Status: Currently Official on 15-Feb-2025
Official Date: Official as of 01-Jun-2023
Document Type: NF Monographs
DocId: GUID-95E9940F-F7E8-41A0-92E5-B5005414EBD7_6_en-US
DOI: https://doi.org/10.31003/USPNF_M39000_06_01
DOI Ref: avc1l

Hydroxyethyl Cellulose

Portions of this monograph that are national *USP* text, and are not part of the harmonized text, are marked with symbols (◆) to specify this fact.

Cellulose, 2-hydroxyethyl ether

CAS RN®: 9004-62-0.

DEFINITION

Partly *O*-(2-hydroxyethylated) cellulose. It may contain suitable pH-stabilizers such as phosphates. It contains 30.0%–70.0% of hydroxyethoxy ($-OC_2H_4OH$) groups (dried substance).

IDENTIFICATION

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197A**
- **B.**

Sample solution: Disperse 1.0 g of the dried substance in 50 mL of carbon dioxide-free water. After 10 min, dilute with carbon dioxide-free water to 100 mL , and stir until dissolution is complete.

Analysis: Heat 10 mL of the *Sample solution* to boiling.

Acceptance criteria: The solution remains clear.

ASSAY

- **Procedure**

[Caution—Hydriodic acid and its reaction byproducts are highly toxic. Perform all steps of the *Standard solution* and the *Sample solution* in a properly functioning hood. Specific safety practices to be followed are to be identified to the analyst performing this test.]

[Note—Prepare the solutions immediately before use.]

◆**Apparatus:** For the reaction vial, use a 5-mL pressure-tight serum vial, 50 mm in height, 20 mm in outside diameter, and 13 mm in inside diameter at the mouth. The vial is equipped with a pressure-tight septum with a polytetrafluoroethylene-faced butyl rubber and an air-tight seal using an aluminum crimp or any sealing system that provides sufficient air-tightness. Use a heater with a heating module that has a square-shape aluminum block with holes 20 mm in diameter and 32 mm in depth, into which the reaction vial fits. The heating module is also equipped with a magnetic stirrer capable of mixing the contents of the vial, or use a reciprocal shaker that performs a reciprocating motion of approximately 100 times per minute.◆

Hydriodic acid: Use a reagent with a typical concentration of hydrogen iodide (HI), about 57%.

Internal standard solution: To 10 mL of *o*-xylene, add 0.5 mL of *n*-octane and dilute in *o*-xylene to 100.0 mL.

Standard solution: Transfer 60 mg of adipic acid and 2.00 mL of *Internal standard solution* to a 5-mL reaction vial, add 1.0 mL of *Hydriodic acid*, and close immediately with a septum. Accurately weigh the vial, then inject 55 µL of iodoethane through the septum in the vial, weigh again accurately, and mix. After phase separation, pierce through the septum of the vial with a cooled syringe, and withdraw a sufficient volume of the upper layer as the *Standard solution*.

Sample solution: To 30.0 mg of the substance to be examined (dried substance), add 60 mg of adipic acid in a 5-mL, pressure-tight reaction vial equipped with a pressure-tight membrane stopper coated with polytetrafluoroethylene and secured with an aluminum crimped cap or any other sealing system providing a sufficient air-tightness. Add 2.00 mL of *Internal standard solution* and 1.0 mL of *Hydriodic acid*, and close immediately. Accurately weigh the reaction vial (total mass before heating). Do not mix the contents of the vial by hand before placing in the oven or the heater. Place the vial in an oven or heat in a suitable heater with continuous mechanical agitation, maintaining an internal temperature of the vial at 165 ± 2° for 2.5 h. Allow to cool and accurately weigh the reaction vial (total mass after heating). If the difference of the total mass before heating to the total mass after heating is more than 10 mg, prepare a new test solution. 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*.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: GC

Detector: Flame ionization

Column: 0.53-mm × 30-m fused silica capillary, coated with a 3-µm layer of phase G1

Carrier gas: Helium

Temperatures

Injection port: 250°

Detector: 280°

Column: See *Table 1*.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
50	0	50	3
50	10	100	—
100	34.9	250	8

Flow rate: 4.2 mL/min

Injection volume: 1 µL

Injection type: Split; spilt ratio, 40:1

Run time: 20.3 min

System suitability

Suitability requirements

Sample: *Standard solution*

[NOTE—The relative retention times for iodoethane and *n*-octane are about 0.6 and 1.0, respectively. The retention time of the internal standard (*n*-octane) is about 10 min.]

