HYDROXYPROPYLMETHYL CELLULOSE

Prepared at the 74th JECFA (2011) and published in FAO JECFA Monographs 11 (2011), superseding the specifications prepared at the 63rd JECFA (2004), published in the Combined Compendium of Food Additive Specifications, FAO JECFA Monographs 1 (2005). A group ADI "not specified" for modified celluloses (ethyl cellulose, ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, methyl ethyl cellulose, and sodium carboxymethyl cellulose) was established at the 35th JECFA (1989).

SYNONYMS INS No. 464

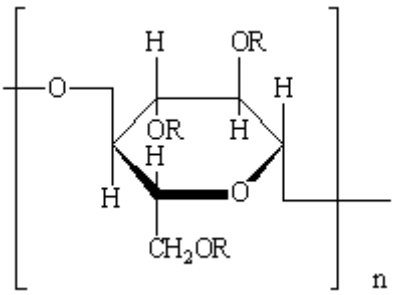
DEFINITION Hydroxypropylmethyl cellulose is a methyl cellulose modified by treatment with alkali and propylene oxide by which a small number of 2-hydroxypropyl groups are attached through ether links to the anhydroglucose units of the cellulose. The article in commerce may be further specified by viscosity.

Chemical names: Hydroxypropylmethyl cellulose, 2-hydroxypropyl ether of methyl cellulose

C.A.S. number: 9004-65-3

Chemical formula: $[C_6H_7O_2(OH)_x(OCH_3)_y(OCH_2CHOHCH_3)_z]_n$
where
z = 0.07 - 0.34
y = 1.12 - 2.03
x = 3-(z + y): (z + y = degree of substitution)

Structural formula:



where R = H or CH_3 or $CH_2CHOHCH_3$

Formula weight: Unsubstituted structural unit: 162.14
Structural unit with 1.19 degree of substitution: approx. 180
Structural unit with 2.37 degree of substitution: approx. 210
Macromolecules: from about 13,000 (n about 70) up to about 200,000 (n about 1000)

Assay: Not less than 19% and not more than 30% of methoxy groups ($-OCH_3$) and not less than 3% and not more than 12% hydroxypropoxy groups ($-OCH_2CHOHCH_3$), on the dried basis

DESCRIPTION Hygroscopic white or off-white powder, or granules or fine fibres

FUNCTIONAL USES Emulsifier, thickening agent, stabiliser

CHARACTERISTICS

IDENTIFICATION

Solubility (Vol. 4)	Swells in water, producing a clear to opalescent, viscous colloidal solution; insoluble in ethanol
Foam formation	A 0.1% solution of the sample is shaken vigorously. A layer of foam appears. This test permits the distinction of sodium carboxymethyl cellulose from other cellulose ethers.
Precipitate formation	To 5 ml of a 0.5% solution of the sample, add 5 ml of a 5% solution of copper sulfate or of aluminium sulfate. No precipitate appears. This test permits the distinction of sodium carboxymethyl cellulose from other cellulose ethers.
Substituents	See description under METHOD OF ASSAY

PURITY

Loss on drying (Vol. 4)	Not more than 10.0% (105° to constant weight)
pH (Vol. 4)	Not less than 5.0 and not more than 8.0 (1 in 100 solution)
Sulfated ash (Vol. 4)	Not more than 1.5% for products with viscosities of 50 centipoise or above, and not more than 3% for products with viscosities below 50 centipoise Test 1 g of the sample
Lead (Vol. 4)	Not more than 2 mg/kg Determine using an AAS/ICP-AES technique appropriate to the specified level. The selection of sample size and method of sample preparation may be based on the principles of the methods described in Volume 4 (under “General Methods, Metallic Impurities”).
Propylene chlorohydrins	Not more than 1 mg/kg See description under TESTS

