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Methylcellulose

Portions of the monograph text 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, methyl ether;

▲◆▲ (USP 1-Aug-2024) Cellulose methyl ether▲◆▲ (USP 1-Aug-2024)

CAS RN®: 9004-67-5.

DEFINITION

Methylcellulose is a methyl ether of cellulose. When dried at 105° for 1 h, it contains NLT 26.0% and NMT 33.0% of methoxy ($-OCH_3$) groups.

IDENTIFICATION

- **A.**

  Sample: 1 g

  Analysis: Evenly distribute the *Sample* onto the surface of 100 mL of water in a beaker, tapping the top of the beaker gently, if necessary, to ensure a uniform layer on the surface, and allow to stand for 1–2 min.

  Acceptance criteria: The powdered material aggregates on the surface.

- **B.**

  Sample: 1 g

  Analysis: Evenly distribute the *Sample* into 100 mL of boiling water and stir the mixture using a magnetic stirrer with a 25-mm long bar. A slurry is formed and the particles do not dissolve. Allow the slurry to cool to 5° and stir using a magnetic stirrer.

  Acceptance criteria: A clear or slightly turbid solution occurs with its thickness dependent on the viscosity grade.

- **C.**

  Solution A: Sulfuric acid and water (9 in 10). [Note—Carefully add the sulfuric acid to the 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 immediately and it does not change 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**—Perform all steps involving hydriodic acid carefully, in a well-ventilated hood. Use goggles, acid-resistant gloves, and other appropriate safety equipment. Be exceedingly careful when handling the hot vials because they are under pressure. In the event of hydriodic exposure, wash with copious amounts of water, and seek medical attention at once.]

Apparatus

Reaction vial: A 5-mL pressure-tight serum vial ▲▲ (USP 1-Aug-2024) equipped with a pressure-tight septum having a polytetrafluoroethylene-faced butyl rubber and an airtight seal using an aluminum crimp or any sealing system that provides sufficient airtightness

Heater: A heating module with a square-shaped aluminum block having holes▲ (USP 1-Aug-2024) , so that the reaction vial fits. The heating module is also equipped with a magnetic stirrer capable of mixing the contents of the vial, or a reciprocal shaker that performs a reciprocating motion approximately 100 times/min can be used.

Hydriodic acid: Use a reagent having a specific gravity of at least 1.69, equivalent to 55%–57% hydrogen iodide (HI).

Internal standard solution: 30 mg/mL of *n*-octane in *o*-xylene

Standard solution: Into a suitable serum vial, weigh 60–100 mg of adipic acid, add 2.0 mL of *Hydriodic acid*, and then pipet 2.0 mL of the *Internal standard solution* into the vial. Close the vial securely with a suitable septum stopper. Weigh the vial and contents, add 45 µL of methyl iodide with a syringe through the septum, weigh again, and calculate the weight of methyl iodide added, by difference. Shake, and allow the layers to separate. Use the upper layer as the *Standard solution*.

Sample solution: Transfer 0.065 g of Methylcellulose to a 5-mL thick-walled reaction vial equipped with a pressure-tight septum closure, add 60–100 mg of adipic acid, and pipet 2.0 mL of the *Internal standard solution* into the vial. Cautiously pipet 2.0 mL of *Hydriodic acid* into the mixture, immediately secure the closure, and weigh accurately. Using the magnetic stirrer from the heating module, or using a reciprocal shaker, mix the contents of the vial continuously for 60 min while heating the block so that the temperature of the contents is maintained at 130 ± 2°. 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 again. If the weight loss is less than 26 mg and there is no evidence of a leak, use the upper layer of the mixture as the *Sample solution*.

Chromatographic system

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: Adjust so that the retention time of the internal standard is about 10 min (about 4.3 mL/min).

Injection volume: 1 or 2 µL

Injection type: Split, split ratio 40:1

Run time: 20.3 min

System suitability

▲**Sample:** *Standard solution*▲ (USP 1-Aug-2024)

Suitability requirements

Resolution: Methyl 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 peak area ratio between methyl iodide and the internal standard

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of methoxy in the portion of Methylcellulose taken:

$$\text{Result} = X \times (R_U/R_S) \times (W_S/W)$$

X = ratio of the formula weights of methoxy to methyl iodide times 100%, 21.864

R_U = peak area ratio of methyl iodide to the internal standard from the *Sample solution*

R_S = peak area ratio of methyl iodide to the internal standard from the *Standard solution*

W_S = weight of methyl iodide in the *Standard solution* (mg)

W = weight of Methylcellulose, calculated on the dried basis, taken for the *Assay* (mg)

Acceptance criteria: 26.0%–33.0% calculated on the dried basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 1.5%

SPECIFIC TESTS

• **Loss on Drying ⟨731⟩**

Analysis: Dry at 105° for 1 h.

Acceptance criteria: NMT 5.0%

• **Viscosity—Capillary Methods ⟨911⟩** and **Viscosity—Rotational Methods ⟨912⟩**

[Note—The density is 1.00 g/mL, so there is no necessity for determining the density at every measurement in the case of having the confirmation data.]

Method 1: This method is applied to samples with a viscosity of less than 600 mPa · s. Weigh a quantity of Methylcellulose, equivalent to 4.000 g, calculated on the dried basis, transfer into a wide-mouth bottle, and add hot water (90°–99°) to obtain the total weight of the sample and water of 200.0 g. Cap the bottle and stir by mechanical means at 400 ± 50 rpm for 10–20 min until 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. Continue the stirring in a cooling water bath equilibrated at a temperature below 5° 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 bubbles. Using a spatula, remove any foam, if present. Perform the test with this solution at 20 ± 0.1° to obtain the kinematic viscosity (ν). Separately, determine the density (ρ) of the solution, and calculate the viscosity (η) as $\eta = \rho\nu$.

Method 2: This method is applied to samples with a viscosity of 600 mPa · s or higher. Weigh a quantity of Methylcellulose, equivalent to 10.00 g, calculated on the dried basis, transfer into a wide-mouth bottle, and add hot water (90°–99°) to obtain the 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 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. Continue the stirring in a cooling water bath equilibrated at a temperature below 5° 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 bubbles. Using a spatula, remove any foam, if present. Determine the viscosity of this solution at 20 ± 0.1° using a single-cylinder type rotational viscometer.

Apparatus: Brookfield type LV model or equivalent. For rotor no., revolution, and calculation multiplier, apply the 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.

Operation of apparatus: 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 to rotate the spindle specified above twice, and average the three readings.

Acceptance criteria: 80.0%–120.0% of that stated on the label for viscosity types less than 600 mPa · s, and 75.0%–140.0% of that stated on the label for viscosity types 600 mPa · s or higher

• **pH ⟨791⟩**

Analysis: Measure the pH of the solution prepared in the test for viscosity. Read the indicated pH value after the probe has been immersed for 5 ± 0.5 min.

Acceptance criteria: 5.0–8.0

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers.

• **Labeling:** Label it to indicate its nominal viscosity value [viscosity of a solution (1 in 50)] in millipascal seconds (mPa · s).

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

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

Chromatographic Database Information: Chromatographic Database

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