

(4) Bromine or chlorine—Place 10 mL of the sample solution obtained in (1) in a glass-stoppered test tube, add 5 drops of potassium iodide TS and 1 mL of chloroform, and shake for 1 minute: the chloroform layer remains free from a purple color.

(5) Heavy metals—Evaporate 5 mL of Hydrochloric Acid on a water bath to dryness, and add 2 mL of dilute acetic acid and water to the residue to make 50 mL. Perform the test using this solution as the test solution. Prepare the control solution as follows: to 3.0 mL of Standard Lead Solution add 2 mL of dilute acetic acid and water to make 50 mL (not more than 5 ppm).

(6) Arsenic—Prepare the test solution with 1.7 mL of Hydrochloric Acid according to Method 1, and perform the test using Apparatus B (not more than 1 ppm).

(7) Mercury—Dilute 20 mL of Hydrochloric Acid with water to make exactly 100 mL, and use the solution as the sample solution. Perform the test with this sample solution as directed under the Atomic Absorption Spectrophotometry (cold vapor type). Place the sample solution in a sample bottle of the atomic absorption spectrophotometer, add 10 mL of tin (II) chloride-sulfuric acid TS, connect the bottle immediately to the spectrophotometer, circulate air, and determine the absorbance  $A_T$  of the sample solution after the recorder reading has risen rapidly, and becomes constant at a wavelength of 253.7 nm. On the other hand, to 8 mL of Standard Mercury Solution add water to make exactly 100 mL, and determine the absorbance  $A_S$  of the solution obtained by the same procedure as used for the sample solution:  $A_T$  is smaller than  $A_S$  (not more than 0.04 ppm).

**Residue on ignition** Pipet 10 mL of Hydrochloric Acid, add 2 drops of sulfuric acid, evaporate to dryness, and ignite: not more than 1.0 mg of residue remains.

**Assay** Weigh accurately a glass-stoppered flask containing 20 mL of water, add about 3 mL of Hydrochloric Acid, and weigh accurately again. Dilute with 25 mL of water, and titrate with 1 mol/L sodium hydroxide VS (indicator: 2 to 3 drops of methyl red TS).

$$\begin{aligned} \text{Each mL of 1 mol/L sodium hydroxide VS} \\ = 36.461 \text{ mg of HCl} \end{aligned}$$

**Containers and storage** Containers—Tight containers.

## Dilute Hydrochloric Acid

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Dilute Hydrochloric Acid contains not less than 9.5 w/v% and not more than 10.5 w/v% of hydrogen chloride (HCl: 36.46).

**Description** Dilute Hydrochloric Acid is a colorless liquid. It is odorless and has a strong acid taste.

Specific gravity  $d_{20}^{20}$ : about 1.05

**Identification** A solution of Dilute Hydrochloric Acid (1 in 30) changes blue litmus paper to red and responds to the Qualitative Tests for chloride.

**Purity** (1) Sulfate—To 3.0 mL of Dilute Hydrochloric Acid add 5 mL of water and 5 drops of barium chloride TS,

and allow to stand for 1 hour: no turbidity is produced.

(2) Sulfite—To 3.0 mL of Dilute Hydrochloric Acid add 5 mL of water and 1 drop of iodine TS: the color of iodine TS does not disappear.

(3) Bromide or iodide—Place 10 mL of Dilute Hydrochloric Acid in a glass-stoppered test tube, add 1 mL of chloroform and 1 drop of 0.002 mol/L potassium permanganate VS, and shake well: the chloroform layer remains colorless.

(4) Bromine or chlorine—Place 10 mL of Dilute Hydrochloric Acid in a glass-stoppered test tube, add 5 drops of potassium iodide TS and 1 mL of chloroform, and shake for 1 minute: the chloroform layer remains free from a purple color.

(5) Heavy metals—Evaporate 9.5 mL of Dilute Hydrochloric Acid on a water bath to dryness, add 2 mL of dilute acetic acid and water to make 50 mL, and perform the test using this solution as the test solution. Prepare the control solution as follows: to 3.0 mL of Standard Lead Solution add 2 mL of dilute acetic acid and water to make 50 mL (not more than 3 ppm).

(6) Arsenic—Prepare the test solution with 4.0 mL of Dilute Hydrochloric Acid according to Method 1, and perform the test using Apparatus B (not more than 0.5 ppm).

(7) Mercury—Dilute 80 mL of Dilute Hydrochloric Acid with water to make exactly 100 mL, and use this solution as the sample solution. Perform the test with this solution according to the Atomic Absorption Spectrophotometry (cold vapor type). Place the sample solution in a sample bottle of the atomic absorption spectrophotometer, add 10 mL of tin (II) chloride-sulfuric acid TS, connect the bottle immediately to the spectrophotometer, circulate air, and read the absorbance  $A_T$  of the sample solution after the recorder reading has risen rapidly and become constant at a wavelength of 253.7 nm. On the other hand, to 8 mL of Standard Mercury Solution add water to make exactly 100 mL, and read the absorbance  $A_S$  of the solution obtained by the same procedure as used for the sample solution:  $A_T$  is smaller than  $A_S$  (not more than 0.01 ppm).

**Residue on ignition** Pipet 10 mL of Dilute Hydrochloric Acid, add 2 drops of sulfuric acid, evaporate to dryness, and ignite: the mass of the residue is not more than 1.0 mg.

