Hydroxyethylcellulose

ヒドロキシエチルセルロース

[*9004-62-0*]

This monograph is harmonized with the European Pharmacopoeia and the U. S. Pharmacopeia.

The parts of the text that are not harmonized among the targeted texts for the harmonization are marked with symbols (◆ ◆), and the texts that are uniquely specified by the JP other than the targeted texts for the harmonization are marked with symbols (◇ ◇).

Hydroxyethylcellulose is partly *O*-(2-hydroxyethylated) cellulose.

It contains not less than 30.0% and not more than 70.0% of hydroxyethoxy group (-OC_2H_4OH: 61.06), calculated on the dried basis.

It may contain suitable pH-stabilizers such as phosphates.

◆The viscosity is shown in millipascal second (mPa･s) on the label.◆

◆**Description** Hydroxyethylcellulose occurs as a white to yellowish white, powder or grains.

It is practically insoluble in ethanol (95).

It forms a viscous liquid upon addition of water.

It is hygroscopic.◆

Identification **(1)** Determine the infrared absorption spectrum of Hydroxyethylcellulose as directed in the ATR method under Infrared Spectrophotometry <*2.25*> and compare the spectrum with the spectrum of Hydroxyethylcellulose RS for Identification: both spectra exhibit similar intensities of absorption at the same wave numbers.

(2) Disperse 1.0 g of Hydroxyethylcellulose in 50 mL of freshly boiled and cooled water. After 10 minutes, add freshly boiled and cooled water to make 100 mL, stir to dissolve completely, and use this solution as the sample solution. Boil 10 mL of the sample solution: the solution is clear.

◆**Viscosity** <*2.53*> Weigh exactly a quantity of Hydroxyethylcellulose, equivalent to 10.00 g calculated on the dried basis, add 400 mL of water, stir to dissolve, and add water to make exactly 500.0 g. Remove air bubbles, and use this solution as the sample solution. Perform the test with the sample solution according to Method 2 at 20 ± 0.1℃, using a beaker with an inside diameter of not less than 70 mm and a single cylinder-type rotational viscometer, according to the following operating conditions: not less than 75% and not more than 140% of the labeled viscosity.

Operating conditions —

Apparatus: Brookfield type viscometer LV and RV model.

Rotor No., rotation frequency and calculation multiplier: According to the following table, depending on the labeled viscosity.

Labeled viscosity (mPa･s)				Model	Rotor No.	Rotation frequency /min	Calculation multiplier
		less than 200		LV	1	30	2
Not less than 200 and less than		4000		LV	3	30	40
〃	4000	〃	10,000	LV	4	30	200
〃	10,000	〃	50,000	RV	6	20	500
〃	50,000			RV	7	20	2000

Procedure of apparatus: Read a value after 2 minutes of rotation, and stop the rotation for at least 2 minutes. Repeat this procedure more two times, and average the three observed values. ◆

pH <*2.54*> The pH of the sample solution obtained in the Identification (2) is between 5.5 and 8.5.

Purity **(1)** Chloride—To 1 mL of the sample solution obtained in the Identification (2) add water to make 30 mL, and use this solution as the sample solution. Separately, to 10 mL of Standard Chloride Solution add 5 mL of water, and use this solution as the control solution. To 15 mL each of the sample solution and the control solution add 1 mL of 2 mol/L nitric acid TS, transfer to test tubes containing 1 mL of a solution of silver nitrate (17 in 1000), allow to stand for 5 minutes protecting from light, and compare the opalescence developed in the both solutions against a black background by viewing transversely: the opalescence developed in the sample solution is not more intense than that of the control solution (not more than 1.0%).

(2) Nitrate—Dissolve 0.50 g of Hydroxyethylcellulose in the diluting solution to make exactly 100 mL, and use this solution as the sample solution. Separately, dissolve 0.8154 g of potassium nitrate in the diluting solution to make 1000 mL, and use this solution as the standard nitrate stock solution. If the viscosity of Hydroxyethylcellulose is not more than 1000 mPa･s, pipet 10 mL, 20 mL and 40 mL of the standard nitrate stock solution, add the diluting solution to each to make exactly 100 mL, and use these solutions as the standard solutions. If the viscosity of Hydroxyethylcellulose is more than 1000 mPa･s, pipet 1 mL, 2 mL and 4 mL of the standard nitrate stock solution, add the diluting solution to each to make exactly 100 mL, and use these solutions as the standard solutions. Perform the test with the sample solution and standard solutions using a nitrate-selective electrode as an indicator electrode, a silver-silver chloride electrode as a reference electrode and diluted ammonium sulfate TS (1 in 30) as reference electrolyte. Calculate the concentration of nitrates in the sample solution using a calibration curve obtained from the potential differences of the standard solutions: not more than

