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develops, and the solution, when viewed under long-wavelength ultraviolet light, exhibits a pale yellow fluorescence.

B: Evaporate 4 mL of the *Assay preparation*, obtained as directed in the *Assay*, on a water bath to dryness, and dissolve the residue in 0.5 mL of chloroform. Apply 10 µL of this solution and 10 µL of a solution of USP Hydroxyprogesterone Caproate RS in chloroform, containing 400 µg per mL, to a thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture, on a line about 2.5 cm from the bottom edge and about 2 cm apart. Place the plate in a developing chamber that contains and that has been equilibrated with a mixture of 3 volumes of chloroform and 1 volume of ethyl acetate. Develop the plate until the solvent front has moved to about 10 cm above the points of application. Remove the plate, mark the solvent front, and dry. Spray the plate with a mixture of 1 volume of sulfuric acid and 3 volumes of alcohol, and heat in an oven at 105° for 5 minutes: the R_f value of the principal yellowish green spot obtained from the solution under test corresponds to that obtained from the Standard solution.

Water, *Method I* ⟨921⟩: not more than 0.2%.

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—

Isoniazid reagent—Dissolve 375 mg of isoniazid and 0.47 mL of hydrochloric acid in 500 mL of methanol.

Standard preparation—Dissolve a suitable quantity of USP Hydroxyprogesterone Caproate RS, accurately weighed, in methanol, and dilute quantitatively and stepwise with methanol to obtain a solution having a known concentration of about 50 µg per mL.

Assay preparation—Transfer to a 250-mL volumetric flask an accurately measured volume of Injection, equivalent to about 250 mg of hydroxyprogesterone caproate, add methanol to volume, and mix. Pipet 5 mL of this solution into a 100-mL volumetric flask, add methanol to volume, and mix.

Procedure—Pipet 5 mL of *Assay preparation* into a glass-stoppered, 50-mL conical flask. Pipet 5 mL of *Standard preparation* into a similar flask. To each flask, add 10.0 mL of *Isoniazid reagent*, mix, and allow to stand in a water bath at 30° for about 45 minutes. Concomitantly determine the absorbances of both solutions at the wavelength of maximum absorbance at about 380 nm, with a suitable spectrophotometer, using as a blank a mixture of 5 mL of methanol and 10 mL of *Isoniazid reagent*. Calculate the quantity, in mg, of $C_{27}H_{40}O_4$ in each mL of the Injection taken by the formula:

$$5(C/V)(A_U/A_S),$$

in which C is the concentration, in µg per mL, of USP Hydroxyprogesterone Caproate RS in the *Standard preparation*, V is the volume, in mL, of Injection taken, and A_U and A_S are the absorbances of the solutions from the *Assay preparation* and the *Standard preparation*, respectively.

Hydroxypropyl Cellulose—*see* Hydroxypropyl Cellulose NF

Hydroxypropyl Cellulose, Low-Substituted—*see* Hydroxypropyl Cellulose, Low-Substituted NF

drops of the solution on a silver chloride plate so that it forms a thin film: the infrared absorption spectrum of the film so obtained exhibits maxima only at the same wavelengths as that of a similar preparation of USP Hydroxypropyl Cellulose RS.

Sterility—It meets the requirements under *Sterility Tests* ⟨71⟩.

Weight variation—Determine the weight of each of a sufficient number of Systems. Not more than 1 out of 20 varies more than 25% from the average or, failing that, not more than 6 out of 60 (including the original 20) vary more than 25% (but none more than 35%) from the average weight.

Assay—

Standard preparation—Dissolve with agitation an accurately weighed quantity of USP Hydroxypropyl Cellulose RS in water to obtain a solution having a known concentration of about 0.05 mg per mL.

Assay preparation—Transfer a sufficient number of Ocular Systems, to provide about 25 mg of hydroxypropyl cellulose, to a 500-mL volumetric flask, add about 250 mL of water, and dissolve with agitation on a mechanical shaker. Dilute with water to volume, and mix.

