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Hypromellose Acetate Succinate

Hydroxypropyl methylcellulose acetate succinate;
Cellulose, 2-hydroxypropyl methyl ether, acetate hydrogen butanedioate;
Cellulose, 2-hydroxypropyl methyl ether, acetate succinate
CAS RN®: 71138-97-1.

DEFINITION

Hypromellose Acetate Succinate is a mixture of acetic acid and monosuccinic acid esters of hydroxypropyl methylcellulose. It contains NLT 12.0% and NMT 28.0% of methoxy groups ($-OCH_3$), NLT 4.0% and NMT 23.0% of hydroxypropoxy groups ($-OCH_2CHOHCH_3$), NLT 2.0% and NMT 16.0% of acetyl groups ($-COCH_3$), and NLT 4.0% and NMT 28.0% of succinoyl groups ($-COC_2H_4COOH$), calculated on the dried basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197A**▲ (CN 1-May-2020)

Sample: Neat. Do not dry specimen.

Analysis: Use a Fourier transform IR spectrophotometer fitted with a suitable accessory for single bounce attenuated total reflectance (see *Mid-Infrared Spectroscopy ⟨854⟩*) with a diamond or germanium crystal. Acquire a background single-beam spectrum with a clean diamond or germanium crystal sampling plate in place. Place the sample on the diamond or germanium crystal sampling surface with a microspatula or equivalent. For best results, the sample should cover the crystal surface under the pressure point tip. Using the pressure device, apply pressure to the sample, making sure the sample remains centered under the pressure tip. Acquire a single-beam spectrum of the sample, and make the necessary corrections for the background. Release the pressure device, and clear it from the sample area. Wipe the sample off the crystal and pressure device tip, and rinse both with acetone.

Acceptance criteria: The IR spectrum of the *Sample* exhibits maxima only at the same wavelengths as a similarly obtained spectrum of USP Hypromellose Acetate Succinate RS.

ASSAY

• **Acetyl and Succinoyl Groups**

Phosphoric acid solution: 1.25 M phosphoric acid and water (2:98)

Buffer: 2.72 g/L of monobasic potassium phosphate

Diluent: Adjust the *Buffer* with 1 N sodium hydroxide to a pH of 7.5.

Acetic acid stock solution: Add approximately 20 mL of water to a stoppered, 100-mL volumetric flask, place the flask on a balance, and tare. Transfer 2.0 mL of glacial acetic acid to the flask, and record the weight of the acid added. Fill the flask with water to volume. Transfer 6 mL of the resulting solution into a 100-mL volumetric flask, and dilute with water to volume.

Succinic acid stock solution: 1.3 mg/mL of succinic acid

Mobile phase: Adjust the *Buffer* to a pH of 2.8 by the dropwise addition of 6 M phosphoric acid. Pass through a 0.22-µm nylon filter.

Standard solution 1: Transfer 4.0 mL of the *Acetic acid stock solution* and 4.0 mL of the *Succinic acid stock solution* to a 25-mL volumetric flask. Dilute with *Mobile phase* to volume, and mix.

Standard solution 2: Prepare as directed for *Standard solution 1*. This solution is prepared as a duplicate.

Sample solution: Weigh 12.4 mg of Hypromellose Acetate Succinate into a glass vial. Transfer 4.0 mL of 1.0 N sodium hydroxide to the vial, and stir the solution for 4 h. Then, add 4.0 mL of 1.25 M phosphoric acid to the same vial to bring the pH of the solution to 3 or less. Invert the test *Sample solution* vial several times to ensure complete mixing, and pass through a filter of 0.22-µm pore size. Use the clear filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 20°–30°

Flow rate: 1 mL/min

Run time: 15 min

Injection volume: 10 µL

System suitability

Samples: *Standard solution 1* and *Standard solution 2*

Suitability requirements

Column efficiency: NLT 8000 theoretical plates, determined from the succinic acid peak, *Standard solution 1*

Tailing factor: 0.9–1.5 for the succinic acid peak, *Standard solution 1*

Relative standard deviation: NMT 2.0% for each peak from six replicate injections, *Standard solution 1*

Peak difference: The difference in peak areas between *Standard solution 1* and *Standard solution 2* for both acetic and succinic acids peaks does not exceed 2%.

[NOTE—After each run sequence, the column should be flushed first by 50% water and 50% acetonitrile for 60 min and then by 100% methanol for 60 min. The column should be stored in 100% methanol.]