3.0%, calculated on the dried basis, if Hydroxyethylcellulose has a viscosity of not more than 1000 mPa·s, and not more than 0.2%, calculated on the dried basis, if Hydroxyethylcellulose has a viscosity of more than 1000 mPa·s. Prepare the solutions before use.

Diluting solution: To a mixture of 50 mL of 1 mol/L sulfuric acid TS and 800 mL of water add 135 g of potassium dihydrogen phosphate, and add water to make 1000 mL. To this solution add water to make exactly 25 times the initial volume.

In order to determine the applicable limit, determine the viscosity using the following procedure.

Introduce a quantity of Hydroxyethylcellulose, equivalent to 2.00 g calculated on the dried basis, into 50 g of water, stir, add water to make 100 g, and stir to dissolve completely. Determine the viscosity using a rotating viscometer at 25℃ and at a shear rate of 100 s^{-1} for substances with an expected viscosity less than 100 mPa·s, at a shear rate of 10 s^{-1} for substances with an expected viscosity not less than 100 mPa·s and not more than 20,000 mPa·s, and at a shear rate of 1 s^{-1} for substances with an expected viscosity more than 20,000 mPa·s. If it is impossible to obtain a shear rate of exactly 10 s^{-1} or 100 s^{-1} respectively, use a rate slightly higher and a rate slightly lower and interpolate.

◇**(3)** Heavy metal *<1.07>*—Proceed with 1.0 g of Hydroxyethylcellulose 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). ◇

(4) Aldehydes—Introduce 1.0 g of Hydroxyethylcellulose into a glass-stoppered test tube, add 10 mL of ethanol (99.5), stopper the tube tightly, and stir for 30 minutes. Centrifuge, and use the supernatant liquid as the sample solution. Use Standard Glyoxal Solution as the control solution. Pipet 2 mL each of the sample solution and the control solution, to each add 5 mL of a solution prepared by dissolving 4 g of 3-methyl-2-benzothiazolonehydrazone hydrochloride monohydrate in diluted acetic acid (100) (4 in 5) to make 1000 mL, shake to become uniform, and allow to stand for 2 hours. Compare the color of these solutions: the sample solution is not more intensely colored than the control solution (not more than 20 ppm).

Loss on drying *<2.41>* Not more than 10.0% (1 g, 105℃, 3 hours).

Residue on Ignition *<2.44>* Not more than 4.0% if the viscosity of Hydroxyethylcellulose is not more than 1000 mPa·s, and not more than 1.0% if the viscosity of Hydroxyethylcellulose is more than 1000 mPa·s (1 g). In order to determine the applicable limit, determine the viscosity according to the method in the Purity (2).

Assay Weigh accurately about 30 mg of Hydroxyethylcellulose, transfer to a 5-mL pressure-tight serum vial, add exactly 60 mg of adipic acid, 2 mL of the internal standard solution and 1 mL of hydroiodic acid, seal the vial immediately with a septum coated with fluororesin and an aluminum cap, and weigh accurately the vial. Place the vial in an oven or heat in a suitable heater with continuous stirring, maintaining the internal temperature of about 165 ± 2℃ for 2.5 hours. Allow to cool and weigh accurately the vial. If the difference of the mass between before heating and after heating is more than 10 mg, prepare a new sample solution. If the difference of the mass between before heating and after heating is not more than 10 mg, after phase separation, pierce through the septum of the vial with a cooled syringe, and withdraw a sufficient volume of the upper phase as the sample solution. Separately, place exactly 60 mg of adipic acid, 2 mL of the internal standard solution and 1 mL of hydroiodic acid in another serum vial, and seal immediately. Weigh accurately the vial, inject 55 μL of iodoethane for assay through the septum in the vial, and weigh again accurately. Shake thoroughly, after phase separation, pierce through the septum of the vial with a cooled syringe, and withdraw a sufficient volume of the upper phase as the standard solution. Perform the test as directed under Gas Chromatography *<2.02>* with 1 μL each of the sample solution and standard solution according to the following conditions, calculate the ratios, Q_T and Q_S, of the peak area of iodoethane to that of the internal standard.

$$\text{Amount (\%) of hydroethoxy group } (-OC_2H_4OH) = M_S / M_T \times Q_T / Q_S \times 39.15$$

M_S: Amount (mg) of iodoethane for assay taken

M_T: Amount (mg) of Hydroxyethylcellulose taken, calculated on the dried basis

Internal standard solution—A solution of *n*-octane in *o*-xylene (1 in 200).

