the dried basis.

Description Ciclosporin occurs as a white powder.

It is very soluble in acetonitrile, in methanol and in ethanol (95), freely soluble in diethyl ether, and practically insoluble in water.

Identification Determine the infrared absorption spectrum of Ciclosporin 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.

Optical rotation $[\alpha]_D^{20}$: -185 – $-193°$ (0.1 g calculated on the dried basis, methanol, 20 mL, 100 mm).

Purity (1) Clarity and color of solution—Dissolve 1.0 g of Ciclosporin in 10 mL of ethanol (95): the solution is clear, and has no more color than the following control solution (1), (2) or (3).

Control solution (1): To exactly 3.0 mL of Ferric Chloride Stock CS and exactly 0.8 mL of Cobaltous Chloride Stock CS add diluted hydrochloric acid (1 in 40) to make exactly 100 mL.

Control solution (2): To exactly 3.0 mL of Ferric Chloride Stock CS, exactly 1.3 mL of Cobaltous Chloride Stock CS and exactly 0.5 mL of Cupric Sulfate Stock CS add diluted hydrochloric acid (1 in 40) to make exactly 100 mL.

Control solution (3): To exactly 0.5 mL of Iron (III) chloride Stock CS and exactly 1.0 mL of Cobaltous Chloride Stock CS add diluted hydrochloric acid (1 in 40) to make exactly 100 mL.

(2) Heavy metals—Proceed with 1.0 g of Ciclosporin according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).

(3) Related substances—Use the sample solution obtained in the Assay as the sample solution. Pipet 2 mL of the sample solution, add a mixture of water and acetonitrile (1:1) to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 20 μL each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions. Determine each peak area of both solutions by the automatic integration method: the total area of all peaks other than the ciclosporin peak from the sample solution is not more than 1.5 times of the peak area of ciclosporin from the standard solution, and the each peak area other than the ciclosporin peak from the sample solution is not more than 0.7 times of the peak area of ciclosporin from the standard solution.

Operating conditions—

Detector, column, column temperature, mobile phase, flow rate, and selection of column: Proceed as directed in the operating conditions in the Assay.

Detection sensitivity: Adjust the detection sensitivity so that the peak height of ciclosporin from 20 μL of the standard solution is about 10 mm.

Time span of measurement: About 2 times as long as the retention time of ciclosporin after the solvent peak.

Loss on drying Not more than 2.0% (1 g, in vacuum at a pressure not exceeding 0.67 kPa, 60°C, 3 hours).

Residue on ignition Not more than 0.1% (0.5 g).

Assay Weigh accurately about 0.03 g each of Ciclosporin and Ciclosporin Reference Standard, previously determined the loss on drying as the same manner as above, and dissolve each in a mixture of water and acetonitrile (1:1) to make exactly 25 mL, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with exactly 20 μL each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas, A_T and A_S, of ciclosporin in each solution.

Amount (mg) of $C_{62}H_{111}N_{11}O_{12}$
= amount (mg) of Ciclosporin Reference Standard, calculated on the dried basis

$$\times \frac{A_S}{A_T}$$

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column about 4 mm in inside diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 to 5 μm in particle diameter). Connect the sample injection port to the column with a stainless steel tube about 0.3 mm in inside diameter and about 1 m in length.

Column temperature: A constant temperature of about 80°C (including the sample injection port and the connecting tube).

Mobile phase: A mixture of water, acetonitrile, *tert*-butyl methyl ether and phosphoric acid (520:430:50:1).

Flow rate: Adjust the flow rate so that the retention time of ciclosporin is about 27 minutes.

Selection of column: Dissolve 3 mg of Ciclosporin U Reference Standard in 2.5 mL of a mixture of water and acetonitrile (1:1), and add 2.5 mL of the standard solution. Proceed with 20 μL of this solution under the above operating conditions, and calculate the resolution. Use the column giving elution of ciclosporin U and ciclosporin in this order with the resolution between these peaks being not less than 1.2.

System repeatability: When the test is repeated 6 times with the standard solution under the above operating conditions, the relative standard deviation of the peak area of ciclosporin is not more than 1.0%.

Containers and storage Containers—Tight containers.

Storage—Light-resistant.

Cimetidine

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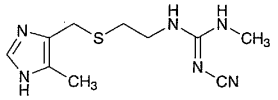

$C_{10}H_{16}N_6S$: 252.34

2-Cyano-1-methyl-3-{2-[(5-methyl-1*H*-imidazol-4-yl)methylsulfanyl]ethyl}guanidine [*51481-61-9*]

Cimetidine, when dried, contains not less than 99.0% of $C_{10}H_{16}N_6S$.

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

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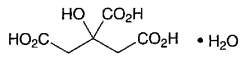

$C_6H_8O_7.H_2O$: 210.14

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