Resolution: NLT 5.0 between the iodoethane and *n*-octane peaks

Relative standard deviation: NMT 2.0%, using the response factor of the principal peak for 6 injections of the *Standard solution*

Analysis

Samples: Upper layer of the *Standard solution* and the *Sample solution*

Calculate the response factor (*F*):

$$\text{Result} = (r_{S1} \times W_1 \times C)/(r_{S2} \times 100)$$

r_{S1} = peak area of the internal standard from the *Standard solution*

W_1 = weight of iodoethane in the *Standard solution* (mg)

C = percentage content of iodoethane from the certificate of the manufacturer

r_{S2} = peak area of iodoethane from the *Standard solution*

Calculate the percentage content (*m/m*) of the hydroxyethoxy groups:

$$\text{Result} = (r_{U1} \times F \times M_1 \times 100)/(r_{U2} \times W_2 \times M_2)$$

r_{U1} = peak area of iodoethane from the *Sample solution*

F = average value of the response factors of the *Standard solution*

M_1 = molar mass of the hydroxyethoxy group, 61.1

r_{U2} = peak area of the internal standard from the *Sample solution*

W_2 = weight of the sample (dried substance) in the *Sample solution* (mg)

M_2 = molar mass of iodoethane, 156.0

Acceptance criteria: 30.0%–70.0% of hydroxyethyoxy groups ($-OC_2H_4OH$) on the dried basis

IMPURITIES

• **Chlorides**

Chloride standard solution (5 ppm chloride)**:** Dissolve 0.824 g of USP Sodium Chloride RS in water to make 1000.0 mL. Immediately before use, dilute 1.0 mL of the solution so obtained with water to 100.0 mL.

Standard solution: Mix 10 mL of the *Chloride standard solution* and 5 mL of water immediately before use.

Sample solution: Dilute 1 mL of the *Sample solution* prepared in *IdentificationB* with water to 30 mL.

Analysis: Add 1 mL of a dilute nitric acid solution (200 g/L) to 15 mL of the *Sample solution*, and pour the mixture as a single addition into a test tube containing 1 mL of silver nitrate solution (17 g/L). Prepare a standard in the same manner. Examine the tubes laterally against a black background.

Acceptance criteria: After standing for 5 min protected from light, any opalescence in the *Sample solution* is not more intense than that in the *Standard solution* (NMT 1.0%).

• **Nitrates**

[Note—Prepare all solutions immediately before use.]

Buffer solution: To a mixture of 50 mL of 1 M sulfuric acid and 800 mL of water, add 135 g of monobasic potassium phosphate, and dilute with water to 1000 mL.

Buffered water: Dilute 80 mL of *Buffer solution* with water to 2000 mL.

Nitrate standard solution (500 ppm nitrate)**:** Dissolve 0.8154 g of potassium nitrate in 500 mL of *Buffered water*, and dilute with the same solvent to 1000.0 mL.

Sample solution: Dissolve 0.50 g of the substance to be examined in *Buffered water*, and dilute with the same solvent to 100.0 mL.

Reference solutions: If hydroxyethyl cellulose has a viscosity of 1000 mPa · s or less, dilute 10.0, 20.0, and 40.0 mL of *Nitrate standard solution* with *Buffered water* to 100.0 mL, and mix. If hydroxyethyl cellulose has a viscosity of more than 1000 mPa · s, dilute 1.0, 2.0, and 4.0 mL of *Nitrate standard solution* with *Buffered water* to 100.0 mL, and mix. To determine the applicable limit, determine the viscosity using the method described in the *Note* in the test for *Viscosity—Rotational Methods* ⟨912⟩.

Analysis: Carry out the measurements for each solution, potentiometrically (see *Titrimetry* ⟨541⟩), using a nitrate selective electrode as an indicator and a silver–silver chloride electrode with 0.1 M ammonium sulfate as a reference electrolyte. Calculate the concentration of nitrates using a calibration curve.

