of Diltiazem Hydrochloride in 20 mL of water: the solution is clear and colorless.

(2) Sulfate—Perform the test with 1.0 g of Diltiazem Hydrochloride. Prepare the control solution with 0.50 mL of 0.005 mol/L sulfuric acid VS (not more than 0.024%).

(3) Heavy metals—Proceed with 2.0 g of Diltiazem Hydrochloride 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) Arsenic—Place 1.0 g of Diltiazem Hydrochloride in a decomposition flask, add 5 mL of nitric acid and 2 mL of sulfuric acid, put a small funnel on the neck of the flask, and heat cautiously until white fumes are evolved. After cooling, add 2 mL of nitric acid, heat, and repeat this procedure twice, add several 2-mL portions of hydrogen peroxide (30), and heat until the solution becomes colorless to pale yellow. After cooling, add 2 mL of saturated solution of ammonium oxalate monohydrate, and heat again until white fumes are evolved. After cooling, add water to make 5 mL, use this solution as the test solution, and perform the test using apparatus B: the test solution has no more color than the following control solution (not more than 2 ppm).

Control solution: Proceed in the same manner as the test solution without Diltiazem Hydrochloride, add 2.0 mL of Standard Arsenic Solution and water to make 5 mL, and proceed in the same manner as the test solution.

(5) Related substances—Dissolve 0.050 g of Diltiazem Hydrochloride in 50 mL of diluted ethanol (95) (4 in 5), and use this solution as the sample solution. Measure exactly 1 mL of the sample solution, add diluted ethanol (95) (4 in 5) 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 automatic integration method: the total peak area of peaks other than the peak of diltiazem obtained from the sample solution is not more than 3/5 of the peak area of diltiazem obtained from the standard solution.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 240 nm).

Column: A stainless steel column about 4 mm in inside diameter and 15 to 30 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 to 10 μm in particle diameter).

Column temperature: A constant temperature of about 50°C.

Mobile phase: Dissolve 8 g of sodium acetate trihydrate and 1.5 g of *d*-camphorsulfonic acid in 500 mL of water, and filter using a membrane filter (0.4 μm in pore size). Add 250 mL each of acetonitrile and methanol to the filtrate, and adjust the solution to a pH of 6.6 by adding sodium acetate trihydrate.

Flow rate: Adjust the flow rate so that the retention time of diltiazem is about 9 minutes.

Selection of column: Weigh 0.03 g of Diltiazem Hydro chloride, 0.02 g of *d*-3-hydroxy-cis-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(*p*-methoxyphenyl)-1,5-benzothiazepin-4-(5*H*)-one hydrochloride and 0.02 g of phenylbenzoate, dissolve in 160 mL of ethanol (99.5), and add water to make 200 mL. Using 20 μL of this solution, perform the test as directed under the Liquid Chromatography under the above operating conditions: *d*-3-hydroxy-cis-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(*p*-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one, diltiazem and phenyl benzoate are eluted in this order, and the resolution of *d*-3-hydroxy-cis-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(*p*-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one and diltiazem and the resolution of diltiazem and phenyl benzoate are not less than 2.5, respectively.

Detection sensitivity: Adjust the detection sensitivity so that the peak height obtained from 20 μL of the standard solution is between 5 mm and 15 mm.

Time span of measurement: About twice as long as the retention time of diltiazem after the solvent peak.

Loss on drying Not more than 0.5% (1 g, 105°C, 2 hours).

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

Assay Weigh accurately about 0.7 g of Diltiazem Hydrochloride, previously dried, dissolve in 2.0 mL of formic acid, add 60 mL of acetic anhydride, 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
= 45.10 mg of $C_{22}H_{26}N_2O_4S.HCl$

Containers and storage Containers—Tight containers.
Storage—Light-resistant.

Dimemorfan Phosphate

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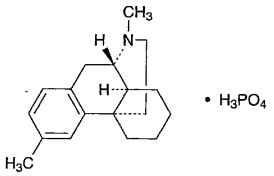


$C_{18}H_{25}N.H_3PO_4$: 353.39
(9*S*,13*S*,14*S*)-3,17-Dimethylmorphinan monophosphate
[*36304-84-4*]

Dimemorfan Phosphate, when dried, contains not less than 98.5% of $C_{18}H_{25}N.H_3PO_4$.

Description Dimemorfan Phosphate occurs as white to pale yellowish white crystals or crystalline powder.

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

Melting point: about 265°C (with decomposition).

Identification (1) Determine the absorption spectrum of a solution of Dimemorfan Phosphate (1 in 5000) as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wavelenghs.

(2) Determine the infrared absorption spectrum of Dimemorfan Phosphate, previously dried, as directed in the potassium bromide disk method under the Infrared Spec-

trophotometry, and compare the spectrum with the Reference Spectrum: both spectra exhibits similar intensities of absorption at the same wave numbers.

(3) To 2 mL of a solution of Dimemorfan Phosphate (1 in 100) add 2 to 3 drops of silver nitrate TS: a yellow precipitate is formed, and it dissolves on the addition of dilute nitric acid.

