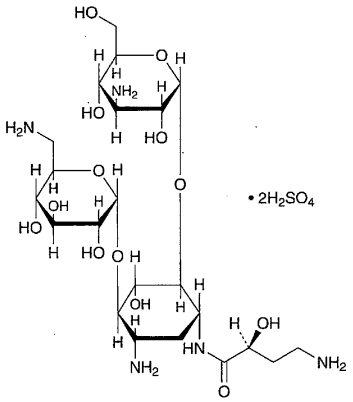
Amikacin Sulfate

硫酸アミカシン



$C_{22}H_{43}N_5O_{13}.2H_2SO_4$: 781.76

O-3-Amino-3-deoxy-α-D-glucopyranosyl-(1→6)-*O*-[6-amino-6-deoxy-α-D-glucopyranosyl-(1→4)]-1-*N*-[(2*S*)-4-amino-2-hydroxybutanoyl]-2-deoxy-D-streptamine disulfate [*39831-55-5*]

Amikacin Sulfate contains not less than 645 μg (potency) per mg, calculated on the dried basis. The potency of Amikacin Sulfate is expressed as mass (potency) of amikacin ($C_{22}H_{43}N_5O_{13}$: 585.60).

Description Amikacin Sulfate occurs as a white to yellowish white powder.

It is very soluble in water, and practically insoluble in ethanol (95).

Identification **(1)** Determine the infrared absorption spectrum of Amikacin Sulfate, previously dried, as directed in the potassium bromide disk method under the Infrared Spectrophotometry, and compare the spectrum with the Reference Spectrum or the spectrum of Amikacin Sulfate Reference Standard previously dried: both spectra exhibit similar intensities of absorption at the same wave numbers.

(2) Dissolve 0.1 g each of Amikacin Sulfate and Amikacin Sulfate Reference Standard in 4 mL of water, and use these solutions as the sample solution and the standard solution. Perform the test with these solutions as directed under the Thin-layer chromatography. Spot 2 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 water, ammonia water (28), methanol and tetrahydrofuran (1:1:1:1) to a distance of about 10 cm, and air-dry the plate. Spray evenly ninhydrin-citric acid-acetic acid TS on the plate, and heat at 100°C for 10 minutes: the principal spots from the sample solution and the standard solution exhibit a red-purple color and show the same *R*f value.

(3) A solution of Amikacin Sulfate (1 in 100) responds to the Qualitative Tests (1) for sulfate.

Optical rotation $[\alpha]_D^{20}$: +76 – +84° (1 g, water, 100 mL, 100 mm).

pH Dissolve 1.0 g of Amikacin Sulfate in 100 mL of water: the pH of the solution is between 6.0 and 7.5.

Purity **(1)** Heavy metals—Proceed with 1.0 g of Amikacin Sulfate according to Method 2, and perform the test. Prepare the control solution with 2.0 mL Standard Lead Solution (not more than 20 ppm).

(2) Related substances—Dissolve 0.10 g of Amikacin Sulfate in 4 mL of a water, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with these solutions as directed under the Thin-layer chromatography. Spot 2 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 water, ammonia water (28), methanol and tetrahydrofuran (1:1:1:1) to a distance of about 10 cm, and air-dry the plate. Spray evenly ninhydrin-citric acid-acetic acid TS on the plate, and heat at 100°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.

Loss on drying Not more than 4.0% (1 g, in vacuum, 60°C, 3 hours).

Assay Weigh accurately an amount of Amikacin Sulfate and Amikacin Sulfate Reference Standard, equivalent to about 0.05 g (potency), dissolve each in water to make exactly 50 mL. Pipet 200 μL each of these solutions in the test tube with glass stopper, add exactly 3 mL of pyridine and exactly 2 mL of a solution of 2,4,6-trinitrobenzenesulfonic acid (1 in 100), stopper tightly, and heat in a water bath at 70°C for 30 minutes. After cooling, add exactly 2 mL each of acetic aid (100), and use these solutions as the sample solution and the standard solution, respectively. Perform the test with 20 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions, and determine the heights, H_T and H_S, of the peak of amikacin derivative.

$$\text{Amount [μg (potency)] of amikacin } (C_{22}H_{43}N_5O_{13}) = \text{amount [mg (potency)] of Amikacin Sulfate Reference Standard} \times \frac{H_T}{H_S} \times 1000$$

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 340 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 35°C.

Mobile phase: Dissolve 2.72 g of potassium dihydrogenphosphate in 800 mL of water, adjust to pH 6.5 with a solution of potassium hydroxide (1 in 40), and add water to make 1000 mL. To 280 mL of this solution add 720 mL of methanol, and mix.

Flow rate: Adjust the flow rate so that the retention time of amikacin derivative is about 9 minutes.