Analysis

Samples: *Standard solution 1* and *Sample solution*

Calculate the percentage of acetic acid, *A*, in the portion of Hypromellose Acetate Succinate taken:

$$A = (r_{UA}/r_{SA}) \times (C_A/C_U) \times 100$$

r_{UA} = peak response for acetic acid from the *Sample solution*

r_{SA} = peak response for acetic acid from *Standard solution 1*

C_A = concentration of acetic acid in *Standard solution 1* (mg/mL)

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

Calculate the percentage of acetyl groups ($-COCH_3$) in the portion of Hypromellose Acetate Succinate taken:

$$\text{Result} = (A - A_{free}) \times (M_{r1}/M_{r2})$$

A = defined above

A_{free} = percentage of free acetic acid, as determined in the test for *Limit of Free Acetic and Succinic Acids*

M_{r1} = molecular weight of the acetyl group, 43.04

M_{r2} = molecular weight of acetic acid, 60.05

Calculate the percentage of succinic acid, *S*, in the portion of Hypromellose Acetate Succinate taken:

$$S = (r_{US}/r_{SS}) \times (C_S/C_U) \times 100$$

r_{US} = peak response for succinic acid from the *Sample solution*

r_{SS} = peak response for succinic acid from *Standard solution 1*

C_S = concentration of succinic acid in *Standard solution 1* (mg/mL)

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

Calculate the percentage of succinoyl groups ($-COC_2H_4COOH$) in the portion of Hypromellose Acetate Succinate taken:

$$\text{Result} = (S - S_{free}) \times (M_{r1}/M_{r2})$$

S = defined above

S_{free} = percentage of free succinic acid, as determined in the test for *Limit of Free Acetic and Succinic Acids*

M_{r1} = molecular weight of the succinoyl group, 101.08

M_{r2} = molecular weight of succinic acid, 118.09

Acceptance criteria

Acetyl groups ($-COCH_3$): 2.0%–16.0% on the dried basis

Succinoyl groups ($-COC_2H_4COOH$): 4.0%–28.0% on the dried basis

- **CONTENT OF METHOXY AND 2-HYDROXYPROPOXY GROUPS**

[**CAUTION—**Hydriodic acid and its reaction byproducts are highly toxic. Perform all steps in the preparation of the *Sample solution* and the *Standard solution* in a properly functioning hood. Specific safety practices to be followed are to be identified to the analyst performing this test.]

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

Solution A: Methanol and water (10:90)

Solution B: Methanol and water (85:15)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	70	30
8	40	60
10	15	85
17	15	85

[Note—These gradient elution times are established on an HPLC system with a dwell volume of approximately 2.0 mL. The injection time can be adjusted relative to the start of a run to accommodate the change in dwell volume from one HPLC system to another to achieve the separation described.]

Standard stock solution: Transfer 2 mL of *o*-xylene into a stoppered, 10-mL volumetric flask, place the flask on a balance, and tare. Add 200 µL of methyl iodide, insert the stopper into the flask, and accurately weigh: the weight of methyl iodide is about 350 mg. Tare the flask again, add 34 µL of isopropyl iodide, and weigh the flask: the recorded weight of isopropyl iodide is 50 mg. Dilute with *o*-xylene to volume, and mix.

Standard solution: Transfer 85 mg of adipic acid into an 8-mL vial (or other suitable container), add 2 mL of *Hydriodic acid*, and add 2.0 mL of the *Standard stock solution*. Shake and allow the phases to separate. Carefully transfer approximately 1.5 mL of the *o*-xylene (top) layer to a small vial, making sure that the bottom aqueous layer is not disturbed. Transfer 1.0 mL of the resulting solution to a 10-mL volumetric flask, and dilute with methanol to volume. [Note—This solution is stable for 8 h at 5°.]

Sample solution: [Caution—Use a cap that has a top safety relief valve, such as a Minniert valve, to prevent accidental explosion of the vial under high pressure when heated.] Weigh 65 mg of Hypromellose Acetate Succinate into a 5-mL reaction vial, and add 2.0 mL of *o*-xylene and about 100 mg of adipic acid. Add 2.0 mL of *Hydriodic acid*, and close the vial tightly with a cap.

Weigh the vial before heating, and place the vial into a heating block at 150°. Shake the vial after 5 min and after 30 min of heating. Remove the vial from the heating block after 1 h of heating, and cool. Weigh the vial. If the weight loss is greater than 10 mg, discard the mixture, and prepare another reaction solution. Carefully transfer approximately 1.5 mL of the top *o*-xylene layer into a small glass vial, making sure that the bottom aqueous layer is not disturbed. Transfer 1.0 mL of this solution into a 10-mL volumetric flask, and dilute with methanol to volume. [Note—This solution is stable for 8 h at 5°.]

