Description Cimetidine occurs as a white crystalline powder. It is odorless, and has a bitter taste.

It is freely soluble in methanol and in acetic acid (100), sparingly soluble in ethanol (95), slightly soluble in water, and practically insoluble in diethyl ether.

It dissolves in dilute hydrochloric acid.

It is gradually colored by light.

Identification (1) To 0.1 mL of a solution of Cimetidine in ethanol (95) (1 in 100) add 5 mL of citric acid-acetic anhydride TS, and heat in a water bath for 15 minutes: a red-purple color develops.

(2) Determine the infrared absorption spectrum of Cimetidine, previously dried, as directed in the potassium bromide disk method under the Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wave numbers.

pH Dissolve 0.5 g of Cimetidine in 50 mL of freshly boiled and cooled water, shake for 5 minutes and filter: the pH of the filtrate is between 9.0 and 10.5.

Melting point 140 - 144°C

Purity (1) Clarity and color of solution—Dissolve 1.0 g of Cimetidine in 10 mL of methanol: the solution is clear and colorless to pale yellow in color.

(2) Heavy metals—Proceed with 2.0 g of Cimetidine according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

(3) Arsenic—Dissolve 1.0 g of Cimetidine in 5 mL of dilute hydrochloric acid, and perform the test with this solution using Apparatus B (not more than 2 ppm).

(4) Related substances—Dissolve 0.5 g of Cimetidine in 10 mL of methanol, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add methanol to make exactly 100 mL. Pipet 1 mL of this solution, add methanol to make exactly 10 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 4 μL each of the sample solution and the standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, methanol and ammonia solution (28) (21:2:2) to a distance of about 15 cm, air-dry the plate, and then dry at 80°C for 30 minutes. Allow the plate to stand in iodine vapor for 45 minutes: the spots other than the principal spot from the sample solution are not more intense than the spot from the standard solution.

Loss on drying Not more than 0.5% (1 g, 105°C, 3 hours).

Residue on ignition Not more than 0.25% (1 g).

Assay Weigh accurately about 0.24 g of Cimetidine, previously dried, dissolve in 75 mL of acetic acid (100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination, and make any necessary correction.

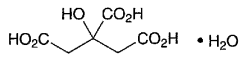
Each mL of 0.1 mol/L perchloric acid VS
= 25.234 mg of $C_{10}H_{16}N_6S$

Containers and storage Containers—Well-closed containers.

Storage—Light-resistant.

Citric Acid

クエン酸



$C_6H_8O_7.H_2O$: 210.14

2-Hydroxypropane-1,2,3-tricarboxylic acid monohydrate [*5949-29-1*]

Citric Acid contains not less than 99.5% of $C_6H_8O_7H_2O$.

Description Citric Acid occurs as colorless crystals, white granules or crystalline powder. It is odorless, and has a strong acid taste.

It is very soluble in water, freely soluble in ethanol (95) and in acetone, and sparingly soluble in diethyl ether.

It is efflorescent in dry air.

Identification A solution of Citric Acid (1 in 20) changes the color of blue litmus paper to red. The solution, made neutral with ammonia TS, responds to the Qualitative Tests for citrate.

Purity (1) Sulfate—Perform the test with 0.5 g of Citric Acid. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid VS (not more than 0.048%).

(2) Oxalate—Dissolve 1.0 g of Citric Acid in 2 mL of dilute ethanol, neutralize with ammonia TS, add 0.2 mL of calcium chloride TS, and allow to stand for 1 hour: no turbidity is produced.

(3) Heavy metals—Proceed with 2.0 g of Citric Acid according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

(4) Calcium—Dissolve 1.0 g of Citric Acid in 10 mL of water, neutralize with ammonia TS, and add 1 mL of ammonium oxalate TS: no turbidity is produced.

(5) Arsenic—Prepare the test solution with 2.0 g of Citric Acid according to Method 1, and perform the test using Apparatus B (not more than 1 ppm).

(6) Related substances—Dry 0.50 g of Citric Acid at 105°C for 3 hours. Cool, dissolve the mass in 10 mL of acetone, and use this solution as the sample solution. Perform the test with this solution as directed under the Paper Chromatography. Spot 5 μL of the sample solution on a filter paper. Develop the paper with the upper layer solution of a mixture of 1-butanol, formic acid and water (8:3:2) to a distance of about 25 cm, and air-dry the filter paper. Spray evenly bromophenol blue TS, pH 7.0, on the paper: any yellow spot other than the principal spot does not appear.

(7) Polycyclic aromatic hydrocarbon—Dissolve 25 g of Citric Acid in 30 mL of water by heating. Cool, extract with three 20-mL portions of hexane for ultraviolet-visible spectrophotometry, and then each time separate the *n*-hexane layer by centrifuging between 2500 and 3000 revolutions per minute for 10 minutes. Combine the *n*-hexane extracts, and concentrate to 1 to 2 mL by evaporating. Cool, dilute with hexane for ultraviolet-visible spectrophotometry to make 10 mL, and use this solution as the sample solution. Determine the absorbance between 260 nm and 350 nm as directed under the Ultraviolet-visible Spectrophotometry using

the solution of *n*-hexane prepared with 30 mL of water in the same manner as the blank: the absorbance is not more than 0.05.

