solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine each peak area of both solutions by the automatic integration method: the total area of the peaks other than meticrane from the sample solution is not larger than the peak area of meticrane from the standard solution.

Operating conditions 1—

Detector: An ultraviolet absorption photometer (wavelength: 230 nm).

Column: A stainless steel column 4.6 in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase: A mixture of water and acetonitrile (17:3).

Flow rate: Adjust the flow rate so that the retention time of meticrane is about 7 minutes.

Selection of column: Dissolve 0.01 g each of Meticrane and caffeine in acetonitrile to make 100 mL. Proceed with 2 μL of this solution under the above operating conditions, and calculate the resolution. Use a column giving elution of caffeine and meticrane in this order with the resolution between these peaks being not less than 10.

Detection sensitivity: Adjust the detection sensitivity so that the peak height of meticrane obtained from 2 μL of the standard solution is 20 - 50% of the full scale.

Time span of measurement: About 4 times as long as the retention time of meticrane, after the solvent peak.

Operating conditions 2—

Detector, column, and column temperature: Proceed as directed in the operating conditions 1.

Mobile phase: A mixture of water and acetonitrile (1:1).

Flow rate: Adjust the flow rate so that the retention time of meticrane is about 2 minutes.

Selection of column: Dissolve 0.02 g each of Meticrane and methyl parahydroxybenzoate in acetonitrile to make 100 mL. Proceed with 2 μL of this solution under the above operating conditions, and calculate the resolution. Use a column giving elution of meticrane and methyl parahydroxybenzoate in this order with the resolution between these peaks being not less than 4.

Detection sensitivity: Adjust the detection sensitivity so that the peak height of meticrane from 2 μL of the standard solution is 20 - 50% of the full scale.

Time span of measurement: About 10 times as long as the retention time of meticrane, after the solvent peak.

Loss on drying Not more than 0.5% (1 g, 105°C, 4 hours).

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

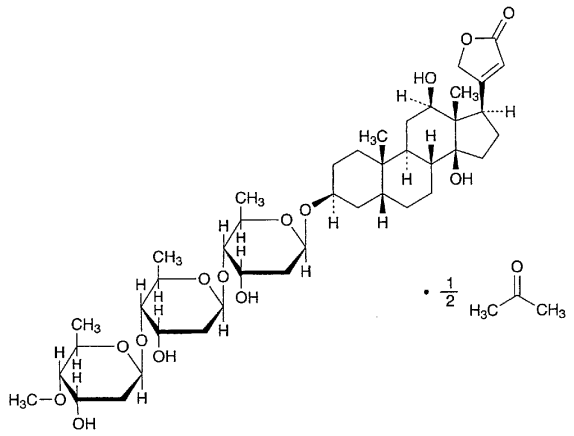
Assay Weigh accurately about 0.5 g of Meticrane, previously dried, dissolve in 50 mL of dimethylformamide, add 5 mL of water, and titrate with 0.1 mol/L potassium hydroxide-ethanol VS (potentiometric titration). Perform a blank determination, and make any necessary correction.

Each mL of 0.1 mol/L potassium hydroxide-ethanol VS
= 27.535 mg of $C_{10}H_{13}NO_4S_2$

Containers and storage Containers—Well-closed containers.

Metildigoxin

メチルジゴキシン



$C_{42}H_{66}O_{14}.½C_3H_6O$: 824.00

3β-[*O*-2,6-Dideoxy-4-*O*-methyl-β-D-*ribo*-hexopyranosyl-(1→4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1→4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyloxy]-12β,14-dihydroxy-5β-card-20(22)-enolide—acetone (2/1) [*30685-43-9*, acetone free]

Metildigoxin contains not less than 96.0% and not more than 103.0% of $C_{42}H_{66}O_{14}.½C_3H_6O$, calculated on the anhydrous basis.

Description Metildigoxin occurs as a white to light yellowish white, crystalline powder.

It is freely soluble in *N,N*-dimethylformamide, in pyridine and in acetic acid (100), soluble in chloroform, sparingly soluble in methanol, slightly soluble in ethanol (95) and in acetone, very slightly soluble in water, and practically insoluble in diethyl ether.

Identification **(1)** Dissolve 2 mg of Metildigoxin in 2 mL of acetic acid (100), shake well with 1 drop of iron (III) chloride TS, and add gently 2 mL of sulfuric acid to divide into two layers: a brown color develops at the interface, and a deep blue color gradually develops in the acetic acid layer.

(2) Dissolve 2 mg of Metildigoxin in 2 mL of 1,3-dinitrobenzene TS, add 2 mL of a solution of tetramethylammonium hydroxide in ethanol (95) (1 in 200), and shake: a purple color gradually develops, and changes to blue-purple.

(3) Determine the absorption spectrum of a solution of Metildigoxin in methanol (1 in 50,000) as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Metildigoxin Reference Standard prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

(4) Determine the infrared absorption spectrum of Metildigoxin as directed in the potassium bromide disk method under the Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum or the spectrum of Metildigoxin Reference Standard: both spectra exhibit similar intensities of absorption at the same wave numbers. If

any difference appears between the spectra, dissolve Metildigoxin and Metildigoxin Reference Standard in acetone, respectively, then evaporate the acetone to dryness, and repeat the test on the residues.

