

Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-Aug-2024
Document Type: USP Monographs
DocId: GUID-6A0B0F3C-FA70-433C-AD55-2020BBC64718_5_en-US
DOI: https://doi.org/10.31003/USPNF_M39215_05_01
DOI Ref: 5eb6m

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Hypromellose

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.

Change to read:

Cellulose, 2-hydroxypropyl methyl ether;
◆▲ (USP 1-Aug-2024) Cellulose hydroxypropyl methyl ether▲◆▲ (USP 1-Aug-2024)
CAS RN[®]: 9004-65-3.

DEFINITION

Hypromellose is a methyl and hydroxypropyl mixed ether of cellulose. It contains, calculated on the dried basis, methoxy (–OCH₃: 31.03) and hydroxypropoxy (–OC₃H₆OH: 75.09) groups conforming to the limits for the types of Hypromellose (hydroxypropyl methylcellulose) set forth in the following table.

Substitution Type	Methoxy (%)		Hydroxypropoxy (%)	
	Min.	Max.	Min.	Max.
1828	16.5	20.0	23.0	32.0
2208	19.0	24.0	4.0	12.0
2906	27.0	30.0	4.0	7.5
2910	28.0	30.0	7.0	12.0

IDENTIFICATION

- A.**
Sample: 1 g
Analysis: Gently add the *Sample* to the top of 100 mL of water in a beaker, and allow to disperse over the surface, tapping the top of the container to ensure an even dispersion of the substance. Allow the beaker to stand for 1–2 min.
Acceptance criteria: The powdered material aggregates on the surface.
- B.**
Sample: 1 g
Analysis: Add the *Sample* to 100 mL of boiling water, and stir the mixture using a magnetic stirrer with a bar 25-mm long.
Acceptance criteria: A slurry is formed, but the powdered material does not dissolve. Cool the slurry to 10°, and stir using a magnetic stirrer. The resulting liquid is a clear or slightly turbid solution with thickness dependent on the viscosity grade.
- C.**
Solution A: [Sulfuric acid](#) and water (9 in 10). [NOTE—Carefully add [sulfuric acid](#) to water.]
Sample solution: 0.1 mL of the solution prepared in *Identification B*
Analysis: To the *Sample solution* add 9 mL of *Solution A*, and shake. Heat in a water bath for exactly 3 min, immediately cool in an ice bath, and add carefully 0.6 mL of [ninhydrin TS](#). Shake, and allow to stand at 25°.
Acceptance criteria: A red color develops at first that changes to purple within 100 min.
- D.**
Sample solution: 2–3 mL of the solution prepared in *Identification B*
Analysis: Pour the *Sample solution* onto a glass slide as a thin film, and allow the water to evaporate.
Acceptance criteria: A coherent, clear film forms on the glass slide.
- E.**
Sample solution: 50 mL of the solution prepared in *Identification B*
Analysis: Add the *Sample solution* to exactly 50 mL of water in a beaker. Insert a thermometer into the solution. Stir the solution on a magnetic stirrer/hot plate, and begin heating at a rate of 2°–5°/min. Determine the temperature at which a turbidity increase begins to

occur, and designate this temperature as the flocculation temperature.

Acceptance criteria: The flocculation temperature is higher than 50°.

ASSAY

Change to read:

• **PROCEDURE**

[**CAUTION**—Hydriodic acid and its reaction byproducts are highly toxic. Perform all steps in the preparation 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.]

Apparatus: For the reaction vial, use a 5-mL pressure-tight serum vial ▲▲ (USP 1-Aug-2024) equipped with a pressure-tight septum with a polytetrafluoroethylene-faced butyl rubber and an airtight seal using an aluminum crimp or any sealing system that provides sufficient airtightness. Use a heater having a heating module that has a square-shaped aluminum block with holes▲▲ (USP 1-Aug-2024) , 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 about 100 times/min.

