002-0901PDG.pdf

HYDROXYPROPYLCELLULOSE, LOW SUBSTITUTED

Stage 4, Revision 1

CP: USP

BRIEFING NOTE

Compared to the Stage 4, document the following changes are proposed:

1. Assay: a determination of the molar substitution has been added based on extensive validation work. The validation report is attached for your information. This assay applies the general principle for determination of alkoxy groups in substituted celluloses (Zeissel-reaction followed by gas chromatography) which has been presented by JPEC for Hydroxypropylcellulose and Hydroxypropylcellulose, low substituted. This method replaces the existing GC method for consistency with the newly proposed method for Hydroxypropylcellulose.

2. In addition, the text has been converted to “global style”.

Hydroxypropyl Cellulose, Low Substitued

DEFINITION

Cellulose, 2-hydroxypropyl ether *[9004-64-21.*

Hydroxypropyl Cellulose, Low substituted is a low- substituted poly(hydroxypropyl) ether of cellulose. It contains not less than 5.0 percent and not more than 16.0 percent of hydroxypropoxy groups, calculated on the dried basis.

Packaging and storage—Preserve in tight containers.

Identification—
A: Infrared absorption spectrophotometry.
B: Shake thoroughly 0.1 g with 10 mL of water. Add 1 g of sodium hydroxide, and shake until it becomes homogeneous. Transfer 5 mL to a suitable container, add 10 mL of a mixture of acetone and methanol (4:1), and shake: a white, flocculent precipitate is formed.

pH between 5.0 and 7.5, in a suspension obtained by shaking 1.0 g with 100 mL of water.

Loss on drying : Dry it at 105º for 1 hour: it loses not more than 5.0% of its weight.

Residue on ignition : not more than 0.8%

Heavy metals, maximum 10 PPM

Standard Preparation—Into a 50-mL color-comparison tube pipet 2 mL of *Standard Lead Solution* (20 µg of Pb), and dilute with water to 25 mL. Using a pH meter or short-range pH indicator paper as external indicator, adjust with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, dilute with water to 40 mL, and mix.

Test Preparation—Transfer 2 g of the substance to a suitable crucible, add sufficient sulfuric acid to wet the substance, and carefully ignite at a low temperature until thoroughly charred. (The crucible may be loosely covered with a suitable lid during the charring.) Add to the carbonized mass 2 mL of nitric acid and 5 drops of sulfuric acid, and heat cautiously until white fumes no longer are evolved. Ignite, preferably in a muffle furnace, at 500° to 600°, until the carbon is completely burned off. Cool, add 4 mL of 6 N hydrochloric acid, cover, digest on a steam bath for 15 minutes, uncover, and slowly evaporate on a steam bath to

dryness. Moisten the residue with 1 drop of hydrochloric acid, add 10 mL of hot water, and digest for 2 minutes. Add 6 N ammonium hydroxide dropwise until the solution is just alkaline to litmus paper, dilute with water to 25 mL, and adjust with 1 N acetic acid to a pH between 3.0 and 4.0, using short-range pH indicator paper as an external indicator. Filter if necessary, rinse the crucible and the filter with 10 mL of water, combine the filtrate and rinsing in a 50-mL color-comparison tube, dilute with water to 40 mL, and mix.

Procedure—To each of the tubes containing the *Standard Preparation* and the *Test Preparation,* add 2 mL of *pH 3.5 Acetate Buffer,* then add 1.2 mL of thioacetamide–glycerin base, dilute with water to 50 mL, mix, allow to stand for 2 minutes, and view downward over a white surface*: the color of the solution from the *Test Preparation* is not darker than that of the solution from the *Standard Preparation*.

Assay for hydroxypropoxy groups—Gas Chromatography
Internal standard solution –methycyclohexane in *o*-xylene (1 in 50)

Test Solution - Weigh accurately 30 mg of hydroxypropylcellulose, Low Substituted previously dried, transfer to the reaction vial, add 60 mg of adipic acid, 2.0 mL of *Internal standard solution*, and 1.0 mL of hydroiodic acid, stopper the vial tightly, and weigh accurately. Shake the vial for 30 seconds, heat at 115 º in a heater capable of maintaining the inside temperature within ± 1 º for 70 minutes with continuous shaking. Allow the vial to cool and weigh accurately. If the loss is less than 5 mg, use the upper layer of the mixture as the test solution.

Standard Solution - Add 60 mg of adipic acid, 2.0 mL of *Internal standard solution*, and 1.0 mL of hydroiodic acid, stopper the vial tightly, and weigh accurately. Add 25 µL of isopropyl iodide for assay, and again weigh accurately. Shake the reaction vial for 30 seconds, and use the upper layer of the content as the standard solution.

Chromatographic Conditions:

Detector: FID
Column: Fused silica, 0.53 mm inside diameter and 30 m in length, coated with 3 µm 100% dimethyl polysiloxane for gas chromatography. Use a guard column if necessary.
Carrier gas: Helium
Flow Rate: Adjust the flow rate so the retention time of the internal standard is about 8 minutes
Split ratio: 1:50.
Temperature:
— *temperature program a*s follows:

	Time (min)	Temperature (°C)
Column	0-3	40
	3-9	40 → 100
	9-12	100 → 250
	12-15	250
Injection port		180
Detector		280

System Suitability:

Resolution, R, between isopropyl iodide and methylcyclohexane is NLT 2 for the Standard Solution. The %RSD of the response factor calculation (F) for 6 injections of the Standard Solution is NMT 2.0%.

Calculations:

Calculate the response factor (F) from the following expression:

$F = (A_1 \times W_1 \times C) / (A_2 \times 100)$

A_1 = peak area of the internal standard peak in the chromatogram of the standard solution.

A_2 = peak area of the isopropyl iodide peak in the chromatogram of the standard solution.

W1 = weight of isopropyl iodide in the standard solution in mg.

C = percentage content of isopropyl iodide from the certificate of the manufacturer.

Calculate the percentage content m/m of the hydroxypropoxy group:

$\%\ \text{hydroxypropxy} = (A_4 \times F \times M_1 \times 100) / (A_3 \times W_2 \times M_2)$

A_3 = peak area of the internal standard peak in the chromatogram of the test solution.

A_4 = peak area of isopropyl iodide peak in the chromatogram of the test solution.

F = response factor calculated from above

M_1 = molar mass of hydroxypropoxy group: 75.1

M_2 = molar mass of isopropyl iodide: 170.0

W_2 = weight of the sample in the test solution, in mg.

Reagents

pH 3.5 Acetate Buffer— Dissolve 25.0 g of ammonium acetate in 25 mL of water, and add 38.0 mL of 6 N hydrochloric acid. Adjust, if necessary, with 6 N

ammonium hydroxide or 6 N hydrochloric acid to a pH of 3.5, dilute with water to 100 mL, and mix.

Thioacetamide–Glycerin Base —

Solution A: Dissolve 4 g of thioacetamide in 100 mL of water.

Solution B: To 200 g of glycerin add water to bring the total weight to 235 g. Add 140 mL of 1 N sodium hydroxide and 50 mL of water.

Mix 0.2 mL of Solution A and 1 mL of Solution B and heat in a boiling water bath for 20 seconds. Use the mixture immediately.