Optical rotation $[\alpha]_{546.1}^{20}$: +22.0 - +25.5° (1 g, calculated on the anhydrous basis, pyridine, 10 mL, 100 mm).

Purity **(1)** Arsenic—Prepare the test solution with 0.5 g of Metildigoxin according to Method 3, and perform the test using Apparatus B (not more than 4 ppm).

(2) Related substances—Dissolve 0.010 g of Metildigoxin 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 50 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin-layer Chromatography. Spot 20 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 2-butanone and chloroform (3:1) to a distance of about 15 cm, and air-dry the plate. Spray evenly dilute sulfuric acid on the plate, and heat at 110°C for 10 minutes: the spots other than the principal spot from the sample solution are not more intense than the spot from the standard solution.

Acetone Weigh accurately about 0.1 g of Metildigoxin, dissolve in exactly 2 mL of the internal standard solution, add *N,N*-dimethylformamide to make 10 mL, and use this solution as the sample solution. Separately, weigh accurately about 0.4 g of acetone in a 50-mL volumetric flask containing about 10 mL of *N,N*-dimethylformamide, and add *N,N*-dimethylformamide to make 50 mL. Pipet 5 mL of this solution, add exactly 20 mL of the internal standard solution, then add *N,N*-dimethylformamide to make 100 mL, and use this solution as the standard solution. Perform the test with 1 μL each of the sample solution and the standard solution as directed under the Gas Chromatography, and calculate the ratios, Q_T and Q_S, of the peak area of acetone to that of the internal standard: the amount of acetone is between 2.0% and 5.0%.

$$\text{Amount (\%) of acetone} = \frac{Q_T}{Q_S} \times \frac{\text{amount (g) of acetone taken}}{\text{amount (g) of the sample taken}}$$

Internal standard solution—A solution of *t*-butanol in *N,N*-dimethylformamide (1 in 2000).

Operating conditions—

Detector: A hydrogen flame-ionization detector.

Column: A glass column about 2 mm in inside diameter and 1 to 2 m in length, packed with porous ethylvinylbenzene-divinylbenzene copolymer for gas chromatography (150 to 180 μm in particle diameter).

Column temperature: A constant temperature between 170°C and 230°C.

Carrier gas: Nitrogen

Flow rate: Adjust the flow rate so that the retention time of acetone is about 2 minutes.

Selection of column: Proceed with 1 μL of the standard solution under the above operating conditions, and calculate the resolution. Use a column giving elution of acetone and *t*-butanol in this order with the resolution between these peaks being not less than 2.0.

Water Not more than 3.0% (0.3 g, direct titration).

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

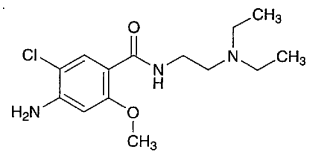
Assay Weigh accurately 0.1 g each of Metildigoxin and Metildigoxin Reference Standard, and dissolve each in methanol to make exactly 50 mL. Pipet 5 mL each of the solutions, add methanol to each to make exactly 100 mL, and use these solutions as the sample solution and the standard solution, respectively. Pipet 5 mL each of the sample solution and the standard solution, add 15 mL of 2,4,6-trinitrophenol-ethanol TS and 2 mL of sodium hydroxide TS to each, shake well, add methanol to make exactly 25 mL, and allow to stand at 20±0.5°C for 20 minutes. Perform the test with these solutions as directed under the Ultraviolet-visible Spectrophotometry using a solution prepared by mixing 15 mL of 2,4,6-trinitrophenol-ethanol TS and 2 mL of sodium hydroxide TS and adding methanol to make exactly 25 mL as the blank. Determine the maximum absorbances, A_T and A_S, of the subsequent solutions obtained from the sample solution and the standard solution, respectively, by measuring every 5 minutes, at 495 nm.

$$\text{Amount (mg) of } C_{42}H_{66}O_{14}\cdot\tfrac{1}{2}C_3H_6O = \text{amount (mg) of Metildigoxin Reference Standard, calculated on the anhydrous basis} \times \frac{A_T}{A_S}$$

Containers and storage Containers—Tight containers.

Metoclopramide

メトクロプラミド



$C_{14}H_{22}ClN_3O_2$: 299.80

4-Amino-5-chloro-*N*-(2-diethylaminoethyl)-2-methoxybenzamide [*364-62-5*]

Metoclopramide, when dried, contains not less than 99.0% of $C_{14}H_{22}ClN_3O_2$.

Description Metoclopramide occurs as white crystals or a crystalline powder, and is odorless.

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

It dissolves in dilute hydrochloric acid.

Identification **(1)** Dissolve 0.01 g of Metoclopramide in 1 mL of dilute hydrochloric acid and 4 mL of water: the solution responds to the Qualitative Tests for Primary Aromatic Amines.

(2) Dissolve 0.01 g of Metoclopramide in 5 mL of dilute hydrochloric acid and 20 mL of water, and to 5 mL of this solution add 1 mL of Dragendorff's TS: a reddish orange precipitate is produced.

(3) Dissolve 0.1 g of Metoclopramide in 1 mL of 1