BRIEFING

**Methylcellulose.** The Japanese Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Methylcellulose monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the ADOPPTION STAGE 6 document, is based on the corresponding monograph for Methylcellulose that was prepared by the Japanese Pharmacopoeia. The Japanese Pharmacopoeia draft was based in part on comments from the European Pharmacopoeia and the United States Pharmacopeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the Japanese Pharmacopoeia. Differences between the Japanese Pharmacopoeia Adoption Stage 6 document and the current USP monograph for Methylcellulose include the following.

1. *Definition.* Changed from NLT 27.5% and NMT 31.5% of methoxy to NLT 26.0% and NMT 33.0% of methoxy groups. Drying time changed from 2 h to 1 h.
2. *Identification.* Replaced three existing methods with five new methods.
5. *Loss on Drying.* Changed time from 2 h to 1 h to align with PDG proposal.
6. *pH.* New method proposed by PDG.
8. *Packaging and Storage.* No change.
9. *Labeling.* Added statement to include units of measurement (mPa·s).

(EM2: K. Moore.)

RTS—C44010

**Add the following:**

▲ **Methylcellulose**

<table>
<thead>
<tr>
<th>Attributes</th>
<th>EP</th>
<th>JP</th>
<th>USP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Labeling</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Identification A</td>
<td>+</td>
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<tr>
<td>Identification B</td>
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<td>Identification C</td>
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<td>Identification D</td>
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<td>Identification E</td>
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<tr>
<td>Apparent Viscosity, Method 1</td>
<td>+</td>
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<tr>
<td>Apparent Viscosity, Method 2</td>
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<tr>
<td>pH</td>
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</table>
**DEFINITION**

Methylcellulose is a methyl ether of cellulose. When dried at $105^\circ$ for 1 h, it contains NLT 26.0% and NMT 33.0% of methoxy ($\text{OCH}_3$) groups.

**IDENTIFICATION**

- **A. PROCEDURE**
  
  **Analysis:** Evenly distribute 1.0 g 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. PROCEDURE**
  
  **Analysis:** Evenly distribute 1.0 g 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 $5^\circ$ and stir using a magnetic stirrer.
  
  **Acceptance criteria:** A clear or slightly turbid solution occurs with its thickness dependent on the viscosity grade.

- **C. PROCEDURE**
  
  **Analysis:** To 0.1 mL of the sample solution obtained in *Identification* test *B* add 9 mL of diluted sulfuric acid (9 in 10), shake, heat in a water bath for exactly 3 min, immediately cool in an ice bath, add carefully 0.6 mL of ninhydrin TS, shake, and allow to stand at $25^\circ$.

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**Legend:** + will adopt and implement; – will not stipulate.

In EP, Viscosity and Assay will be dealt with in the non-mandatory Functionality-Related Characteristics section. The assay limits will not be included in the Definition (EP).

**Nonharmonized attributes:** Packaging and storage

**Specific local attributes:** Appearance of solution (EP), Description (JP), Limit of glyoxal (EP).

Cellulose, methyl ether; Cellulose methyl ether [9004-67-5].
Acceptance criteria: A red color develops immediately, and it does not change to purple within 100 min.

D. Procedure

Analysis: Add 2–3 mL of the solution obtained in Identification test B 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. Procedure

Analysis: Add exactly 50 mL of the sample solution obtained in Identification test A 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°/min to 5°/min. Determine the temperature at which a turbidity increase begins to occur and designate the temperature as the flocculation temperature.

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

ASSAY

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, 20 mm in outside diameter, 50 mm in height, and 20 mm in outside diameter and 13 mm in inside diameter at the mouth, equipped with a pressure-tight septum having a polytetrafluoroethylene-faced butyl rubber, and air-tight sealing by an aluminum crimp or another sealing system providing a sufficient air-tightness.

Heater: A heating module with a square-shaped aluminum block having holes 20 mm in diameter and 32 mm in depth, so that the reaction vial fits. Capable of mixing the contents of the vial using a magnetic stirrer equipped in the heating module or using a reciprocal shaker which performs a reciprocating motion approximately 100 times/min.

