

solution with 0.25 mL of 0.01 mol/L hydrochloric acid VS (not more than 0.011%).

(3) Heavy metals—Dissolve 1.0 g of Tegafur in 40 mL of water by warming, cool, filter if necessary, and add 2 mL of dilute acetic acid and water to make 50 mL. Perform the test using this solution as the test solution. Prepare the control solution with 1.0 mL of Standard Lead Solution (not more than 10 ppm).

(4) Arsenic—To 1.0 g of Tegafur in a crucible add 10 mL of a solution of magnesium nitrate hexahydrate in ethanol (95) (1 in 10), fire the ethanol to burn, and incinerate by ignition between 750°C and 850°C. If a carbonized substance remains, moisten it with a small quantity of nitric acid, and ignite again to incinerate. After cooling, dissolve the residue in 10 mL of dilute hydrochloric acid by warming on a water bath, and perform the test with this solution using Apparatus B (not more than 2 ppm).

(5) Related substances—Dissolve 0.10 g of Tegafur 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 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 μ L each of the sample solution and the standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of chloroform and ethanol (95) (5:1) to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm): 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, 4 hours).

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

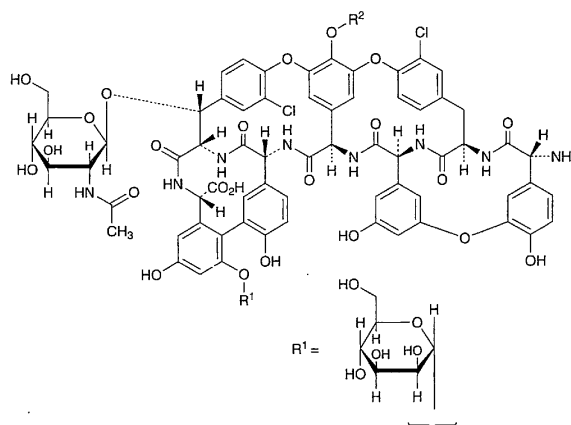
Assay Weigh accurately about 0.15 g of Tegafur, previously dried, place in an iodine bottle, dissolve in 75 mL of water, and add exactly 25 mL of 1/60 mol/L potassium bromate VS. Add rapidly 1.0 g of potassium bromide and 12 mL of hydrochloric acid, stopper the bottle tightly at once, and allow to stand for 30 minutes with occasional shaking. To this solution add 1.6 g of potassium iodide, shake gently, allow to stand for exactly 5 minutes, and titrate the liberated iodine with 0.1 mol/L sodium thiosulfate VS (indicator: 2 mL of starch TS). Perform a blank determination.

Each mL of 1/60 mol/L potassium bromate VS
= 10.008 mg of C₈H₉FN₂O₃

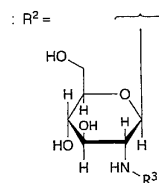
Containers and storage Containers—Tight containers.

Teicoplanin

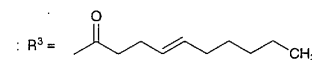
テイコプラニン



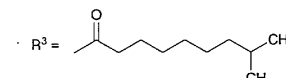
Teicoplanin Agroup



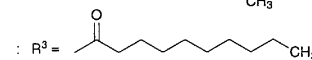
Teucoplanin A₂₋₁



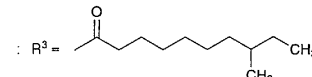
Teucoplanin A₂₋₂



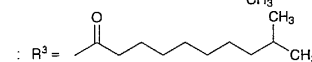
Teucoplanin A₂₋₃



Teucoplanin A₂₋₄



Teucoplanin A₂₋₅



Teucoplanin A₃₋₁

: R² = H

Teicoplanin A₂₋₁

C₈₈H₉₅Cl₂N₉O₃₃: 1877.64

(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50*aR*)-34-(2-Acetylamino-2-deoxy- β -D-glucopyranosyloxy)-15-amino-22,31-dichloro-56-[2-(*Z*)-dec-4-enoylamino-2-deoxy- β -D-glucopyranosyloxy]-2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-6,11,40,44-tetrahydroxy-42-(α -D-mannopyranosyloxy)-2,16,36,50,51,59-hexaoxo-1*H*,15*H*,34*H*-20,23:30,33-dietheno-3,18:35,48-bis(iminomethano)-4,8:10,14:25,28:43,47-tetrametheno-28*H*-[1,14,6,22]dioxadiazacyclooctacosino[4,5-*m*][10,2,16]benzoxadiazacyclotetracosine-38-carboxylic acid [91032-34-7]

