1995

USP 23

NF 18

THE UNITED STATES PHARMACOPEIA

THE NATIONAL FORMULARY

By authority of the United States Pharmacopeial Convention, Inc., meeting at Washington, D.C., March 8–10, 1990. Prepared by the Committee of Revision and published by the Board of Trustees

Official from January 1, 1995

UNITED STATES PHARMACOPEIAL CONVENTION, INC.
12601 Twinbrook Parkway, Rockville, MD 20852

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ISSN 0195-7996
ISBN 0-913595-76-4 (cloth)
0-913595-81-0 (leather)

Printed by Rand McNally, 1133 County Street, Taunton, MA 02780-3795

molar heat of fusion of the major component, R = gas constant, and K = distribution ratio of solute between the solid and liquid phases.

Assuming that the temperature range is small and that no solid solutions are formed ($K = 0$), integration of the van't Hoff equation yields the following relationship between mole fraction of impurity and the melting-point depression:

$$X_2 = \frac{(T_o - T_m)\Delta H_f}{RT_o^2}, \qquad (2)$$

in which T_o = melting point of the pure compound, in °K, and T_m = melting point of the test specimen, in °K.

With no solid solution formation, the concentration of impurity in the liquid phase at any temperature during the melting is inversely proportional to the fraction melted at that temperature, and the melting-point depression is directly proportional to the mole fraction of impurity. A plot of the observed test specimen temperature, T_s, versus the reciprocal of the fraction melted, $1/F$, at temperature T_s, should yield a straight line with the slope equal to the melting-point depression ($T_o - T_m$). The theoretical melting point of the pure compound is obtained by extrapolation to $1/F = 0$:

$$T_s = T_o - \frac{RT_o^2X_2(1/F)}{\Delta H_f}. \qquad (3)$$

Substituting the experimentally obtained values for $T_o - T_m$, ΔH_f, and T_o in Equation 2 yields the mole fraction of the total eutectic impurity, which, when multiplied by 100, gives the mole percentage of total eutectic impurities.

Deviations from the theoretical linear plot also may be due to solid solution formation ($K \neq 0$), so that care must be taken in interpreting the data.

To observe the linear effect of the impurity concentration on the melting-point depression, the impurity must be *soluble* in the liquid phase or melt of the compound, but *insoluble* in the solid phase, i.e., no solid solutions are formed. Some chemical similarities are necessary for solubility in the melt. For example, the presence of ionic compounds in neutral organic compounds and the occurrence of thermal decomposition may not be reflected in purity estimates. The extent of these theoretical limitations has been only partially explored.

Impurities present from the synthetic route often are similar to the end product, hence there usually is no problem of solubility in the melt. Impurities consisting of molecules of the same shape, size, and character as those of the major component can fit into the matrix of the major component without disruption of the lattice, forming solid solutions or inclusions; such impurities are not detectable by DSC. Purity estimates are too high in such cases. This is more common with less-ordered crystals as indicated by low heats of fusion.

Impurity levels calculated from thermograms are reproducible and probably reliable within 0.1% for ideal compounds. Melting-point determinations by scanning calorimetry have a reproducibility with a standard deviation of about 0.2°. Calibration against standards may allow about 1° accuracy for the melting point, so that this technique is comparable to other procedures.

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 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

The uniformity of dosage units can be demonstrated by either of two methods, weight variation or content uniformity. The requirements of this chapter apply both to dosage forms containing a single active ingredient and to dosage forms containing two or more active ingredients.

Weight Variation requirements may be applied where the product is a liquid-filled soft capsule, or where the product to be tested contains 50 mg or more of an active ingredient comprising 50% or more, by weight, of the dosage-form unit. Uniformity with respect to other active ingredients, if present in lesser proportions, is demonstrated by *Content Uniformity* requirements. *Weight Variation* requirements may be applied to solids (including sterile solids) that contain no inactive or active added substances.

Weight Variation requirements may be applied to solids (including sterile solids), with or without inactive or active added substances, that have been prepared from true solutions and freeze-dried in the final containers, and labeled to indicate this method of preparation.

Content Uniformity requirements may be applied in all cases. The test for *Content Uniformity* is required for all coated tablets, including film-coated tablets, for transdermal systems, for suspensions in single-unit containers or in soft capsules, and for pressurized metered-dose inhalers. The test for *Content Uniformity* is required for solids (including sterile solids) that contain inactive or active added substances, except that the test for *Weight Variation* may be applied for special situations as stated above.

WEIGHT VARIATION

For the determination of dosage-form uniformity by weight variation, select not less than 30 units, and proceed as follows for the dosage form designated. [NOTE—Specimens other than these test units may be drawn from the same batch for *Assay* determinations.]