Optical rotation $[\alpha]_D^{20}$: +25 - +27° (after drying, 1 g, methanol, 100 mL, 100 mm).

pH Dissolve 1.0 g of Dimemorfan Phosphate in 100 mL of water: the pH of this solution is between 4.0 and 5.0.

Purity **(1)** Heavy metals—Proceed with 1.0 g of Dimemorfan Phosphate according to Method 1, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).

(2) Arsenic—Prepare the test solution with 1.0 g of Dimemorfan Phosphate according to Method 3, and perform the test using Apparatus B. Use 10 mL of a solution of magnesium nitrate hexahydrate in ethanol (95) (1 in 10) (not more than 2 ppm).

(3) Related substances—Dissolve 0.10 g of Dimemorfan Phosphate 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, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 10 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 methanol, chloroform and ammonia solution (28) (150:150:1) to a distance of about 10 cm, and air-dry the plate. Spray evenly the plate with Dragendorff's TS for spraying: 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).

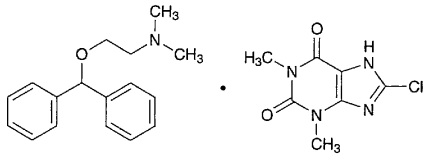
Assay Weigh accurately about 0.6 g of Dimemorfan Phosphate, previously dried, dissolve in 100 mL of acetic acid (100), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination, and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 35.340 mg of $C_{18}H_{25}N.H_3PO_4$

Containers and storage Containers—Tight containers.

Dimenhydrinate

ジメンヒドリナート



$C_{17}H_{21}NO.C_7H_7ClN_4O_2$: 469.96
N-[2-(Diphenylmethyloxy)ethyl]-*N*,*N*-dimethylamine—8-chloro-3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dione (1/1) [*523-87-5*]

Dimenhydrinate, when dried, contains not less than 53.0% and not more than 55.5% of diphenhydramine ($C_{17}H_{21}NO$: 255.36), and not less than 44.0% and not more than 47.0% of 8-chlorotheophylline ($C_7H_7ClN_4O_2$: 214.61).

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

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

Identification **(1)** Dissolve 0.5 g of Dimenhydrinate in 30 mL of dilute ethanol, add 30 mL of water, and use this solution as the sample solution. Transfer 30 mL of the sample solution to a separator, and add 2 mL of ammonia solution (28). Extract with two 10-mL portions of diethyl ether, combine the diethyl ether extracts, wash the combined extracts with 5 mL of water, and then extract the combined extracts with 15 mL of diluted hydrochloric acid (1 in 100). With this acid extract perform the following tests.

(i) To 5 mL of this acid extract add 5 drops of Reinecke salt TS: a light red precipitate is produced.

(ii) To 10 mL of this acid extract add 10 mL of 2,4,6-trinitrophenol TS dropwise, and allow to stand for 30 minutes. Collect the precipitate by filtrating, recrystallize from dilute ethanol, and dry at 105°C for 30 minutes: the crystals melt between 128°C and 133°C.

(2) To 30 mL of the sample solution obtained in the Identification (1) add 2 mL of dilute sulfuric acid, and cool for 30 minutes. Scratch the inside wall of the container frequently to facilitate crystallization. Filter, and wash the white crystals with a small amount of ice-cooled water. Dry the crystals for 1 hour at 105°C: the crystals melt between 300°C and 305°C with decomposition.

(3) To 0.01 g of the crystals obtained in the Identification (2) add 10 drops of hydrogen peroxide TS and 1 drop of hydrochloric acid, and evaporate on a water bath to dryness: the residue shows a yellow-red color. When the dish containing the residue is held over a vessel containing 2 to 3 drops of ammonia TS, the color changes to red-purple, which is discharged on the addition of 2 to 3 drops of sodium hydroxide TS.

(4) Mix well 0.05 g of the crystals obtained in the Identification (2) with 0.5 g of sodium peroxide in a nickel crucible, and heat until the mass melts. Cool, dissolve the melted mass in 20 mL of water, and acidify with dilute nitric acid: the solution responds to the Qualitative Tests for chloride.

Melting point 102 - 107°C

Purity **(1)** Chloride—Transfer 50 mL of the filtrate obtained in the Assay (2) to a Nessler tube, add 1 mL of nitric acid, and allow to stand for 5 minutes: the turbidity of the solution is not greater than that of the following control solution.

Control solution: Dilute 0.25 mL of 0.01 mol/L hydrochloric acid VS with 6 mL of dilute nitric acid and with water to make 50 mL, add 1 mL of silver nitrate TS, and allow to stand for 5 minutes (not more than 0.044%).

(2) Bromide and iodide—Place 0.10 g of Dimenhydrinate in a glass-stoppered test tube, and add 0.05 g of sodium nitrite, 10 mL of chloroform and 10 mL of dilute hydrochloric acid. Stopper, shake well, and allow to stand: the chloroform layer remains colorless.

Loss on drying Not more than 0.5% (3 g, in vacuum, phosphorus (V) oxide, 24 hours).