Teicoplanin A₂₋₂

C₈₈H₉₇Cl₂N₉O₃₃: 1879.66

(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50*aR*)-34-

(2-Acetylamino-2-deoxy- β -D-glucopyranosyloxy)-15-amino-22,31-dichloro-56-[2-deoxy-2-(8-methylnonanoylamino)- β -D-glucopyranosyloxy]-2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-6,11,40,44-tetrahydroxy-42-(α -D-mannopyranosyloxy)-2,16,36,50,51,59-hexaoxo-1*H*,15*H*,34*H*-20,23:30,33-dietheno-3,18:35,48-bis(iminomethano)-4,8:10,14:25,28:43,47-tetrametheno-28*H*-[1,14,6,22]dioxadiazacyclooctacosino[4,5-*m*][10,2,16]benzoxadiazacyclotetracosine-38-carboxylic acid [91032-26-7]

Teicoplanin A₂₋₃

C₈₈H₉₇Cl₂N₉O₃₃: 1879.66
(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50*aR*)-34-(2-Acetylamino-2-deoxy- β -D-glucopyranosyloxy)-15-amino-22,31-dichloro-56-(2-decanoylamino-2-deoxy- β -D-glucopyranosyloxy)-2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-6,11,40,44-tetrahydroxy-42-(α -D-mannopyranosyloxy)-2,16,36,50,51,59-hexaoxo-1*H*,15*H*,34*H*-20,23:30,33-dietheno-3,18:35,48-bis(iminomethano)-4,8:10,14:25,28:43,47-tetrametheno-28*H*-[1,14,6,22]dioxadiazacyclooctacosino[4,5-*m*][10,2,16]benzoxadiazacyclotetracosine-38-carboxylic acid [91032-36-9]

Teicoplanin A₂₋₄

C₈₉H₉₉Cl₂N₉O₃₃: 1893.68
(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50*aR*)-34-(2-Acetylamino-2-deoxy- β -D-glucopyranosyloxy)-15-amino-22,31-dichloro-56-[2-deoxy-2-(8-methyldecanoylamino)- β -D-glucopyranosyloxy]-2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-6,11,40,44-tetrahydroxy-42-(α -D-mannopyranosyloxy)-2,16,36,50,51,59-hexaoxo-1*H*,15*H*,34*H*-20,23:30,33-dietheno-3,18:35,48-bis(iminomethano)-4,8:10,14:25,28:43,47-tetrametheno-28*H*-[1,14,6,22]dioxadiazacyclooctacosino[4,5-*m*][10,2,16]benzoxadiazacyclotetracosine-38-carboxylic acid [91032-37-0]

Teicoplanin A₂₋₅

C₈₉H₉₉Cl₂N₉O₃₃: 1893.68
(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50*aR*)-34-(2-Acetylamino-2-deoxy- β -D-glucopyranosyloxy)-15-amino-22,31-dichloro-56-[2-deoxy-2-(9-methyldecanoylamino)- β -D-glucopyranosyloxy]-2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-6,11,40,44-tetrahydroxy-42-(α -D-mannopyranosyloxy)-2,16,36,50,51,59-hexaoxo-1*H*,15*H*,34*H*-20,23:30,33-dietheno-3,18:35,48-bis(iminomethano)-4,8:10,14:25,28:43,47-tetrametheno-28*H*-[1,14,6,22]dioxadiazacyclooctacosino[4,5-*m*][10,2,16]benzoxadiazacyclotetracosine-38-carboxylic acid [91032-38-1]

Teicoplanin A₃₋₁

C₇₂H₆₈Cl₂N₈O₂₈: 1564.25
(3*S*,15*R*,18*R*,34*R*,35*S*,38*S*,48*R*,50*aR*)-34-(2-Acetylamino-2-deoxy- β -D-glucopyranosyloxy)-15-amino-22,31-dichloro-2,3,16,17,18,19,35,36,37,38,48,49,50,50a-tetradecahydro-

