BRIEFING

Ethylcellulose, *NF 20* page 2545. The European Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the *Ethylcellulose* monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the **Adoption Stage 6** document, is based on the corresponding monograph for *Ethylcellulose* prepared by the European Pharmacopoeia. The European Pharmacopoeia draft was based in part on comments from the Japanese Pharmacopoeia and the United States Pharmacopeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the European Pharmacopoeia.

Differences between the Adoption Stage 6 document and the current *NF* monograph include the following:

1. Definition— Revisions are made to make the definition more specific.
2. *Packaging and storage*— No change.
3. *Labeling*— The requirement that ethoxy content be stated on the label is deleted.
4. *USP Reference standards*— No change.
5. *Identification*— The identification test is replaced with a more definitive infrared absorption test.
6. *Viscosity*— This test is modified to comply with EP and JP standards.
7. *Acidity or alkalinity*— This test is added to comply with EP standards.
8. *Loss on drying*— No change.
9. *Residue on ignition*— The standards for this test are modified to comply with those of EP.
10. *Lead*— This test is deleted, based on comments received that the test is not needed.
11. *Heavy metals*— No change.
12. *Organic volatile impurities*— This test is deleted, based on comments received that the test is not needed.
13. *Acetaldehyde*— This test is added to comply with EP standards.
14. *Chlorides*— This test is added to comply with EP standards.
15. *Assay*— The current *NF* test is replaced with a more specific chromatographic procedure, in part to comply with EP standards.

(EMC: J. Lane) RTS—37582-1

Change to read:

■ **Ethylcellulose**

Cellulose, ethyl ether.
Cellulose ethyl ether [*9004-57-3*].

» Ethylcellulose is a partly *O*-ethylated cellulose. It contains not less than 44.0 percent and not more than 51.0 percent of ethoxy (– OC_2H_5) groups, calculated with reference to the dried substance.

Packaging and storage — Preserve in well-closed containers.

Labeling — Label it to indicate its nominal viscosity in millipascal seconds for a 5 percent m/m solution.

USP Reference standards ⟨11⟩ — *USP Ethylcellulose RS.*

Identification — *Infrared Absorption* ⟨197K⟩ .

Viscosity ⟨911⟩ — Shake a quantity of ethylcellulose equivalent to 5.00 g of the dried substance with 95 g of a mixture of 20 g of alcohol and 80 g of toluene until the substance is dissolved. Determine the viscosity using a capillary viscometer. The viscosity, determined at 25° and expressed in mPa·s, is not less than 80.0% and not more than 120.0% of that stated on the label for a nominal viscosity greater than 6 mPa·s; and not less than 75.0% and not more than 140.0% of that stated on the label for a nominal viscosity not greater than 6 mPa·s.

Acidity or alkalinity — To 0.5 g of ethylcellulose, accurately weighed, add 25 mL of carbon dioxide–free water and shake for 15 minutes. Filter through a sintered-glass filter (40). To 10 mL of this solution, add 0.1 mL of *Phenolphthalein solution* and 0.5 mL of 0.01 N sodium hydroxide. The solution is pink. To 10 mL of this solution, add 0.1 mL of *Methyl red solution* and 0.5 mL of 0.01 N hydrochloric acid. The solution is red.

Phenolphthalein solution— Dissolve 100 mg of phenolphthalein in 80 mL of alcohol and dilute to 100 mL with water.

Methyl red solution— Dissolve 50 mg of methyl red in a mixture of 1.86 mL of 0.1 N sodium hydroxide and 50 mL of alcohol and dilute to 100 mL with water.

Loss on drying ⟨731⟩ — Dry it at 105° for 2 hours: it loses not more than 3.0% of its weight.

Residue on ignition ⟨281⟩ : not more than 0.5%, determined on 1.0 g.

Heavy metals, *Method II* ⟨231⟩ : 20 µg per g.

Acetaldehyde — Introduce 3.0 g into a 250 mL conical flask with a ground-glass stopper, add 10 mL of water, and stir mechanically for 1 hour. Allow to stand for 24 hours, filter, and dilute the filtrate to 100.0 mL with water. Transfer 5.0 mL to a 25 mL volumetric flask, add 5 mL of a 0.5 g/L solution of methylbenzothiazolone hydrazone hydrochloride and heat in a water bath at 60° for 5 minutes. Add 2 mL of *Ferric chloride–sulfamic acid reagent* and heat again at 60° for 5 minutes. Cool and dilute to 25.0 mL with water. The solution is not more intensely colored than a standard prepared at the same time and in the same manner using, instead of the 5.0 mL of filtrate, 5.0 mL of a reference solution prepared by diluting 3.0 mL of *Acetaldehyde standard solution* to 100.0 mL with water (100 ppm).

