In addition, the method is reliable when the purity of the major component is greater than 98.5 mol% and the materials are not decomposed during the melting phase.

Impurity levels calculated from thermograms are reproducible and generally reliable within 0.1% for ideal compounds.

Compounds that exist in polymorphic form cannot be used in purity determination unless the compound is completely converted to one form. On the other hand, DSC and DTA are inherently useful for detecting, and therefore monitoring, polymorphism.

Procedure—The actual procedure and the calculations to be employed for eutectic impurity analysis are dependent on the particular instrument used. Consult the manufacturer's literature and/or the thermal analysis literature for the most appropriate technique for a given instrument. In any event, it is imperative to keep in mind the limitations of solid solution formation, insolubility in the melt, polymorphism, and decomposition during the analysis.

⟨905⟩ UNIFORMITY OF DOSAGE UNITS

This general chapter is harmonized with the corresponding texts of the *European Pharmacopoeia* and the *Japanese Pharmacopoeia*. Portions of the general chapter text that are national *USP* text, and are not part of the harmonized text, are marked with symbols (✦✦) to specify this fact.

✦NOTE—In this chapter, *unit* and *dosage unit* are synonymous.✦

To ensure the consistency of dosage units, each unit in a batch should have a drug substance content within a narrow range around the label claim. Dosage units are defined as dosage forms containing a single dose or a part of a dose of drug substance in each unit. The uniformity of dosage units specification is not intended to apply to suspensions, emulsions, or gels in unit-dose containers intended for external, cutaneous administration.

The term "uniformity of dosage unit" is defined as the degree of uniformity in the amount of the drug substance among dosage units. Therefore, the requirements of this chapter apply to each drug substance being comprised in dosage units containing one or more drug substances, unless otherwise specified elsewhere in this Pharmacopeia.

The uniformity of dosage units can be demonstrated by either of two methods, *Content Uniformity* or ✦*Weight✦ Variation* (see *Table 1*). The test for *Content Uniformity* of preparations presented in dosage units is based on the assay of the individual content of drug substance(s) in a number of dosage units to determine whether the individual content is within the limits set. The *Content Uniformity* method may be applied in all cases.

The test for ✦*Weight✦ Variation* is applicable for the following dosage forms:

(W1)	Solutions enclosed in unit-dose containers and into soft capsules;
(W2)	Solids (including powders, granules, and sterile solids) that are packaged in single-unit containers and contain no active or inactive added substances;
(W3)	Solids (including sterile solids) that are packaged in single-unit containers, with or without active or inactive added substances, that have been prepared from true solutions and freeze-dried in the final containers and are labeled to indicate this method of preparation; and
(W4)	Hard capsules, uncoated tablets, or film-coated tablets, containing 25 mg or more of a drug substance comprising 25% or more, by weight, of the dosage unit or, in the case of hard capsules, the capsule contents, except that uniformity of other drug substances present in lesser proportions is demonstrated by meeting the requirements for *Content Uniformity*.

The test for *Content Uniformity* is required for all dosage forms not meeting the above conditions for the ✦*Weight✦ Variation* test.[1]

Table 1. Application of Content Uniformity (CU) and Weight Variation (WV) Tests for Dosage Forms

Dosage Form	Type	Subtype	Dose & Ratio of Drug Substance: ≥25 mg and ≥25%	Dose & Ratio of Drug Substance: <25 mg or <25%
Tablets	Uncoated		WV	CU
	Coated	Film	WV	CU
		Others	CU	CU
Capsules	Hard		WV	CU
	Soft	Suspension, emulsion, or gel	CU	CU
		Solutions	WV	WV
Solids in single-unit containers	Single component		WV	WV
	Multiple components	Solution freeze-dried in final container	WV	WV
		Others	CU	CU
Solutions in unit-dose containers ✦and into soft capsules✦			WV	WV
Others			CU	CU

CONTENT UNIFORMITY

Select not fewer than 30 units, and proceed as follows for the dosage form designated.

Where different procedures are used for assay of the preparation and for the *Content Uniformity* test, it may be necessary to establish a correction factor to be applied to the results of the latter.

[1] ✦European Pharmacopoeia and Japanese Pharmacopoeia text not accepted by the United States Pharmacopeia: Alternatively, products listed in item (4) above that do not meet the 25 mg/25% threshold limit may be tested for uniformity of dosage units by Mass Variation instead of the Content Uniformity test if the concentration relative standard deviation (RSD) of the drug substance in the final dosage units is not more than 2%, based on process validation data and development data, and if there has been regulatory approval of such a change. The concentration RSD is the RSD of the concentration per dosage unit (w/w or w/v), where concentration per dosage unit equals the assay result per dosage unit divided by the individual dosage unit weight. See the RSD formula in *Table 2*.✦

Solid Dosage Forms

Assay 10 units individually using an appropriate analytical method. Calculate the acceptance value (see *Table 2*).

Liquid or Semi-Solid Dosage Forms

Assay 10 units individually using an appropriate analytical method. Carry out the assay on the amount of well-mixed material that is removed from an individual container in conditions of normal use, and express the results as delivered dose. Calculate the acceptance value (see *Table 2*).

Calculation of Acceptance Value

Calculate the acceptance value by the formula:

$$\left|M - \overline{X}\right| + ks$$

in which the terms are as defined in *Table 2*.

