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

SINCE 1820

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

General Notices and Requirements

Applying to Standards, Tests, Assays, and Other Specifications of the United States Pharmacopeia

Guide to GENERAL NOTICES AND REQUIREMENTS

The *General Notices and Requirements* (hereinafter referred to as the *General Notices*) provide in summary form the basic guidelines for the interpretation and application of the standards, tests, assays, and other specifications of the *United States Pharmacopeia* and obviate the need to repeat throughout the book those requirements that are pertinent in numerous instances.

Where exceptions to the *General Notices* are made, the wording in the individual monograph or general test chapter takes precedence and specifically indicates the directions or the intent. To emphasize that such exceptions do exist, the *General Notices* employ where indicated a qualifying expression such as "unless otherwise specified." Thus, it is understood that the specific wording of standards, tests, assays, and other specifications is binding wherever deviations from the *General Notices* exist. By the same token, where no language is given specifically to the contrary, the *General Notices* apply.

TITLE

The full title of this book, including its supplements, is The Pharmacopeia of the United States of America, Twenty-third Revision. This title may be abbreviated to *United States Pharmacopeia*, Twenty-third Revision, or to *USP 23*. The *United States Pharmacopeia*, Twenty-third Revision, supersedes all earlier revisions. Where the term USP is used, without further qualification, during the period in which this Pharmacopeia is official, it refers only to *USP 23* and any supplement(s) thereto.

"OFFICIAL" AND "OFFICIAL ARTICLES"

The word "official," as used in this Pharmacopeia or with reference hereto, is synonymous with "Pharmacopeial," with "USP," and with "compendial."

The designation USP in conjunction with the official title on the label of an article means that the article purports to comply with USP standards; such specific designation on the label does not constitute a representation, endorsement, or incorporation by the manufacturer's labeling of the informational material contained in the USP monograph, nor does it constitute assurance by USP that the article is known to comply with USP standards. The standards apply equally to articles bearing the official titles or names derived by transposition of the definitive words of official titles or transposition in the order of the names of two or more active ingredients in official titles, whether or not the added designation "USP" is used. Names considered to be synonyms of the official titles may not be used for official titles.

Where an article differs from the standards of strength, quality, and purity, as determined by the application of the assays and tests set forth for it in the Pharmacopeia, its difference shall be plainly stated on its label. Where an article fails to comply in identity with the identity prescribed in the USP, or contains an added substance that interferes with the prescribed assays and tests, such article shall be designated by a name that is clearly distinguishing and differentiating from any name recognized in the Pharmacopeia.

Articles listed herein are official and the standards set forth in the monographs apply to them only when the articles are intended or labeled for use as drugs, as nutritional supplements, or as medical devices and when bought, sold, or dispensed for these purposes or when labeled as conforming to this Pharmacopeia.

An article is deemed to be recognized in this Pharmacopeia when a monograph for the article is published in it, including its supplements, addenda, or other interim revisions, and an official date is generally or specifically assigned to it.

The following terminology is used for distinguishing the articles for which monographs are provided: an *official substance* is an active drug entity, a recognized nutrient, or a pharmaceutic ingredient (see also *NF 18*) or a component of a finished device for which the monograph title includes no indication of the nature of the finished form; an *official preparation* is a *drug product*, a *nutritional supplement*, or a *finished device*. It is the finished or partially finished (e.g., as in the case of a sterile solid to be constituted into a solution for administration) preparation or product of one or more official substances formulated for use on or for the patient or consumer; an *article* is an item for which a monograph is provided, whether an official substance or an official preparation.

Nutritional Supplements—The designation of an official preparation containing recognized nutrients as "USP" or the use of the designation "USP" in conjunction with the title of such nutritional supplement preparation may be made only if the article contains two or more of the recognized nutrients and the preparation meets the applicable requirements contained in the individual Class Monograph and General Chapters. Any additional ingredient in such article that is not recognized in the pharmacopeia and for which nutritional value is claimed, shall not be represented nor imply that it is of USP quality or recognized by USP. If a preparation does not comply with applicable requirements but contains nutrients that are recognized in the USP, the article may not designate the individual nutrients as complying with USP standards or being of USP quality without designating on the label that the article itself does not comply with USP standards.

ATOMIC WEIGHTS AND CHEMICAL FORMULAS

The atomic weights used in computing molecular weights and the factors in the assays and elsewhere are those recommended in 1991 by the IUPAC Commission on Atomic Weights and Isotopic Abundances. Chemical formulas, other than those in the Definitions, tests, and assays, are given for purposes of information and calculation. The format within a given monograph is such that after the official title the primarily informational portions of the text ap-

pear first, followed by the text comprising requirements, the latter section of the monograph being introduced by a boldface double-arrow symbol ». (Graphic formulas and chemical nomenclature provided as information in the individual monographs are discussed in the *Preface*.)

ABBREVIATIONS

The term RS refers to a USP Reference Standard as stated under *Reference Standards* in these *General Notices* (see also *USP Reference Standards* ⟨11⟩).

The terms CS and TS refer to Colorimetric Solution and Test Solution, respectively (see under *Reagents, Indicators, and Solutions*). The term VS refers to Volumetric Solution as stated under *Solutions* in the *General Notices*.