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

Internal standard solution: 30 mg/mL of *n*-octane in [o-xylene](#)

Standard solution: Into a suitable serum vial, weigh between 60 and 100 mg of [adipic acid](#), and add 2.0 mL of *Hydriodic acid* and 2.0 mL of *Internal standard solution*. Close the vial securely with a suitable septum stopper. Weigh the vial and contents, add between 15 and 22 µL of [isopropyl iodide](#) through the septum with a syringe, weigh again, and calculate the weight of [isopropyl iodide](#) added, by difference. Add 45 µL of methyl iodide similarly, weigh again, and calculate the weight of methyl iodide added, by difference. Shake the reaction vial well, and allow the layers to separate. Use the upper layer as the *Standard solution*.

Sample solution: Transfer 0.065 g of Hypromellose to a 5-mL thick-walled reaction vial equipped with a pressure-tight septum-type closure, add between 60 and 100 mg of [adipic acid](#), and pipet 2.0 mL of *Internal standard solution* into the vial. Cautiously pipet 2.0 mL of *Hydriodic acid* into the mixture, immediately cap the vial tightly, and weigh. Using the magnetic stirrer equipped in the heating module, or using a reciprocal shaker, mix the contents of the vial continuously, heating and maintaining the temperature of the contents at 130 ± 2° for 60 min. If a reciprocal shaker or magnetic stirrer cannot be used, shake the vial well by hand at 5-min intervals during the initial 30 min of the heating time. Allow the vial to cool, and weigh. If the weight loss is ≥26 mg or there is evidence of a leak, discard the mixture, and prepare another *Sample solution*.

Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

Mode: GC

Detector: Thermal conductivity or hydrogen flame-ionization

Column: 0.53-mm × 30-m fused silica capillary, coated with a 3-µm layer of phase G1. Use a guard column if necessary.

Temperatures

Injection port: 250°

Detector: 280°

Column: See the temperature program shown in [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

Carrier gas: Helium

Flow rate: With the *Standard solution*, adjust the flow rate so that the retention time of the internal standard is about 10 min (about 4.3 mL/min).

Injection volume: 1–2 µL

Injection type: Split, split ratio 40:1

Run time: 20.3 min

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: Methyl iodide, isopropyl iodide, and the internal standard are eluted in this order, with resolution NLT 5 between these peaks.

Relative standard deviation: NMT 2.0% for 6 injections of the *Standard solution*, using the ratio of the peak area of methyl iodide, isopropyl iodide to that of the internal standard.

Analysis

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

Calculate the percentage of methoxy ($-\text{OCH}_3$) in the portion of Hypromellose taken:

$$\text{Result} = 21.864 \times (R_{Ua}/R_{Sa}) \times (W_{Sa}/W_U)$$

R_{Ua} = peak area ratio of methyl iodide to *n*-octane from the *Sample solution*

R_{Sa} = peak area ratio of methyl iodide to *n*-octane from the *Standard solution*

W_{Sa} = weight of methyl iodide in the *Standard solution* (mg)

W_U = weight of Hypromellose, calculated on the dried basis, taken for the *Sample solution* (mg)

Calculate the percentage of hydroxypropoxy ($-\text{OC}_3\text{H}_6\text{OH}$) in the portion of Hypromellose taken:

$$\text{Result} = 44.17 \times (R_{Ub}/R_{Sb}) \times (W_{Sb}/W_U)$$

R_{Ub} = peak area ratio of isopropyl iodide to *n*-octane from the *Sample solution*

R_{Sb} = peak area ratio of isopropyl iodide to *n*-octane from the *Standard solution*

W_{Sb} = weight of isopropyl iodide in the *Standard solution* (mg)

W_U = weight of Hypromellose, calculated on the dried basis, taken for the *Sample solution* (mg)

Acceptance criteria: See the limits, calculated on the dried basis, in the table in the *Definition*.

IMPURITIES

- [RESIDUE ON IGNITION \(281\)](#).

Sample: 1.0 g

Acceptance criteria: NMT 1.5%

SPECIFIC TESTS

- [pH \(791\)](#).

Sample: Use the solution prepared in the tests for *Viscosity—Capillary Methods* and *Viscosity—Rotational Methods*.

Analysis: Read the indicated pH value after the probe has been immersed for 5 ± 0.5 min.