TESTS

PURITY TESTS

Propylene chlorohydrins	Determine by Gas Chromatography–Mass Spectrometry (GC-MS) (Vol. 4) using the following procedure. **Note**: Propylene chlorohydrins (PCH) are present as 2 isomers namely: 1-chloro-2-propanol (1C2P) and 2-chloro-1-propanol (2C1P). Internal standard solutions *Internal Standard Stock Solution #1 (1 mg/ml):* Weigh 0.1 g to nearest 0.1 mg (approximately 100 µl) of o-xylene-d_{10} (CAS 56004-61-6) into a 100 ml volumetric flask and make up to volume with methanol. *Internal Standard Stock Solution #2 (100 µg/ml):* Pipette 5ml of Internal Standard Stock Solution #1 into a 50 ml volumetric flask and make up to volume with methanol. *Internal Standard Stock Solution #3 (4 µg/ml):* Pipette 1 ml of Internal

Standard Stock Solution #2 into a 25 ml volumetric flask and make up to volume with methanol:

Internal Standard Solution #4 (16 ng/ml): Add 1 ml of Internal Standard Stock Solution #3 into a 250 ml volumetric flask and dilute to volume with diethyl ether.

Internal Standard Solution #5 (8 ng/ml): Pipette 25 ml of Internal Standard Stock Solution #4 into a 50 ml volumetric flask and dilute to volume with diethyl ether.

Standards

Stock Standard Solution #1 (1mg/ml): Weigh 0.1 g to the nearest 0.1 mg of propylene chlorohydrin, mixture of 1-Chloro-2-propanol-75% and 2-Chloro-1-propanol-25%, Eastman Kodak, Cat. # P1325 or equivalent) into a 100 ml volumetric flask and make up to volume with diethyl ether.

Stock Standard Solution #2 (100 µg/ml): Pipette 5 ml of Standard Stock Solution #1 into a 50 ml volumetric flask and make up to volume with diethyl ether.

Stock Standard Solution #3 (10 µg/ml): Pipette 5 ml of Standard Stock Solution #2 into a 50 ml volumetric flask and make up to volume with diethyl ether.

Stock Standard Solution #4 (500 ng/ml): Pipette 5 ml of Standard Stock Solution #3 into a 100 ml volumetric flask and make up to volume with diethyl ether.

Note: All standard solutions should be prepared with diethyl ether of the highest purity available.

Prepare working standard solutions by pipetting the volumes shown in the table below in to a 10 ml volumetric flask and make up to volume with diethyl ether.

Vol. of Stock Standard Solution #4, ml	Vol. of Internal standard solution #4, ml	Vol. made up, ml	Conc. of Standard (ng/ml)	Conc. of Internal Standard (ng/ml)
0.50	5.0	10.0	25	8
1.0	5.0	10.0	50	8
2.0	5.0	10.0	100	8
4.0	5.0	10.0	200	8
5.0	5.0	10.0	300	8

Instrument:

A gas chromatograph with a mass selective detector (GCMS) in Selective Ion Monitoring (SIM) mode, Electron impact ionisation (EI) source, pulsed-splitless injector and a data station.

GCMS Conditions:

	Inlet temperature	225°
	Pulse pressure	50 psi until 2 min
	Inlet purge flow	40 ml/min at 2 min
	Injection volume	5 µl
Guard Column	Deactivated fused silica, 10 m x 0.25 mm i.d. x 0.35 mm o.d.	
Column	30 m x 0.25 mm i.d. x 1.4 µm film DB-624 or equivalent	
Temperature programming:	Initial temperature	40°
	Initial hold Time	5.0 min
	Ramp rate	10°/min
	Temperature 2	80°
	Hold time	3.0 min
	Ramp rate	25°/min
	Final temperature	230°
	Final hold time	5.0 min
Carrier	Gas	Helium
	Flow rate	1.4 ml/min
	Column head pressure	11.5 psi
Detector	Ion source temperature.	230°
	Transfer line temperature	260°
SIM ions:	o-Xylene-d_{10}	Target ion m/z = 116
		Qualifier ion m/z = 98
	1-Chloro-2-Propanol	Target ion m/z = 79
		Qualifier ion m/z = 81
	2-Chloro-1-Propanol	Target ion m/z= 58
		Qualifier ion m/z= 31
Retention times	o-Xylene-d_{10}	13.7 min
	1-Chloro-2-Propanol	9.5 min
	2-Chloro-1-Propanol	10.4 min

Procedure:

Weigh about 1.00 g, to nearest 0.1 mg, of sample into a glass vial. Pipette 5.0 ml of Internal Standard Solution #5 into the vial, securely close the vial and sonicate for 10 minutes. Centrifuge the vial to separate the mixture. Remove a portion of the diethyl ether layer for GCMS analysis.

