

Hyoscyamine Sulfate Tablets

» Hyoscyamine Sulfate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of hyoscyamine sulfate [(C₁₇H₂₃NO₃)₂ · H₂SO₄ · 2H₂O].

Packaging and storage—Preserve in tight, light-resistant containers.

USP Reference standards (11)—

USP Hyoscyamine Sulfate RS

Identification—

A: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay*.

B: A filtered solution of Tablets meets the requirements of the tests for *Sulfate* (191).

Disintegration (701): 15 minutes.

Uniformity of dosage units (905): meet the requirements.

Assay—

Diluent, Buffer solution, Mobile phase, Standard stock preparation, and Standard preparation—Proceed as directed in the *Assay* under *Hyoscyamine Sulfate Injection*.

Tropic acid solution—Dissolve an accurately weighed quantity of tropic acid in *Diluent* to obtain a solution having a concentration of about 3 µg of tropic acid per mL.

System suitability preparation—Transfer 3.0 mL of the *Standard stock preparation* into a 100-mL volumetric flask, add 4.0 mL of the *Tropic acid solution*, dilute with *Diluent*, to volume and mix.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed quantity of the powder, equivalent to about 0.125 mg of hyoscyamine sulfate, to a 25-mL volumetric flask. Add about 20 mL of the *Diluent*, and sonicate for 15 minutes with occasional swirling. Allow to cool to room temperature, dilute with *Diluent* to volume, and mix. Pass an aliquot through a 0.45-µm filter, discarding the first 5 mL of the filtrate.

Chromatographic system—The liquid chromatograph is equipped with a 205-nm detector and a 4.6-mm × 15-cm column that contains 4-µm packing L11 and a 3-mm × 4-mm guard column that contains packing L11. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 30°. Chromatograph the *System suitability preparation*, and record the peak responses as directed for *Procedure*: the elution order is the tropic acid peak, followed by the hyoscyamine peak; the resolution, *R*, between tropic acid and hyoscyamine is not less than 1.5; the tailing factor for the hyoscyamine peak is not more than 1.8; and the relative standard deviation for six replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the area responses for the major peaks. Calculate the quantity, in mg, of hyoscyamine sulfate [(C₁₇H₂₃NO₃)₂ · H₂SO₄ · 2H₂O] in the portion of Tablets taken by the formula:

$$25 \times 1.053 \times C(r_u / r_s)$$

in which 1.053 is the ratio of the molecular weight of hydrated hyoscyamine sulfate to that of anhydrous hyoscyamine sulfate; *C* is as defined under *Standard preparation*; and *r_u* and *r_s* are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Hypromellose

Attribute	JP	EP	USP
Definition	+	+	+
Labeling	+	+	+
Identification (A)	+	+	+
Identification (B)	+	+	+
Identification (C)	+	+	+
Identification (D)	+	+	+
Identification (E)	+	+	+
Viscosity, Method 1	+	+	+
Viscosity, Method 2	+	+	+
pH	+	+	+
Heavy Metals	+	+	+
Loss on Drying	+	+	+
Residue on Ignition	+	+	+
Assay	+	+	+

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

Nonharmonized attributes: Packaging and Storage

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

Cellulose, 2-hydroxypropyl methyl ether;
Cellulose hydroxypropyl methyl ether [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 table below.

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. PROCEDURE

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. PROCEDURE

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. PROCEDURE

Solution A: Sulfuric acid and water (9:1). [NOTE—Carefully add sulfuric acid to water.]

Sample solution: 0.1 mL of the solution prepared for *Identification test 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. PROCEDURE

Sample solution: 2–3 mL of the solution prepared for *Identification test 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. PROCEDURE

Sample solution: 50 mL of the solution prepared in *Identification test 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° to 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

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, 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 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-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 about 100 times/min.

Hydriodic acid: Use a reagent having a typical concentration of 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 μ L and 22 μ L of isopropyl iodide through the septum with a syringe, weigh again, and calculate the weight of isopropyl iodide added, by difference. Add 45 μ L 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 dried 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 \pm 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 \geq 0.50% of the contents 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: 3- to 4-mm \times 1.8- to 3-m glass column packed with 20% liquid phase G28 on 100- to 120-mesh support S1C that is not silanized

[NOTE—Use a column giving well-resolved peaks of methyl iodide, isopropyl iodide, and the internal standard, in that order.]

