

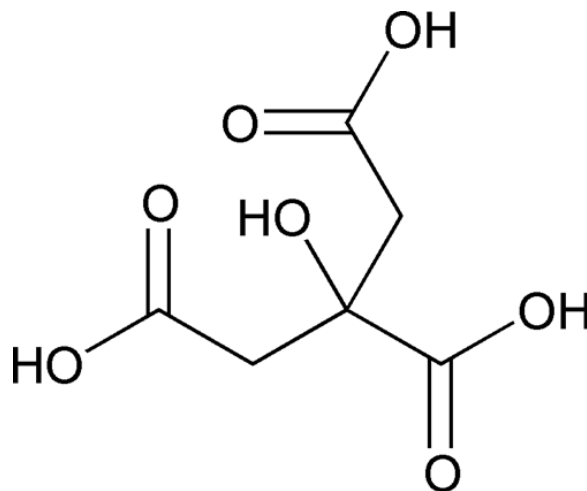
BRIEFING

Anhydrous Citric Acid, *USP 28* page 483 and page 1851 in *PF 30(5)* [Sept.–Oct. 2004]. The test for *Organic volatile impurities* is omitted to comply with the Stage 6 Harmonization Draft. It is proposed to implement the revision via the *Fourth Interim Revision Announcement* pertaining to *USP 28–NF 23*, with an official date of Aug. 1, 2005.

(EMC: J. Lane) RTS—42152-1

Add the following:

▲ Anhydrous Citric Acid



$C_6H_8O_7$ 192.13

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

» Anhydrous Citric Acid contains not less than 99.5 percent and not more than 100.5 percent of $C_6H_8O_7$, calculated on the anhydrous basis.

Add the following:

■ **Packaging and storage**—Preserve in tight containers. No storage requirements specified. ■_{2S} (*USP28*)

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*.

Clarity of solution—[NOTE—The *Test solution* is to be compared to *Reference suspension A* in diffused daylight 5 minutes after preparation of *Reference suspension A*.]

Hydrazine sulfate solution—Transfer 1.0 g of hydrazine sulfate to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Allow to stand for 4 to 6 hours 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—[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.] 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 hours.

Opalescence standard—[NOTE—This suspension should not be used beyond 24 hours after preparation.] Transfer 15.0 mL of the *Primary opalescent suspension* to a 1000-mL volumetric flask, dilute with water to volume, and mix.

Reference suspensions—Transfer 5.0 mL of the *Opalescence standard* to a 100-mL volumetric flask, dilute with water to volume, and mix to obtain *Reference suspension A*. Transfer 10.0 mL of the *Opalescence standard* to a second 100-mL volumetric flask, dilute with water to volume, and mix to obtain *Reference suspension B*.

Test solution—Dissolve 2.0 g of Anhydrous Citric Acid in about 5 mL of water, dilute with water to 10 mL, and mix.

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

Color of solution—

Standard stock solutions—Prepare three solutions, *A*, *B*, and *C*, containing, respectively, the following parts of ferric chloride CS, cobaltous chloride CS, cupric sulfate CS, and dilute hydrochloric acid (10 g per L):

A—2.4:0.6:0:7.0.

B—2.4:1.0:0.4:6.2.

C—9.6:0.2:0.2:0.

Standard solutions—[NOTE—Prepare the *Standard solutions* immediately before use.] Transfer 2.5 mL of *Standard stock solution A* to a 100-mL volumetric flask, dilute with dilute hydrochloric acid (10 g per L) to volume, and mix to obtain *Standard solution A*. Transfer 2.5 mL of *Standard stock solution B* to a 100-mL volumetric flask, dilute with dilute hydrochloric acid (10 g per L) to volume, and mix to obtain *Standard solution B*. Transfer 0.75 mL of *Standard stock solution C* to a 100-mL volumetric flask, dilute with dilute hydrochloric acid (10 g per L) to volume, and mix to obtain *Standard solution C*.

Test solution—Use the *Test solution* prepared as directed in the test for *Clarity of solution*.

