**Hypromellose**

*Add the following:*

<table>
<thead>
<tr>
<th>Attribute</th>
<th>JP</th>
<th>EP</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>
<td>+</td>
</tr>
<tr>
<td>Identification (A)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Identification (B)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Identification (C)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Identification (D)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Identification (E)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Viscosity, Method 1</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Viscosity, Method 2</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>pH</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Residue on ignition</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Assay</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

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

**Nonharmonized attributes:** Packaging and storage

**Specific local attributes:** Appearance of solution (EP), OVI (USP), Description (JP), Limit of glyoxal (EP)·25 (USP·25)

**Change to read:**

» Hypromellose is a propylene glycol ether of methylcellulose. When dried at 105°C for 2 hours, it contains methoxy (–OCH3) and hydroxypropoxy (–OCH2CHOHCH3).

- 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 accompanying table.

<table>
<thead>
<tr>
<th>Substitution Type</th>
<th>Methoxy (percent)</th>
<th>Hydroxypropoxy (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Min.</td>
<td>Max.</td>
</tr>
<tr>
<td>1828</td>
<td>16.5</td>
<td>20.0</td>
</tr>
<tr>
<td>2208</td>
<td>19.0</td>
<td>24.0</td>
</tr>
<tr>
<td>2906</td>
<td>27.0</td>
<td>30.0</td>
</tr>
<tr>
<td>2910</td>
<td>28.0</td>
<td>30.0</td>
</tr>
</tbody>
</table>
No change:

Packaging and storage—Preserve in well-closed containers. No storage requirements specified.

Change to read:

Labeling—Label it to indicate its substitution type and its viscosity type (viscosity of a solution (1 in 50)).

- **nominal viscosity value in milli-Pascal per second (mPa·s)**

Change to read:

**Identification**

**A:** Gently add 1 g of Hypromellose 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 until the substance becomes transparent and mucilaginous (about 5 hours), and then add the beaker to wet the remaining substance. Add a stirring bar, and stir until solution is complete: the mixture remains stable when an equal volume of 1 N sodium hydroxide or 1 N hydrochloric acid is added.

- **for 1 to 2 minutes; the powder aggregate on the surface.**

**B:** Add 1 g of Hypromellose to 100 mL of boiling water, and stir the mixture to form a clear or slightly turbid solution with thickness dependent on the viscosity grade.

- **C:** Pour a few mL of the mixture prepared for Identification test B onto a glass plate, and allow the water to evaporate: a thin, self-sustaining film results.

**Sulfuric acid, 90%**—Carefully add 9 mL of sulfuric acid to 1 mL of water. To 0.1 mL of the solution prepared for Identification test B, add 9 mL of Sulfuric acid, 90%, and shake. Heat in a water bath for exactly 3 minutes, immediately cool in an ice bath, and add carefully 0.6 mL of ninhydrin TS. Shake, and allow to stand at 25°C: a red color develops at first that changes to purple within 100 minutes.

**D:** Pour 2 to 3 mL of the solution prepared for Identification test B onto a glass slide as a thin film, and allow the water to evaporate: a coherent, clear film forms on the glass slide.

**E:** Add exactly 50 mL of the solution prepared in Identification test B 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 to 5°C per minute. Determine the temperature at which a turbidity increase begins to occur and designate this temperature as the flocculation temperature: the flocculation temperature is higher than 50°C.

**Change to read:**

Viscosity (911) — Place a quantity, accurately weighed and equivalent to 2 g of solids on the dried basis, in a tared, wide-mouth centrifuge bottle, and add 98 g of water previously heated to 50 to 60°C. Stir with a propeller type stirs for 10 minutes, place the bottle in an ice bath, continue the stirring, and allow to remain in the ice bath for 40 minutes to ensure that hydration and solution are complete. Adjust the weight of the solution to 100 g, if necessary, and centrifuge the solution to expel any entrapped air. Adjust the temperature of the solution to 20 ± 0.1°C, and determine the viscosity in a suitable viscometer of the Ubbelohde type as directed for Procedure for Cellulose Derivatives under Viscosity (911). Its apparent viscosity is not less than 80.0% and not more than 120.0% of that stated on the label for viscosity types of 100 centipoises or less, and not less than 25.0% and not more than 140.0% of that stated on the label for viscosity types higher than 100 centipoises.

**FOR HYPROMELLOSE SAMPLES HAVING A VISCOSITY TYPE OF LESS THAN 600 mPa·s**—Transfer an accurately weighed quantity of Hypromellose, equivalent to 4 g of solids, calculated on the dried basis, to a tared, wide-mouth centrifuge bottle. Add hot water 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 to 20 minutes 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°C for another 20 to 40 minutes. Adjust the solution weight, if necessary, to 200.0 g using cold water. Centrifuge the solution to expel any entrapped air. If any foam is present, remove with a spatula. Determine the viscosity in a suitable viscometer of the Ubbelohde type as directed for Procedure for Cellulose Derivatives under Viscosity (911): the viscosity is not less than 80% and not more than 120% of that stated on the label.