System suitability—

System performance: Dissolve about 5 mg (potency) of Amikacin Sulfate and about 5 mg (potency) of Kanamycin Sulfate in 5 mL of water. Transfer 200 μL of this solution in a glass-stopperd test tube, add 3 mL of pyridine and 2 mL of a solution of 2,4,6-trinitrobenzenesulfonic acid (1 in 100),

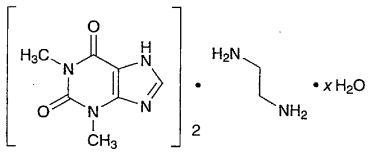
stopper tightly, heat in a water bath at 70°C for 30 minutes. After cooling, add 2 mL of acetic acid (100). When the procedure is run with 20 μL of this solution under the above operating conditions, amikacin derivative and kanamycin derivative are eluted in this order with the resolution between these peaks being not less than 5.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratios of the peak height of amikacin derivative is not more than 2.0%.

Containers and storage Containers—Hermetic containers.

Aminophylline

アミノフィリン



$C_{14}H_{16}N_8O_4.C_2H_8N_2.xH_2O$
3,7-Dihydro-1,3-dimethyl-1*H*-purine-2,6-dione hemi(ethylenediamine) hydrate [*5877-66-5*, dihydrate]

Aminophylline contains not less than 84.0% and not more than 86.0% of theophylline ($C_7H_8N_4O_2$: 180.17), and not less than 14.0% and not more than 15.0% of ethylenediamine ($C_2H_8N_2$: 60.10), calculated on the anhydrous basis.

Description Aminophylline occurs as white to pale yellow granules or powder. It is odorless or slightly ammonia-like odor, and has a bitter taste.

It is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol (95) and in diethyl ether.

To 1 g of Aminophylline add 5 mL of water, and shake: it dissolves almost completely. Separation of crystals begins in 2 to 3 minutes, and these crystals dissolve on the addition of a small amount of ethylenediamine.

It is gradually affected by light, and gradually loses ethylenediamine in air.

Identification **(1)** Dissolve 0.75 g of Aminophylline in 30 mL of water, and use this solution as the sample solution. To 20 mL of the sample solution add 1 mL of dilute hydrochloric acid: a precipitate is gradually formed. Filter the precipitate, recrystallize from water, and dry at 105°C for 1 hour: the crystals so obtained melt between 271°C and 275°C.

(2) Dissolve 0.1 g of the crystals obtained in (1) in 50 mL of water, and to 2 mL of this solution add tannic acid TS dropwise: a white precipitate is produced, and this precipitate dissolves upon dropwise addition of tannic acid TS.

(3) To 0.01 g of the crystals obtained in (1) add 10 drops of hydrogen peroxide TS and 1 drop of hydrochloric acid, and evaporate on a water bath to dryness: the residue shows a yellow-red color. Invert the dish containing the residue over a vessel containing 2 to 3 drops of ammonia TS: the color of the residue changes to red-purple, which is destroyed on the addition of 2 to 3 drops of sodium hydroxide TS.

(4) Dissolve 0.01 g of the crystals obtained in (1) in 5 mL of water, add 3 mL of ammonia-ammonium chloride buffer solution, pH 8.0, and 1 mL of copper (II) sulfate-pyridine TS, and mix. Add 5 mL of chloroform to the mixture, and shake: the chloroform layer develops a green color.

(5) To 5 mL of the sample solution obtained in (1) add 2 drops of copper (II) sulfate TS: a purple color develops. Add 1 mL of copper (II) sulfate TS: the color changes to blue, and green precipitates are formed on standing.

pH Dissolve 1.0 g of Aminophylline in 25 mL of water: the pH of the solution is between 8.0 and 9.5.

Purity **(1)** Clarity and color of solution—Dissolve 1.0 g of Aminophylline in 10 mL of hot water: the solution is clear and colorless to pale yellow.

(2) Heavy metals—Proceed with 1.0 g of Aminophylline according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 20 ppm).

Water Not more than 7.9% (0.3 g, direct titration).

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

Assay **(1)** Theophylline—Weigh accurately about 0.25 g of Aminophylline, and dissolve in 50 mL of water and 8 mL of ammonia TS by gentle warming on a water bath. Add exactly 20 mL of 0.1 mol/L silver nitrate VS, warm on a water bath for 15 minutes, allow to stand between 5°C and 10°C for 20 minutes, collect the precipitate by suction, and wash with three 10-mL portions of water. Combine the filtrate and washings, and add dilute nitric acid to make neutral. Add 3 mL of dilute nitric acid, and titrate the excess silver nitrate with 0.1 mol/L ammonium thiocyanate VS (indicator: 2 mL of ammonium iron (III) sulfate TS). Perform a blank determination.

Each mL of 0.1 mol/L silver nitrate VS
= 18.017 mg of $C_7H_8N_4O_2$

(2) Ethylenediamine—Weigh accurately about 0.5 g of Aminophylline, dissolve in 30 mL of water, and titrate with 0.1 mol/L hydrochloric acid VS (indicator: 3 drops of bromophenol blue TS).

Each mL of 0.1 mol/L hydrochloric acid VS
= 3.0049 mg of $C_2H_8N_2$

Containers and storage Containers—Tight containers.
Storage—Light-resistant.

Aminophylline Injection

アミノフィリン注射液

Aminophylline Injection is an aqueous solution for injection. It contains not less than 75% and not more than 86% of the labeled amount of theophylline ($C_7H_8N_4O_2$: 180.17), and not less than 13% and not more than 20% of ethylenediamine ($C_2H_8N_2$: 60.10).