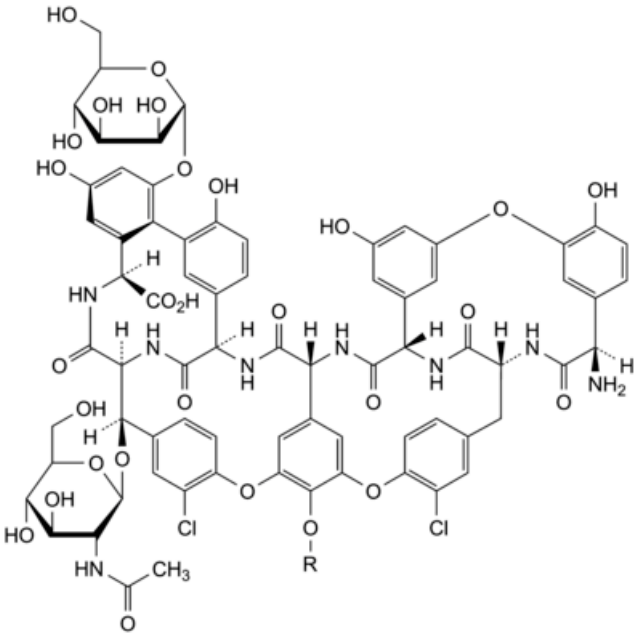
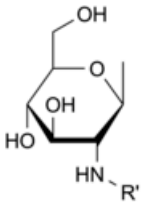
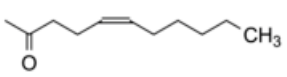
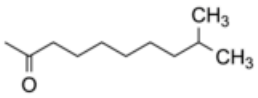
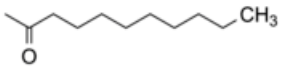
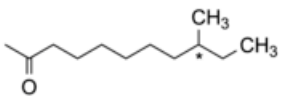
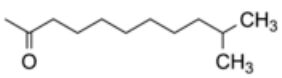
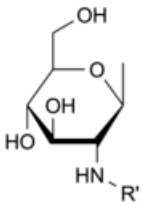
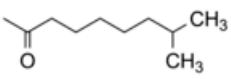
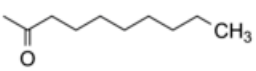
Edition: BP 2025 (Ph. Eur. 11.6 update)

Teicoplanin

General Notices

(Ph. Eur. monograph 2358)



teicoplanin	R	R'
$A_{2\text{-}1}$ $C_{88}H_{95}Cl_2N_9O_{33}$ M_r 1878		
$A_{2\text{-}2}$ $C_{88}H_{97}Cl_2N_9O_{33}$ M_r 1880		
$A_{2\text{-}3}$ $C_{88}H_{97}Cl_2N_9O_{33}$ M_r 1880		
$A_{2\text{-}4}$ $C_{89}H_{99}Cl_2N_9O_{33}$ M_r 1894		
$A_{2\text{-}5}$ $C_{89}H_{99}Cl_2N_9O_{33}$ M_r 1894		
$A_{3\text{-}1}$ $C_{72}H_{68}Cl_2N_8O_{28}$ M_r 1564	H	
$A_{2\text{-}1a}$ $C_{87}H_{95}Cl_2N_9O_{33}$ M_r 1866		
$A_{2\text{-}1b}$ $C_{87}H_{95}Cl_2N_9O_{33}$ M_r 1866		

61036-62-2

Action and use

Glycopeptide antibacterial.

Preparation

Teicoplanin for Injection

Ph Eur

DEFINITION

Mixture of glycopeptides produced by certain strains of *Actinoplanes teichomyceticus sp.*; the 6 principal components of the mixture are teicoplanins A_{2-1} to A_{2-5} and teicoplanin A_{3-1}, and 2 minor components are teicoplanins A_{2-1a} and A_{2-1b}.

Fermentation product.

Potency

Minimum 900 IU/mg (anhydrous and sodium chloride-free substance).

CHARACTERS

Appearance

White or yellowish, amorphous powder.

Solubility

Freely soluble in water, sparingly soluble in dimethylformamide, practically insoluble in ethanol (96 per cent).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *teicoplanin for identification CRS*.

B. Examine the chromatograms obtained in the test for composition.

Results The principal peaks (teicoplanins A_{3-1}, A_{2-1}, A_{2-2}, A_{2-3}, A_{2-4} and A_{2-5}) and the 2 minor peaks (teicoplanins A_{2-1a} and A_{2-1b}) in the chromatogram obtained with the test solution are similar in retention time and size to the principal peaks in the chromatogram obtained with reference solution (a).

TESTS

Appearance of solution

The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_3 or B_4 (*2.2.2, Method I*).

Dissolve 0.8 g in 10 mL of *water R*.

pH (*2.2.3*)

6.5 to 7.5.

Dissolve 0.50 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

Composition

Liquid chromatography (*2.2.29*): use the normalisation procedure.

