

(2) Chloride—To 1.0 g of Hydroxypropylmethylcellulose 2906 add 30 mL of hot water, stir well, heat on a water bath for 10 minutes, filter by decantation while hot, wash the residue well with hot water, combine the washings with the filtrate, and add water to make 100 mL after cooling. To 5 mL of the solution add 6 mL of dilute nitric acid and water to make 50 mL, and perform the test using this solution as the test solution. Prepare the control solution with 0.40 mL of 0.01 mol/L hydrochloric acid VS (not more than 0.284%).

(3) Heavy metals—Proceed with 2.0 g of Hydroxypropylmethylcellulose 2906 according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

(4) Iron—Prepare the test solution with 0.20 g of Hydroxypropylmethylcellulose 2906 according to Method 3, and perform the test according to Method A. Prepare the control solution with 2.0 mL of Standard Iron Solution (not more than 100 ppm).

(5) Arsenic—Prepare the test solution with 1.0 g of Hydroxypropylmethylcellulose 2906 according to Method 3, and perform the test using apparatus B (not more than 2 ppm).

**Loss on drying** Not more than 5.0% (1 g, 105°C, 1 hour).

**Residue on ignition** Not more than 1.5% (1.0 g).

**Assay (i) Apparatus**—Reaction flask: A 5-mL screw-cap pressure-tight glass bottle, having an inverted conical bottom inside, 20 mm in outside diameter, 50 mm in height up the neck, 2 mL in capacity up to a height of about 30 mm, equipped with a pressure-tight septum of heat-resisting resin and also with an inside stopper or sealer of fluoroplastic.

**Heater**: A square-shaped aluminum block 60 to 80 mm thick, having holes 20.6 mm in diameter and 32 mm in depth, capable of maintaining the inside temperature within  $\pm 1^\circ\text{C}$ .

(ii) Procedure—Weigh accurately about 0.065 g of Hydroxypropylmethylcellulose 2906, previously dried, transfer to the reaction flask, add 0.065 g of adipic acid, 2.0 mL of the internal standard solution and 2.0 mL of hydroiodic acid, stopper the flask tightly, and weigh accurately. Shake the flask for 30 seconds, heat at 150°C on the heater for 30 minutes with repeated shaking at 5-minute intervals, and continue heating for an additional 30 minutes. Allow the flask to cool, and again weigh accurately. If the mass loss is less than 10 mg, use the upper layer of the mixture as the sample solution. Separately, take 0.065 g of adipic acid, 2.0 mL of the internal standard solution and 2.0 mL of hydroiodic acid in another reaction flask, and weigh accurately. Add 15  $\mu\text{L}$  of isopropyl iodide for assay, weigh accurately, add 45  $\mu\text{L}$  of iodomethane for assay in the same manner, and again weigh accurately. Shake the reaction flask for 30 seconds, and use the upper layer of the content as the standard solution. Perform the test with 2  $\mu\text{L}$  each of the sample solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the ratios,  $Q_{\text{Ta}}$  and  $Q_{\text{Tb}}$ , of the peak area of iodomethane from the sample solution to that of the internal standard, and  $Q_{\text{Sa}}$  and  $Q_{\text{Sb}}$ , of the peak area of iodomethane and isopropyl iodide from the standard solution to that of the internal standard.

$$\begin{aligned} &\text{Content (\%)} \text{ of methoxyl group} \\ &= \frac{Q_{\text{Ta}}}{Q_{\text{Sa}}} \times \frac{W_{\text{Sa}}}{\text{amount (mg) of the sample}} \times 21.864 \end{aligned}$$

Content (%) of hydroxypropoxyl group

$$= \frac{Q_{\text{Tb}}}{Q_{\text{Sb}}} \times \frac{W_{\text{Sb}}}{\text{amount (mg) of the sample}} \times 44.17$$

$W_{\text{Sa}}$ : Amount (mg) of iodomethane in the standard solution.

$W_{\text{Sb}}$ : Amount (mg) of isopropyl iodide in the standard solution.

**Internal standard solution**—A solution of *n*-octane in *o*-xylene (1 in 25).

**Operating conditions**—

**Detector**: A thermal conductivity detector or hydrogen flame-ionization detector.

**Column**: A glass column about 3 mm in inside diameter and about 3 m in length, packed with siliceous earth for gas chromatography, 180 to 250  $\mu\text{m}$  in diameter, coated with methyl silicone polymer at the ratio of 20%.

