(2) To 5 mL of a solution of Dilazep Hydrochloride (3 in 500) add 0.3 mL of Reinecke salt TS: a light red precipitate is formed.

(3) Determine the absorption spectrum of a solution of Dilazep Hydrochloride (1 in 50,000) 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 wavelengths.

(4) Determine the infrared absorption spectrum of Dilazep Hydrochloride as directed in the potassium chloride 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.

(5) A solution of Dilazep Hydrochloride (1 in 50) responds to the Qualitative Tests for chloride.

pH Dissolve 1.0 g of Dilazep Hydrochloride in 100 mL of water: the pH of this solution is between 3.0 and 4.0.

Purity (1) Clarity and color of solution—Dissolve 1.0 g of Dilazep Hydrochloride in 20 mL of water: the solution is clear and colorless.

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

(3) Heavy metals—Proceed with 2.0 g of Dilazep Hydrochloride according to Method 1, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

(4) Arsenic—Prepare the test solution with 1.0 g of Dilazep Hydrochloride according to Method 3, and perform the test using Apparatus B (not more than 2 ppm).

(5) Related substances—Dissolve 0.40 g of Dilazep Hydrochloride in 10 mL of chloroform, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add chloroform to make exactly 200 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 5 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, ethyl acetate, dichloromethane and hydrochloric acid (500:200:100:1) to a distance of about 10 cm, and air-dry the plate. Spray evenly Dragendorff's TS for spraying on the plate: 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 2.0 - 3.0% (1 g, 105°C, 3 hours).

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

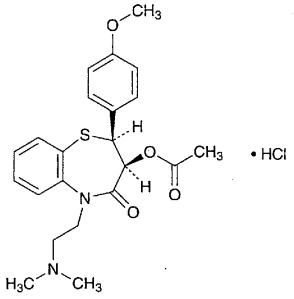
Assay Weigh accurately about 0.3 g of Dilazep Hydrochloride, dissolve in 40 mL of a mixture of acetic anhydride and acetic acid (100) (7:3), and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination, and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 33.881 mg of $C_{31}H_{44}N_2O_{10}.2HCl$

Containers and storage Containers—Tight containers.

Diltiazem Hydrochloride

塩酸ジルチアゼム



$C_{22}H_{26}N_2O_4S.HCl$: 450.98

(2*S*,3*S*)-5-[2-(Dimethylamino)ethyl]-2,3,4,5-tetrahydro-2-(4-methoxyphenyl)-4-oxo-1,5-benzothiazepin-3-yl acetate monohydrochloride [*42399-41-7*]

Diltiazem Hydrochloride, when dried, contains not less than 98.5% of $C_{22}H_{26}N_2O_4S.HCl$.

Description Diltiazem Hydrochloride occurs as white crystals or crystalline powder. It is odorless.

It is very soluble in formic acid, freely soluble in water, in methanol and in chloroform, sparingly soluble in acetonitrile, slightly soluble in acetic anhydride and in ethanol (99.5), and practically insoluble in diethyl ether.

Identification (1) Dissolve 0.05 g of Diltiazem Hydrochloride in 1 mL of 1 mol/L hydrochloric acid TS, add 2 mL of ammonium thiocyanate-cobaltous nitrate TS and 5 mL of chloroform, shake well, and allow to stand: a blue color develops in the chloroform layer.

(2) Proceed as directed under the Oxygen Flask Combustion Method with 0.03 g of Diltiazem Hydrochloride, using 20 mL of water as the absorbing liquid, and prepare the test solution: the test solution responds to the Qualitative Tests (1) for sulfate.

(3) Dissolve 0.01 g of Diltiazem Hydrchloride in 0.01 mol/L hydrochloric acid TS to make 100 mL. To 2 mL of the solution add 0.01 mol/L hydrochloric acid TS to make 20 mL. Determine the absorption spectrum of the solution 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 wavelengths.

(4) Determine the infrared absorption spectrum of Diltiazem Hydrochloride, previously dried, as directed in the potassium bromide disk method under the Infrared Spectrophotometry: it exhibits absorption at the wave numbers of about 1741 cm^{-1}, 1678 cm^{-1}, 1252 cm^{-1} and 1025 cm^{-1}.

(5) A solution of Diltiazem Hydrochloride (1 in 50) responds to the Qualitative Tests (2) for chloride.

Optical rotation $[\alpha]_D^{20}$: +115 - +120° (after drying, 0.20 g, water, 20 mL, 100 mm).

Melting point 210 - 215°C (with decomposition).

pH Dissolve 1.0 g of Diltiazem Hydrochloride in 100 mL of water: the pH of this solution is between 4.3 and 5.3.

Purity (1) Clarity and color of solution—Dissolve 1.0 g

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).

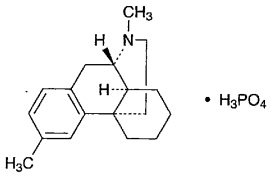
Assay Weigh accurately about 0.7 g of Diltiazem Hydrochloride, previously dried, dissolve in 2.0 mL of formic acid, add 60 mL of acetic anhydride, and titrate with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination, and make any necessary correction.

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

リン酸ジメモルファン



$C_{18}H_{25}N.H_3PO_4$: 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-