6,11,40,44,56-pentahydroxy-42-(α -D-mannopyranosyloxy)-2,16,36,50,51,59-hexaoxo-1*H*,15*H*,34*H*-20,23:30,33-dietheno-3,18:35,48-bis(iminomethano)-4,8:10,14:25,28:43,47-tetrametheno-28*H*-[1,14,6,22]dioxadiazacyclooctacosino[4,5-*m*][10,2,16]benzoxadiazacyclotetracosine-38-carboxylic acid [93616-27-4]

[61036-62-2, Teicoplanin]

Teicoplanin, contains not less than 80.0% of teicoplanin A₂ group (A₂₋₁, A₂₋₂, A₂₋₃, A₂₋₄, A₂₋₅), contains not less than 15.0% of teicoplanin A₃₋₁, and contains not less than 900 μ g (potency) per mg, calculated on the anhydrous, de-sodium chloride and de-residual solvents basis. The potency of Teicoplanin is expressed as mass (potency) of teicoplanin (C₇₂₋₈₉H₆₈₋₉₉Cl₂N₈₋₉O₂₈₋₃₃).

Description Teicoplanin occurs as a white to light yellowish white powder.

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

Identification (1) To 1 mL of a solution of Teicoplanin (1 in 100) add 2 mL of ninhydrin TS, and warm for 5 minutes: a blue-purple color develops.

(2) To 1 mL of a solution of Teicoplanin (3 in 100) add slowly 2 mL of anthrone TS, and shake gently: a dark brown color develops.

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

pH Dissolve 0.5 g of Teicoplanin in 10 mL of water: the pH of the solution is between 6.3 and 7.7.

Content ratio of the active principle Dissolve about 0.02 g of Teicoplanin in water to make 10 mL, and use this solution as the sample solution. Perform the test with 20 μ L of the sample solution as directed under the Liquid Chromatography according to the following conditions, and calculate the sum of peak areas of teicoplanin A₂ group, S₁, the sum of peak areas of teicoplanin A₃ group, S₂, and the sum of peak areas of other contents, S₃ from the sample solution by the automatic integration method. Calculate the content ratio of them by the formula given below: teicoplanin A₂ group, teicoplanin A₃ group, and the other are not less than 80.0%, not less than 15.0% and not more than 5.0%, respectively.

The elution order of each content and the relative retention time of each content to the retention time of teicoplanin A₂₋₂ are shown in the following table.

Name of content	Elution order	Relative retention time
teicoplanin A ₃ group		≤ 0.42
teicoplanin A ₃₋₁	1	0.29
teicoplanin A ₂ group		0.42 < , ≤ 1.25
teicoplanin A ₂₋₁	2	0.91
teicoplanin A ₂₋₂	3	1.00
teicoplanin A ₂₋₃	4	1.04
teicoplanin A ₂₋₄	5	1.17
teicoplanin A ₂₋₅	6	1.20
other		1.25 <

Content ratio (%) of teicoplanin A₂ group

$$= \frac{S_1}{S_1 + 0.83 \times S_2 + S_3} \times 100$$

Content ratio (%) of teicoplanin A₃ group

$$= \frac{0.83 \times S_2}{S_1 + 0.83 \times S_2 + S_3} \times 100$$

Content ratio (%) of other contents

$$= \frac{S_3}{S_1 + 0.83 \times S_2 + S_3} \times 100$$

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

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

Mobile phase A: Dissolve 7.80 g of sodium dihydrogenphosphate dihydrate in 1650 mL of water, add 300 mL of acetonitrile, adjust the pH to 6.0 with sodium hydroxide TS, and add water to make 2000 mL.

Mobile phase B: Dissolve 7.80 g of sodium dihydrogenphosphate dihydrate in 550 mL of water, add 1400 mL of acetonitrile, adjust the pH to 6.0 with sodium hydroxide TS, and add water to make 2000 mL.

Flowing of the mobile phase: Flow mobile phase A for 10 minutes before injection. After injection, control the gradient by mixing the mobile A and B as directed in the following table.

Time after injection of the sample (min)	Mobile phase A (%)	Mobile phase B (%)
0 – 32	100→70	0→30
32 – 40	70→50	30→50
40 – 42	50→100	50→0

Flow rate: 1.8 mL per minute.

Time span of measurement: About 1.7 times as long as the retention time of teicoplanin A₂₋₂ after the solvent peak.

System suitability—

Test for required detection: Confirm that the peak height of teicoplanin A₂₋₂ obtained from the sample solution is equivalent to 90% of the full scale.