Procedure—Separately pipet 2 mL of the *Standard preparation*, the *Assay preparation*, and water, to provide a blank, into individual 50-mL centrifuge tubes. Add to each tube 6.0 mL of a 1 in 2000 solution of anthrone in sulfuric acid, and mix on a vortex mixer. After 40 minutes, again mix, and concomitantly determine the absorbances of the solutions obtained from the *Standard preparation* and the *Assay preparation* at 620 nm, with a suitable spectrophotometer, against the solution from the blank. Calculate the quantity, in mg, of hydroxypropyl cellulose in each Ocular System taken by the formula:

$$(500)(C/N)(A_U/A_S),$$

in which C is the concentration, in mg per mL, of USP Hydroxypropyl Cellulose RS in the *Standard preparation*, N is the number of Ocular Systems taken for the *Assay*, and A_U and A_S are the absorbances of the solutions from the *Assay preparation* and the *Standard preparation*, respectively.

Hydroxypropyl Methylcellulose

Cellulose, 2-hydroxypropyl methyl ether.
Cellulose hydroxypropyl methyl ether [*9004-65-3*].

» Hydroxypropyl Methylcellulose is a propylene glycol ether of methylcellulose. When dried at 105° for 2 hours, it contains methoxy (–OCH_3) and hydroxypropoxy (–$OCH_2CHOHCH_3$) groups conforming to the limits for the types of Hydroxypropyl Methylcellulose set forth in the accompanying table.

Packaging and storage—Preserve in well-closed containers.

Labeling—Label it to indicate its substitution type and its viscosity type [viscosity of a solution (1 in 50)].

Identification—

A: Gently add 1 g 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 until the substance becomes transparent and mucilaginous (about 5 hours), and swirl the beaker to wet the remaining substance, add a stirring bar, and stir until solution is complete: the mixture remains stable when an equal volume of 1 *N* sodium hydroxide or 1 *N* hydrochloric acid is added.

B: Add 1 g to 100 mL of boiling water, and stir the mixture: a slurry is formed, but the powdered material does not dissolve. Cool the slurry to 20°, and stir: the resulting liquid is a clear or opalescent mucilaginous colloidal mixture.

C: Pour a few mL of the mixture prepared for *Identification* test *B* onto a glass plate, and allow the water to evaporate: a thin, self-sustaining film results.

Apparent viscosity—Place a quantity, accurately weighed and equivalent to 2 g of solids on the dried basis in a tared, wide-mouth, 250-mL centrifuge bottle, and add 98 g of water previously heated to 80° to 90°. Stir with a propeller-type stirrer for 10 minutes, place the bottle in an ice bath, continue the stirring, and allow to remain in the ice bath for 40 minutes to ensure that hydration and solution are complete. Adjust the weight of the solution to 100 g, if necessary, and centrifuge the solution to expel any entrapped air. Adjust the temperature of the solution to 20 ± 0.1°, and determine the viscosity in a suitable viscosimeter of the Ubbelohde type as directed for *Procedure for Cellulose Derivatives* under *Viscosity* ⟨911⟩. Its viscosity is not less than 80.0% and not more than 120.0% of that stated on the label for viscosity types of 100 centipoises or less, and not less than 75.0% and not more than 140.0% of that stated on the label for viscosity types higher than 100 centipoises.

Loss on drying ⟨731⟩—Dry it at 105° for 2 hours: it loses not more than 5.0% of its weight.

Residue on ignition ⟨281⟩: not more than 1.5% for Hydroxypropyl Methylcellulose having a labeled viscosity of greater than 50 centipoises, not more than 3% for Hydroxypropyl Methylcellulose having a labeled viscosity of 50 centipoises or less, and not more than 5% for Hydroxypropyl Methylcellulose 1828 of all labeled viscosities.

Arsenic, *Method II* ⟨211⟩: 3 ppm.

Heavy metals, *Method II* ⟨231⟩: 0.001%, 1 mL of hydroxylamine hydrochloride solution (1 in 5) being added to the solution of the residue.

Assay—[*Caution—Hydriodic acid and its reaction byproducts are highly toxic. Perform all steps of the Assay preparation and the Standard preparation 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% HI.