Operating conditions—

Detector: A hydrogen flame-ionization detector.

Column: A fused silica column 0.53 mm in inside diameter and 30 m in length, coated with dimethylpolysiloxane for gas chromatography in 3 μm thickness.

Column temperature: Maintain the temperature at 50℃ for 3 minutes, raise the temperature to 100℃ at a rate of 10℃ per minute, then to 250℃ at a rate of 35℃ per minute, and maintain at 250℃ for 8 minutes.

Injection port temperature: A constant temperature of about 250℃.

Detector temperature: A constant temperature of about 280℃.

Carrier gas: Helium.

Flow rate: 4.2 mL per minutes (the retention time of the internal standard is about 10 minutes).

Split ratio: 1:40.

System suitability—

System performance: When the procedure is run with 1 μL of the standard solution under the above operating conditions, iodoethane and the internal standard are eluted in this order with the relative retention time of iodoethane to that of the internal standard being about 0.6 and the resolution between these peaks being not less than 5.0.

System repeatability: When the test is repeated 6 times with 1 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of iodoethane to that of the internal standard is not more than 2.0%.

◆**Containers and storage** Containers—Tight containers. ◆

Add the following to 9.01 Reference Standards (1):

Hydroxyethylcellulose RS for Identification

Add the following to 9.22 Standard Solutions:

Standard Chloride Solution Pipet 10 mL of Standard Chloride Stock Solution, add water to make exactly 1000 mL. Prepare before use. Each mL of this solution contains 5 μg of chloride (Cl).

Standard Chloride Stock Solution Weigh accurately 0.842 g of sodium chloride, previously dried at 130℃ for 2 hours, and dissolve in water to make exactly 1000 mL.

Standard Glyoxal Solution Dilute Standard Glyoxal Stock Solution to 10 times with ethanol (99.5). Prepare before use. Each mL of this solution contains 0.002 mg of glyoxal ($C_2H_2O_2$).

Standard Glyoxal Stock Solution Transfer a quantity of 40% glyoxal TS, equivalent to 0.200 g of glyoxal, in a 100-mL volumetric flask, and dilute to 100 mL with ethanol (99.5). Dilute to 100-fold with ethanol (99.5) before use. Each mL of this solution contains 0.02 mg of glyoxal ($C_2H_2O_2$).

Add the following to 9.41 Reagents, Test Solutions:

40% glyoxal TS *Content*: 38 – 42%. Assay—Put 1.000 g of 40% glyoxal TS in a glass-stoppered flask, add 20 mL of a solution of hydroxylammonium chloride (7 in 100) and 50 mL of water. Stopper tightly, allow to stand for 30 minutes, titrate <*2.50*> with 1 mol/L sodium hydroxide VS (indicator: 1.0 mL of methyl red-methylene blue TS). Perform a blank determination in the same manner, and make any necessary correction.

Each mL of 1 mol/L sodium hydroxide VS
= 29.02 mg of $C_2H_2O_2$

Iodoethane for assay C_2H_5I Colorless to slightly yellow liquid, turning brown on exposure to air and light. Miscible with ethanol (95). Boiling point: about 72℃; Specific gravity d_{20}^{20}: about 1.95.

Refractive index <*2.45*> n_D^{20}: about 1.513.

Content: not less than 99.0%. Assay—Proceed as directed in the Assay under isopropyl iodide for assay.

Each mL of 0.1 mol/L silver nitrate VS
= 15.60 mg of C_2H_5I

Storage—Preserve in tight, light-resistant containers.

3-Methyl-2-benzothiazolonehydrazone hydrochloride monohydrate $C_8H_{10}ClN_3S.H_2O$ A white to light yellow-white crystalline powder.

Melting point <*2.60*>: about 270℃ (with decomposition).