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1 in 50 solution of α-bromo-2′-acetonaphthone in acetonitrile. Swirl to wash down the sides of the vial. Add 50 µL of a freshly prepared 1 in 100 solution of diisopropylethylamine in acetonitrile, swirl again, and place the vial in a suitable heating device maintained at a temperature of 30° to 35° for not less than 15 minutes. Evaporate the acetonitrile from the vial with the aid of a stream of nitrogen, add 2.0 mL of *Internal standard preparation*, mix, and filter the resulting solution through a fine-porosity filter. Protect the filtered solution from light prior to injection to prevent degradation of the naphthacyl ester of carboprost.

Assay preparation—Using Carboprost Tromethamine, proceed as directed under *Standard preparation*.

Procedure—As a system suitability test, chromatograph different volumes of the *Standard preparation* using a suitable microsyringe or sampling valve to determine appropriate volume and other operating parameters. The retention times for guaifenesin and the 2-naphthacyl ester of carboprost are about 7 minutes and 11 minutes, respectively. In a suitable chromatogram, the resolution factor between these two peaks is not less than 4.0 and the relative standard deviation for four replicate injections of the *Standard preparation* show a relative standard deviation of not more than 2.0%. Use a suitable high-pressure liquid chromatograph of the general type (see *Chromatography* ⟨621⟩) capable of providing column pressure up to about 1500 psig operated at room temperature and equipped with an ultraviolet detector capable of monitoring absorption at 254 nm, a suitable recorder, and a 4-mm × 30-cm stainless steel column that contains 10-µm packing L3. Chromatograph equal volumes of the *Standard preparation* and the *Assay preparation*. Calculate the quantity, in mg, of $C_{25}H_{47}NO_8$, in the portion of Carboprost Tromethamine taken by the formula:

$$W_S(R_U/R_S),$$

in which W_S is the weight, in mg, of USP Carboprost Tromethamine RS used in the *Standard preparation*, and R_U and R_S are the ratios of the peak responses of the 2-naphthacyl ester of carboprost and the internal standard obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Carboprost Tromethamine Injection

» Carboprost Tromethamine Injection is a sterile solution of Carboprost Tromethamine in aqueous solution, which may contain also benzyl alcohol, sodium chloride, and tromethamine. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of carboprost ($C_{21}H_{36}O_5$).

Packaging and storage—Preserve in single-dose or in multiple-dose containers, preferably of Type I glass, in a refrigerator.

USP Reference standards ⟨11⟩—*USP Carboprost Tromethamine RS*. *USP Endotoxin RS*.

Identification—Extract a volume of Injection equivalent to about 2.5 mg of carboprost tromethamine with 1.5 to 2 times its volume of chloroform. Discard the chloroform layer, and acidify the aqueous layer with 3 to 5 drops of hydrochloric acid. Extract the acidified solution with an equivalent volume of chloroform. Filter the chloroform layer through a pledget of cotton, and concentrate it to a volume of less than 1 mL. Combine the resulting solution with 150 to 180 mg of potassium bromide. Dry the potassium bromide mixture in vacuum overnight, and prepare a potassium bromide pellet from the dried mixture: the infrared absorption spectrum of the resulting pellet exhibits maxima at the same wavelengths as that of a similar preparation of USP Carboprost Tromethamine RS.

Bacterial endotoxins ⟨85⟩—It contains not more than 714.3 USP Endotoxin Units per mg of carboprost tromethamine.

pH ⟨791⟩: between 7.0 and 8.0.

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

Assay—

Mobile solvent and *Citrate buffer*—Prepare as directed for *Mobile solvent* and *Citrate buffer* in the *Assay* under *Carboprost Tromethamine*.

Internal standard preparation—Using the *Mobile solvent*, prepare a solution containing approximately 3 mg of guaifenesin per mL.