Test solution Dissolve 0.100 g of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a) Dissolve 20 mg of *teicoplanin for identification CRS* in *water R* and dilute to 10.0 mL with the same solvent.

Reference solution (b) Dilute 1.0 mL of reference solution (a) to 10.0 mL with *water R*. Dilute 1.0 mL of this solution to 20.0 mL with *water R*.

Reference solution (c) Dissolve 50.0 mg of *mesityl oxide CRS* (impurity A) in *water R* and dilute to 25.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with *water R*. Dilute 1.0 mL of this solution to 100.0 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: spherical *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: mix 900 mL of a 3.0 g/L solution of *anhydrous sodium dihydrogen phosphate R*, adjusted to pH 6.0 with a 40 g/L solution of *sodium hydroxide R*, and 100 mL of *acetonitrile R*;

— *mobile phase B*: mix 300 mL of a 3.0 g/L solution of *anhydrous sodium dihydrogen phosphate R*, adjusted to pH 6.0 with a 40 g/L solution of *sodium hydroxide R*, and 700 mL of *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	100 → 50	0 → 50
30 - 31	50 → 10	50 → 90
31 - 35	10	90

Flow rate 2.3 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 20 µL of the test solution and reference solutions (a) and (b).

Identification Use the chromatogram supplied with *teicoplanin for identification CRS* and the chromatogram obtained with reference solution (a) to identify the groups and components.

Relative retention With reference to teicoplanin A_{2-2} (retention time = about 18 min):

— teicoplanin A_3 group ≤ 0.70:

— teicoplanin A_{3-1} = about 0.43.

— teicoplanin A_2 group > 0.70 including:

— teicoplanin A_{2-1} group > 0.70 and < 1.00:

— teicoplanin A_{2-1a} = about 0.85;

— teicoplanin A_{2-1b} = about 0.88;

— teicoplanin A_{2-1} = about 0.93;

— teicoplanin A_{2-2} = 1.00;

— teicoplanin A_{2-3} group > 1.00 and < 1.12:

— teicoplanin A_{2-3} = about 1.03;

— teicoplanin A_{2-4} = about 1.12;

— teicoplanin A_{2-5} group > 1.12 and < 1.25:

— teicoplanin A_{2-5} = about 1.15;

— teicoplanin A_{2-6} group ≥ 1.25:

— teicoplanin-like related substance RS A_{2-6a} = about 1.25;

— teicoplanin-like related substance RS A_{2-6b} = about 1.30;

— teicoplanin-like related substance RS A_{2-6c} = about 1.38.

System suitability:

— the chromatogram obtained with reference solution (a) is similar to the chromatogram supplied with *teicoplanin for identification CRS*;

— *resolution*: minimum 1.0 between the peaks due to teicoplanin A_{2-4} and teicoplanin A_{2-5} in the chromatogram obtained with reference solution (a);

— *signal-to-noise ratio*: minimum 40 for the peak due to teicoplanin A_{2-2} in the chromatogram obtained with reference solution (b).

Calculate the percentage contents using the following equations:

teicoplanin A_3 group = _____

teicoplanin A_2 group = _____

teicoplanin A_{2-1} group = _____

teicoplanin A_{2-1a} = _____

teicoplanin A_{2-1b} = _____

teicoplanin A_{2-1} = _____

teicoplanin A_{2-2} = _____

teicoplanin A_{2-3} group = _____

teicoplanin A_{2-3} = _____

teicoplanin A_{2-4} = _____

teicoplanin A_{2-5} group = _____

teicoplanin A_{2-5} = _____

teicoplanin A_{2-6} group = _____

S_2	=	sum of the areas of the peaks due to teicoplanin A_2 group in the chromatogram obtained with the test solution;
S_3	=	sum of the areas of the peaks due to teicoplanin A_3 group in the chromatogram obtained with the test solution; disregard any peak due to impurity A;
$S_{2\text{-}6}$	=	sum of the areas of the peaks with a relative retention greater than or equal to 1.25 in the chromatogram obtained with the test solution;
$S_{2\text{-}1}$	=	sum of the areas of the peaks due to teicoplanin $A_{2\text{-}1}$ group in the chromatogram obtained with the test solution;
$A_{2\text{-}1a}$	=	area of the peak due to teicoplanin $A_{2\text{-}1a}$ in the chromatogram obtained with the test solution;
$A_{2\text{-}1b}$	=	area of the peak due to teicoplanin $A_{2\text{-}1b}$ in the chromatogram obtained with the test solution;
$A_{2\text{-}1}$	=	area of the peak due to teicoplanin $A_{2\text{-}1}$ in the chromatogram obtained with the test solution;
$A_{2\text{-}2}$	=	area of the peak due to teicoplanin $A_{2\text{-}2}$ in the chromatogram obtained with the test solution;
$S_{2\text{-}3}$	=	sum of the areas of the peaks due to teicoplanin $A_{2\text{-}3}$ group in the chromatogram obtained with the test solution;
$A_{2\text{-}3}$	=	area of the peak due to teicoplanin $A_{2\text{-}3}$ in the chromatogram obtained with the test solution;
$A_{2\text{-}4}$	=	area of the peak due to teicoplanin $A_{2\text{-}4}$ in the chromatogram obtained with the test solution;
$S_{2\text{-}5}$	=	sum of the areas of the peaks due to teicoplanin $A_{2\text{-}5}$ group in the chromatogram obtained with the test solution;
$A_{2\text{-}5}$	=	area of the peak due to teicoplanin $A_{2\text{-}5}$ in the chromatogram obtained with the test solution.

