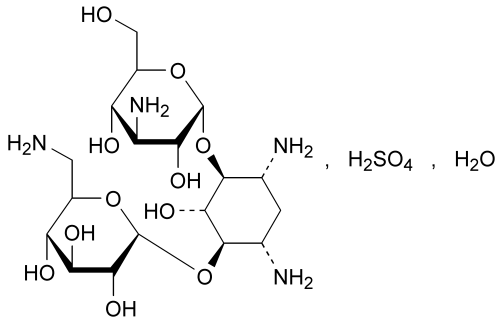
01/2008:0032

KANAMYCIN MONOSULPHATE

Kanamycini monosulfas



$C_{18}H_{38}N_4O_{15}S,H_2O$ M_r 601

DEFINITION

Kanamycin monosulphate is 6-*O*-(3-amino-3-deoxy-α-D-glucopyranosyl)-4-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl)-2-deoxy-D-streptamine sulphate, an antimicrobial substance produced by the growth of certain strains of *Streptomyces kanamyceticus*. The potency is not less than 750 IU/mg, calculated with reference to the dried substance.

PRODUCTION

It is produced by methods of manufacture designed to eliminate or minimise substances lowering blood pressure.

The method of manufacture is validated to demonstrate that the product if tested would comply with the following test:

Abnormal toxicity (*2.6.9*). Inject into each mouse 0.5 ml of a solution containing 2 mg per millilitre of the substance to be examined.

CHARACTERS

A white or almost white, crystalline powder, soluble in about 8 parts of water, practically insoluble in acetone and in alcohol.

IDENTIFICATION

A. Examine by thin-layer chromatography (*2.2.27*), using a plate coated with a 0.75 mm layer of the following mixture: mix 0.3 g of *carbomer R* with 240 ml of *water R* and allow to stand, with moderate shaking, for 1 h; adjust to pH 7 by the gradual addition, with continuous shaking, of *dilute sodium hydroxide solution R* and add 30 g of *silica gel H R*.

Heat the plate at 110 °C for 1 h, allow to cool and use immediately.

Test solution. Dissolve 10 mg of the substance to be examined in *water R* and dilute to 10 ml with the same solvent.

Reference solution (a). Dissolve 10 mg of *kanamycin monosulphate CRS* in *water R* and dilute to 10 ml with the same solvent.

Reference solution (b). Dissolve 10 mg of *kanamycin monosulphate CRS*, 10 mg of *neomycin sulphate CRS* and 10 mg of *streptomycin sulphate CRS* in *water R* and dilute to 10 ml with the same solvent.

Apply separately to the plate 10 µl of each solution. Develop over a path of 12 cm using a 70 g/l solution of *potassium dihydrogen phosphate R*. Dry the plate in a current of warm air and spray with a mixture of equal volumes of a 2 g/l solution of *dihydroxynaphthalene R* in *alcohol R* and a 460 g/l solution of *sulphuric acid R*. Heat at 150 °C for 5 min to 10 min. The principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a). The test is not valid unless the chromatogram obtained with reference solution (b) shows three clearly separated spots.

B. Dissolve 0.5 g in 10 ml of *water R*. Add 10 ml of *picric acid solution R*. Initiate crystallisation if necessary by scratching the wall of the tube with a glass rod and allow to stand. Collect the crystals, wash with 20 ml of *water R* and filter. Dry at 100 °C. The crystals melt (*2.2.14*) at about 235 °C, with decomposition.

C. Dissolve about 50 mg in 2 ml of *water R*. Add 1 ml of a 10 g/l solution of *ninhydrin R* and heat for a few minutes on a water-bath. A violet colour develops.

D. It gives the reactions of sulphates (*2.3.1*).

TESTS

Solution S. Dissolve 0.20 g in *carbon dioxide-free water R* and dilute to 20.0 ml with the same solvent.

pH (*2.2.3*). The pH of solution S is 6.5 to 8.5.

