dine, dissolve in the mobile phase to make exactly 50 mL, and use this solution as the sample solution. Separately, take exactly 0.025 g of Cefalexin Reference Standard, dissolve in the mobile phase to make exactly 250 mL, and use this solution as the standard solution. Perform the test with 5 μL each of these solutions as directed under the Liquid Chromatography according to the following conditions, and calculate the areas of each peak by the automatic integration method: the peak area of cefalexin from the sample solution is not more than the peak area of cefalexin from the standard solution.

Operating conditions—

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

Column: A stainless steel column 4.6 mm in inside diameter and 15 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: Dissolve 6.8 g of potassium dihydrogenphosphate in 800 mL of water, adjust the pH to 3.0 with diluted phosphoric acid (1 in 10), and add water to make 1000 mL. To 700 mL of this solution add 100 mL of acetonitrile.

Flow rate: Adjust the flow rate so that the retention time of cefalexin is about 10 minutes.

System suitability—

System performance: When the procdure is run with 5 μL of the sample solution under the above operating conditions, cefalexin and cefradine are eluted in this order with the resolution between these peaks being not less than 4.

System repeatability: When the test is repeated 6 times with 5 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak areas of cefalexin is not more than 2.0%.

Water Not more than 6.0% (0.2 g, volumetric titration, direct titration).

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. Adjust the pH of the medium so that it will be 6.2 to 6.4 after sterilization.

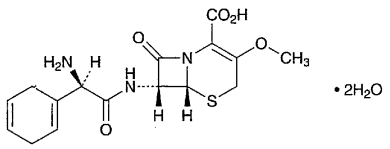
(3) Standard solution—Weigh accurately an amount of Cefradine Reference Standard equivalent to about 0.02 g (potency), dissolve in phosphate buffer solution, pH 6.0 to make exactly 50 mL. Take exactly a suitable amount of this solution, add phosphate buffer solution, pH 6.0 to make solutions so that each mL contains 20 μg (potency) and 5 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 Cefradine equivalent to about 0.02 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 20 μg (potency) and 5 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.

Cefroxadine

セフロキサジン



$C_{16}H_{19}N_3O_5S.2H_2O$: 401.43

(6*R*,7*R*)-7-[(2*R*)-2-Amino-2-cyclohexa-1,4-dienylacetylamino]-3-methoxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid dihydrate [*51762-05-1*, anhydride]

Cefroxadine conforms to the requirements of Cefroxadine in the Requirements for Antibiotic Products of Japan.

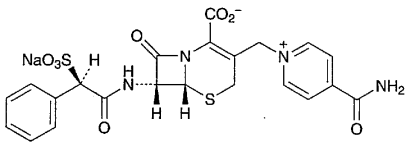
Description Cefroxadine occurs as pale yellowish white to light yellow crumbly, crystalline grains or powder. It has a characteristic odor.

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

It dissolves in 0.1 mol/L hydrochloric acid TS.

Cefsulodin Sodium

セフスロジンナトリウム



$C_{22}H_{19}N_4NaO_8S_2$: 554.53

Monosodium (6*R*,7*R*)-3-(4-carbamoylpyridinium-1-ylmethyl)-8-oxo-7-[(2*R*)-2-phenyl-2-sulfonatoacetylamino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate [*52152-93-9*]

Cefsulodin Sodium contains not less than 864 μg (potency) per mg, calculated on the anhydrous basis. The potency of Cefsulodin Sodium is expressed as mass (potency) of cefsulodin ($C_{22}H_{20}N_4O_8S_2$: 532.55).

Description Cefsulodin Sodium occurs as white to light yellow, crystals or crystalline powder.

It is freely soluble in water and in formamide, slightly soluble in methanol, and very slightly soluble in ethanol (95).

It is hygroscopic.

Identification **(1)** Determine the absorption spectrum of a solution of Cefsulodin Sodium (1 in 50,000) as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum or the spectrum

of Cefsulodin Sodium Reference Standard: both spectra exhibit similar intensities of absorption at the same wavelength.

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

(3) Determine the spectrum of a solution of Cefsulodin Sodium in heavy water for nuclear magnetic resonance spectroscopy (1 in 10) as directed under the Nuclear Magnetic Resonance Spectroscopy (^{1}H), using sodium 3-trimethylsilylpropanesulfonate for nuclear magnetic resonance spectroscopy as an internal reference compound: it exhibits a multiple signal A between δ 7.3 ppm and δ 7.7 ppm, and double signals, B and C, at around δ 8.4 ppm and at around δ 9.1 ppm, respectively. The ratio of integrated intensity of these signals, A:B:C, is about 5:2:2.

(4) Cefsulodin Sodium responds to the Qualitative Test (1) for sodium salt.