Limits:

— *teicoplanin A_2 group*: 84.0 per cent to 98.0 per cent;

— *teicoplanin $A_{2\text{-}2}$*: 37.0 per cent to 50.0 per cent;

— *teicoplanin $A_{2\text{-}1}$ group*: 10.0 per cent to 19.0 per cent;

— *teicoplanin $A_{2\text{-}5}$ group*: 7.0 per cent to 17.0 per cent;

— *teicoplanin $A_{2\text{-}4}$*: 7.0 per cent to 15.0 per cent;

— *teicoplanin $A_{2\text{-}5}$*: 7.0 per cent to 15.0 per cent;

— *teicoplanin $A_{2\text{-}3}$ group*: 5.0 per cent to 11.0 per cent;

— *teicoplanin A_3 group*: 4.0 per cent to 12.0 per cent;

— *teicoplanin $A_{2\text{-}3}$*: 4.0 per cent to 8.5 per cent;

— *teicoplanin $A_{2\text{-}1}$*: 2.0 per cent to 7.0 per cent;

— *teicoplanin $A_{2\text{-}1a}$*: 0.5 per cent to 5.5 per cent;

— *teicoplanin $A_{2\text{-}1b}$*: 0.5 per cent to 4.0 per cent;

— *teicoplanin $A_{2\text{-}6}$ group*: maximum 5.0 per cent;

— *disregard limit*: 0.25 per cent.

Related substances

Liquid chromatography (2.2.29) as described in the test for composition. Use the normalisation procedure.

Use the chromatogram obtained with reference solution (a) to identify all peaks present above the disregard limit as teicoplanin-like related substances. Any peak present in any part of the chromatogram obtained with the test solution that cannot be correlated to a peak above the disregard limit in reference solution (a) should be considered as a non-teicoplanin-like impurity, unless it is characterized by other means.

A teicoplanin-like related substance is defined as a substance that shares the same glycopeptide core structure of the parent molecule, composed of a linear heptapeptide aglycone, an α-D-mannose and an acetyl-β-D-glucosamine.

The R′ side chains in the teicoplanin-like related substances RS $A_{2\text{-}6a}$, RS $A_{2\text{-}6b}$ and RS $A_{2\text{-}6c}$ are unknown.

Calculate the percentage contents using the following equations:

teicoplanin-like related substance (x)	=	———
A_{RSTLx}	=	area of the peak due to the teicoplanin-like related substance (x) in the chromatogram obtained with the test solution;
non-teicoplanin-like impurity (x)	=	———
A_{Ix}	=	area of the peak due to the non-teicoplanin-like impurity (x) in the chromatogram obtained with the test solution.

Limits:

— *teicoplanin-like related substance RS $A_{2\text{-}6c}$*: maximum 2.5 per cent;

— *teicoplanin-like related substance RS $A_{2\text{-}6a}$*: maximum 1.5 per cent;

— *teicoplanin-like related substance RS $A_{2\text{-}6b}$*: maximum 1.5 per cent;

— *any non-teicoplanin-like impurity other than impurity A*: maximum 0.5 per cent;

— *total non-teicoplanin-like impurities other than impurity A*: maximum 1.5 per cent.

Impurity A

Liquid chromatography (*2.2.29*) as described in the test for composition with the following modifications.

Injection 20 µL of the test solution and reference solution (c).

Relative retention With reference to teicoplanin $A_{2\text{-}2}$ (retention time = about 18 min): impurity A = about 0.6.

Calculation of percentage content:

— for impurity A, use the concentration of impurity A in reference solution (c).

Limit:

— *impurity A*: maximum 0.2 per cent.

Chlorides

Maximum 5.0 per cent, expressed as sodium chloride (anhydrous substance).

Dissolve 1.000 g in 300 mL of *water R*, stir and acidify with 2 mL of *nitric acid R*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M silver nitrate* is equivalent to 5.844 mg of NaCl.

Water (*2.5.12*)

Maximum 15.0 per cent, determined on 0.300 g.

ASSAY

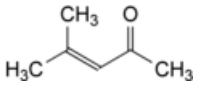
Carry out the microbiological assay of antibiotics (2.7.2), using the diffusion method. Use *teicoplanin CRS* as the reference substance.

STORAGE

Protected from light, at a temperature of 2 °C to 8 °C.

IMPURITIES

Specified impurities *A.*



A. 4-methylpent-3-en-2-one (mesityl oxide).

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