Ferric chloride–sulfamic acid reagent— Prepare a solution containing 10 g/L of ferric chloride and 10 g/L of sulfamic acid.

Acetaldehyde standard solution— Dissolve 1.0 g of acetaldehyde in 2-propanol and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of the solution to 500.0 mL with water. Prepare immediately before use.

Chorides — Disperse 250 mg in 50 mL of water, heat to boiling, and allow to cool, shaking occasionally. Filter and discard the first 10 mL of the filtrate. Dilute 10 mL of the filtrate to 15 mL with water. Add 1 mL of *Dilute nitric acid* and pour the mixture as a single addition into a test tube containing 1 mL of 0.1 N Silver Nitrate VS. Prepare a standard in the same manner using 10 mL of *Chloride standard solution* and 5 mL of water. Examine the tubes laterally against a black background. After standing for 5 minutes protected from light, any opalescence in the test solution is not more intense than that in the standard (0.1 %).

Dilute nitric acid— Dilute 20 mL of nitric acid with water to 100 mL.

Chloride standard solution— Immediately before use, dilute with water to 100 times its volume a solution containing sodium chloride equivalent to 0.824 g/L of sodium chloride.

Assay —

NOTE—Hydriodic acid and its reaction byproducts are highly toxic. Perform all steps of the *Test solution* preparation and the *Reference solution* preparation in a properly functioning hood.

Internal standard solution— Dilute 120 µL of toluene to 10 mL with *o*-xylene.

Test solution— Transfer 50.0 mg of ethylcellulose, 50 mg of adipic acid and 2.0 mL of the *Internal standard solution* into a suitable 5 mL thick-walled reaction vial, with a pressure-tight septum closure. Cautiously add 2.0 mL of hydriodic acid, immediately close the vial tightly, and weigh the contents and the vial accurately. Shake the vial for 30 seconds, heat to 125° for 10 minutes, allow to cool for 2 minutes, shake again for 30 seconds, and heat to 125° for 10 minutes. Afterwards allow to cool for 2 minutes and repeat shaking and heating for a third time. Allow the vial to cool for 45 minutes and reweigh. If the loss is greater than 10 mg, discard the mixture and prepare another. Use the upper layer for analysis.

Reference solution— Transfer 100.0 mg of adipic acid, 4.0 mL of the *Internal standard solution* and 4.0 mL of hydriodic acid into a suitable 10 mL thick-walled reaction vial with a pressure-tight septum closure. Close the vial tightly and weigh the vial and contents accurately. Afterwards inject 50 µL of the iodoethane through the septum with a syringe, weight the vial again and calculate the mass of iodoethane added, by difference. Shake well and allow the layers to separate.

Chromatographic system (see *Chromatography* ⟨621⟩)— The gas chromatograph is equipped with a flame-ionization detector and a 2-mm × 5.0-m stainless steel column packed with 3% G2 on 150 µm to 180 µm mesh support S1A. The carrier gas is nitrogen, flowing at a rate of about 15 mL per second. The injection port and detector temperatures are both maintained at 200°. The column temperature is maintained at 80°.

Procedure— Inject 1 µL of the upper layer of the *Reference solution* into the chromatograph, record the chromatogram, and record the areas of the peaks. The relative retention times are as follows: iodoethane 0.6, toluene 1.0, and *o*-xylene 2.3. Adjust the sensitivity of the system so that the heights of the two principal peaks are at least 50 percent of the full scale of the recorder. The test is not valid unless the resolution between the peaks corresponding to iodoethane and toluene is at least 2.0. Inject 1 µL of the *Test solution* into the chromatograph, and record the chromatogram as directed for *Standard solution*. Use the retention times observed in the chromatogram of the *Standard solution* to identify the peaks in the chromatogram of the *Test solution*. Calculate the percent of ethoxy groups by the formula:

$$[451000/312][Q_1 m_2]/[Q_2 m_1(100 - d)],$$

where Q_1 is the ratio of the iodoethane peak area to the toluene peak area in the chromatogram obtained with the *Test solution*, Q_2 is the ratio of the iodoethane peak area to the toluene peak area in the chromatogram obtained with the *Reference solution*, m_1 is the mass of ethylcellulose used in the *Test solution* in milligrams, m_2 is the mass of iodoethane used in the *Reference solution* in milligrams, and d is the loss on drying as a percentage. ■2

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