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Citric Acid Monohydrate

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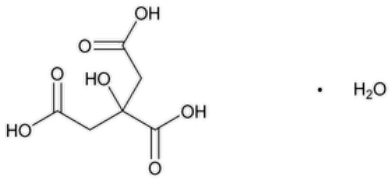

$C_6H_8O_7 \cdot H_2O$ 210.14

1,2,3-Propanetricarboxylic acid, 2-hydroxy-, monohydrate CAS RN®: 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

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**▲ (CN 1-May-2020) **:** 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. Titrate 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

• **Residue on Ignition ⟨281⟩:** NMT 0.1%, determined on 1.0 g

• **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. To 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 the *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).

• **Limit of Oxalic Acid**

Sample stock solution: 0.80 g of Citric Acid Monohydrate in 4 mL of water

Sample solution: To the *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. Transfer 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 the *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.

Change to read:

• **Clarity of Solution**

[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 in water. 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 of *Hydrazine sulfate solution* to the *Methenamine solution* in the 100-mL glass-stoppered flask. Mix, and allow to stand for 24 h. [Note—This suspension is stable for 2 months, provided it is stored in a glass container free from surface 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 95 mL of water.

Standard suspension B: Dilute 10.0 mL of *Opalescence standard* with 90 mL of water.

Sample solution: 200 mg/mL of Citric Acid Monohydrate in water

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 ▲*Visual Comparison ⟨630⟩*▲ (CN 1-May-2019)). [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 or its opalescence is not more pronounced than *Standard suspension A*.

Change to read:

• **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: Prepare as directed in the test for *Clarity of Solution*.

Analysis 1

Samples: 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 water to a separate matching test tube. Compare the *Sample solution* and water in diffused daylight, viewing vertically against a white background (see ▲*Visual Comparison ⟨630⟩*▲ (CN 1-May-2019)).

Acceptance criteria 1: The *Sample solution* is not more intensely colored than water. If more intensely colored, follow *Analysis 2*.

Analysis 2

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

Transfer a sufficient portion of *Standard solution A*, *Standard solution B*, and *Standard solution C* to separate test tubes of colorless, transparent, neutral glass with a flat base and an internal diameter of 15–25 mm to obtain a depth of 40 mm. Compare the *Sample solution* from *Analysis 1* to *Standard solution A*, *Standard solution B*, and *Standard solution C* in diffused daylight, viewing vertically against a white background (see ▲*Visual Comparison ⟨630⟩*▲ (CN 1-May-2019)).

Acceptance criteria 2: The *Sample solution* is not more intensely colored than *Standard solutions A, B,* and *C*.

• **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⟩**

Sample: 0.5 g of Citric Acid Monohydrate

Acceptance criteria: 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

♦

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
CITRIC ACID MONOHYDRATE	Documentary Standards Support	SE2020 Simple Excipients

Chromatographic Database Information: Chromatographic Database

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