Value under *Content Uniformity* or under ✦*Weight*✦ *Variation*. Unless otherwise specified, L1 is 15.0 and L2 is 25.0.

⟨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:

$$k = v/d\ t$$

in which v 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.

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* 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.

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

⟨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.

In the original titrimetric solution, known as Karl Fischer Reagent, the sulfur dioxide and iodine are dissolved in pyridine and methanol. The test specimen may be titrated with the *Reagent* directly, or the analysis may be carried out by a residual titration procedure. The stoichiometry of the reaction is not exact, and the reproducibility of a determination depends upon such factors as the relative concentrations of the *Reagent* ingredients, the nature of the inert solvent used to dissolve the test specimen, and the technique used in the particular determination. Therefore, an empirically standardized technique is used in order to achieve the desired accuracy. Precision in the method is governed largely by the extent to which atmospheric moisture is excluded from the system. The titration of water is usually carried out with the use of anhydrous methanol as the solvent for the test specimen; however, other suitable solvents may be used for special or unusual test specimens.

Apparatus—Any apparatus may be used that provides for adequate exclusion of atmospheric moisture and determination of the endpoint. In the case of a colorless solution that is titrated directly, the endpoint may be observed visually as a change in color from canary yellow to amber. The reverse is observed in the case of a test specimen that is titrated residually. More commonly, however, the endpoint is determined electrometrically with an apparatus employing a simple electrical circuit that serves to impress about 200 mV of applied potential between a pair of platinum electrodes immersed in the solution to be titrated. At the endpoint of the titration a slight excess of the reagent increases the flow of current to between 50 and 150 microamperes for 30 seconds to 30 minutes, depending upon the solution being titrated. The time is shortest for substances that dissolve in the reagent. With some automatic titrators, the abrupt change in current or potential at the endpoint serves to close a solenoid-operated valve that controls the buret delivering the titrant. Commercially available apparatus generally comprises a closed system consisting of one or two automatic burets and a tightly covered titration vessel fitted with the necessary electrodes and a magnetic stirrer. The air in the system is kept dry with a suitable desiccant, and the titration vessel may be purged by means of a stream of dry nitrogen or current of dry air.

Reagent—Prepare the Karl Fischer Reagent as follows. Add 125 g of iodine to a solution containing 670 mL of methanol and 170 mL of pyridine, and cool. Place 100 mL of pyridine in a 250-mL graduated cylinder, and, keeping the pyridine cold in an ice bath, pass in dry sulfur dioxide until the volume reaches 200 mL. Slowly add this solution, with shaking, to the cooled iodine mixture. Shake to dissolve the iodine, transfer the solution to the apparatus, and allow the solution to stand overnight before standardizing. One mL of this solution when freshly prepared is equivalent to approximately 5 mg of water, but it deteriorates gradually; therefore, standardize it within 1 hour before use, or daily if in continuous use. Protect from light while in use. Store any bulk stock of the reagent in a suitably sealed, glass-stoppered container, fully protected from light, and under refrigeration.

A commercially available, stabilized solution of Karl Fischer type reagent may be used. Commercially available reagents containing solvents or bases other than pyridine or alcohols other than methanol may be used also. These may be single solutions or reagents formed in situ by combining the components of the reagents present in two discrete solutions. The diluted *Reagent* called for in some monographs should be diluted as directed by the manufacturer. Either methanol or other suitable solvent, such as ethylene glycol monomethyl ether, may be used as the diluent.

Test Preparation—Unless otherwise specified in the individual monograph, use an accurately weighed or measured amount of the specimen under test estimated to contain 2 to 250 mg of water. The amount of water depends on the water equivalency factor of the *Reagent* and on the method of endpoint determination. In most cases, the minimum amount of specimen, in mg, can be estimated using the formula:

$$FCV/KF$$

in which F is the water equivalency factor of the *Reagent,* in mg per mL; C is the used volume, in percent, of the capacity of the buret; V is the buret volume, in mL; and KF is the limit or reasonable expected water content in the sample, in percent. C is generally between 30% and 100% for manual titration, and between 10% and 100% for the instrumental method endpoint determination. [NOTE—It is recommended that the product of FCV be greater than or equal to 200 for the calculation to ensure that the minimum amount of water titrated is greater than or equal to 2 mg.]

Where the specimen under test is an aerosol with propellant, store it in a freezer for not less than 2 hours, open the container, and test 10.0 mL of the well-mixed specimen. In titrating the specimen, determine the endpoint at a temperature of 10° or higher.

Where the specimen under test is capsules, use a portion of the mixed contents of not fewer than 4 capsules.

Where the specimen under test is tablets, use powder from not fewer than 4 tablets ground to a fine powder in an atmosphere of temperature and relative humidity known not to influence the results.

Where the monograph specifies that the specimen under test is hygroscopic, use a dry syringe to inject an appropriate volume of methanol, or other suitable solvent, accurately measured, into a tared container, and shake to dissolve the specimen. Using the same syringe, remove the solution from the container and transfer it to a titration vessel prepared as directed for *Procedure.* Repeat the procedure