Table 2

Variable	Definition	Conditions	Value
$\overline{X}$	Mean of individual contents (χ_1, χ_2, …, χ_n), expressed as a percentage of the label claim		
χ_1, χ_2, …, χ_n	Individual contents of the units tested, expressed as a percentage of the label claim		
n	Sample size (number of units in a sample)		
k	Acceptability constant	If n = 10, then k =	2.4
		If n = 30, then k =	2.0
s	Sample standard deviation		$\left[\frac{\sum_{i=1}^{n}(\chi_i - \overline{X})^2}{n-1}\right]^{\frac{1}{2}}$
RSD	Relative standard deviation (the sample standard deviation expressed as a percentage of the mean)		$100s/\overline{X}$
M (case 1) to be applied when T ≤101.5	Reference value	If 98.5% ≤$\overline{X}$ ≤101.5%, then	M = $\overline{X}$ (AV = ks)
		If $\overline{X}$ <98.5%, then	M = 98.5% (AV = 98.5 – $\overline{X}$ + ks)
		If $\overline{X}$ >101.5%, then	M = 101.5% (AV = $\overline{X}$ – 101.5 + ks)
M (case 2) to be applied when T >101.5	Reference value	If 98.5 ≤$\overline{X}$ ≤T, then	M = $\overline{X}$ (AV = ks)
		If $\overline{X}$ <98.5%, then	M = 98.5% (AV = 98.5 – $\overline{X}$ + ks)
		If $\overline{X}$ >T, then	M = T% (AV = $\overline{X}$ – T + ks)
Acceptance value (AV)			General formula: $\left\|M - \overline{X}\right\| + ks$ (Calculations are specified above for the different cases.)
L1	Maximum allowed acceptance value		L1 = 15.0 unless otherwise specified

Table 2 *(Continued)*

Variable	Definition	Conditions	Value
L2	Maximum allowed range for deviation of each dosage unit tested from the calculated value of M	On the low side, no dosage unit result can be less than [1–(0.01)(L2)]M, while on the high side, no dosage unit result can be greater than [1 + (0.01)(L2)]M. (This is based on an L2 value of 25.0.)	L2 = 25.0 unless otherwise specified
T	Target content per dosage unit at the time of manufacture, expressed as a percentage of the label claim. Unless otherwise stated, T is 100.0%, or T is the manufacturer's approved target content per dosage unit.		

✦WEIGHT✦ VARIATION

Carry out an assay for the drug substance(s) on a representative sample of the batch using an appropriate analytical method. This value is result A, expressed as percentage of label claim (see *Calculation of Acceptance Value*). Assume that the concentration (weight of drug substance per weight of dosage unit) is uniform. Select not fewer than 30 dosage units, and proceed as follows for the dosage form designated.

Uncoated or Film-Coated Tablets

Accurately weigh 10 tablets individually. Calculate the content, expressed as percentage of label claim, of each tablet from the ✦weight✦ of the individual tablet and the result of the *Assay*. Calculate the acceptance value.

Hard Capsules

Accurately weigh 10 capsules individually, taking care to preserve the identity of each capsule. Remove the contents of each capsule by a suitable means. Accurately weigh the emptied shells individually, and calculate for each capsule the net ✦weight✦ of its contents by subtracting the ✦weight✦ of the shell from the respective gross ✦weight✦. Calculate the drug substance content of each capsule from the ✦net weight✦ of the individual capsule ✦content✦ and the result of the *Assay*. Calculate the acceptance value.

Soft Capsules

Accurately weigh 10 intact capsules individually to obtain their gross ✦weights✦, taking care to preserve the identity of each capsule. Then cut open the capsules by means of a suitable clean, dry cutting instrument such as scissors or a sharp open blade, and remove the contents by washing with a suitable solvent. Allow the occluded solvent to evaporate from the shells at room temperature over a period of about 30 minutes, taking precautions to avoid uptake or loss of moisture. Weigh the individual shells, and calculate the net contents. Calculate the drug substance content in each capsule from the ✦weight✦ of product removed from the individual capsules and the result of the *Assay*. Calculate the acceptance value.

Solid Dosage Forms Other Than Tablets and Capsules

Proceed as directed for *Hard Capsules*, treating each unit as described therein. Calculate the acceptance value.

Liquid Dosage Forms

Accurately weigh the amount of liquid that is removed from each of 10 individual containers in conditions of normal use. If necessary, compute the equivalent volume after determining the density. Calculate the drug substance content in each container from the mass of product removed from the individual containers and the result of the *Assay*. Calculate the acceptance value.

Calculation of Acceptance Value

Calculate the acceptance value as shown in *Content Uniformity*, except that the individual contents of the units are replaced with the individual estimated contents defined below.

$\chi_1, \chi_2, \ldots, \chi_n$	=	individual estimated contents of the units tested, where $\chi_i = w_i \times A/\overline{W}$
$w_1, w_2, \ldots, w_n$	=	individual ✦weights✦ of the units tested
A	=	content of drug substance (% of label claim) obtained using an appropriate analytical method
$\overline{W}$	=	mean of individual ✦weights✦ $(w_1, w_2, \ldots, w_n)$

CRITERIA

Apply the following criteria, unless otherwise specified.

Solid, Semi-Solid, and Liquid Dosage Forms

The requirements for dosage uniformity are met if the acceptance value of the first 10 dosage units is less than or equal to L1%. If the acceptance value is > L1%, test the next 20 units, and calculate the acceptance value. The requirements are met if the final acceptance value of the 30 dosage units is ≤ L1%, and no individual content of ✦any✦ dosage unit is less than [1 – (0.01)(L2)]M nor more than [1 + (0.01)(L2)]M ✦as specified✦ in the *Calculation of Acceptance*

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.

* 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.