Hydriodic acid: Use a reagent having a specific gravity of at least 1.69, equivalent to 55%–57% 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, then pipet 2.0 mL of Internal standard solution into the vial, and 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 Internal standard solution into the vial. Cautiously pipet 2.0 mL of Hydriodic acid into the mixture, immediately secure the closure, and weigh it. Using a magnetic stirrer equipped in 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°C. 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 again weigh. If the weight loss is less than 0.50% of the contents 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: 1.8 to 3 m × 3 to 4-mm column packed with 10%–20% liquid phase G1, 125–150 µm in diameter on 100- to 120-mesh support S1A

Column temperature: 100°C

Carrier gas: Helium for the thermal conductivity detector, and helium or nitrogen for the hydrogen flame ionization detector

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

Injection size: 1 or 2 µL

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of methoxy in the Methylcellulose taken:

Result = 21.864 × (Q_T/Q_S) × (W_S/W)

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

Q_T = ratio of the peak area of methyl iodide to that of internal standard in the Sample solution

Q_S = ratio of the peak area of methyl iodide to that of internal standard in 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%

IMPURITIES

Inorganic Impurities

• Residue on Ignition 〈281〉: NMT 1.5%

• Heavy Metals, Method III 〈231〉: For the Standard Preparation, add the Standard Lead Solution prior to digestion. Omit the Monitor Preparation.

Acceptance criteria: The color of the test solution is not darker than that of the control solution (NMT 20 ppm).
**SPECIFIC TESTS**

- **Loss on Drying (731):** Dry a sample at 105°C for 1 h: it loses NMT 5.0% of its weight.

- **pH:** Measure the pH of the solution prepared in the test for Viscosity at 20 ± 2°C. Read the indicated pH value after the probe has been immersed for 5 ± 0.5 min.

  **Acceptance criteria:** 5.0–8.0

- **Viscosity (911)**

  [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 to obtain the total weight of the sample and water of 200.0 g. Capping the bottle, stir by mechanical means at 400 ± 50 rpm for 10 or 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, and continue the stirring in a cooling water bath equilibrated at a temperature below 5°C 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°C to obtain the kinematic viscosity, \( \nu \). Separately, determine the density, \( \rho \), of the solution, and calculate the viscosity, \( \eta \), 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 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, and continue the stirring in a cooling water bath equilibrated at a temperature below 5°C 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°C using a single cylinder type rotational viscometer.

**Apparatus:** Brookfield type LV model or equivalent. Rotor No., revolution, and calculation multiplier: apply the conditions specified in the following table.

<table>
<thead>
<tr>
<th>Labeled Viscosity(^a)-(mPa·s)</th>
<th>Rotor No.</th>
<th>Revolution (rpm)</th>
<th>Calculation Multiplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>600 or more and less than 1400</td>
<td>3</td>
<td>60</td>
<td>20</td>
</tr>
<tr>
<td>1400 or more and less than 3500</td>
<td>3</td>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>3500 or more and less than 9500</td>
<td>4</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>9500 or more and less than 99,500</td>
<td>4</td>
<td>6</td>
<td>1000</td>
</tr>
<tr>
<td>99,500 or more</td>
<td>4</td>
<td>3</td>
<td>2000</td>
</tr>
</tbody>
</table>

\(^a\)Viscosity measured at 20°C.
**Labeled Viscosity**\(^a\) (mPa·s) | **Rotor No.** | **Revolution (rpm)** | **Calculation Multiplier**
---|---|---|---

\(^a\) 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 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

**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage:** Preserve in well-closed containers. *
- **Labeling:** Label it to indicate its nominal viscosity type [viscosity of a solution (1 in 50)] in milli-Pascal second (mPa·s).

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

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<td>Monograph</td>
<td><strong>Kevin T. Moore, Ph.D.</strong>&lt;br&gt;Senior Scientist&lt;br&gt;1-301-816-8369</td>
<td>(EM205) Excipient Monographs 2</td>
</tr>
</tbody>
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