Calculations:

Calculate the ratios of detector responses for 1C2P and 2C1P versus detector response for o-xylene-d_{10} at each working standard concentration using the following equation:

$$AR_{(std)} = R_{(std)}/R_{(IS)}$$

where

$AR_{(std)}$ is the ratio of detector response for 1C2P or 2C1P versus

the detector response for o-xylene-d_{10} in the standard;
$R_{(std)}$ is the detector response of the target ion for 1C2P or 2C1P in the standard; and
$R_{(IS)}$ is the detector response of the target ion for o-xylene-d_{10} in the standard.

Prepare standard curves for 1C2P and 2C1P by plotting the concentration of 1C2P or 2C1P (ng/ml) versus the ratios of detector response ($AR_{(std)}$) for each isomer in the working standards

Calculate the ratio of detector response for 1C2P and 2C1P versus the detector response for o-xylene-d_{10} in the sample using the following equation:

$$AR_{(sample)} = R_{(Sample)}/R_{(IS)}$$

where
$AR_{(sample)}$ is the ratio of detector response for 1C2P or 2C1P versus the detector response for o-xylene-d_{10} in the sample;
$R_{(sample)}$ is the detector response of the target ion for 1C2P or 2C1P in the sample; and
$R_{(IS)}$ is the detector response of the target ion for o-xylene-d_{10} in the sample.

From the linear regression of the standard curves for each isomer, calculate ng/g using the following equation:

$$ng/g = (V \times (AR_{(sample)} - b)/m)/W$$

where
$AR_{(sample)}$ is the Ratio of detector response for 1C2P or 2C1P versus the detector response for o-xylene-d_{10} in the sample;
b is the y-intercept of the linear regression curve;
m is the slope of the linear regression curve;
V is the final volume (5.0 ml); and
W is the weight of the sample in grams.

Report the PCH content in mg/kg as the sum of the 2 isomers (1C2P and 2C1P).

METHOD OF ASSAY

Determination of the content of hydroxypropoxy groups

Apparatus

The apparatus for hydroxypropoxy group determination is shown in the accompanying diagram. The boiling flask, D, is fitted with an aluminium foil-covered Vigreux column, E, on the sidearm and with a bleeder tube through the neck and to the bottom of the flask for the introduction of steam and nitrogen. A steam generator, B, is attached to the bleeder tube through Tube C, and a condenser, F, is attached to the Vigreux column. The boiling flask and steam generator are immersed in an oil bath, A, equipped with a thermo-regulator such that a temperature of 155° and the desired heating rate may be maintained. The distillate is collected in a 150 ml beaker, G, or other suitable container.

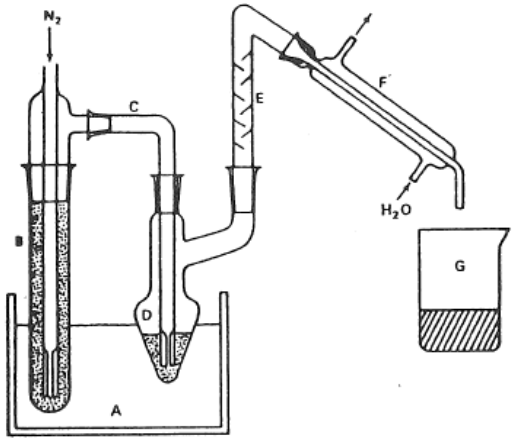


Figure. Apparatus for hydroxypropyl determination

Procedure

Accurately weigh about 100 mg of the sample, previously dried at 105° for 2 h, transfer into the boiling flask and add 10 ml of chromium trioxide solution (60 g in 140 ml of water). Immerse the steam generator and the boiling flask in the oil bath (at room temperature) to the level of the top of the chromium trioxide solution. Start cooling water through the condenser and pass nitrogen gas through the boiling flask at the rate of one bubble per sec. Starting at room temperature, raise the temperature of the oil bath to 155° over a period of not less than 30 min, and maintain this temperature until the end of the determination. Distil until 50 ml of the distillate is collected. Detach the condenser from the Vigreux column, and wash it with water, collecting the washings in the distillate container. Titrate the combined washings and distillate with 0.02 N sodium hydroxide to a pH of 7.0, using a pH meter set at the expanded scale.

