C. Dissolve about 10 mg in 2 ml of *dilute hydrochloric acid R* and heat on a water-bath for 3 min. Add 3 ml of *sodium carbonate solution R* and 1 ml of a 20 g/l solution of *sodium nitroprusside R*. A violet-red colour develops.

D. Dissolve 0.1 g in *water R* and dilute to 10 ml with the same solvent. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

pH (*2.2.3*): 3.0 to 5.0.

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 10 ml with the same solvent.

Specific optical rotation (*2.2.7*): + 135 to + 150 (anhydrous substance).

Dissolve 1.000 g in *water R* and dilute to 25.0 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 ml with the mobile phase.

Reference solution (a). Dissolve 50.0 mg of *clindamycin hydrochloride CRS* in the mobile phase and dilute to 50.0 ml with the mobile phase.

Reference solution (b). Dilute 2.0 ml of the test solution to 100.0 ml with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm,
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: mix 45 volumes of *acetonitrile R* and 55 volumes of a 6.8 g/l solution of *potassium dihydrogen phosphate R* adjusted to pH 7.5 with a 250 g/l solution of *potassium hydroxide R*.

Flow rate: 1 ml/min.

Detection: spectrophotometer at 210 nm.

Injection: 20 µl.

Run time: twice the retention time of clindamycin.

System suitability: reference solution (a):

– *relative retention* with reference to clindamycin (retention time = about 10 min): impurity A = about 0.4; impurity B = about 0.65; impurity C = about 0.8.

Limits:

– *impurity B*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (2.0 per cent),
– *impurity C*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (4.0 per cent),
– *any other impurity*: not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent),
– *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (6.0 per cent),
– *disregard limit*: 0.025 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*): 3.0 per cent to 6.0 per cent, determined on 0.500 g.

Sulphated ash (*2.4.14*): maximum 0.5 per cent, determined on 1.0 g.

ASSAY

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

Injection: 20 µl of the test solution and reference solution (a).

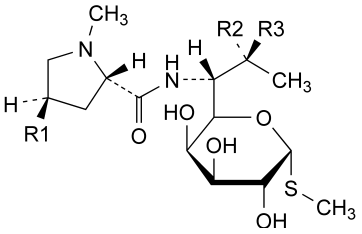
System suitability:

– *repeatability*: maximum relative standard deviation of 0.85 per cent after 6 injections of reference solution (a).

STORAGE

In an airtight container.

IMPURITIES



A. R1 = CH_2-CH_2-CH_3, R2 = OH, R3 = H: methyl 6,8-dideoxy-6-[[[(2*S*,4*R*)-1-methyl-4-propylpyrrolidin-2-yl]carbonyl]amino]-1-thio-D-*erythro*-α-D-*galacto*-octopyranoside (lincomycin),

B. R1 = C_2H_5, R2 = H, R3 = Cl: methyl 7-chloro-6,7,8-trideoxy-6-[[[(2*S*,4*R*)-4-ethyl-1-methylpyrrolidin-2-yl]carbonyl]amino]-1-thio-L-*threo*-α-D-*galacto*-octopyranoside (clindamycin B),

C. R1 = CH_2-CH_2-CH_3, R2 = Cl, R3 = H: methyl 7-chloro-6,7,8-trideoxy-6-[[[(2*S*,4*R*)-1-methyl-4-propylpyrrolidin-2-yl]carbonyl]amino]-1-thio-D-*erythro*-α-D-*galacto*-octopyranoside (7-epiclindamycin).

01/2005:0985
corrected

CROSCARMELLOSE SODIUM

Carmellosum natricum conexum

DEFINITION

Croscarmellose sodium (cross-linked sodium carboxymethylcellulose) is the sodium salt of a cross-linked, partly *O*-carboxymethylated cellulose.

CHARACTERS

A white or greyish-white powder, practically insoluble in acetone, in anhydrous ethanol and in toluene.

IDENTIFICATION

A. Shake 1 g with 100 ml of a solution containing 4 ppm of *methylene blue R* and allow to settle. The substance to be examined absorbs the methylene blue and settles as a blue, fibrous mass.

B. Shake 1 g with 50 ml of *water R*. Transfer 1 ml of the mixture to a test-tube, add 1 ml of *water R* and 0.05 ml of a freshly prepared 40 g/l solution of *α-naphthol R* in *methanol R*. Incline the test-tube and add carefully 2 ml of *sulphuric acid R* down the side so that it forms a lower layer. A reddish-violet colour develops at the interface.

C. The solution prepared from the sulphated ash in the test for heavy metals (see Tests) gives reaction (a) of sodium (*2.3.1*).

TESTS

pH (*2.2.3*). Shake 1 g with 100 ml of *carbon dioxide-free water R* for 5 min. The pH of the suspension is 5.0 to 7.0.

Degree of substitution. Place 1.000 g in a 500 ml conical flask, add 300 ml of a 100 g/l solution of *sodium chloride R*, 25.0 ml of *0.1 M sodium hydroxide*, stopper the flask and allow to stand for 5 min, shaking occasionally. Add 0.05 ml of *m-cresol purple solution R* and about 15 ml of *0.1 M hydrochloric acid* from a burette. Insert the stopper and shake. If the solution is violet, add *0.1 M hydrochloric acid* in 1 ml portions until the solution becomes yellow, shaking after each addition. Titrate with *0.1 M sodium hydroxide* until the colour turns to violet.

Calculate the number of milliequivalents (*M*) of base required for the neutralisation equivalent to 1 g of dried substance.