**Column temperature**: A constant temperature of about 100°C.

**Carrier gas**: Helium

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

**Selection of column**: Proceed with 2  $\mu\text{L}$  of the standard solution under the above operating conditions. Use a column giving well-resolved peaks of iodomethane, isopropyl iodide and the internal standard in this order.

**Containers and storage** Containers—Well-closed containers.

## Hydroxypropylmethylcellulose 2910

ヒドロキシプロピルメチルセルロース 2910

Hydroxypropylmethylcellulose 2910 is a methyl and hydroxypropyl mixed ether of cellulose. When dried, it contains not less than 28.0% and not more than 30.0% of methoxyl group ( $-\text{OCH}_3$ : 31.03), and not less than 7.0% and not more than 12.0% of hydroxypropoxyl group ( $-\text{OC}_3\text{H}_6\text{OH}$ : 75.09).

The kinematic viscosity of Hydroxypropylmethylcellulose 2910 is shown in square millimeter second ( $\text{mm}^2/\text{s}$ ) on the label.

**Description** Hydroxypropylmethylcellulose 2910 occurs as white to yellowish white, powder or granules. It is odorless or has a slight, characteristic odor. It is tasteless.

It is practically insoluble in ethanol (99.5) and in diethyl ether.

It swells in water and a clear or slightly turbid, viscous solution is produced.

**Identification (1)** To 1 g of Hydroxypropylmethylcellulose 2910 add 100 mL of hot water, cool to room temperature with stirring, and use this as the sample solution. Add anthrone TS gently to 5 mL of the sample solution: a blue to blue-green color is produced at the zone of contact.

(2) To 0.1 mL of the sample solution obtained in (1) add 9 mL of diluted sulfuric acid (9 in 10), shake, heat in a water bath for exactly 3 minutes, immediately cool in an ice bath, add carefully 0.6 mL of ninhydrin TS, shake, and allow to

stand at 25°C: a red color develops at first, and it changes to purple within 100 minutes.

(3) Take 5 mg of Hydroxypropylmethylcellulose 2910 in a small test tube, add 2 drops of a solution of 25% hydrated benzoyl peroxide in acetone (1 in 10), evaporate on a water bath to dryness, fix a glass rod, which is moistened with disodium chlomotropate TS at the lower end, into the small test tube with a cork stopper, and heat in a bath at 125°C for 5 to 6 minutes: a red-purple color develops in disodium chlomotropate TS.

(4) Heat the sample solution obtained in (1) in a water bath: a white turbidity or precipitate is produced, which disappears upon cooling the solution.

**Viscosity** Weigh exactly Hydroxypropylmethylcellulose 2910, equivalent to 2.000 g of dried solid, calculated on the dried basis, add 98 mL of water previously heated to 85°C, and stir by mechanical means for 10 minutes. Continue the stirring for another 40 minutes in an ice bath until the solution is complete, add water to make 100.0 g, and if necessary, centrifuge the solution to expel any entrapped air. Determine the viscosity as directed in Method 1 under the Viscosity at 20°C. The viscosity of Hydroxypropylmethylcellulose 2910 is not less than 80% and not more than 120% of that stated on the label.

**pH** To 1.0 g of Hydroxypropylmethylcellulose 2910 add 100 mL of hot water, shake to form a suspension, and cool to room temperature: the pH of the solution thus obtained is between 5.0 and 8.0.

**Purity (1) Clarity and color of solution**—To 0.5 g of Hydroxypropylmethylcellulose 2910 add 20 mL of hot water, and stir well to disperse by heating on a water bath. Cool to 5°C, add water to make 50 mL, transfer to a Nessler tube, and observe transversely the turbidity of the solution: the solution is not more intense than the following control solution.

Control solution: To 2.0 mL of 0.005 mol/L sulfuric acid VS add 1 mL of dilute hydrochloric acid, 45 mL of water and 2 mL of barium chloride TS, mix, allow to stand for 10 minutes, and shake before use.

(2) Chloride—To 1.0 g of Hydroxypropylmethylcellulose 2910 add 30 mL of hot water, stir well, heat on a water bath for 10 minutes, filter by decantation while hot, wash the residue well with hot water, combine the washings with the filtrate, and add water to make 100 mL after cooling. To 5 mL of the solution add 6 mL of dilute nitric acid and water to make 50 mL, and perform the test using this solution as the test solution. Prepare the control solution with 0.40 mL of 0.01 mol/L hydrochloric acid VS (not more than 0.284%).

(3) Heavy metals—Proceed with 2.0 g of Hydroxypropylmethylcellulose 2910 according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

(4) Iron—Prepare the test solution with 0.20 g of Hydroxypropylmethylcellulose 2910 according to Method 3, and perform the test according to Method A. Prepare the control solution with 2.0 mL of Standard Iron Solution (not more than 100 ppm).

