

Hyromellose Acetate Succinate

Hydroxypropyl methylcellulose acetate succinate.
Cellulose, 2-hydroxypropyl methyl ether, acetate hydrogen butanedioate.
Cellulose, 2-hydroxypropyl methyl ether, acetate succinate [71138-97-1].

» Hyromellose Acetate Succinate is a mixture of acetic acid and monosuccinic acid esters of hydroxypropyl methylcellulose. It contains not less than 12.0 percent and not more than 28.0 percent of methoxy groups ($-\text{OCH}_3$), not less than 4.0 percent and not more than 23.0 percent of hydroxypropoxy groups ($-\text{OCH}_2\text{CHOHCH}_3$), not less than 2.0 percent and not more than 16.0 percent of acetyl groups ($-\text{COCH}_3$), and not less than 4.0 percent and not more than 28.0 percent of succinoyl groups ($-\text{COC}_2\text{H}_4\text{COOH}$), calculated on the dried basis.

Packaging and storage— Preserve in tight containers. No storage requirements specified.

Labeling— Label it to indicate its nominal viscosity type.

USP Reference standards $\langle 11 \rangle$ — USP Hyromellose Acetate Succinate RS.

Identification, Infrared Absorption $\langle 197A \rangle$ — Do not dry specimens. Use a Fourier transform IR spectrometer fitted with a suitable accessory for single bounce attenuated total reflectance (see *Spectrophotometry and Light-Scattering* $\langle 851 \rangle$) 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. The IR spectrum so obtained exhibits maxima only at the same wavelengths as a similarly obtained spectrum of USP Hyromellose Acetate Succinate RS.

Viscosity $\langle 911 \rangle$ —

Sodium hydroxide solution— Immediately before use, dissolve 4.3 g of sodium hydroxide in carbon dioxide-free water to make 1000 mL.

Procedure— To 2.00 g of Hyromellose 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 minutes. Adjust the temperature of the solution to $20 \pm 0.1^\circ$, and determine the viscosity in a suitable viscosimeter, as directed for Procedure for Cellulose Derivatives under *Viscosity* $\langle 911 \rangle$. Its viscosity is not less than 80% and not more than 120% of that stated on the label.

Loss on drying $\langle 731 \rangle$ — Dry it at 105° for 1 hour; it loses not more than 5.0% of its weight.

Residue on ignition $\langle 281 \rangle$: not more than 0.20%, determined at $600 \pm 50^\circ$.

Heavy metals, Method II $\langle 231 \rangle$: 0.001%.

Limit of free acetic and succinic acids—

Phosphoric acid solution— Transfer 1.0 mL of 1.25 M phosphoric acid into a 50-mL volumetric flask, and dilute with water to volume.

0.02 M Phosphate buffer— Dissolve 5.44 g of monobasic potassium phosphate in 2 L of water.

Diluent— Adjust 0.02 M Phosphate 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 the glacial acetic acid to the flask, and record the weight of the acid added. Fill the flask with water to volume. Transfer 6.0 mL of this solution into a 100-mL volumetric flask, and dilute with water to volume.

Succinic acid stock solution— Accurately weigh about 130 mg of succinic acid into a 100-mL volumetric flask. Add about 50 mL of water, and swirl the contents until the succinic acid is fully dissolved. Fill the flask with water to volume.

Mobile phase— Adjust the 0.02 M Phosphate buffer to a pH of 2.8 by the dropwise addition of 8 M phosphoric acid. Pass through a 0.22- μm nylon filter.

Standard solution— Transfer 4.0 mL of the Acetic acid stock solution into a 25-mL volumetric flask. To the same flask, transfer 4.0 mL of the Succinic acid stock solution, dilute with Mobile phase to volume, and mix. Prepare this solution in duplicate.

Test solution— Accurately weigh about 102 mg of Hyromellose Acetate Succinate into a glass vial. Transfer 4.0 mL of Diluent to the vial, and stir the content for 2 hours. Then, transfer 4.0 mL of the Phosphoric acid solution to the same vial to bring the pH of the Test solution to 3 or less. Invert the vial several times to ensure complete mixing, centrifuge, and use the clear supernatant as the Test solution.

Chromatographic system (see *Chromatography* $\langle 821 \rangle$) — The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm \times 15-cm column that contains 5- μm packing L1. The column temperature is maintained between 20° and 30° . The flow rate is about 1 mL per minute, and the run time is about 15 minutes. Chromatograph the first preparation of the Standard solution, and record the peak responses as directed for Procedure; the column efficiency, determined from the succinic acid peak, is not less than 8000 theoretical plates; the tailing factor of this peak is between 0.9 and 1.5, and the relative standard deviation for six replicate injections is not more than 2.0% for each peak. Chromatograph the second preparation of the Standard solution; the difference in peak areas between the two standard solutions for both acetic and succinic acid peaks does not exceed 2%. [NOTE—After each run sequence, the column should be flushed first by 50% water and 50% acetonitrile for 80 minutes and then by 100% methanol for 80 minutes. The column should be stored in 100% methanol.]

Procedure— Separately inject equal volumes (about 10 μL) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak areas corresponding to acetic and succinic acids. Calculate the percentage of free acetic acid, A_{free} , in the portion of Hyromellose Acetate Succinate taken by the formula:

$$0.0768(W_A / W)(r_{1A} / r_{2A}),$$

in which W_A is the weight of glacial acetic acid, in mg, used to prepare the Acetic acid stock solution; W is the weight of Hyromellose Acetate Succinate, in mg, used to prepare the Test solution; and r_{1A} and r_{2A} are the peak responses for acetic acid obtained from the Test solution and the Standard solution, respectively. Calculate the percentage of free succinic acid, S_{free} , in the portion of Hyromellose Acetate Succinate taken by the formula:

$$1.28(W_S / W)(r_{1S} / r_{2S}),$$

in which W_S is the weight of succinic acid, in mg, used to prepare the Succinic acid stock solution; r_{1S} and r_{2S} are the peak responses for succinic acid obtained from the Test solution and the Standard solution, respectively; and W is as defined above; the sum of free acetic acid and free succinic acid found does not exceed 1.0%.