UNCOATED TABLETS—Weigh accurately 10 tablets individually, and calculate the average weight. From the result of the *Assay*, obtained as directed in the individual monograph, calculate the content of active ingredient in each of the 10 tablets, assuming homogeneous distribution of the active ingredient.

HARD CAPSULES—Weigh accurately 10 capsules individually, taking care to preserve the identity of each capsule. Remove the contents of each capsule by a suitable means. Weigh accurately 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. From the results of the *Assay*, obtained as directed in the individual monograph, calculate the content of active ingredient in each of the capsules, assuming homogeneous distribution of the active ingredient.

SOFT CAPSULES—Determine the net weight of the contents of individual capsules as follows. Weigh accurately the 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. From the results of the *Assay*, obtained as directed in the individual monograph, calculate the content of active ingredient in each of the capsules, assuming homogeneous distribution of the active ingredient.

SOLIDS IN SINGLE-UNIT CONTAINERS and STERILE SOLIDS FOR PARENTERAL USE—Proceed as directed under *Hard Capsules*, treating each unit as described therein.

CONTENT UNIFORMITY

For the determination of dosage-form uniformity by assay of individual units, select not less than 30 units, and proceed as follows for the dosage form designated.

UNCOATED AND COATED TABLETS, HARD AND SOFT CAPSULES, SUPPOSITORIES, TRANSDERMAL SYSTEMS, SUSPENSIONS IN SINGLE-UNIT CONTAINERS, PRESSURIZED METERED-DOSE INHALERS, INHALATIONS IN SINGLE-UNIT CONTAINERS, and SOLIDS (INCLUDING STERILE SOLIDS) IN SINGLE-UNIT CONTAINERS—Assay 10 units individually as directed in the *Assay* in the individual monograph, unless otherwise specified in the test for *Content uniformity*. Where the amount of

active ingredient in a single dose unit is less than required in the *Assay*, adjust the degree of dilution of the solutions and/or the volume of aliquots so that the concentration of the active ingredients in the final solution is of the same order as that obtained in the *Assay* procedure; or, in the case of a titrimetric assay, use a more dilute titrant, if necessary, so that an adequate volume of titrant is required (see *Titrimetry* ⟨541⟩); see also *Procedures* under *Tests and Assays* in the *General Notices and Requirements*. If any such modifications are made in the *Assay* procedure set forth in the individual monograph, make the appropriate corresponding changes in the calculation formula and titration factor.

Where a special procedure is specified in the test for *Content uniformity* in the individual monograph, make any necessary correction of the results obtained as follows.

(1) Prepare a composite specimen of a sufficient number of dosage units to provide the amount of specimen called for in the *Assay* in the individual monograph plus the amount required for the special procedure given in the test for *Content uniformity* in the monograph by finely powdering tablets or mixing the contents of capsules or suspensions or solids in single-unit containers to obtain a homogeneous mixture. If a homogeneous mixture cannot be obtained in this manner, use suitable solvents or other procedures to prepare a solution containing all of the active ingredient, and use appropriate aliquot portions of this solution for the specified procedures.

(2) Assay separate, accurately measured portions of the composite specimen of capsules or tablets or suspensions or inhalations or solids in single-unit containers, both (a) as directed in the *Assay*, and (b) using the special procedure given in the test for *Content uniformity* in the monograph.

(3) Calculate the weight of active ingredient equivalent to 1 average dosage unit, by (a) using the results obtained by the *Assay* procedure, and by (b) using the results obtained by the special procedure.

(4) Calculate the correction factor, F, by the formula:

$$F = A/P,$$

in which A is the weight of active ingredient equivalent to 1 average dosage unit obtained by the *Assay* procedure, and P is the weight of active ingredient equivalent to 1 average dosage unit obtained by the special procedure.

$$\text{If } \frac{(100|A-P|)}{A} > 10,$$

the use of a correction factor is not valid.

(5) A valid correction may be applied only if F is not less than 1.03 nor greater than 1.10, or, not less than 0.900 nor greater than 0.970, and if F is between 0.970 and 1.030 no correction is required.

(6) If F lies between 1.03 and 1.10, or between 0.900 and 0.970, calculate the weight of active ingredient in each dosage unit by multiplying each of the weights found using the special procedure by F.

Calculation of the Relative Standard Deviation

The use of preprogrammed calculators or computers is acceptable. A manual mathematical method is as follows:

s = sample standard deviation.

RSD = relative standard deviation (the sample standard deviation expressed as a percentage of the mean).