Specific optical rotation (*2.2.7*). +112 to +123, determined on solution S and calculated with reference to the dried substance.

Kanamycin B. Examine by thin-layer chromatography (*2.2.27*), using a plate prepared as prescribed under identification test A. Heat the plate at 110 °C for 1 h, allow to cool and use immediately.

Test solution. Dissolve 0.1 g of the substance to be examined in *water R* and dilute to 20 ml with the same solvent.

Reference solution. Dissolve 4 mg of *kanamycin B sulphate CRS* in *water R* and dilute to 20 ml with the same solvent.

Apply separately to the plate 4 µl of each solution. Develop over a path of 12 cm using a 70 g/l solution of *potassium dihydrogen phosphate R*. Dry the plate in a current of warm air and spray with *ninhydrin and stannous chloride reagent R*. Heat the plate at 110 °C for 15 min. Any spot corresponding to kanamycin B in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with the reference solution.

Loss on drying (*2.2.32*). Not more than 1.5 per cent, determined on 1.00 g by drying at 60 °C at a pressure not exceeding 670 Pa for 3 h.

Sulphated ash (*2.4.14*). Not more than 0.5 per cent, determined on 1.0 g.

Sulphate. 15.0 per cent to 17.0 per cent of sulphate (SO_4), calculated with reference to the dried substance. Dissolve 0.250 g in 100 ml of *water R* and adjust the solution to pH 11 using *concentrated ammonia R*. Add 10.0 ml of *0.1 M barium chloride* and about 0.5 mg of *phthalein purple R*. Titrate with *0.1 M sodium edetate* adding 50 ml of *alcohol R* when the colour of the solution begins to change and continue the titration until the violet-blue colour disappears.

1 ml of *0.1 M barium chloride* is equivalent to 9.606 mg of sulphate (SO_4).

Pyrogens (*2.6.8*). If intended for use in the manufacture of parenteral dosage forms without a further appropriate procedure for the removal of pyrogens, it complies with the test for pyrogens. Inject per kilogram of the rabbit's mass 1 ml of a solution in *water for injections R* containing 10 mg per millilitre of the substance to be examined.

ASSAY

Carry out the microbiological assay of antibiotics (*2.7.2*).

STORAGE

If the substance is sterile, store in a sterile, tamper-proof container.

01/2008:0503

KAOLIN, HEAVY

Kaolinum ponderosum

DEFINITION

Purified, natural, hydrated aluminium silicate of variable composition.

CHARACTERS

Appearance: fine, white or greyish-white, unctuous powder.

Solubility: practically insoluble in water and in organic solvents.

IDENTIFICATION

A. To 0.5 g in a metal crucible add 1 g of *potassium nitrate R* and 3 g of *sodium carbonate R* and heat until the mixture melts. Allow to cool. To the residue add 20 ml of boiling *water R*, mix and filter. Wash the residue with 50 ml of *water R*. To the residue add 1 ml of *hydrochloric acid R* and 5 ml of *water R*. Filter. To the filtrate add 1 ml of *strong sodium hydroxide solution R* and filter. To the filtrate add 3 ml of *ammonium chloride solution R*. A gelatinous white precipitate is formed.

B. Add 2.0 g in 20 portions to 100 ml of a 10 g/l solution of *sodium laurilsulfate R* in a 100 ml graduated cylinder about 30 mm in diameter. Allow 2 min between additions for each portion to settle. Allow to stand for 2 h. The apparent volume of the sediment is not greater than 5 ml.

C. 0.25 g gives the reaction of silicates (*2.3.1*).

TESTS

Solution S. To 4 g add a mixture of 6 ml of *acetic acid R* and 34 ml of *distilled water R*, shake for 1 min and filter.

Acidity or alkalinity. To 1.0 g add 20 ml of *carbon dioxide-free water R*, shake for 2 min and filter. To 10 ml of the filtrate add 0.1 ml of *phenolphthalein solution R*. The solution is colourless. Not more than 0.25 ml of *0.01 M sodium hydroxide* is required to change the colour of the indicator to pink.