Internal standard solution—Transfer about 2.5 g of toluene, accurately weighed, to a 100-mL volumetric flask containing 10 mL of *o*-xylene, dilute with *o*-xylene to volume, and mix.

Standard preparation—Into a suitable serum vial weigh about 135 mg of adipic acid and 4.0 mL of *Hydriodic acid*, pipet 4 mL of *Internal standard solution* into the vial, and close the vial securely with a suitable septum stopper. Weigh the vial and contents accurately, add 30 µL of isopropyl iodide through the septum with a syringe, again weigh, and calculate the weight of isopropyl iodide added, by difference. Add 90 µL of methyl iodide similarly, again weigh, and calculate the weight of methyl iodide added, by difference. Shake, and allow the layers to separate.

Assay preparation—Transfer about 0.065 g of dried Hydroxypropyl Methylcellulose, accurately weighed, to a 5-mL thick-walled vial. Cautiously pipet 2 mL of *Hydriodic acid* into the mixture, immediately cap the vial tightly, and weigh accurately. Mix the contents of the vial continuously while heating at 150°, for 60 minutes. Allow the vial to cool for about 45 minutes, and again weigh. If the weight loss is greater than 10 mg, discard the mixture, and prepare another *Assay preparation.*

Chromatographic system—Use a gas chromatograph equipped with a thermal conductivity detector. Under typical conditions, the instrument contains a 1.8-m × 4-mm glass column packed with 20 percent liquid phase G28 on 100- to 120-mesh support S1C that is not silanized, the column is maintained at 130°, and helium is used as the carrier gas. In a suitable system, the resolution, *R* (see *Chromatography* ⟨621⟩), between the toluene and isopropyl iodide peaks is not less than 2.0.

Calibration—Inject about 2 µL of the upper layer of the *Standard preparation* into the gas chromatograph, and record the chromatogram. Under the conditions described above, the relative retention times of methyl iodide, isopropyl iodide, toluene, and *o*-xylene are approximately 1.0, 2.2, 3.6, and 8.0, respectively. Calculate the relative response factor, F_{mi}, of equal weights of toluene and methyl iodide taken by the formula:

$$Q_{smi}/A_{smi},$$

in which Q_{smi} is the quantity ratio of methyl iodide to toluene in the *Standard preparation*, and A_{smi} is the peak area ratio of methyl iodide to toluene obtained from the *Standard preparation.* Similarly, calculate the relative response factor, F_{ii}, of equal weights of toluene and isopropyl iodide taken by the formula:

$$Q_{sii}/A_{sii},$$

in which Q_{sii} is the quantity ratio of isopropyl iodide to toluene in the *Standard preparation*, and A_{sii} is the peak area ratio of isopropyl iodide to toluene obtained from the *Standard preparation.*

Procedure—Inject about 2 µL of the upper layer of the *Assay preparation* into the gas chromatograph, and record the chromatogram. Calculate the percentage of methoxy in the Hydroxypropyl Methylcellulose taken by the formula:

$$2(31/142)F_{mi}A_{umi}(W_t/W_u),$$

in which 31/142 is the ratio of the formula weights of methoxy and methyl iodide, F_{mi} is defined under *Calibration*, A_{umi} is the ratio of the area of the methyl iodide peak to that of the toluene peak obtained from the *Assay preparation*, W_t is the weight, in g, of toluene in the *Internal standard solution*, and W_u is the weight, in g, of Hydroxypropyl Methylcellulose taken for the *Assay*. Similarly, calculate the percentage of hydroxypropoxy in the Hydroxypropyl Methylcellulose taken by the formula:

$$2(75/170)F_{ii}A_{uii}(W_t/W_u),$$

in which 75/170 is the ratio of the formula weights of hydroxypropoxy and isopropyl iodide, F_{ii} is defined under *Calibration*, A_{uii} is the ratio of the area of the isopropyl iodide peak to that of the toluene peak obtained from the *Assay preparation*, W_t is the weight, in g, of toluene in the *Internal standard solution*, and W_u is the weight, in g, of Hydroxypropyl Methylcellulose taken

in this Pharmacopeia, see the monograph *Hydroxypropyl Methylcellulose.*

Hydroxypropyl Methylcellulose Ophthalmic Solution

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

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩—*USP Hydroxypropyl Methylcellulose RS.*

Identification—

A: It responds to *Identification* test *C* under *Hydroxypropyl Methylcellulose*.