Column temperature: 100°

Carrier gas: Use helium with the thermal conductivity detector; helium or nitrogen can be used for the hydrogen flame-ionization detector.

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

Injection size: 1–2 μ L

Analysis

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

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

$$\text{Result} = 44.17 \times (R_{Uib}/R_{Sib}) \times (W_{Sib}/W_U)$$

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

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

W_{Sib} = 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

Inorganic Impurities

- **RESIDUE ON IGNITION** <281>: NMT 1.5% on a 1.0-g sample
- **HEAVY METALS**, *Method III* <231>: NMT 20 ppm

SPECIFIC TESTS

- **pH** (791): 5.0–8.0, measured on the solution prepared in the tests for *Viscosity* at a temperature of 20 \pm 2°. Read the indicated pH value after the probe has been immersed for 5 \pm 0.5 min.
- **LOSS ON DRYING** (731): Dry 1.0 g at 105° for 1 h: it loses NMT 5.0% of its weight.
- **VISCOSITY** (911)

For hypromellose samples having a viscosity type of less than 600 mPa \cdot 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 to obtain a total weight of the sample and water of 200.0 g. Capping the bottle, stir by mechanical means at 400 \pm 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 to expel any entrapped air. If any foam is present, remove with a spatula.

Analysis: Determine the viscosity in a suitable viscosimeter of the Ubbelohde type as directed under *Viscosity* (911).

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

For hypromellose samples having a viscosity type of 600 mPa · 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 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 viscosimeter (Brookfield type LV Model, or equivalent), and determine the viscosity of this solution at 20 ± 0.1° under the operating conditions specified in the table below.

Labeled Viscosity* (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

* 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 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 millipascals per second (mPa · s).

Hypromellose Ophthalmic Solution

» Hypromellose Ophthalmic Solution is a sterile solution of Hypromellose. It contains not less than 85.0 percent and not more than 115.0 percent of the labeled amount of Hypromellose (hydroxypropyl methylcellulose). It may contain suitable antimicrobial, buffering, and stabilizing agents.

Packaging and storage—Preserve in tight containers.

USP Reference standards (11)—
USP Hypromellose RS

Identification—

A: Pour a few mL of Ophthalmic Solution onto a glass plate, and allow the water to evaporate: a thin, self-sustaining film results.

B: Heat 5 mL of Ophthalmic Solution in a test tube over a low flame: the warm solution turns cloudy but clears upon chilling.

Sterility (71): meets the requirements.

pH (791): between 6.0 and 7.8.

Assay—

Standard preparation—Dissolve a suitable quantity of USP Hypromellose RS, accurately weighed, in water, and dilute quantitatively with water to obtain a solution having a known concentration of about 100 µg per mL.

Assay preparation—Dilute an accurately measured volume of Ophthalmic Solution quantitatively with water to obtain a solution having an equivalent concentration of about 100 µg of hypromellose per mL.

Procedure—Pipet 2 mL each of the *Standard preparation*, the *Assay preparation*, and water to provide a blank, into separate, glass-stoppered test tubes. To each tube add 5.0 mL of diphenylamine solution (prepared by dissolving 3.75 g of colorless diphenylamine crystals in 150 mL of glacial acetic acid and diluting the solution with 90 mL of hydrochloric acid), mix, and immediately insert the tubes into an oil bath at 105° to 110° for 30 minutes, the temperature being kept uniform within 0.1° during heating. Remove the tubes, and place them in an ice-water bath for 10 minutes or until thoroughly cool. At room temperature and using a suitable spectrophotometer, concomitantly determine the absorbances of the solutions from the *Standard preparation* and the *Assay preparation* at 635 nm, using the water solution as the blank. Calculate the quantity, in mg, of hypromellose in each mL of the Ophthalmic Solution taken by the formula:

$$0.001 C d (A_u / A_s)$$

in which C is the concentration, in µg per mL, of USP Hypromellose RS in the *Standard preparation*; d is the dilution factor used to obtain the *Assay preparation*; and A_u and A_s are the absorbances of the solutions from the *Assay preparation* and the *Standard preparation*, respectively.