Acceptance criteria: NMT 3.0% (dried substance), if hydroxyethyl cellulose has a viscosity of 1000 mPa · s or less; and NMT 0.2% (dried substance), if hydroxyethyl cellulose has a viscosity of more than 1000 mPa · s.

• **Aldehydes**

Standard stock solution (20 ppm glyoxal)**:** In a 100-mL graduated flask, weigh a quantity of glyoxal solution [40% (w/w)] corresponding to 0.200 g of glyoxal ($C_2H_2O_2$), and dilute with anhydrous ethanol to volume. Immediately before use dilute the solution with the same solvent to 100 times its volume.

Standard solution (2 ppm glyoxal)**:** Immediately before use, dilute the *Standard stock solution* with anhydrous ethanol to 10 times its volume.

Sample solution: Transfer 1.0 g of Hydroxyethyl Cellulose to a test tube with a ground-glass stopper, and add 10.0 mL of anhydrous ethanol. Stopper the tube, and stir by mechanical means for 30 min. Centrifuge, and retain the supernatant.

Analysis: To 2.0 mL of the *Sample solution*, add 5.0 mL of a 4-g/L solution of methylbenzothiazolone hydrazone hydrochloride in an 80% (v/v) solution of glacial acetic acid in water. Shake to homogenize. After 2 h, the solution is not more intensely colored than a standard prepared at the same time and in the same manner using 2.0 mL of the *Standard solution* instead of 2.0 mL of the *Sample solution*.

Acceptance criteria: NMT 20 ppm, expressed as glyoxal

• **Residue on Ignition** ⟨281⟩**:** NMT 4.0% if hydroxyethyl cellulose has a viscosity of 1000 mPa · s or less and NMT 1.0% if hydroxyethyl cellulose has a viscosity of more than 1000 mPa · s, determined on 1.0 g. In order to determine the applicable limit, determine the viscosity using the method described in the *Note* in the test for *Viscosity—Rotational Methods* ⟨912⟩.

Change to read:

• ◆▲**Lead** ⟨251⟩, *Procedures, Procedure 1*▲ (CN 1-Jun-2023) **:** NMT 10 µg/g◆

SPECIFIC TESTS

• **pH ⟨791⟩**

Sample solution: Use the *Sample solution* prepared in *IdentificationB* (10 mg/mL).

Acceptance criteria: 5.5–8.5

• **Loss on Drying ⟨731⟩**

Sample: 1.000 g

Analysis: Dry the *Sample* at 105° for 3 h.

Acceptance criteria: NMT 10.0%

• **Viscosity—Rotational Methods ⟨912⟩:** When determined at the concentration and under the conditions specified in the labeling, its viscosity is 50%–150% of the labeled viscosity, where stated as a single value, or it is between the maximum and minimum values, where stated as a range of viscosities.

[Note—To determine the applicable limit for the tests for *Nitrates* and *Residue on Ignition* ⟨281⟩, determine the viscosity using the following procedure.]

While stirring transfer a quantity of the substance to be examined, equivalent to 2.00 g of the dried substance, to 50 g of water. Dilute with water to 100.0 g, and stir until dissolution is complete. Determine the viscosity using a rotating viscometer at 25° and at a shear rate of 100 s^{-1} for substances with an expected viscosity up to 100 mPa · s, at a shear rate of 10 s^{-1} for substances with an expected viscosity between 100 mPa · s and 20,000 mPa · s and at a shear rate of 1 s^{-1} for substances with an expected viscosity above 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.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers.

• **Labeling:** The labeling indicates its viscosity, under specified conditions, in aqueous solution. The indicated viscosity may be in the form of a range encompassing 50%–150% of the labeled value. The label states the name and concentration of any added pH-stabilizer.

• **USP Reference Standards ⟨11⟩**

USP Hydroxyethyl Cellulose RS

USP Sodium Chloride RS

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
HYDROXYETHYL CELLULOSE	Documentary Standards Support	CE2020 Complex Excipients
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	CE2020 Complex Excipients

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 34(6)

Current DocID: GUID-95E9940F-F7E8-41A0-92E5-B5005414EBD7_6_en-US

DOI: https://doi.org/10.31003/USPNF_M39000_06_01

DOI ref: avc1l