(5) Arsenic—Prepare the test solution with 1.0 g of Hydroxypropylmethylcellulose 2910 according to Method 3, and perform the test using apparatus B (not more than 2 ppm).

**Loss on drying** Not more than 5.0% (1 g, 105°C, 1 hour).

**Residue on ignition** Not more than 1.5% (1.0 g).

**Assay (i) Apparatus**—Reaction flask: A 5-mL screw-cap pressure-tight glass bottle, having an inverted conical bottom inside, 20 mm in outside diameter, 50 mm in height up the neck, 2 mL in capacity up to a height of about 30 mm, equipped with a pressure-tight septum of heat-resisting resin and also with an inside stopper or sealer of fluoroplastic.

Heater: A square-shaped aluminum block 60 to 80 mm thick, having holes 20.6 mm in diameter and 32 mm in depth, capable of maintaining the inside temperature within  $\pm 1^\circ\text{C}$ .

(ii) Procedure—Weigh accurately about 0.065 g of Hydroxypropylmethylcellulose 2910, previously dried, transfer to the reaction flask, add 0.065 g of adipic acid, 2.0 mL of the internal standard solution and 2.0 mL of hydroiodic acid, stopper the flask tightly, and weigh accurately. Shake the flask for 30 seconds, heat at 150°C on the heater for 30 minutes with repeated shaking at 5-minute intervals, and continue heating for an additional 30 minutes. Allow the flask to cool, and again weigh accurately. If the mass loss is less than 10 mg, use the upper layer of the mixture as the sample solution. Separately, take 0.065 g of adipic acid, 2.0 mL of the internal standard solution and 2.0 mL of hydroiodic acid in another reaction flask, and weigh accurately. Add 15  $\mu\text{L}$  of isopropyl iodide for assay, weigh accurately, add 45  $\mu\text{L}$  of iodomethane for assay in the same manner, and again weigh accurately. Shake the reaction flask for 30 seconds, and use the upper layer of the content as the standard solution. Perform the test with 2  $\mu\text{L}$  each of the sample solution and the standard solution as directed under the Gas Chromatography according to the following conditions, and calculate the ratios,  $Q_{\text{Ta}}$  and  $Q_{\text{Tb}}$ , of the peak area of iodomethane from the sample solution to that of the internal standard, and  $Q_{\text{Sa}}$  and  $Q_{\text{Sb}}$ , of the peak area of iodomethane and isopropyl iodide from the standard solution to that of the internal standard.

$$\begin{aligned} & \text{Content (\% of methoxyl group)} \\ &= \frac{Q_{\text{Ta}}}{Q_{\text{Sa}}} \times \frac{W_{\text{Sa}}}{\text{amount (mg) of the sample}} \times 21.864 \end{aligned}$$

$$\begin{aligned} & \text{Content (\% of hydroxypropoxyl group)} \\ &= \frac{Q_{\text{Tb}}}{Q_{\text{Sb}}} \times \frac{W_{\text{Sb}}}{\text{amount (mg) of the sample}} \times 44.17 \end{aligned}$$

$W_{\text{Sa}}$ : Amount (mg) of iodomethane in the standard solution.

$W_{\text{Sb}}$ : Amount (mg) of isopropyl iodide in the standard solution.

**Internal standard solution**—A solution of n-octane in o-xylene (1 in 25).

**Operating conditions**—

Detector: A thermal conductivity detector or hydrogen flame-ionization detector.

Column: A glass column about 3 mm in inside diameter and about 3 m in length, packed with siliceous earth for gas chromatography, 180 to 250  $\mu\text{m}$  in diameter, coated with methyl silicone polymer at the ratio of 20%.

Column temperature: A constant temperature of about 100°C.

Carrier gas: Helium

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

Selection of column: Proceed with 2  $\mu\text{L}$  of the standard solution under the above operating conditions. Use a column giving well-resolved peaks of iodomethane, isopropyl iodide and the internal standard in this order.

**Containers and storage** Containers—Well-closed containers.

## Hydroxypropylmethylcellulose Phthalate

ヒドロキシプロピルメチルセルロースフタレート

Hydroxypropyl methylcellulose benzene-1,2-dicarboxylate  
[9050-31-1]

Hydroxypropylmethylcellulose Phthalate is a monophthalic acid ester of hydroxypropyl methylcellulose.