Organic impurities. Heat 0.3 g to redness in a calcination tube. The residue is only slightly more coloured than the original substance.

Adsorption power. To 1.0 g in a ground-glass-stoppered test-tube add 10.0 ml of a 3.7 g/l solution of *methylene blue R* and shake for 2 min. Allow to settle. Centrifuge and dilute the solution 1 to 100 with *water R*. The solution is not more intensely coloured than a 0.03 g/l solution of *methylene blue R*.

Swelling power. Triturate 2 g with 2 ml of *water R*. The mixture does not flow.

Substances soluble in mineral acids: maximum 1 per cent.

To 5.0 g add 7.5 ml of *dilute hydrochloric acid R* and 27.5 ml of *water R* and boil for 5 min. Filter, wash the residue on the filter with *water R* and dilute the combined filtrate and washings to 50.0 ml with *water R*. To 10.0 ml of the solution add 1.5 ml of *dilute sulphuric acid R*, evaporate to dryness on a water-bath and ignite. The residue weighs a maximum of 10 mg.

Chlorides (*2.4.4*): maximum 250 ppm.

Dilute 2 ml of solution S to 15 ml with *water R*.

Sulphates (*2.4.13*): maximum 0.1 per cent.

Dilute 1.5 ml of solution S to 15 ml with *distilled water R*.

Calcium (*2.4.3*): maximum 250 ppm.

Dilute 4 ml of solution S to 15 ml with *distilled water R*.

Heavy metals (*2.4.8*): maximum 50 ppm.

To 5 ml of the solution prepared for the test for substances soluble in mineral acids add 5 ml of *water R*, 10 ml of *hydrochloric acid R* and 25 ml of *methyl isobutyl ketone R*. Shake for 2 min. Separate the layers. Evaporate the aqueous layer to dryness on a water-bath. Dissolve the residue in 1 ml of *acetic acid R* and dilute to 25 ml with *water R*. Filter. 12 ml of the solution complies with test A. Prepare the reference solution using *lead standard solution (1 ppm Pb) R*.

If intended for internal use, the above test is replaced by the following test for heavy metals (*2.4.8*): maximum 25 ppm.

To 10 ml of the solution prepared for the test for substances soluble in mineral acids add 10 ml of *water R*, 20 ml of *hydrochloric acid R* and 25 ml of *methyl isobutyl ketone R*. Shake for 2 min. Separate the layers. Evaporate the aqueous layer to dryness on a water-bath. Dissolve the residue in 1 ml of *acetic acid R* and dilute to 25 ml with *water R*. Filter. 12 ml of the solution complies with test A. Prepare the reference solution using *lead standard solution (1 ppm Pb) R*.

Microbial contamination. Total viable aerobic count (*2.6.12*) not more than 10^3 micro-organisms per gram, determined by plate-count.

LABELLING

The label states, where applicable, that the substance is suitable for internal use.

01/2008:1426
corrected 6.0

KELP

Fucus vel Ascophyllum

DEFINITION

Fragmented dried thallus of *Fucus vesiculosus* L. or *F. serratus* L. or *Ascophyllum nodosum* Le Jolis.

Content: minimum 0.03 per cent and maximum 0.2 per cent of total iodine (A_r 126.9) (dried drug).

CHARACTERS

Salty and mucilaginous taste.

Unpleasant marine odour.

IDENTIFICATION

A. The drug consists of fragments with a corneous consistency, blackish-brown to greenish-brown, sometimes covered with whitish efflorescence. The thallus consists of a ribbon-like blade, branching dichotomously with prominent central ribs (pseudoveins). *F. vesiculosus* typically shows a foliose blade with smooth edges and bears occasional ovoid, single or paired, air vesicles. The ends of certain branches are of ovoid shape and a little widened. They bear numerous reproductive organs (conceptacles). *F. serratus* has a foliose blade with