System performance: When the procedure is run with 20

μL of the sample solution under the above operating conditions, the symmetry coefficient of the peak of teicoplanin A₃₋₁ is not more than 2.2.

System repeatability: When the test is repeated 3 times with 20 μL of the sample solution under the above operating conditions, the relative standard deviation of the peak areas of teicoplanin A₂₋₂ is not more than 2.0%.

Purity (1) Clarity and color of solution—Being specified separately.

(2) Sodium chloride—Weigh accurately about 0.5 g of Teicoplanin, dissolve in 50 mL of water, titrate with 0.1 mol/L silver nitrate VS (indicator: 1 mL of potassium chromate TS), and calculate an amount of sodium chloride: not more than 5.0%.

$$\begin{aligned} \text{Each mL of 0.1 mol/L silver nitrate VS} \\ = 5.844 \text{ mg of NaCl} \end{aligned}$$

(3) Heavy metals—Being specified separately.

(4) Arsenic—Being specified separately.

(5) Residual solvents—Weigh accurately about 0.1 g of Teicoplanin, dissolve in *N,N*-dimethylformamide to make exactly 10 mL, and use this solution as the sample solution. Separately, weigh accurately about 1 g each of methanol and acetone, and add *N,N*-dimethylformamide to make exactly 100 mL. Pipet 1 mL of this solution, add *N,N*-dimethylformamide to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 4 μL each of the sample solution and the standard solution as directed under the Gas Chromatography according to the following condition. Calculate the peak area of methanol, A₁, and the peak area of acetone, A₂, obtained from the sample solution, and the peak area of methanol, A_{S1}, and the peak area of acetone, A_{S2}, obtained from the standard solution by the automatic integration method, and calculate the amounts of methanol and acetone by the following formula: not more than 0.5% and not more than 1.0%, respectively.

Amount (%) of methanol

$$= \frac{\text{amount (g) of methanol}}{\text{amount (g) of Teicoplanin}} \times 100$$

$$\times \frac{A_1}{A_{S1}} \times 0.001 \times \frac{1}{\text{amount (g) of Teicoplanin}} \times 100$$

Amount (%) of acetone

$$= \frac{\text{amount (g) of acetone}}{\text{amount (g) of Teicoplanin}} \times 100$$

$$\times \frac{A_2}{A_{S2}} \times 0.001 \times \frac{1}{\text{amount (g) of Teicoplanin}} \times 100$$

Operating conditions—

Detector: Hydrogen flame-ionization detector.

Column: A glass column 2 mm in inside diameter and 3 m in length, packed with graphite carbon for gas chromatography, 150 to 180 μm in particle diameter, coated with 0.1% of polyethylene glycol esterified.

Column temperature: Inject the sample at a constant temperature of about 70°C, maintain the temperature for 4 minutes, then program to increase the temperature at the rate of 8°C per minute to 210°C.

Detector temperature: A constant temperature of about 240°C.

Carrier gas: Nitrogen

Flow rate: Adjust the flow rate so that the retention times of methanol and acetone are about 2 minutes and 5 minutes, respectively.

System suitability—

Test for required detection: Confirm that the peak height of acetone obtained from 4 μL of the standard solution is equivalent to about the full scale.

System performance: When the procedure is run with 4 μL of the standard solution under the above operating conditions, methanol and acetone are eluted in this order with the resolution between these peaks being not less than 2.0.

System repeatability: When the test is repeated 3 times with 4 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak areas of acetone is not more than 3%.

Water Not more than 15.0% (0.2 g, volumetric titration, direct titration).

Bacterial endotoxins Less than 0.73 EU/mg (potency).

Blood pressure depressant Being specified separately.

Assay Perform the test according to the Cylinder-plate method as directed under the Microbial Assay for Antibiotics according to the following conditions.

(1) Test organism—*Bacillus subtilis* ATCC 6633

(2) Culture medium—Use the medium i in 1) Medium for test organism [5] under (1) Agar media for seed and base layer.

(3) Standard solution—Weigh accurately an amount of Teicoplanin Reference Standard equivalent to about 0.05 g (potency), dissolve in phosphate buffer solution, pH 6.0 to make exactly 50 mL, and use this solution as the standard stock solution. Keep the standard stock solution at not exceeding 5°C and use within 14 days. Take exactly a suitable amount of this solution before use, add phosphate buffer solution, pH 6.0 to make solutions so that each mL contains 160 μg (potency) and 40 μg (potency), and use these solutions as the high concentration standard solution and the low concentration standard solution, respectively.