Content of acetyl and succinoyl groups—

Phosphoric acid solution, Acetic acid stock solution, Succinic acid stock solution, Mobile phase, Standard solution, and Chromatographic system— Proceed as directed in the test for Limit of free acetic and succinic acids.

Test solution— Accurately weigh about 12.4 mg of Hyromellose 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 hours. 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 0.22- μm filter. Use the clear filtrate as the Test solution.

Procedure— Separately inject equal volumes (about 10 μL) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak areas corresponding to acetic and succinic acids. Calculate the percentage of acetic acid, A , in the portion of Hyromellose Acetate Succinate taken by the formula:

$$0.0768(W_A / W)(r_{1A} / r_{2A}),$$

in which W_A is the weight of acetic acid, in mg, used to prepare the Acetic acid stock solution; W is the weight of Hyromellose Acetate Succinate, in mg, used to prepare the Test solution; and r_{1A} and r_{2A} are the peak responses for acetic acid obtained from the Test solution and the Standard solution, respectively. Calculate the percentage of acetyl groups ($-\text{COCH}_3$) in the portion of Hydroxypropyl Methylcellulose Acetate Succinate taken by the formula:

$$0.717(A - A_{\text{free}}),$$

in which A_{free} is the percentage of free acetic acid, as determined in the test for Limit of free acetic and succinic acids; and A is as defined above. Calculate the percentage of succinic acid, S , in the portion of Hyromellose Acetate Succinate taken by the formula:

$$1.28(W_S / W)(r_{1S} / r_{2S}),$$

in which W_S is the weight of succinic acid, in mg, used to prepare the Succinic acid stock solution; W is as defined above; and r_{1S} and r_{2S} are the peak responses for succinic acid obtained from the Test solution and the Standard solution, respectively. Calculate the percentage of succinoyl groups ($-\text{COC}_2\text{H}_4\text{COOH}$) in the portion of Hydroxypropyl Methylcellulose Acetate Succinate taken by the formula:

$$0.856(S - S_{\text{free}}),$$

in which S is as defined above; and S_{free} is the percentage of free succinic acid, as determined in the test for Limit of free acetic and succinic acids.

Content of methoxy and 2-hydroxypropoxy groups— [Caution—Hydroiodic acid and its reaction byproducts are highly toxic. Perform all steps in the preparation of the Test solution and the Standard solution in a properly functioning hood. Specific safety practices to be followed are to be identified to the analyst]

Content of methoxy and 2-hydroxypropoxy groups— [Caution—Hydroiodic acid and its reaction byproducts are highly toxic. Perform all steps in the preparation of the Test 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.]

Hydroiodic acid— Use a reagent having a specific gravity of at least 1.60, equivalent to 55% hydrogen iodide.

Solution A— Prepare a mixture of water and methanol (90:10).

Solution B— Prepare a mixture of methanol and water (85:15).

Mobile phase— Use variable mixtures of Solution A and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography, § 821).

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 about 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 about 34 µL of isopropyl iodide, and accurately weigh the flask; the recorded weight of isopropyl iodide is about 50 mg. Dilute with o-xylene to volume, and mix.

Standard solution— Transfer about 85 mg of adipic acid into an 8-mL vial (or other suitable container), add 2 mL of Hydroiodic 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 this solution into a 10-mL volumetric flask, and dilute with methanol to volume. [NOTE—This solution is stable for 8 hours at 5°.]

Test solution— Accurately weigh about 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 Hydroiodic acid, and close the vial tightly with a cap. [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 the vial before heating, and place the vial into a heating block at 150°. Shake the vial after 5 minutes and after 30 minutes of heating. Remove the vial from the heating block after 1 hour 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 hours at 5°.]

Chromatographic system (see Chromatography, § 821)— The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The column temperature is maintained at 30°. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	Solution A (%)	Solution B (%)	Elution
0	70	30	equilibration
0–8	70→40	30→60	linear gradient
8–10	40→15	60→85	linear gradient
10–17	15	85	isocratic

[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.] Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the column efficiency, determined from the methyl iodide peak, is not less than 10,000 theoretical plates; the tailing factor of this peak is between 0.9 and 1.5; and the relative standard deviation for replicate injections is not more than 2.0% for each peak.

Procedure— Separately inject equal volumes (about 10 µL) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak areas corresponding to methyl iodide and isopropyl iodide. Calculate the percentage of methoxy groups (–OCH₃) in the portion of Hypromellose Acetate Succinate taken by the formula:

$$4.38(W_{II} / W)(r_{UI} / r_{SI}),$$

in which W_{II} is the weight of methyl iodide, in mg, used to prepare the Standard stock solution; W is the weight of Hypromellose Acetate Succinate, in mg, used to prepare the Test solution; and r_{UI} and r_{SI} are the peak responses for methyl iodide obtained from the Test solution and the Standard solution, respectively. Calculate the percentage of 2-hydroxypropoxy groups (–OCH₂CHOHCH₃) in the portion of Hypromellose Acetate Succinate taken by the formula:

$$8.84(W_I / W)(r_{II} / r_{SI}),$$

in which W_I is the weight of isopropyl iodide, in mg, used to prepare the Standard stock solution; r_{II} and r_{SI} are the peak responses for isopropyl iodide obtained from the Test solution and the Standard solution, respectively; and W is as defined above.