Optical rotation $[\alpha]_D^{20}$: +16.5 - +20.0° (0.10 g calculated on the anhydrous basis, water, 10 mL, 100 mm).

pH Dissolve 1.0 g of Cefsulodin Sodium in 10 mL of water: the pH of the solution is not less than 3.3 and not more than 4.8.

Purity **(1)** Clarity of solution—Dissolve 1.0 g of Cefsulodin Sodium in 10 mL of water: the solution is clear.

(2) Heavy metals—To 1.0 g of Cefsulodin Sodium add 10 mL of a solution of magnesium nitrate hexahydrate in ethanol (95) (1 in 5), mix, fire the ethanol to burn, then heat gradually to carbonize. After cooling, add 2 mL of nitric acid, heat carefully, then heat at 500 - 600°C to incinerate. If a carbonized residue still retains, add a little amount of nitric acid, and heat again to incinerate. After cooling, add 6 mL of hydrochloric acid to the residue, heat to dryness on a water bath, then moisten the residue with 3 drops of hydrochloric acid, add 10 mL of hot water, and heat on a water bath to dissolve. Add ammonia TS dropwise to adjust to pH 3 - 4, and add 2 mL of dilute acetic acid. If necessary, filter, wash the crucible and residue on the filter with 10 mL of water, transfer the filtrate and washings into a Nessler tube, add water to make 50 mL, and use this solution as the test solution. Prepare the control solution as follows: To 2.0 mL of Standard Lead Solution add 10 mL of a solution of magnesium nitrate hexahydrate in ethanol (95) (1 in 5), fire the ethanol to burn. After cooling, add 2 mL of nitric acid, heat carefully, then heat at 500 - 600°C. After cooling, add 6 mL of hydrochloric acid, then proceed in the same manner as for the preparation of the test solution (not more than 20 ppm).

(3) Arsenic—Prepare the test solution with 1.0 g of Cefsulodin Sodium according to Method 3, using a solution of magnesium nitrate hexahydrate in ethanol (95) (1 in 5) and 15 mL of dilute hydrochloric acid instead of a solution of magnesium nitrate hexahydrate in ethanol (95) (1 in 50) and 3 mL of hydrochloric acid, and perform the test (not more than 2 ppm).

(4) Related substances—Weigh accurately about 0.10 g of Cefsulodin Sodium, dissolve in water to make exactly 50 mL, and use this solution as the sample solution. Separately, weigh accurately about 0.02 g of isonicotinic acid amide and about 0.02 g of Cefsulodin Sodium Reference Standard (separately determine the water content in the same manner as Cefsulodin Sodium), and dissolve in water to make exactly 100 mL. Pipet 10 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with 10 μL each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the areas of each peak by the automatic integration method. Calculate the amount of the related substances by the following formula: the amount of isonicotinic acid amide is not more than 1.0%, and the total of other related substances is not more than 1.2%.

$$\text{Amount (\%) of isonicotinic acid amide} = \frac{A}{B_I} \times \frac{W_I}{W_T} \times 5$$

$$\text{Total amount (\%) of the other related substances} = \frac{B}{B_S} \times \frac{W_S}{W_T} \times 5$$

A: Peak area of isonicotinic acid amide from the sample solution

B: Total peak area other than cefsulodin and other than isonicotinic acid amide from the sample solution

B_I: Peak area of isonicotinic acid amide from the standard solution

B_S: Peak area of cefsulodin from the standard solution

W_T: Amount (g) of the sample

W_S: Amount (g) of Cefsulodin Sodium Reference Standard

W_I: Amount (g) of isonicotinic acid amide

Operating conditions—

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

Column: A stainless steel column 4 mm in inside diameter and 15 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: A mixture of a solution of ammonium sulfate (1 in 100) and acetonitrile (97:3).

Mobile phase B: A mixture of a solution of ammonium sulfate (1 in 100) and acetonitrile (92:8).

Flowing of the mobile phase: Change the mobile phase A to B at 14 minutes after the injection of sample.

Flow rate: Adjust the flow rate so that the retention time of cefsulodin is about 9.

Time span of measurement: About 4 times as long as the retention time of cefsulodin.

System suitability—

Test for required detection: Pipet 1 mL of the standard solution, add water to make exactly 10 mL. Confirm that the peak areas of isonicotinic acid amide and cefsulodin obtained from 10 μL of this solution are equivalent to 7 to 13% of those of isonicotinic acid amide and cefsulodin obtained from 10 μL of the standard solution.

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, isonicotinic acid amide and cefsulodin are eluted in this order with the resolution between these peaks being not less than 5.

System repeatability: When the test is repeated 5 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak areas of cefsulodin is not more than 1.0%.

