Stage 4 Harmonization
Official: May 1, 2023

Hypromellose Phthalate

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.

DEFINITION

Hypromellose Phthalate is a monophthalic acid ester of hydroxypropyl methylcellulose. It contains methoxy ($-OCH_3$), hydroxypropoxy ($-OCH_2CHOHCH_3$), and phthalyl (*o*-carboxybenzoyl; $C_8H_5O_3$) groups. It contains NLT 21.0% and NMT 35.0% of phthalyl groups, calculated on the anhydrous basis.

IDENTIFICATION

● ◆ **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K. Do not dry specimens. ◆

ASSAY

● **Phthalyl Content**

Sample: 1 g

Analysis: Transfer the *Sample* to a conical flask, dissolve in 50 mL of a mixture of alcohol, acetone, and water (2:2:1), add phenolphthalein TS, and titrate with 0.1 N sodium hydroxide VS. Perform a blank determination (see *Titrimetry* ⟨541⟩).

Calculate the percentage of phthalyl groups in the portion of Hypromellose Phthalate taken:

$$\text{Result} = [0.01 \times M_{r1} \times (V/W)] - [2 \times (M_{r1}/M_{r2}) \times P]$$

M_{r1} = molecular weight of the phthalyl group, 149.1
V = volume of 0.1 N sodium hydroxide consumed after correction for the blank (mL)
W = weight of Hypromellose Phthalate taken, calculated on the anhydrous basis (g)
M_{r2} = molecular weight of phthalic acid, 166.1
P = percentage of free phthalic acid found as directed in the test for *Limit of Free Phthalic Acid*

Acceptance criteria: 21.0%–35.0% on the anhydrous basis

IMPURITIES

● **Residue on Ignition ⟨281⟩:** NMT 0.20%

● **Chloride and Sulfate ⟨221⟩, *Chloride***

Sample solution: Dissolve 1.0 g in 40 mL of 0.2 N sodium hydroxide, add 1 drop of phenolphthalein TS, and add 2 N nitric acid dropwise, with stirring, until the red color is discharged. Add an additional 20 mL of 2 N nitric acid with stirring. Heat on a water bath, with stirring, until the gel-like precipitate formed becomes granular. Cool the mixture, and centrifuge. Separate the liquid phase, and wash the residue with three successive 20-mL portions of water, separating the washings by centrifuging. Dilute the combined liquids with water to 200 mL, mix, and filter.

Standard solution: Treat 0.50 mL of 0.01 N hydrochloric acid with 10 mL of 0.2 N sodium hydroxide, add 7 mL of 2 N nitric acid, and dilute with water to 50 mL.

Analysis: Add 1 mL of silver nitrate TS to the *Standard solution*. Add 1 mL of silver nitrate TS to a 50-mL portion of the *Sample solution*. After mixing, allow each solution to stand for 5 min protected from direct sunlight. Compare the turbidity of the solutions.

Acceptance criteria: A 50-mL portion of the *Sample solution* shows no more chloride than the *Standard solution* (0.07%).

Change to read:

- **Limit of Free Phthalic Acid**

Mobile phase: 0.1% trifluoroacetic acid and acetonitrile (90:10)

Standard solution: Weigh accurately and transfer 12.5 mg of phthalic acid to a 250-mL volumetric flask, and add 125 mL of acetonitrile. Add 25 mL of water, and dilute with acetonitrile to volume.

Sample solution: Weigh accurately and transfer 200 mg of Hypromellose Phthalate to a 100-mL volumetric flask. Add 50 mL of acetonitrile, and sonicate to dissolve partially. Add 10 mL of water, and sonicate to dissolve. Cool to room temperature, and dilute with acetonitrile to volume.

Chromatographic system

(See *Chromatography* ⟨621⟩*, System Suitability*.)

Mode: LC

Detector: UV 235 nm

Column: 4.6-mm × 25-cm; packing L1 with a high carbon load

Flow rate: 2 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 1.0% for ▲5▲ (NF 1-May-2023) replicate injections

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of phthalic acid in the portion of Hypromellose Phthalate taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of phthalic acid from the *Sample solution*

r_S = peak response of phthalic acid from the *Standard solution*

C_S = concentration of phthalic acid in the *Standard solution* (mg/mL)

C_U = concentration of Hypromellose Phthalate in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 1.0%

SPECIFIC TESTS

- **Water Determination** ⟨921⟩*, Method I*: NMT 5.0%

- **Viscosity—Capillary Methods** ⟨911⟩

Sample solution: Dissolve 10 g, previously dried at 105° for 1 h, in 90 g of a mixture of methanol and methylene chloride (1:1 w/w) by mixing and shaking.

Analysis: Determine the viscosity at 20 ± 0.1°.

Acceptance criteria: 80%–120% of that indicated by the label

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers.
- ◆ **Labeling:** Label it to indicate its viscosity and nominal phthalyl content.◆
- ◆**USP Reference Standards** ⟨11⟩
  USP Hypromellose Phthalate RS
- ◆

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Not Applicable

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