$\overline{X}$ = mean of the values obtained from the units tested, expressed as a percentage of the label claim.

n = number of units tested.

$x_1, x_2, x_3 \ldots x_n$ = individual values (x_i) of the units tested, expressed as a percentage of the label claim.

$$s = \left[\frac{\Sigma(x_i - \overline{X})^2}{n-1}\right]^{1/2}$$

$$RSD = \frac{100s}{\overline{X}}.$$

Criteria

Apply the following criteria, unless otherwise specified in the individual monograph.

(*A*) *If the Average of the Limits Specified in the Potency Definition in the Individual Monograph is 100.0 Percent or Less*—

COMPRESSED TABLETS (COATED OR UNCOATED), SUPPOSITORIES, SUSPENSIONS IN SINGLE-UNIT CONTAINERS, SOLIDS (INCLUDING STERILE SOLIDS) IN SINGLE-UNIT CONTAINERS, and STERILE SOLIDS FOR PARENTERAL USE—Unless otherwise specified in the individual monograph, the requirements for dose uniformity are met if the amount of the active ingredient in each of the 10 dosage units as determined from the *Weight Variation* or the *Content Uniformity* method lies within the range of 85.0% to 115.0% of the label claim and the *Relative standard deviation* is less than or equal to 6.0%.

If 1 unit is outside the range of 85.0% to 115.0% of label claim and no unit is outside the range of 75.0% to 125.0% of label claim, or if the *Relative standard deviation* is greater than 6.0%, or if both conditions prevail, test 20 additional units. The requirements are met if not more than 1 unit of the 30 is outside the range of 85.0% to 115.0% of label claim and no unit is outside the range of 75.0% to 125.0% of label claim and the *Relative standard deviation* of the 30 dosage units does not exceed 7.8%.

CAPSULES, TRANSDERMAL SYSTEMS, INHALATIONS, AND MOLDED TABLETS—Unless otherwise specified in the individual monograph, the requirements for dose uniformity are met if the amount of the active ingredient in not less than 9 of the 10 dosage units as determined from the *Weight Variation* or the *Content Uniformity* method lies within the range of 85.0% to 115.0% of label claim and no unit is outside the range of 75.0% to 125.0% of label claim and the *Relative standard deviation* of the 10 dosage units is less than or equal to 6.0%.

If 2 or 3 dosage units are outside the range of 85.0% to 115.0% of label claim, but not outside the range of 75.0% to 125.0% of label claim, or if the *Relative standard deviation* is greater than 6.0% or if both conditions prevail, test 20 additional units. The requirements are met if not more than 3 units of the 30 are outside the range of 85.0% to 115.0% of label claim and no unit is outside the range of 75.0% to 125.0% of label claim, and the *Relative standard deviation* of the 30 dosage units does not exceed 7.8%.

PRESSURIZED METERED-DOSE INHALERS—[NOTE—A dosage unit is defined as the discharged spray obtained by actuation of the valve that number of times defined in the labeling as the recommended dose. Follow the labeled instructions for shaking and firing the inhaler. For collection of the dosage unit from the inhaler, proceed as directed in the test for *Uniformity of Unit Spray Content* under *Aerosols* ⟨601⟩.] Unless otherwise specified in the individual monograph, the requirements for dose uniformity are met if the amount, of the active ingredient discharged in not more than 1 of the 10 dosage units as determined from the *Content Uniformity* method lies outside the range of 75.0% to 125.0% of the label claim and no unit is outside the range of 65.0% to 135.0% of the label claim. If 2 or 3 dosage units are outside the range of 75.0% to 125.0% of label claim, but not outside the range of 65.0% to 135.0% of label claim, test 20 additional units. The requirements are met if not more than 3 units of the 30 are outside the range of 75.0% to 125.0% of label claim and no unit is outside the range of 65.0% to 135.0% of label claim.

(*B*) *If the Average of the Limits Specified in the Potency Definition in the Individual Monograph is Greater than 100.0 Percent*—

(1) If the average value of the dosage units tested is 100.0 percent or less, the requirements are as in (*A*).

(2) If the average value of the dosage units tested is greater than or equal to the average of the limits specified in the potency definition in the individual monograph, the requirements are as in (*A*), except that the words "label claim" are replaced by the words "label claim multiplied by the average of the limits specified in the potency definition in the monograph divided by 100."

(3) If the average value of the dosage units tested is between 100 percent and the average of the limits specified in the potency definition in the individual monograph, the requirements are as in (*A*), except that the words "label claim" are replaced by the words "label claim multiplied by the average value of the dosage units tested (expressed as a percent of label claim) divided by 100."