Acceptance criteria: 5.0–8.0

- [LOSS ON DRYING \(731\)](#).

Sample: 1.0 g

Analysis: Dry the *Sample* at 105° for 1 h.

Acceptance criteria: NMT 5.0%

- [VISCOSITY—CAPILLARY METHODS \(911\)](#) and [VISCOSITY—ROTATIONAL METHODS \(912\)](#).

Method 1: This method is applied to Hypromellose samples with a viscosity type of less than $600 \text{ mPa} \cdot \text{s}$.

Sample solution: Transfer a quantity of Hypromellose equivalent to 4 g of solids, calculated on the dried basis, to a tared, wide-mouth centrifuge bottle. Add hot water (90° – 99°) to obtain a total weight of the sample and water of 200.0 g. Capping the bottle, stir by mechanical means at 400 ± 50 rpm for 10–20 min until the particles are thoroughly dispersed and wetted out. Scrape down the walls of the bottle with a spatula, if necessary, to ensure that there is no undissolved material on the sides of the bottle, and continue the stirring in a cooling water bath equilibrated at a temperature below 10° for another 20–40 min. Adjust the solution weight, if necessary, to 200.0 g, using cold water. Centrifuge the solution, if necessary, to expel any entrapped air. If any foam is present, remove with a spatula.

Analysis: Determine the viscosity at $20 \pm 0.1^\circ$ in a suitable viscometer of the Ubbelohde type as directed in [Viscosity—Capillary Methods \(911\)](#).

Acceptance criteria: 80%–120% of the viscosity stated on the label

Method 2: This method is applied to Hypromellose samples with a viscosity type of $600 \text{ mPa} \cdot \text{s}$ or higher.

Sample solution: Transfer a quantity of Hypromellose equivalent to 10 g of solids, calculated on the dried basis, to a tared, wide-mouth centrifuge bottle, and add hot water (90° – 99°) to obtain a total weight of the sample and water of 500.0 g. Capping the bottle, stir by mechanical means at 400 ± 50 rpm for 10–20 min until the particles are thoroughly dispersed and wetted out. Scrape down the walls of the bottle with a spatula, if necessary, to ensure that there is no undissolved material on the sides of the bottle, and continue the stirring in a cooling water bath equilibrated at a temperature below 10° for another 20–40 min. Adjust the solution weight, if necessary, to 500.0 g, using cold water. Centrifuge the solution, if necessary, to expel any entrapped air. If any foam is present, remove with a spatula.

Analysis: Equip a suitable single-cylinder type rotational viscometer¹, and determine the viscosity of this solution at $20 \pm 0.1^\circ$ under the operating conditions specified in [Table 2](#).

Table 2

Labeled Viscosity ^a (mPa · s)	Rotor No.	Revolution (rpm)	Calculation Multiplier
600 or more and less than 1400	3	60	20
1400 or more and less than 3500	3	12	100
3500 or more and less than 9500	4	60	100
9500 or more and less than 99,500	4	6	1000
99,500 or more	4	3	2000

^a The labeled viscosity is based on the manufacturer's specifications.
Allow the spindle to rotate for 2 min before taking the measurement. Allow a rest period of at least 2 min between subsequent measurements. Repeat the operation twice to rotate the spindle as specified above, and average the three readings.
Acceptance criteria: 75%–140% of the viscosity stated on the label

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. No storage requirements are specified.
- **LABELING:** Label it to indicate its substitution type and its nominal viscosity value in millipascal seconds (mPa · s).

¹ Brookfield type LV model, or equivalent.

Auxiliary Information - Please [check for your question in the FAQs](#) before contacting USP.

Topic/Question	Contact	Expert Committee
HYPROMELLOSE	Documentary Standards Support	CE2020 Complex Excipients

Chromatographic Database Information: [Chromatographic Database](#)

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 42(5)

Current DocID: GUID-6A0B0F3C-FA70-433C-AD55-2020BBC64718_5_en-US
DOI: https://doi.org/10.31003/USPNF_M39215_05_01
DOI ref: [5eb6m](#)