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HYDROXYPROPYLCELLULOSE

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 and comparative studies with the existing titration method. 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 titration method which required the highly toxic reagent chromic acid.

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

Hydroxypropyl Cellulose

DEFINITION

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

Hydroxypropyl Cellulose is a partially substituted poly(hydroxypropyl) ether of cellulose. It contains not less than 53.4 percent and not more than 80.5 percent of hydroxypropoxy groups, calculated on the dried basis. It may contain suitable anticaking agents.

Packaging and storage—Preserve in well-closed containers.

Labeling—Label it to indicate the normal viscosity in an aqueous solution of stated concentration and temperature. Suitable anticaking agents should be stated on the label.

Identification—

A: Dissolve 1 g of Hydroxypropyl Cellulose in 100 mL of water. Transfer 10 mL of this solution to a suitable container. Heat the solution to 45º: the solution becomes cloudy or a flocculent precipitate is formed, and the turbidity or precipitate disappears on cooling.

B: Transfer 1 mL of the solution from *Identification* test *A* to a glass plate, and allow the water to evaporate: a thin, self-sustaining film is formed.

C: Infrared absorption spectrophotometry.

Viscosity : not less than 50% and not more than 150% of the labeled claim; use an LV-type rotational viscometer with the spindle and speed combination for materials with labeled viscosity of 75cp or higher.

pH between 5.0 and 8.0 for a 1% solution.

Loss on drying : Dry it at 105º for 4 hours: it loses not more than 5.0% of its weight.

Residue on ignition : not more than 0.8%

Heavy metals, maximum 20 PPM

Standard Preparation—Transfer a mixture of 8 mL of sulfuric acid and 10 mL of nitric acid to a clean, dry, 100-mL Kjeldahl flask, and add a further volume of nitric acid equal to the incremental volume of nitric acid added to the Test Preparation. Heat the solution to the production of dense, white fumes; cool; cautiously add 10 mL of water; and, if hydrogen peroxide was used in treating the

Test Preparation, add a volume of 30 percent hydrogen peroxide equal to that used for the substance being tested. Boil gently to the production of dense, white fumes. Again cool, cautiously add 5 mL of water, mix, and boil gently to the production of dense, white fumes and to a volume of 2 to 3 mL. Cool, dilute cautiously with a few mL of water, add 2.0 mL of Standard Lead Solution (20 µg of Pb), and mix. Transfer to a 50-mL color-comparison tube, rinse the flask with water, adding the rinsing to the tube until the volume is 25 mL, and mix.

Test Preparation—Transfer 1 g of the test substance to a clean, dry, 100-mL Kjeldahl flask. [note—A 300-mL flask may be used if the reaction foams excessively.] Clamp the flask at an angle of 45°, and add a sufficient quantity of a mixture of 8 mL of sulfuric acid and 10 mL of nitric acid to moisten the substance thoroughly. Warm gently until the reaction commences, allow the reaction to subside, and add portions of the same acid mixture, heating after each addition, until a total of 18 mL of the acid mixture has been added. Increase the amount of heat, and boil gently until the solution darkens. Cool, add 2 mL of nitric acid, and heat again until the solution darkens. Continue the heating, followed by addition of nitric acid until no further darkening occurs, then heat strongly to the production of dense, white fumes. Cool, cautiously add 5 mL of water, boil gently to the production of dense, white fumes, and continue heating until the volume is reduced to a few mL. Cool, cautiously add 5 mL of water, and examine the color of the solution. If the color is yellow, cautiously add 1 mL of 30 percent hydrogen peroxide, and again evaporate to the production of dense, white fumes and a volume of 2 to 3 mL. If the solution is still yellow, repeat the addition of 5 mL of water and the peroxide treatment. Cool, dilute cautiously with a few mL of water, and rinse into a 50-mL color-comparison tube, taking care that the combined volume does not exceed 25 mL.

Monitor Preparation—Proceed with the digestion, using the same amount of sample and the same procedure as directed in the subsection If the substance is a solid in the section Test Preparation, until the step “Cool, dilute cautiously with a few mL of water.” Add 2.0 mL of Lead Standard Solution (20 µg of lead), and mix. Transfer to a 50-mL color comparison tube, rinse the flask with water, adding the rinsing to the tube until the volume is 25 mL, and mix.

Procedure—Treat the Test Preparation, the Standard Preparation, and the Monitor Preparation as follows. Using a pH meter or short-range pH indicator paper as external indicator, adjust the solution to a pH between 3.0 and 4.0 with ammonium hydroxide (a dilute ammonia solution may be used, if desired, as the specified range is approached), dilute with water to 40 mL, and mix.

To each tube 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 Test Preparation is not darker than that of the Standard Preparation, and the color of the Monitor Preparation is equal to or darker than that of 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 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 ° in a heater capable of maintaining the inside temperature within ± 1 ° 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:

$\%\ \text{hydroxypropxy} = (1.1 \times A_4 \times F \times M_1 \times 100) / (A_3 \times W_2 \times M_2)$

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.

1.1 = Correction Factor to correlate results to previous titration assay which was replaced by this method.

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.