Calculate the degree of acid carboxymethyl substitution (*A*) from the expression:

$$\frac{1150M}{(7102 - 412M - 80C)}$$

C = sulphated ash as a percentage.

Calculate the degree of sodium carboxymethyl substitution (*S*) from the expression:

$$\frac{(162 + 58A)\,C}{(7102 - 80C)}$$

The degree of substitution is the sum of *A* + *S* and it is between 0.60 and 0.85, calculated with reference to the dried substance.

Sodium chloride and sodium glycollate. The sum of the percentage contents of sodium chloride and sodium glycollate is maximum 0.5 per cent, calculated with reference to the dried substance.

Sodium chloride. Place 5.00 g in a 250 ml conical flask, add 50 ml of *water R* and 5 ml of *strong hydrogen peroxide solution R* and heat on a water-bath for 20 min, stirring occasionally to ensure total hydration. Cool, add 100 ml of *water R* and 10 ml of *nitric acid R*. Titrate with *0.05 M silver nitrate* determining the end-point potentiometrically (*2.2.20*) using a silver indicator electrode and a double-junction reference electrode containing a 100 g/l solution of *potassium nitrate R* in the outer jacket and a standard filling solution in the inner jacket, and stirring constantly.

1 ml of *0.05 M silver nitrate* is equivalent to 2.922 mg of NaCl.

Sodium glycollate. Place a quantity of the substance to be examined equivalent to 0.500 g of the dried substance in a 100 ml beaker. Add 5 ml of *glacial acetic acid R* and 5 ml of *water R* and stir to ensure total hydration (about 15 min). Add 50 ml of *acetone R* and 1 g of *sodium chloride R*. Stir for several minutes to ensure complete precipitation of the carboxymethylcellulose. Filter through a fast filter paper impregnated with *acetone R* into a volumetric flask, rinse the beaker and filter with 30 ml of *acetone R* and dilute the filtrate to 100.0 ml with the same solvent. Allow to stand for 24 h without shaking. Use the clear supernatant to prepare the test solution.

Prepare the reference solutions as follows: in a 100 ml volumetric flask, dissolve 0.100 g of *glycollic acid R*, previously dried *in vacuo* over *diphosphorus pentoxide R*, in *water R* and dilute to 100.0 ml with the same solvent. Use the solution within 30 days. Transfer 1.0 ml, 2.0 ml, 3.0 ml and 4.0 ml of the solution to separate volumetric flasks; dilute the contents of each flask to 5.0 ml with *water R*, add 5 ml of *glacial acetic acid R*, dilute to 100.0 ml with *acetone R* and mix.

Transfer 2.0 ml of the test solution and 2.0 ml of each of the reference solutions to separate 25 ml volumetric flasks. Heat the uncovered flasks for 20 min on a water-bath to eliminate acetone. Allow to cool and add 5.0 ml of *2,7-dihydroxynaphthalene solution R* to each flask. Mix, add a further 15.0 ml of *2,7-dihydroxynaphthalene solution R* and mix again. Close the flasks with aluminium foil and heat on a water-bath for 20 min. Cool and dilute to 25.0 ml with *sulphuric acid R*.

Measure the absorbance (*2.2.25*) of each solution at 540 nm. Prepare a blank using 2.0 ml of a solution containing 5 per cent *V/V* each of *glacial acetic acid R* and *water R* in *acetone R*. Prepare a standard curve using the absorbances obtained with the reference solutions. From the standard curve and the absorbance of the test solution, determine the mass *a*, in milligrams, of glycollic acid in the substance to be examined, and calculate the content of sodium glycollate from the expression:

$$\frac{10 \times 1.29 \times a}{(100 - b)\,m}$$

1.29 = the factor converting glycollic acid to sodium glycollate,

b = loss on drying as a percentage,

m = mass of the substance to be examined, in grams.

Water-soluble substances: maximum 10.0 per cent. Disperse 10.00 g in 800.0 ml of *water R* and stir for 1 min every 10 min during the first 30 min. Allow to stand for 1 h and centrifuge, if necessary. Decant 200.0 ml of the supernatant liquid onto a fast filter paper in a vacuum filtration funnel, apply vacuum and collect 150.0 ml of the filtrate. Evaporate to dryness and dry the residue at 100 °C to 105 °C for 4 h.

Heavy metals (*2.4.8*). To the residue obtained in the determination of the sulphated ash add 1 ml of *hydrochloric acid R* and evaporate on a water-bath. Take up the residue in 20 ml of *water R*. 12 ml of the solution complies with test A for heavy metals (10 ppm). Prepare the reference solution using *lead standard solution (1 ppm Pb) R*.

Loss on drying (*2.2.32*): maximum 10.0 per cent, determined on 1.000 g by drying in an oven at 100 °C to 105 °C for 6 h.

Sulphated ash (*2.4.14*): 14.0 per cent to 28.0 per cent, determined on 2.000 g, using a mixture of equal volumes of *sulphuric acid R* and *water R*, and calculated with reference to the dried substance.

Settling volume. Place 75 ml of *water R* in a 100 ml graduated cylinder and add 1.5 g of the substance to be examined in 0.5 g portions, shaking vigorously after each addition. Dilute to 100.0 ml with *water R* and shake again until the substance is homogeneously distributed. Allow to stand for 4 h. The settling volume is between 10.0 ml and 30.0 ml.

Microbial contamination. Total viable aerobic count (*2.6.12*) not more than 10^3 bacteria and 10^2 fungi per gram, determined by plate count. It complies with the test for *Escherichia coli* (*2.6.13*).