**FOR HYPROMELLOSE SAMPLES HAVING A VISCOSITY TYPE OF 600 mPa·s OR HIGHER**—Transfer an accurately weighed 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 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 to 20 minutes 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°C for another 20 to 40 minutes. 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. Equip a suitable single cylinder type rotational viscosimeter (Brookfield type LV Model, or equivalent), and determine the viscosity of this solution at 20 + 0.1°C under the following operating conditions specified in the table below.

<table>
<thead>
<tr>
<th>Labeled Viscosity* ( (\text{mPa} \cdot \text{s}) )</th>
<th>Revolution ( (\text{rpm}) )</th>
<th>Calculation</th>
<th>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>

* NOTE: The Labeled Viscosity is based on the manufacture’s specifications.

Allow the spindle to rotate for 2 minutes before taking the measurement. Allow a rest period of 2 minutes between subsequent measurements. Repeat the operation twice to rotate the spindle as specified above, and average the three readings:

the viscosity is not less than 75% and not more than 140% of that stated on the label. ■S (USP30)

**Add the following:**

**pH** (791): between 5.0 and 8.0 measured on the solution prepared in the test for **Viscosity** at a temperature of 20 + 2°C.

Read the indicated pH value after the probe has been immersed for 5 + 0.5 minutes. ■S (USP30)

**Change to read:**

**Heavy metals, Method II** (211): **Method III** (231): ■S (USP30)

0.001%, 1 mL of hydroxylamine hydrochloride solution (1 in 5) being added to the solution of the residue.

not more than 20 ppm. ■S (USP30)

**Change to read:**

**Loss on drying** (731): Dry it at 105° for 2 hours:

Dry 1.0 g at 105° for 1 hour. ■S (USP30) it loses not more than 5.0% of its weight.

**Change to read:**

**Residue on ignition** (281): not more than 1.5% for Hypromellose having a labeled viscosity of greater than 50 centipoises, not more than 3% for Hypromellose having a labeled viscosity of 50 centipoises or less, and not more than 5% for Hypromellose 1828 of all labeled viscosities.

not more than 1.5% on a 1.0-g sample. ■S (USP30)

**No change:**

**Organic volatile impurities, Method IV** (467): meets the requirements.

**Change to read:**

**Assay**—(Caution—Hydriodic acid and its reaction byproducts are highly toxic. Perform all steps of the Assay preparation and the Standard preparation 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, 50 mm in height, 20 mm in outside diameter, and 13 mm in inside diameter at the mouth. The vial is equipped with a pressure-tight septum having a polytetrafluoroethylene-faced butyl rubber and an air-tight seal using an aluminum crimp or any sealing system that provides a sufficient air-tightness. Use a heater having a heating module that has a square-shape aluminum block with holes 20 mm in diameter and 32 mm in depth, 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 approximately 100 times per minute.**USP30**

**Hydriodic acid**—Use a reagent having a specific gravity of at least 1.65, equivalent to 55% HI.

A typical concentration of HI about 57%.**USP30**

**Internal standard solution**—Transfer about 2.5 g of toluene.

3 g of n-octane,**USP30** accurately weighed, to a 100-mL volumetric flask containing 10 mL of o-xylene, dilute with o-xylene to volume, and mix.

**Standard preparation**—Into a suitable serum vial weigh about 1.35 mg of adipic acid and 1.0 mL of internal standard solution into the vial, and close the vial securely with a suitable septum stopper. Weigh the vial and contents accurately, add 20 μL of isopropyl iodide through the septum with a syringe, again weigh, and calculate the weight of isopropyl iodide added, by difference. Add 30 μL of methyl iodide similarly, again weigh, and calculate the weight of methyl iodide added, by difference. Shake, and allow the layers to separate.

Between 60 and 100 mg of adipic acid and add 2.0 mL of Hydriodic acid and 2.0 mL of Internal standard solution into the vial. Close the vial securely with a suitable septum stopper.

Weigh the vial and contents accurately, add between 15 μL to 22 μL of isopropyl iodide through the septum with a syringe, again weigh, 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 preparation.

**Assay preparation**—Transfer about 0.065 g of dried Hypromellose, accurately weighed, to a 5-mL thick-walled reaction vial equipped with a pressure-tight septum-type closure, add an amount of adipic acid equal to the weight of the test specimen.

Between 60 and 100 mg of adipic acid,**USP30** 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 accurately. Mix the contents of the vial continuously, while heating at 150° for 60 minutes. Allow the vial to cool for about 45 minutes, and again weigh. If the weight loss is greater than 10 mg, discard the mixture, and prepare another Assay preparation.