Note: Phenolphthalein TS may be used for this titration instead of pH meter, if it is also used for all standards and blanks.

Record the volume, V_a of the 0.02 N sodium hydroxide used. Add 500 mg of sodium bicarbonate and 10 ml of dilute sulfuric acid TS, and then after evolution of carbon dioxide has ceased, add 1 g of potassium iodide. Stopper the flask, shake the mixture, and allow it to stand in the dark for 5 min. Titrate the liberated iodine with 0.02 N sodium thiosulfate to the sharp disappearance of the yellow colour, confirming the end-point by the addition of a few drops of starch TS. Record the volume of 0.02 N sodium thiosulfate required as Y_a.

Make several reagent blank determinations, using only the chromium trioxide solution in the above procedure. The ratio of the sodium hydroxide titration (V_b) to the sodium thiosulfate titration (Y_b), corrected for variation in normalities, will give the acidity-to-oxidizing ratio, $V_b/Y_b = K$, for the chromium trioxide carried over in the distillation. The factor K should be constant for all determinations.

Make a series of blank determinations using 100 mg of methyl cellulose (containing no foreign material) in place of the sample, recording the average volume of 0.02 N sodium hydroxide required as V_m and the average volume of 0.02 N sodium thiosulfate required as

Y_m.

Calculate the content of hydroxypropoxy groups (in mg) in the sample using the formula:

$$75.0 \times [N_1 (V_a - V_m) - k\, N_2 (Y_a - Y_m)]$$

where

N_1 is the exact normality of the 0.02 N sodium hydroxide solution;
N_2 is the exact normality of the 0.02 N sodium thiosulfate solution; and
k is $V_b N_1 / Y_b N_2$

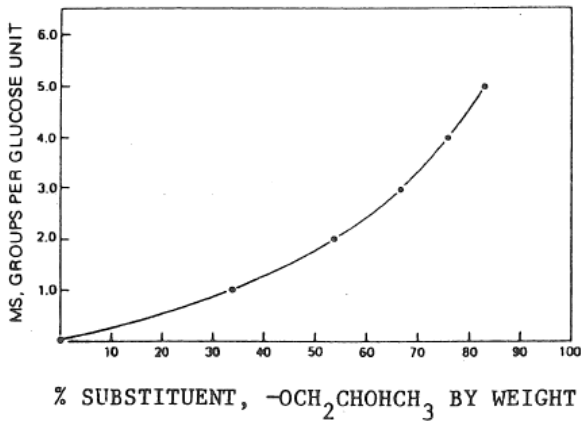


Chart for converting percentage of substitution, by weight, of hydroxypropoxy groups to molecular substitution per glucose unit.

Determination of the content of methoxy groups
Volume 4, under ASSAY METHODS, Cellulose Derivatives Assay, *Ethoxyl and Methoxyl Group Determination*.

See Apparatus and Procedure in *Ethoxy and Methoxy Group Determination* and determine the content of methoxy groups ($-OCH_3$).

Calculation
Calculate as percentage. Correct the % of methoxy groups thus determined by the formula:

$$A - (B \times 0.93 \times 31 / 75)$$

where

A is the total % of $-OCH_3$ groups determined;
B is the % of $-OCH_2CHOHCH_3$ determined in the Method of Assay for hydroxypropoxy group content; and
0.93 is an average obtained by determining, on a large number of samples, the propylene produced from the reaction of hydriodic acid with hydroxypropoxy groups during the Method of Assay for methoxy groups ($-OCH_3$).