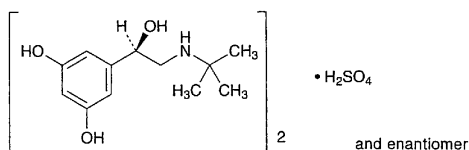
(4) Sample solution—Weigh accurately an amount of Teicoplanin equivalent to about 0.05 g (potency), dissolve in phosphate buffer solution, pH 6.0 to make exactly 50 mL. Take exactly a suitable amount of this solution, add phosphate buffer solution, pH 6.0 to make solutions so that each mL contains 160 μg (potency) and 40 μg (potency), and use these solutions as the high concentration sample solution and the low concentration sample solution, respectively.

Containers and storage Containers—Tight containers.

Storage—Light-resistant, and not exceeding 5°C.

Terbutaline Sulfate

硫酸テルブタリン



$(\text{C}_{12}\text{H}_{19}\text{NO}_3)_2 \cdot \text{H}_2\text{SO}_4$: 548.65

(*RS*)-2-*tert*-Butylamino-1-(3,5-dihydroxyphenyl)ethanol hemisulfate [23031-32-5]

Terbutaline Sulfate contains not less than 98.5% of $(\text{C}_{12}\text{H}_{19}\text{NO}_3)_2 \cdot \text{H}_2\text{SO}_4$, calculated on the anhydrous basis.

Description Terbutaline Sulfate is white to slightly brownish white crystals or crystalline powder. It is odorless or has a faint odor of acetic acid.

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

It is gradually colored by light and by air.

Melting point: about 255°C (with decomposition).

Identification (1) Dissolve 1 mg of Terbutaline Sulfate in 1 mL of water, and add 5 mL of Tris buffer solution, pH 9.5, 0.5 mL of 4-aminoantipyrine solution (1 in 50) and 2 drops of potassium hexacyanoferrate (III) solution (2 in 25): a reddish purple color is produced.

(2) Determine the absorption spectrum of a solution of Terbutaline Sulfate in 0.01 mol/L hydrochloric acid TS (1 in 10,000) 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. This maximum can be biphasic.

(3) A solution of Terbutaline Sulfate (1 in 50) responds to the Qualitative Tests for sulfate.

pH Dissolve Terbutaline Sulfate in 10 mL of water: the pH of this solution is between 4.0 and 4.8.

Purity (1) Clarity and color of solution—Dissolve 0.10 g of Terbutaline Sulfate in 10 mL of water: the solution is clear and colorless or slightly yellow.

(2) Chloride—Perform the test with 2.0 g of Terbutaline Sulfate. Prepare the control solution with 0.25 mL of 0.01 mol/L hydrochloric acid VS (not more than 0.004%).

(3) Acetic acid—Dissolve 0.50 g of Terbutaline Sulfate in a solution of phosphoric acid (59 in 1000) to make exactly 10 mL, and use this solution as the sample solution. Separately, dissolve 1.50 g of acetic acid (100) in a solution of phosphoric acid (59 in 1000) to make exactly 100 mL. Dilute 2 mL of this solution, accurately measured, with a solution of phosphoric acid (59 in 1000) to make exactly 200 mL, and use this solution as the standard solution. Perform the test with 2 μL each of the sample solution and the standard solution as directed under the Gas Chromatography according to the following operating conditions. Measure the peak areas, A_T and A_S , of acetic acid for the two solutions: A_T is not larger than A_S .

Operating conditions—

Detector: A hydrogen flame-ionization detector.

Column: A glass column 3 mm in inside diameter and 1 m in length, packed with 10% of macrogol 6000 on 180- to 250- μm terephthalic acid for gas chromatography.

Column temperature: A constant temperature at about 120°C.

Carrier gas: Nitrogen.

Flow rate: Adjust the flow rate so that the retention time of acetic acid is about 5 minutes.

System suitability—

System performance: Mix 0.05 g each of acetic acid (100) and propionic acid in 100 mL of diluted phosphoric acid (59 in 1000). When the procedure is run with 2 μL of this solution under the above conditions, acetic acid and propionic