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 10,000 theoretical plates, determined from the methyl iodide peak

Tailing factor: 0.9–1.5 for the methyl iodide peak

Relative standard deviation: NMT 2.0% for each peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of methoxy groups ($-OCH_3$) in the portion of Hypromellose Acetate Succinate taken:

$$\text{Result} = (r_{UM}/r_{SM}) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_{UM} = peak response for methyl iodide from the *Sample solution*

r_{SM} = peak response for methyl iodide from the *Standard solution*

C_S = concentration of methyl iodide in the *Standard solution* (mg/mL)

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

M_{r1} = molecular weight of the methoxy group, 31.03

M_{r2} = molecular weight of methyl iodide, 141.94

Calculate the percentage of 2-hydroxypropoxy groups ($-OCH_2CHOHCH_3$) in the portion of Hypromellose Acetate Succinate taken:

$$\text{Result} = (r_{UI}/r_{SI}) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_{UI} = peak response for isopropyl iodide from the *Sample solution*

r_{SI} = peak response for isopropyl iodide from the *Standard solution*

C_S = concentration of isopropyl iodide in the *Standard solution* (mg/mL)

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

M_{r1} = molecular weight of the 2-hydroxypropoxy group, 75.09

M_{r2} = molecular weight of isopropyl iodide, 169.99

Acceptance criteria

Methoxy groups ($-OCH_3$): 12.0%–28.0% on the dried basis

Hydroxypropoxy groups ($-OCH_2CHOHCH_3$): 4.0%–23.0% on the dried basis

IMPURITIES

• **Residue on Ignition ⟨281⟩**

Analysis: Determine at 600 ± 50°.

Acceptance criteria: NMT 0.20%

• **Limit of Free Acetic and Succinic Acids**

Phosphoric acid solution, Buffer, Diluent, Acetic acid stock solution, Succinic acid stock solution, Mobile phase, Standard solution, and **Chromatographic system:** Proceed as directed in the *Assay* for *Acetyl and Succinoyl Groups*.

Sample solution: Weigh 102 mg of Hypromellose Acetate Succinate into a glass vial. Transfer 4.0 mL of *Diluent* to the vial, and stir the content for 2 h. Then, transfer 4.0 mL of the *Phosphoric acid solution* to the same vial to bring the pH of the *Sample solution* to 3 or less. Invert the vial several times to ensure complete mixing, centrifuge, and use the clear supernatant.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of free acetic acid, A_{free}, in the portion of Hypromellose Acetate Succinate taken:

$$A_{free} = (r_{UA}/r_{SA}) \times (C_A/C_U) \times 100$$

r_{UA} = peak response for acetic acid from the *Sample solution*

r_{SA} = peak response for acetic acid from the *Standard solution*

C_A = concentration of acetic acid in the *Standard solution* (mg/mL)

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

Calculate the percentage of free succinic acid, S_{free}, in the portion of Hypromellose Acetate Succinate taken:

$$S_{free} = (r_{US}/r_{SS}) \times (C_S/C_U) \times 100$$

r_{US} = peak response for succinic acid from the *Sample solution*

r_{SS} = peak response for succinic acid from the *Standard solution*

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

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

Acceptance criteria: The sum of free acetic acid and free succinic acid is NMT 1.0%.

SPECIFIC TESTS

• **Loss on Drying ⟨731⟩**

Analysis: Dry at 105° for 1 h.

Acceptance criteria: NMT 5.0%

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

Sodium hydroxide solution: Immediately before use, prepare 4.3 mg/mL of sodium hydroxide in carbon dioxide-free water.

Analysis: To 2.00 g of Hypromellose Acetate Succinate, previously dried, add *Sodium hydroxide solution* to make 100.0 g, insert a stopper into the vessel, and dissolve by constant shaking for 30 min. Adjust the temperature of the solution to 20 ± 0.1°, and determine the viscosity in a suitable viscometer.

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

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers. No storage requirements specified.

• **Labeling:** Label it to indicate its nominal viscosity type.

• **USP Reference Standards ⟨11⟩**

USP Hypromellose Acetate Succinate RS

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

Topic/Question	Contact	Expert Committee
HYPROMELLOSE ACETATE SUCCINATE	Documentary Standards Support	SE2020 Simple Excipients

Chromatographic Database Information: Chromatographic Database

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