

**Sensitivity solution:** 0.05 µg/mL of citalopram hydrobromide from *Standard solution* in *Mobile phase*

**Sample solution:** Transfer 10 Tablets to a 200-mL volumetric flask, add 25 mL of *Buffer*, and shake by mechanical means until disintegrated. Add 100 mL of a mixture of methanol and water (1:1), mix, and sonicate for about 5 min. Allow to cool, dilute with a mixture of methanol and water (1:1) to volume, and mix thoroughly. Allow the excipients to settle. Dilute with *Mobile phase* as necessary to obtain a final concentration of 0.5 mg/mL of citalopram. Pass a portion of this solution through a polytetrafluoroethylene (PTFE) membrane filter having a 0.45-µm or finer pore size, and use the filtrate.

#### Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

**Mode:** LC

**Detector:** UV 239 nm

**Column:** 4.6-mm × 15-cm; 5-µm packing L1

**Column temperature:** 45°

**Flow rate:** 0.8 mL/min

**Injection size:** 20 µL

#### System suitability

**Samples:** *System suitability solution*, *Standard solution*, and *Sensitivity solution*

[NOTE—The relative retention times are given in *Impurity Table 1*.]

#### Suitability requirements

**Resolution:** NLT 3 between citalopram related compound C and citalopram, *System suitability solution*

**Tailing factor:** NMT 1.5, *Standard solution*

**Relative standard deviation:** NMT 5%, *Standard solution*

**Signal-to-noise ratio:** NLT 3, *Sensitivity solution*

#### Analysis

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in each T ablet taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

$r_U$  = peak response for each citalopram related compound from the *Sample solution*

$r_S$  = peak response of the corresponding peak in the *Standard solution*

$C_S$  = concentration of citalopram hydrobromide in the *Standard solution* (mg/mL)

$C_U$  = nominal concentration of citalopram hydrobromide in the *Sample solution* (mg/mL)

$M_{r1}$  = molecular weight of citalopram, 324.39

$M_{r2}$  = molecular weight of citalopram hydrobromide, 405.30

$F$  = relative response factor for each impurity relative to citalopram (free base)

#### Acceptance criteria

**Individual impurities:** See *Impurity Table 1*.

**Total impurities:** NMT 0.8%

**Impurity Table 1**

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Citalopram related compound A	0.43	0.77	0.2
Citalopram related compound B	0.60	0.98	0.25
Citalopram related compound C	0.83	0.69	0.25

**Impurity Table 1** (Continued)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Citalopram	1.0	—	—
Citalopram related compound E	1.32	0.91	0.1
Any other individual unidentified impurity	—	1.0	0.2

#### ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature.

• **USP REFERENCE STANDARDS** <11>

USP Citalopram Hydrobromide RS

USP Citalopram Related Compound A RS

1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carboxamide.

$C_{20}H_{23}FN_2O_2$  342.22

USP Citalopram Related Compound B RS

1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-3-hydroxy-1,3-dihydroisobenzofuran-5-carbonitrile.

$C_{20}H_{21}FN_2O_2$  340.22

USP Citalopram Related Compound C RS

3-(3-*N,N*-Dimethylamino)-1-(4-fluorophenyl)-6-cyano-1(3*H*)-isobenzofuranone.

$C_{20}H_{19}FN_2O_2$  338.22

USP Citalopram Related Compound E RS

1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydrobenzofuran-5-carbonitrile-*N*-oxide.

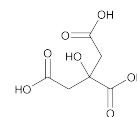
$C_{20}H_{21}FN_2O_2$  340.22

USP Citalopram Related Compound F RS

Dimethyl-(1-methyl-3,3-diphenylallyl)amine hydrochloride.

$C_{18}H_{21}NHCl$  286.64

## Anhydrous Citric Acid



$C_6H_8O_7$

1,2,3-Propanetricarboxylic acid, 2-hydroxy-; Citric acid [77-92-9].

192.13

#### DEFINITION

Anhydrous Citric Acid 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 Anhydrous Citric Acid; record weight accurately.

**Analysis:** Dissolve the *Sample* in 50 mL of water. 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

### 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 in water. 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

**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 for the *Sample solution*, except use 15 mL of *Standard sulfate solution B* instead of the *Sample stock solution*.

### Analysis

**Samples:** *Standard solution* and *Sample 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, dilute with water to volume, and mix. 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.

**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.

**Sample solution:** Dissolve 20.0 g of Anhydrous Citric Acid 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.

**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 *Sample solution*, dilute the combined extracts with chloroform to volume, and mix.

### Fluorometric conditions

**Excitation wavelength:** 392 nm

**Emission wavelength:** 518 nm

### Analysis

**Samples:** *Standard solution* and *Sample 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 Anhydrous Citric Acid in water

**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. 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:** *Standard solution* and *Sample 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 Anhydrous Citric Acid is used can be met. Where the label states that Anhydrous Citric Acid 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 Anhydrous Citric Acid is used can be met.

- **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 to 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 25.0 mL of *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 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 Anhydrous Citric Acid 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 *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  $90 \pm 1^\circ$  for  $60 \pm 0.5$  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)**

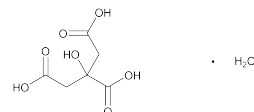
USP Citric Acid RS

USP Endotoxin RS

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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  
[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  $105^\circ$  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****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. 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 *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%).