Standard preparation—Using an accurately weighed quantity of the Reference Standard, prepare an aqueous Standard solution containing approximately 0.332 mg of USP Carboprost Tromethamine RS and 9 mg of benzyl alcohol per mL. Pipet 2 mL of the resulting solution into a stoppered centrifuge tube. Add 20.0 mL of methylene chloride and 1.0 mL of *Citrate buffer*, shake the stoppered tube for about 10 minutes, and centrifuge. Remove and discard the top (aqueous) layer, transfer an 8.0-mL aliquot of the lower (methylene chloride) layer to a suitable vial, and evaporate the solution with the aid of a stream of nitrogen. (The residue does not evaporate to dryness because of the presence of benzyl alcohol.) Add 100 µL of a freshly prepared 1 in 50 solution of α-bromo-2′acetonaphthone in acetonitrile, and swirl to wash down the sides of the vial. Add 50 µL of a freshly prepared 1 in 100 solution of diisopropylethylamine in acetonitrile. Swirl again, and place the vial in a suitable heating device maintained at a temperature of 30° to 35° for not less than 15 minutes. Evaporate the acetonitrile from the vial with the aid of a stream of nitrogen, add 1.0 mL of *Internal standard solution*, mix, and filter the resulting solution through a fine-porosity filter. Protect the filtered solution from light prior to injection to prevent degradation of the naphthacyl ester of carboprost.

Assay preparation—Pipet a volume of Injection, equivalent to about 500 µg of carboprost, to a stoppered, 50-mL centrifuge tube. Proceed as directed for *Standard preparation*, beginning with "Add 20.0 mL of methylene chloride."

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Carboprost Tromethamine*. Calculate the quantity, in µg, of carboprost in each mL of the Injection taken by the formula:

$$(368.51/489.65)(C)(R_U/R_S),$$

in which 368.51 and 489.65 are the molecular weights of carboprost and carboprost tromethamine, respectively, C is the concentration, in µg per mL, of USP Carboprost Tromethamine RS in the Standard solution used to prepare the naphthacyl ester, and R_U and R_S are the ratios of the peak responses of the 2-naphthacyl ester of carboprost and the internal standard obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Carboxymethylcellulose Calcium—*see* Carboxymethylcellulose Calcium NF

Carboxymethylcellulose Sodium

Cellulose, carboxymethyl ether, sodium salt.
Cellulose carboxymethyl ether sodium salt [*9004-32-4*].

» Carboxymethylcellulose Sodium is the sodium salt of a polycarboxymethyl ether of cellulose. It contains not less than 6.5 percent and not more than 9.5 percent of sodium (Na), calculated on the dried basis.

Packaging and storage—Preserve in tight containers.

Labeling—Label it to indicate the viscosity in solutions of stated concentrations.

Identification—Add about 1 g of powdered Carboxymethylcellulose Sodium to 50 mL of water, while stirring to produce a

uniform dispersion. Continue the stirring until a clear solution is produced, and use the solution for the following tests.

A: To 1 mL of the solution, diluted with an equal volume of water, in a small test tube, add 5 drops of 1-naphthol TS. Incline the test tube, and carefully introduce down the side of the tube 2 mL of sulfuric acid so that it forms a lower layer: a red-purple color develops at the interface.

B: To 5 mL of the solution add an equal volume of barium chloride TS: a fine, white precipitate is formed.

C: A portion of the solution responds to the tests for *Sodium* ⟨191⟩.

Viscosity ⟨911⟩—Determine the viscosity in a water solution at the concentration stated on the label. Using undried Carboxymethylcellulose Sodium, weigh accurately the amount which, on the dried basis, will provide 200 g of solution of the stated concentration. Add the substance in small amounts to about 180 mL of stirred water contained in a tared, wide-mouth bottle, continue stirring rapidly until the powder is well wetted, add sufficient water to make the mixture weigh 200 g, and allow to stand, with occasional stirring, until solution is complete. Adjust the temperature to 25 ± 0.2°, and determine the viscosity, using a rotational type of viscosimeter, making certain that the system reaches equilibrium before taking the final reading. The viscosity of solutions of 2% or higher concentration is not less than 80.0% and not more than 120.0% of that stated on the label; the viscosity of solutions of 1% concentration is not less than 75.0% and not more than 140.0% of that stated on the label.

pH ⟨791⟩: between 6.5 and 8.5 in a solution (1 in 100).