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 minutes. If a reciprocal shaker or magnetic stirrer cannot be used, shake the vial well by hand at 5-minute intervals during the initial 30 minutes of the heating time. Allow the vial to cool, and weigh accurately. If the weight loss is greater than or equal to 0.50% of the contents or there is evidence of a leak, discard the mixture, and prepare another Assay preparation.**USP30**

**Chromatographic system** (see Chromatography (621))—The gas chromatograph is equipped with a thermal conductivity detector and a 1.8-mm × 2.0-mm glass column packed with 20% liquid phase G28 on 100- to 120-mesh support S1C that is not silanized. Helium is used as the carrier gas and the temperature of the column is maintained at 120°. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure; the relative retention times are about 1.0, 2.2, 3.6, and 8.0 for methyl iodide, isopropyl iodide, toluene, and o-xylene, respectively; and the resolution, R, between toluene and isopropyl iodide is not less than 2.0.

**or** hydrogen flame-ionization detector and a 3- to 4-mm × 1.8- to 3-mm glass column packed with 20% liquid phase G28 on 100- to 120-mesh support S1C that is not silanized. Helium is used as the carrier gas for use with the thermal conductivity detector; helium or nitrogen can be used for the hydrogen flame-ionization detector. The temperature of the column is maintained at 100°. Chromatograph the Standard preparation, and adjust the flow rate so that the retention time of the internal standard is about 10 minutes. Use a column giving well resolved peaks of methyl iodide, isopropyl iodide, and the internal standard in this order.**USP30**

**Calibration**—Inject about 2 μL of the upper layer of the Standard preparation into the gas chromatograph, and record the chromatogram. Calculate the relative response factor, F, of equal weights of toluene and methyl iodide taken by the formula:

\[
F_{MI/MI} = \frac{R_{MI}}{R_{MI}}
\]

in which \(Q_{MI} \) is the quantity ratio of methyl iodide to toluene in the Standard preparation, and \(R_{MI} \) is the peak area ratio of methyl iodide to toluene obtained from the Standard preparation. Similarly, calculate the relative response factor, \(F_{SI/MI} \) of equal weights of toluene and isopropyl iodide taken by the formula:

\[
F_{SI/MI} = \frac{R_{SI}}{R_{SI}}
\]

in which \(Q_{SI} \) is the quantity ratio of isopropyl iodide to toluene in the Standard preparation, and \(R_{SI} \) is the peak area ratio of isopropyl iodide to toluene obtained from the Standard preparation.

**Assay preparation**—Transfer about 2 μL of the upper layer of the Assay preparation into the gas chromatograph, and record the chromatogram. Calculate the percentage of methoxy- (OCH\( _3 \)) and hydroxypropoxy- (\( \text{OCH} \text{CHOCH} \)) in the Hypromellose taken by the formula:

\[
2\times \left( \frac{31\times 142}{75\times 170} \right) F_{MI/MI}(W_{MI}/W_{MI})
\]

in which 31/142 is the ratio of the formula weights of methoxy and methyl iodide; \(F_{MI/MI} \) is the ratio of the area of the methyl iodide peak to that of the toluene peak obtained from the Assay preparation; \(W_{MI} \) is the weight, in g, of toluene in the internal standard solution; and \(W_{MI} \) is the weight, in g, of Hypromellose taken for the Assay. Similarly, calculate the percentage of hydroxypropoxy- (\( \text{OCH} \text{CHOCH} \)) in the Hypromellose taken by the formula:

\[
2\times \left( \frac{75\times 170}{31\times 142} \right) F_{SI/MI}(W_{SI}/W_{SI})
\]

in which 75/170 is the ratio of the formula weights of hydroxypropoxy and isopropyl iodide; \(F_{SI/MI} \) is the ratio of the area of the isopropyl iodide peak to that of the toluene peak obtained from the Assay preparation.
Separately inject about 1 to 2 μL of the upper layer of the Standard preparation and the Assay preparation into the gas chromatograph, and record the chromatograms. Calculate the following.

\[ Q_{Ta} \]

which is the ratio of the peak areas of methyl iodide to \( n \)-octane in the Assay preparation;

\[ Q_{Ts} \]

which is the ratio of the peak areas of isopropyl iodide to \( n \)-octane in the Assay preparation;

\[ Q_{Sa} \]

which is the ratio of the peak areas of methyl iodide to \( n \)-octane in the Standard preparation; and

\[ Q_{Sb} \]

which is the ratio of the peak areas of isopropyl iodide to \( n \)-octane in the Standard preparation. Calculate the percentage of methoxy (–OCH₃) in the Hypromellose taken by the formula:

\[ 21.864 \left( \frac{Q_{Ta}}{Q_{Sa}} \right) \left( \frac{W_{Sa}}{W_U} \right) \]

in which \( W_{Sa} \) is the weight, in mg, of methyl iodide in the Standard preparation; and \( W_U \) is the weight, in mg, of Hypromellose, calculated on the dried basis, taken for the Assay preparation. Similarly, calculate the percentage of hydroxypropoxy (–OC₃H₆OH) in the Hypromellose taken by the formula:

\[ 44.17 \left( \frac{Q_{Ts}}{Q_{Sb}} \right) \left( \frac{W_{Sb}}{W_U} \right) \]

in which \( W_{Sb} \) is the weight, in mg, of isopropyl iodide in the Standard preparation; and \( W_U \) is the weight, in mg, of Hypromellose, calculated on the dried basis, taken for the Assay preparation. **(USP10)**