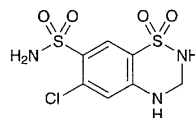
**Assay** Measure exactly 10 mL of Dilute Hydrochloric Acid, and dilute with 20 mL of water. Titrate with 1 mol/L sodium hydroxide VS (indicator: 2 to 3 drops of methyl red TS).

$$\begin{aligned} \text{Each mL of 1 mol/L sodium hydroxide VS} \\ = 36.461 \text{ mg of HCl} \end{aligned}$$

**Containers and storage** Containers—Tight containers.

## Hydrochlorothiazide

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$C_7H_8ClN_3O_4S_2$ : 297.74  
6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide [58-93-5]

Hydrochlorothiazide, when dried, contains not less than 99.0% of  $C_7H_8ClN_3O_4S_2$ .

**Description** Hydrochlorothiazide occurs as white crystals or crystalline powder. It is odorless, and has a slightly bitter taste.

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

It dissolves in sodium hydroxide TS.

Melting point: about 267°C (with decomposition).

**Identification (1)** To 5 mg of Hydrochlorothiazide add 5 mL of disodium chlomotropate TS, and allow to stand for 5 minutes: a purple color develops.

**(2)** Fuse a mixture of 0.1 g of Hydrochlorothiazide and 0.5 g of sodium carbonate decahydrate cautiously: the gas evolved changes moistened red litmus paper to blue. After cooling, crush with a glass rod, add 10 mL of water, stir, and filter. To 4 mL of the filtrate add 2 drops of hydrogen peroxide (30), 5 mL of diluted hydrochloric acid (1 in 5) and 2 to 3 drops of barium chloride TS: a white precipitate is produced.

**(3)** To 4 mL of the filtrate obtained in (2) add 5 mL of dilute nitric acid and 3 drops of silver nitrate TS: a white precipitate is produced.

**(4)** Dissolve 0.012 g of Hydrochlorothiazide in 100 mL of sodium hydroxide TS. Dilute 10 mL of the solution with water to make 100 mL. Determine the absorption spectrum of the solution as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Hydrochlorothiazide Reference Standard prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

**Purity (1) Chloride**—Dissolve 1.0 g of Hydrochlorothiazide in 30 mL of acetone, add 6 mL of dilute nitric acid and water to make 50 mL, and perform the test using this solution as the test solution. Prepare the control solution as follows: to 1.0 mL of 0.01 mol/L hydrochloric acid VS add 30 mL of acetone, 6 mL of dilute nitric acid and water to make 50 mL (not more than 0.036%).

**(2) Sulfate**—Dissolve 1.0 g of Hydrochlorothiazide in 30 mL of acetone, add 1 mL of dilute hydrochloric acid and water to make 50 mL, and perform the test using this solution as the test solution. Prepare the control solution as follows: to 1.0 mL of 0.005 mol/L sulfuric acid VS add 30 mL of acetone, 1 mL of dilute hydrochloric acid and water to make 50 mL (not more than 0.048%).

**(3) Heavy metals**—Proceed with 1.0 g of Hydrochlorothiazide 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).

**(4) Primary aromatic amines**—Dissolve 0.08 g of Hydrochlorothiazide in acetone to make exactly 100 mL. Measure exactly 1 mL of the solution, add 3.0 mL of dilute hydrochloric acid, 3.0 mL of water and 0.15 mL of sodium nitrite TS, shake, and allow to stand for 1 minute. Shake this solution with 1.0 mL of ammonium amidosulfate TS, al-

low to stand for 3 minutes, then add 1.0 mL of *N*-(1-naphthyl)-*N'*-diethylethylenediamine oxalate TS, shake, and allow to stand for 5 minutes. Perform the test with this solution as directed under the Ultraviolet-visible Spectrophotometry, using a solution prepared with 1.0 mL of acetone in the same manner as the blank: the absorbance at 525 nm is not more than 0.10.

**Loss on drying** Not more than 1.0% (1 g, 105°C, 2 hours).

**Residue on ignition** Not more than 0.10% (1 g).

**Assay** Weigh accurately about 0.03 g each of Hydrochlorothiazide and Hydrochlorothiazide Reference Standard, previously dried, and dissolve in 150 mL of the mobile phase, add exactly 10 mL each of the internal standard solution, then add the mobile phase to make 200 mL, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with 20  $\mu$ L each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the ratios,  $Q_T$  and  $Q_S$ , of the peak area of hydrochlorothiazide to that of the internal standard.

$$\begin{aligned} &\text{Amount (mg) of } C_7H_8ClN_3O_4S_2 \\ &= \text{amount (mg) of Hydrochlorothiazide} \\ &\quad \text{Reference Standard} \\ &\quad \times \frac{Q_T}{Q_S} \end{aligned}$$

**Internal standard solution**—A solution of 4-aminoacetophenone in acetonitrile (9 in 2000).

**Operating conditions**—

**Detector:** An ultraviolet absorption photometer (wavelength: 254 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 (5  $\mu$ m in particle diameter).

**Column temperature:** A constant temperature of about 25°C.

**Mobile phase:** A mixture of 0.1 mol/L sodium dihydrogenphosphate TS, pH 3.0 and acetonitrile (9:1).

**Flow rate:** Adjust the flow rate so that the retention time of hydrochlorothiazide is about 10 minutes.

**Selection of column:** Proceed with 20  $\mu$ L of the standard solution under the above operating conditions, and calculate the resolution. Use a column giving elution of hydrochlorothiazide and the internal standard in this order with the resolution between these peaks being not less than 4.

**Containers and storage** Containers—Well-closed containers.

## Hydrocortisone

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