Loss on drying ⟨731⟩—Dry it at 105° for 3 hours: it loses not more than 10.0% of its weight.

Heavy metals—Determine as directed in the test for *Heavy metals* under *Methylcellulose*, using a 500-mg specimen: the limit is 0.004%.

Assay—Transfer to a beaker about 500 mg of Carboxymethylcellulose Sodium, accurately weighed, add 80 mL of glacial acetic acid, heat the mixture on a boiling water bath for 2 hours, cool to room temperature, and titrate with 0.1 *N* perchloric acid VS, determining the endpoint potentiometrically. Each mL of 0.1 *N* perchloric acid is equivalent to 2.299 mg of Na.

Carboxymethylcellulose Sodium Paste

» Carboxymethylcellulose Sodium Paste contains not less than 16.0 percent and not more than 17.0 percent of carboxymethylcellulose sodium.

Packaging and storage—Preserve in well-closed containers, and avoid prolonged exposure to temperatures exceeding 30°.

Identification—Digest a quantity of Paste, equivalent to about 1 g of carboxymethylcellulose sodium, with 50 mL of water until solution is virtually complete, and filter: the filtrate responds to the following tests.

A: To about 30 mL of the solution add 3 mL of hydrochloric acid: a white precipitate is formed.

B: To the remainder of the solution add an equal volume of barium chloride TS: a fine, white, precipitate is formed.

C: The filtrate from *Identification* test *A* responds to the tests for *Sodium* ⟨191⟩.

Consistency—Determine as directed in the test for *Consistency* under *White Petrolatum:* the final average of the trials is not less than 30.0 mm and not more than 36.0 mm, indicating a consistency value between 300 and 360.

Microbial limits ⟨61⟩—The total bacterial count does not exceed 1000 per g, and the tests for *Salmonella* species and *Escherichia coli* are negative.

Loss on drying ⟨731⟩—Dry it at 105° for 3 hours: it loses not more than 2.0% of its weight.

Heavy metals ⟨231⟩—Determine as directed in the test for *Heavy metals* under *Methylcellulose*, using a 400-mg specimen: the limit is 0.005%.

Assay—Transfer about 2 g of Paste, accurately weighed, to a glass-stoppered, 250-mL conical flask. Add 75 mL of glacial acetic acid, attach a condenser, and reflux for 2 hours. Cool, transfer the mixture to a 250-mL beaker with the aid of small volumes of glacial acetic acid, and titrate with 0.1 *N* perchloric acid in dioxane VS, determining the endpoint potentiometrically. Each mL of 0.1 *N* perchloric acid is equivalent to 29.67 mg of carboxymethylcellulose sodium.

Carboxymethylcellulose Sodium Tablets

» Carboxymethylcellulose Sodium Tablets contain an amount of sodium (Na) equivalent to not less than 6.5 percent and not more than 9.5 percent of the labeled amount of carboxymethylcellulose sodium.

Packaging and storage—Preserve in tight containers.

Identification—Digest a quantity of powdered Tablets, equivalent to about 1 g of carboxymethylcellulose sodium, with 50 mL of water until solution is virtually complete, and filter: the filtrate responds to the following tests.

A: To about 30 mL of the solution add 3 mL of hydrochloric acid: a white precipitate is formed.

B: To the remainder of the solution add an equal volume of barium chloride TS: a fine, white precipitate is formed.

C: The filtrate from *Identification* test *A* responds to the tests for *Sodium* ⟨191⟩.

Disintegration ⟨701⟩: 2 hours.

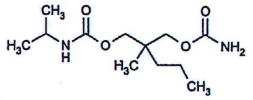
Uniformity of dosage units ⟨905⟩: meet the requirements.