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—It meets the requirements under *Sterility Tests* ⟨71⟩.

pH ⟨791⟩: between 6.0 and 7.8.

Assay—

Standard preparation—Dissolve a suitable quantity of USP Hydroxypropyl Methylcellulose 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 quantitatively an accurately measured volume of Ophthalmic Solution with water to obtain a solution having an equivalent concentration of approximately 100 µg of hydroxypropyl methylcellulose per mL.

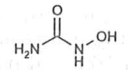
Procedure—Pipet 2 mL each of the *Standard preparation*, the *Assay preparation*, and water to provide a blank, into separate, glass-stoppered test tubes. To each tube add 5.0 mL of diphenylamine solution (prepared by dissolving 3.75 g of colorless diphenylamine crystals in 150 mL of glacial acetic acid 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. Concomitantly determine, at room temperature, the absorbances of the solutions from the *Standard preparation* and the *Assay preparation* at 635 nm, with a suitable spectrophotometer, using the water solution as the blank. Calculate the quantity, in mg, of hydroxypropyl methylcellulose in each mL of the Ophthalmic Solution taken by the formula:

$$0.001C(d/V)(A_U/A_S),$$

in which C is the concentration, in µg per mL, of USP Hydroxypropyl Methylcellulose RS in the Standard solution, d is

Hydroxypropyl Methylcellulose Phthalate 220824—*see* Hydroxypropyl Methylcellulose Phthalate 220824 NF

Hydroxyurea



$CH_4N_2O_2$ 76.06

Urea, hydroxy-.

Hydroxyurea [*127-07-1*].

» Hydroxyurea contains not less than 97.0 percent and not more than 103.0 percent of $CH_4N_2O_2$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers, in a dry atmosphere.

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

Identification, *Infrared Absorption* ⟨197K⟩.

Loss on drying ⟨731⟩—Dry it in vacuum at 60° for 3 hours: it loses not more than 1.0% of its weight.

Residue on ignition ⟨281⟩: not more than 0.50%.

Heavy metals ⟨231⟩: not more than 0.003%.

Urea and related compounds—

Developing solvent—Shake equal volumes of isobutyl alcohol and water in a separator and allow the layers to separate. Use the upper layer as the *Mobile phase* and the lower layer as the *Stationary phase.*

p-Dimethylaminobenzaldehyde solution, 1%—Dissolve 1.0 g of *p*-dimethylaminobenzaldehyde in 50 mL of alcohol, add 2 mL of hydrochloric acid, and dilute with alcohol to 100.0 mL.

pH 6.5 buffer solution—Mix 700 mL of 0.2 *M* dibasic sodium phosphate and 300 mL of 0.1 *M* citric acid.

Standard preparation—Prepare a solution of urea in water, containing 0.1 mg per mL.

Test preparation—Dissolve 10.0 mg of Hydroxyurea in 1.0 mL of water.

Procedure—Treat a suitable chromatographic paper strip (Whatman No. 1 or equivalent) by dipping it in *pH 6.5 buffer solution.* Dry the paper strip, and apply 100 µL of the *Test preparation* and 50 µL of the *Standard preparation.* Place the strip in a chromatographic chamber for descending chromatography containing the *Stationary phase* in the bottom of the chamber and the *Mobile phase* in the trough. Develop for 24 hours, remove the strip from the chamber, air-dry, and develop again for 24 hours. Remove the strip, air-dry, spray with *p-Dimethylaminobenzaldehyde solution, 1%*, and heat at 90° for 1 to 2 minutes. Not more than two spots, other than the major component, are present in the *Test preparation*, and their intensities are not greater than the intensity of the spot from the *Standard preparation* (0.5% of each impurity). The R_f values relative to hydroxyurea, the principal spot, are 0.65 and 1.26 (urea).