It contains methoxyl group ( $-\text{OCH}_3$ : 31.03), hydroxypropoxyl group ( $-\text{OC}_3\text{H}_6\text{OH}$ : 75.09), and carboxybenzoyl group ( $-\text{COC}_6\text{H}_4\text{COOH}$ : 149.12).

There are two substitution types, 200731 and 220824, and each type contains indicated amount of carboxybenzoyl group in the accompanying table, calculated on the anhydrous basis.

Substitution Type	Carboxybenzoyl group (%)	
	Min.	Max.
200731	27.0	35.0
220824	21.0	27.0

Its substitution type and its viscosity are shown in square mm per second ( $\text{mm}^2/\text{s}$ ) on the label.

**Description** Hydroxypropylmethylcellulose Phthalate occurs as white powder or granules. It is odorless and tasteless.

It is practically insoluble in acetonitrile, in ethanol (99.5), and hexane.

It becomes a viscous liquid when a mixture of methanol and dichloromethane (1:1) or a mixture of ethanol (99.5) and acetone (1:1).

It dissolves in sodium hydroxide TS.

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

**Viscosity** To 10 g of Hydroxypropylmethylcellulose Phthalate, previously dried at 105°C for 1 hour, add 90 g of a mixture of methanol and dichloromethane in equal mass ratio, and shake to dissolve. Determine the viscosity at  $20 \pm 0.1^\circ\text{C}$  as directed in the Capillary-Type Viscosimeter under the Viscosity Determination: the viscosity is not less than 80% and not more than 120% of the labeled unit.

**Purity (1) Chloride**—Dissolve 1.0 g of Hydroxypropylmethylcellulose Phthalate in 40 mL of 0.2 mol/L sodium hydroxide VS, add 1 drop of phenolphthalein TS, and add dilute nitric acid dropwise with vigorous stirring until the red color is discharged. Further add 20 mL of dilute nitric acid with stirring. Heat on a water bath with stirring until the gelatinous precipitate formed turns to granular particles. After cooling, centrifuge, and take off the supernatant liquid. Wash the precipitate with three 20-mL portions of water by centrifuging each time, combine the supernatant liquid and the washings, add water to make 200 mL, and filter. Perform the test with 50 mL of the filtrate. Control solution: To 0.50 mL of 0.01 mol/L hydrochloric acid VS add 10 mL of 0.2 mol/L sodium hydroxide VS, 7 mL of dilute nitric acid and water to make 50 mL (not more than 0.07%).

(2) Heavy metals—Proceed with 2.0 g of Hydroxypropylmethylcellulose Phthalate according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

(3) Phthalic acid—Weigh accurately about 200 mg of Hydroxypropylmethylcellulose Phthalate, add about 50 mL of acetonitrile to dissolve partially with the aid of ultrasonicator, add 10 mL of water, and dissolve further with the ultrasonicator. After cooling, add acetonitrile to make exactly 100 mL, and use this solution as the sample solution. Separately, weigh accurately about 12.5 mg of phthalic acid, dissolve in about 125 mL of acetonitrile by mixing, add 25 mL of water and acetonitrile to make exactly 250 mL, and use this solution as the standard solution. Perform the test with 10  $\mu\text{L}$  each of the sample solution and the standard solution as directed under the Liquid Chromatography according to the following conditions, and determine the peak areas of phthalic acid,  $A_T$  and  $A_S$ , of both solutions: amount of phthalic acid ( $\text{C}_8\text{H}_6\text{O}_4$ : 166.13) is not more than 1.0%.

Amount (%) of phthalic acid

$$= \frac{C}{W} \times \frac{A_T}{A_S} \times 10$$

C: concentration of phthalic acid in the standard solution ( $\mu\text{g}/\text{mL}$ )

W: amount (mg) of the sample, calculated on the anhydrous basis

**Operating conditions**—

Detector: An ultraviolet absorption photometer (wavelength: 235 nm).

Column: A stainless steel column about 4 mm in inside diameter and about 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 to 10  $\mu\text{m}$  in particle diameter).

Column temperature: A constant temperature of about 20°C.

Mobile phase: A mixture of 0.1 mol/L cyanoacetic acid and acetonitrile (17:3).

Flow rate: About 2.0 mL per minute.

System repeatability: Repeat the test six times with the standard solution under the above operating conditions: the relative standard deviation of the peak area of phthalic acid is not more than 1.0%.

**Water** Not more than 5.0% (1 g, direct titration, using a mixture of ethanol (99.5) and dichloromethane (3:2) instead of methanol for Karl Fischer method).

**Residue on ignition** Not more than 0.20% (1 g).