Assay—Weigh and finely powder not less than 20 Tablets. Weigh accurately a portion of the powder, equivalent to about 500 mg of carboxymethylcellulose sodium, add 80 mL of glacial acetic acid, heat the mixture on a steam bath for 2 hours, cool to room temperature, and titrate with 0.1 *N* perchloric acid VS, determining the endpoint potentiometrically. Each mL of 0.1 *N* perchloric acid is equivalent to 2.299 mg of Na.

Carboxymethylcellulose Sodium, Microcrystalline Cellulose and—*see* Microcrystalline and Carboxymethylcellulose Sodium NF

Carboxymethylcellulose Sodium 12—*see* Carboxymethylcellulose Sodium 12 NF

Carisoprodol



$C_{12}H_{24}N_2O_4$ 260.34

(±)-2-Methyl-2-propyl-1,3-propanediol carbamate isopropylcarbamate [*78-44-4*].

» Carisoprodol contains not less than 98.0 percent and not more than 102.0 percent of $C_{12}H_{24}N_2O_4$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩—*USP Carisoprodol RS. USP Meprobamate RS.*

⟨911⟩ VISCOSITY

Viscosity is a property of liquids that is closely related to the resistance to flow. It is defined in terms of the force required to move one plane surface continuously past another under specified steady-state conditions when the space between is filled by the liquid in question. It is defined as the shear stress divided by the rate of shear strain. The basic unit is the *poise;* however, viscosities commonly encountered represent fractions of the poise, so that the *centipoise* (1 poise = 100 centipoises) proves to be the more convenient unit. The specifying of temperature is important because viscosity changes with temperature; in general, viscosity decreases as temperature is raised. While on the absolute scale viscosity is measured in poises or centipoises, for convenience the kinematic scale, in which the units are *stokes* and *centistokes* (1 stoke = 100 centistokes) commonly is used. To obtain the kinematic viscosity from the absolute viscosity, the latter is divided by the density of the liquid at the same temperature, i.e., kinematic viscosity = (absolute viscosity)/(density). The sizes of the units are such that viscosities in the ordinary ranges are conveniently expressed in centistokes. The approximate viscosity in centistokes at room temperature of ether is 0.2; of water, 1; of kerosene, 2.5; of mineral oil, 20 to 70; and of honey, 10,000.

Absolute viscosity can be measured directly if accurate dimensions of the measuring instruments are known, but it is more common practice to calibrate the instrument with a liquid of known viscosity and to determine the viscosity of the unknown fluid by comparison with that of the known.

Many substances, such as the gums employed in pharmacy, have variable viscosity, and most of them are less resistant to flow at higher flow rates. In such cases, a given set of conditions is selected for measurement, and the measurement obtained is considered to be an apparent viscosity. Since a change in the conditions of measurement would yield a different value for the apparent viscosity of such substances, the instrument dimensions and conditions for measurement must be closely adhered to by the operator.

Measurement of Viscosity—The usual method for measurement of viscosity involves the determination of the time required for a given volume of liquid to flow through a capillary. Many capillary-tube viscosimeters have been devised, but Ostwald and Ubbelohde viscosimeters are among the most frequently used. Several types are described, with directions for their use, by the American Society for Testing and Materials (ASTM, D-445). The viscosity of oils is expressed on arbitrary scales that vary from one country to another, there being several corresponding instruments. The most widely used are the Redwood No. I and No. II, the Engler, the Saybolt Universal, and the Saybolt Furol. Each of these instruments uses arbitrary units that bear the name of the instrument. Standard temperatures are adopted as a matter of convenience with these instruments. For the Saybolt instruments, measurements usually are made at 100°F and 210°F; Redwood instruments may be used at several temperatures up to 250°F; and values obtained on the Engler instrument usually are reported at 20°C and 50°C. A particularly convenient and rapid type of instrument is a rotational viscosimeter, which utilizes a bob or spindle immersed in the test specimen and measures the resistance to movement of the rotating part. Different spindles are available for given viscosity ranges, and several rotational speeds generally are available. Other rotational instruments may have a stationary bob and a rotating cup. The Brookfield, Rotouisco, and Stormer viscosimeters are examples of rotating-bob instruments, and the MacMichael is an example of the rotating-cup instrument. Numerous other rotational instruments of advanced design with special devices for reading or recording, and with wide ranges of rotational speed, have been devised.