(8) Readily carbonizable substances—Perform the test with 0.5 g of Citric Acid, provided that the solution is heated at 90°C for 1 hour: the solution has no more color than Matching Fluid K.

Residue on ignition Not more than 0.10% (2 g).

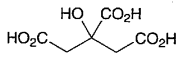
Assay Weigh accurately about 1.5 g of Citric Acid, dissolve in 25 mL of water, and titrate with 1 mol/L sodium hydroxide VS (indicator: 2 drops of phenolphthalein TS).

Each mL of 1 mol/L sodium hydroxide VS
= 70.05 mg of $C_6H_8O_7.H_2O$

Containers and storage Containers—Tight containers.

Anhydrous Citric Acid

無水クエン酸



$C_6H_8O_7$: 192.12
2-Hydroxypropane-1,2,3-tricarboxylic acid [*77-92-9*]

Anhydrous Citric Acid contains not less than 99.5% of $C_6H_8O_7$, calculated on the anhydrous basis.

Description Anhydrous Citric Acid occurs as colorless crystals, white granules or crystalline powder. It is odorless, and has a strong acid taste.

It is very soluble in water, freely soluble in methanol, in ethanol (95) and in acetone, and slightly soluble in diethyl ether.

Identification A solution of Anhydrous Citric Acid (1 in 20) changes the color of the blue litmus paper to red. The solution, made neutral with ammonia TS, responds to the Qualitative Tests for citrate.

Purity **(1)** Sulfate—Perform the test with 0.5 g of Anhydrous Citric Acid. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid VS (not more than 0.048%).

(2) Oxalate—Dissolve 1.0 g of Anhydrous Citric Acid in 2 mL of dilute ethanol, neutralize with ammonia TS, add 0.2 mL of calcium chloride TS, and allow to stand for 1 hour: no turbidity is produced.

(3) Heavy metals—Proceed with 2.0 g of Anhydrous Citric Acid according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

(4) Calcium—Dissolve 1.0 g of Anhydrous Citric Acid in 10 mL of water, neutralize with ammonia TS, and add 1 mL of ammonium oxalate TS: no turbidity is produced.

(5) Arsenic—Prepare the test solution with 2.0 g of Anhydrous Citric Acid according to Method 1, and perform the test using Apparatus B (not more than 1 ppm).

(6) Related substances—Dry 0.50 g of Anhydrous Citric Acid at 105°C for 3 hours. After cooling, dissolve the mass in exactly 10 mL of acetone, and use this solution as the sample solution. Perform the test with this solution as directed under the Paper Chromatography. Spot 5 μL of the sample solution on a filter paper. Develop the paper with the upper layer of a mixture of 1-butanol, formic acid and water (8:3:2) to a distance of about 25 cm, and air-dry the filter paper. Spray evenly bromophenol blue TS, pH 7.0, on the paper: any yellow spot other than the principal spot does not appear.

(7) Polycyclic aromatic hydrocarbon—Dissolve 25 g of Anhydrous Citric Acid in 30 mL of water by heating at about 50°C, cool, and extract with three 20-mL portions of hexane for ultraviolet-visible spectrophotometry. Each time separate the *n*-hexane layer by centrifuging between 2500 and 3000 revolutions per minute for 10 minutes. Combine the *n*-hexane extracts, and concentrate to 1 to 2 mL by evaporating. Cool, dilute with hexane for ultraviolet-visible spectrophotometry to make exactly 10 mL, and use this solution as the sample solution. Determine the absorbance between 260 nm and 350 nm as directed under the Ultraviolet-visible Spectrophotometry using the solution of *n*-hexane prepared with 30 mL of water in the same manner as the blank: the absorbance is not more than 0.05.

(8) Readily carbonizable substances—Perform the test with 0.5 g of Anhydrous Citric Acid, provided that the solution is heated at 90°C for 1 hour: the solution has no more color than Matching Fluid K.

Water Not more than 0.5% (2 g, direct titration).

Residue on ignition Not more than 0.10% (2 g).

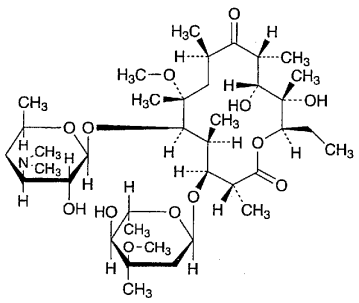
Assay Weigh accurately about 1.5 g of Anhydrous Citric Acid, dissolve in 25 mL of water, and titrate with 1 mol/L sodium hydroxide VS (indicator: 2 drops of phenolphthalein TS).

Each mL of 1 mol/L sodium hydroxide VS
= 64.04 mg of $C_6H_8O_7$

Containers and storage Containers—Tight containers.

Clarithromycin

クラリスロマイシン



$C_{38}H_{69}NO_{13}$: 747.95
(2*R*,3*S*,4*S*,5*R*,6*R*,8*R*,10*R*,11*R*,12*S*,13*R*)-5-(3,4,6-Trideoxy-3-dimethylamino-β-D-*xylo*-hexopyranosyloxy)-3-(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyloxy)-11,12-dihydroxy-6-methoxy-2,4,6,8,10,12-hexamethyl-9-oxopentadecan-13-olide
[*81103-11-9*]