Procedure—Transfer a sufficient portion of the *Test solution* to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 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 *Test solution*, *Standard solution A*, *Standard solution B*, *Standard solution C*, and water in diffused daylight, viewing vertically against a white background (see *Visual Comparison* under *Spectrophotometry and Light-Scattering* (851)). The *Test solution* is not more intensely colored than *Standard solutions A*, *B*, *C* or water.

Identification, Infrared Absorption (197K)—Dry the substance to be examined at 105° for 2 hours.

Bacterial endotoxins (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.

Sterility (71)—Where the label states that Anhydrous Citric Acid is sterile, it meets the requirements for *Sterility* (71) in the relevant dosage form monograph(s) in which Anhydrous Citric Acid is used.

Water, Method I (921): not more than 1.0%.

Residue on ignition (281): not more than 0.1%, determined on 1.0 g.

Readily carbonizable substances—Transfer 1.0 g of powdered Anhydrous Citric Acid to a 22- × 175-mm test tube previously rinsed with 10 mL of sulfuric acid TS and allowed to drain for 10 minutes. Add 10 mL of sulfuric acid TS, agitate until solution is complete, and immerse in a water bath at $90 \pm 1^\circ$ for 60 ± 0.5 minutes, 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: 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.

Sulfate—

Standard sulfate solution A—To 181 mg of dibasic potassium sulfate in a 100-mL volumetric flask, add a few mL of 30% alcohol, swirl to dissolve, dilute with 30% alcohol to volume, and mix. 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 of sulfate per mL.

Standard sulfate solution B—To 181 mg of dibasic potassium sulfate in a 100-mL volumetric flask, add a few mL of water, swirl to dissolve, dilute with water to volume, and mix. 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 of sulfate per mL.

Citric acid solution—Dissolve 2.0 g of Anhydrous Citric Acid in about 10 mL of water, dilute with water to 30 mL, and mix.

Procedure—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 minute. To 2.5 mL of the resulting suspension, add 15 mL of the *Citric acid solution* and 0.5 mL of 5 N acetic acid, and mix (test solution). Prepare the Standard solution in the same manner, except use 15 mL of *Standard sulfate solution B* instead of the *Citric acid solution*: any turbidity produced in the test solution after 5 minutes standing is not greater than that produced in the Standard solution (0.015%).

Heavy metals (231): 0.001%.

Limit of oxalic acid—Prepare a citric acid solution by dissolving 800 mg of Anhydrous Citric Acid in 4 mL of water. Add 3 mL of hydrochloric acid and 1 g of granular zinc, boil for 1 minute, and allow to stand for 2 minutes. 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 minutes (test solution). Concomitantly prepare a control solution in the same manner, except use 4 mL of an oxalic acid solution containing 0.10 mg per mL, equivalent to 0.0714 mg of anhydrous oxalic acid per mL, instead of the citric acid solution: any pink color produced in the test solution is not more intense than that produced in the control solution (0.036%).

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, transfer 1.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix.

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.

Test 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.


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

Procedure—Determine the fluorescence intensities of the *Test solution* and the *Standard solution* in a fluorometer set at an excitation wavelength of 392 nm and an emission wavelength of 518 nm, using the *Blank solution* to set the instrument to zero. The fluorescence of the *Test solution* does not exceed that of the *Standard solution* (0.2 µg per g).

Delete the following:

* ~~Organic volatile impurities, Method IV (467): meets the requirements. 4~~

Assay—Place about 0.550 g of Anhydrous Citric Acid in a tared flask, and weigh accurately. Dissolve in 50 mL of water, add 0.5 mL of phenolphthalein TS, and titrate with 1 N sodium hydroxide VS. Each mL of 1 N sodium hydroxide is equivalent to 64.03 mg of C₆H₈O₇.  USP28

Auxiliary Information— *Staff Liaison* : [Justin Lane, B.S., Scientific Associate](#)

Expert Committee : (EMC) Excipients: Monograph Content

USP28–NF23 Page 483

Pharmacopeial Forum : Volume No. 31(2) Page 607

Phone Number : 1-301-816-8323