Water Not more than 5.0% (1 g, volumetric titration, direct titration, avoiding moisture absorption of the sample, using a mixture of formamide for water determination and methanol for water determination (2:1) instead of methanol for water determination).

Assay Weigh accurately an amount of Cefsulodin Sodium and Cefsulodin Sodium Reference Standard, equivalent to about 0.1 g (potency), dissolve each in water to make exactly 50 mL, and use these solutions as the sample solution and the standard solution. Perform the test with 10 μL each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and calculate the peak areas, A_T and A_S, of cefsulodin of each solution.

$$\text{Amount [}\mu\text{g (potency)] of } C_{22}H_{20}N_4O_8S_2 = \text{amount [mg (potency)] of Cefsulodin Sodium Reference Standard} \times \frac{A_T}{A_S} \times 1000$$

Operating conditions—

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

Column: A stainless steel column 4 mm in inside diameter and 15 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 mixture of a solution of ammonium sulfate (1 in 100) and acetonitrile (97:3).

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

System suitability—

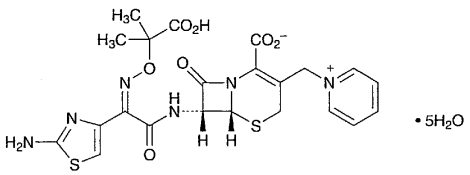
System performance: Dissolve 0.040 g of isonicotinic acid amide in 25 mL of the standard solution. When the procedure is run with 10 μL of this solution under the above operating conditions, isonicotinic acid amide and cefsulodin are eluted in this order with the resolution between these peaks being not less than 5.

System repeatability: When the test is repeated 5 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak areas of cefsulodin is not more than 1.0%.

Containers and storage Containers—Hermetic containers.

Ceftazidime

セフタジジム



$C_{22}H_{22}N_6O_7S_2.5H_2O$: 636.65

(6*R*,7*R*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino)acetylamino]-3-(pyridinium-1-ylmethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate pentahydrate [*72558-82-8*]

Ceftazidime contains not less than 950 μg (potency) per mg, calculated on the dried basis. The potency of Ceftazidime is expressed as mass (potency) of ceftazidime ($C_{22}H_{22}N_6O_7S_2$: 546.58).

Description Ceftazidime occurs as a white to light yellowish white crystalline powder.

It is slightly soluble in water, and very slightly soluble in acetonitrile and in ethanol (95).

Identification **(1)** Determine the absorption spectrum of a solution of Ceftazidime in phosphate buffer solution, pH 6.0 (1 in 100,000) as directed under the Ultraviolet-visible Spectrophotometry, and compare the spectrum with the Reference Spectrum or the spectrum of Ceftazidime Reference Standard: both spectra exhibit similar intensities of absorption at the same wavelength.

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

(3) To 0.05 g of Ceftazidime add 5 mg of dried sodium carbonate, and add 0.5 mL of heavy water for nuclear magnetic resonance spectroscopy to dissolve. Determine the spectrum of this solution as directed under the Nuclear Magnetic Resonance Spectroscopy (^1H), using sodium 3-trimethylsilylpropanesulfonate for nuclear magnetic resonance spectroscopy as an internal reference compound: it exhibits single signals, A and B, at around δ 1.5 ppm and at around δ 6.9 ppm, and a multiple signal C between δ 7.9 ppm and δ 9.2 ppm. The ratio of integrated intensity of each signal, A:B:C, is about 6:1:5.

Optical rotation $[\alpha]_D^{20}$: −28 – −34° (0.5 g calculated on the dried bases, phosphate buffer solution, pH 6.0, 100 mL, 100 mm).

pH Dissolve 0.5 g of Ceftazidime in 100 mL of water: the pH of the solution is between 3.0 and 4.0.

Purity **(1)** Clarity and color of solution—Dissolve 1.0 g of Ceftazidime in 10 mL of a solution obtained by dissolving 5 g of anhydrous disodium hydrogenphosphate and 1 g of potassium dihydrogenphosphate in water to make 100 mL: the solution is clear, and its absorbance at 420 nm is not more than 0.20.

(2) Heavy metals—Proceed with 1.0 g of Ceftazidime 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).

(3) Arsenic—Prepare the test solution with 1.0 g of Ceftazidime according to Method 3, and perform the test using Apparatus B (not more than 2 ppm).

(4) Related substances 1) Trityl-*t*-butyl substance and *t*-butyl substance—Dissolve 0.10 g of Ceftazidime in 2 mL of diluted disodium hydrogenphosphate TS (1 in 3), and use this solution as the sample solution. Pipet 1 mL of the sample solution, add diluted disodium hydrogenphosphate TS