Where only a particular type of instrument is suitable, the individual monograph so indicates.

For measurement of viscosity or apparent viscosity, the temperature of the substance being measured must be accurately controlled, since small temperature changes may lead to marked changes in viscosity. For usual pharmaceutical purposes, the temperature should be held to within ±0.1°.

Procedure for Cellulose Derivatives—Measurement of the viscosity of solutions of the high-viscosity types of methylcellulose is a special case, since they are too viscous for the commonly available viscosimeters. The Ubbelohde viscosimeter may be adapted (cf. ASTM, D-1347) to the measurement of the ranges of viscosity encountered in methylcellulose solutions.

Calibration of Capillary-Type Viscosimeters—Determine the viscosimeter constant, k, for each viscosimeter by the use of an oil of known viscosity.*

Ostwald-Type Viscosimeter—Fill the tube with the exact amount of oil (adjusted to 20.0 ± 0.1°) as specified by the manufacturer. Adjust the meniscus of the column of liquid in the capillary tube to the level of the top graduation line with the aid of either pressure or suction. Open both the filling and capillary tubes in order to permit the liquid to flow into the reservoir against atmospheric pressure. [NOTE—Failure to open either of these tubes will yield false values.] Record the time, in seconds, for liquid to flow from the upper mark to the lower mark in the capillary tube.

Ubbelohde-Type Viscosimeter—Place a quantity of the oil (adjusted to 20.0 ± 0.1°) in the filling tube, and transfer to the capillary tube by gentle suction, taking care to prevent bubble formation in the liquid by keeping the air vent tube closed. Adjust the meniscus of the column of liquid in the capillary tube to the level of the top graduation line. Open both the vent and capillary tubes in order to permit the liquid to flow into the reservoir against atmospheric pressure. [NOTE—Failure to open the vent tube before releasing the capillary tube will yield false values.] Record the time, in seconds, for the liquid to flow from the upper mark to the lower mark in the capillary tube.

Calculations—

Calculate the viscosimeter constant, k, from the equation:

$$k = \nu/dt,$$

in which ν is the known viscosity of the liquid in centipoises, d is the specific gravity of the liquid tested at 20°/20°, and t is the time in seconds for the liquid to pass from the upper mark to the lower mark.

If a viscosimeter is repaired, it must be recalibrated, since even minor repairs frequently cause significant changes in the value of its constant, k.

* Oils of known viscosities may be obtained from the Cannon Instrument Co., Box 16, State College, PA 16801. For methylcellulose, choose an oil the viscosity of which is as close as possible to that of the type of methylcellulose to be determined.

⟨921⟩ WATER DETERMINATION

Many Pharmacopeial articles either are hydrates or contain water in adsorbed form. As a result, the determination of the water content is important in demonstrating compliance with the Pharmacopeial standards. Generally one of the methods given below is called for in the individual monograph, depending upon the nature of the article. In rare cases, a choice is allowed between two methods. When the article contains water of hydration, the Method I (Titrimetric), the Method II (Azeotropic), or the Method III (Gravimetric) is employed, as directed in the individual monograph, and the requirement is given under the heading *Water*.

The heading *Loss on drying* (see *Loss on Drying* ⟨731⟩) is used in those cases where the loss sustained on heating may be not entirely water.

METHOD I (TITRIMETRIC)

Determine the water by *Method Ia*, unless otherwise specified in the individual monograph.

Method Ia (Direct Titration)

Principle—The titrimetric determination of water is based upon the quantitative reaction of water with an anhydrous solution of sulfur dioxide and iodine in the presence of a buffer that reacts with hydrogen ions.

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