The term *PF* refers to *Pharmacopeial Forum*, the journal of standards development and official compendia revision (see *Pharmacopeial Forum* in these *General Notices*).

Abbreviations for the names of many institutions, organizations, and publications are used for convenience throughout *USP* and *NF*. An alphabetized tabulation follows.

Abbreviation	Institution, Organization, or Publication
AAMI	Association for the Advancement of Medical Instrumentation
ACS	American Chemical Society
ANSI	American National Standards Institute
AOAC	AOAC International (formerly Association of Official Analytical Chemists)
ASTM	American Society for Testing and Materials
ATCC	American Type Culture Collection
CAS	Chemical Abstracts Service
CFR	U.S. Code of Federal Regulations
EPA	U.S. Environmental Protection Agency
FCC	Food Chemicals Codex
FDA	U.S. Food and Drug Administration
HIMA	Health Industry Manufacturers Association
ISO	International Standards Organization
IUPAC	International Union of Pure and Applied Chemistry
NBS	National Bureau of Standards
NIST	National Institute of Standards and Technology (formerly NBS)
USAN	United States Adopted Names
WHO	World Health Organization

Abbreviated Statements in Monographs—Incomplete sentences are employed in various portions of the monographs for directness and brevity. Where the limit tests are so abbreviated, it is to be understood that the chapter numbers (shown in angle brackets) designate the respective procedures to be followed, and that the values specified after the colon are the required limits.

SIGNIFICANT FIGURES AND TOLERANCES

Where limits are expressed numerically herein, the upper and lower limits of a range include the two values themselves and all intermediate values, but no values outside the limits. The limits expressed in monograph definitions and tests, regardless of whether the values are expressed as percentages or as absolute numbers, are considered significant to the last digit shown.

Equivalence Statements in Titrimetric Procedures—The directions for titrimetric procedures conclude with a statement of the weight of the analyte that is equivalent to each mL of the standardized titrant. In such an equivalence statement, it is to be understood that the number of significant figures in the concentration of the titrant corresponds to the number of significant figures in the weight of the analyte. Blank corrections are to be made for all titrimetric assays where appropriate (see *Titrimetry* ⟨541⟩).

Tolerances—The limits specified in the monographs for Pharmacopeial articles are established with a view to the use of these articles as drugs, except where it is indicated otherwise. The use of the molecular formula for the active ingredient(s) named in defining the required strength of a Pharmacopeial article is intended to designate the chemical entity or entities, as given in the complete chemical name of the article, having absolute (100 percent) purity.

A dosage form shall be formulated with the intent to provide 100 percent of the quantity of each ingredient declared on the label. Where the content of an ingredient is known to decrease with time, an amount in excess of that declared on the label may be introduced into the dosage form at the time of manufacture to assure compliance with the content requirements of the monograph throughout the expiration period. The tolerances and limits stated in the definitions in the monographs for Pharmacopeial articles allow for such overages and for analytical error, for unavoidable variations in manufacturing and compounding, and for deterioration to an extent considered acceptable under practical conditions.

The specified tolerances are based upon such attributes of quality as might be expected to characterize an article produced from suitable raw materials under recognized principles of good manufacturing practice.

The existence of compendial limits or tolerances does not constitute a basis for a claim that an official substance that more nearly approaches 100 percent purity "exceeds" the Pharmacopeial quality. Similarly, the fact that an article has been prepared to closer tolerances than those specified in the monograph does not constitute a basis for a claim that the article "exceeds" the Pharmacopeial requirements.

Interpretation of Requirements—Analytical results observed in the laboratory (or calculated from experimental measurements) are compared with stated limits to determine whether there is conformance with compendial assay or test requirements. The observed or calculated values usually will contain more significant figures than there are in the stated limit, and an observed or calculated result is to be rounded off to the number of places that is in agreement with the limit expression by the following pro-

cedure. [NOTE—Limits, which are fixed numbers, are not rounded off.]

When rounding off is required, consider only one digit in the decimal place to the right of the last place in the limit expression. If this digit is smaller than 5, it is eliminated and the preceding digit is unchanged. If this digit is greater than 5, it is eliminated and the preceding digit is increased by one. If this digit equals 5, the 5 is eliminated and the preceding digit is increased by one.

Illustration of Rounding Numerical Values for Comparison with Requirements

Compendial Requirement	Unrounded Value	Rounded Result	Conforms
Assay limit ≥98.0%	97.96%	98.0%	Yes
	97.92%	97.9%	No
	97.95%	98.0%	Yes
Assay limit ≤101.5%	101.55%	101.6%	No
	101.46%	101.5%	Yes
	101.45%	101.5%	Yes
Limit test ≤0.02%	0.025%	0.03%	No
	0.015%	0.02%	Yes
	0.027%	0.03%	No
Limit test ≤3 ppm	0.00035%	0.0004%	No
	0.00025%	0.0003%	Yes
	0.00028%	0.0003%	Yes

GENERAL CHAPTERS

Each general chapter is assigned a number that appears in brackets adjacent to the chapter name (e.g., ⟨601⟩ *Aerosols*). General chapters that include general *requirements* for tests and assays are numbered from ⟨1⟩ to ⟨999⟩, chapters that are *informational* are numbered from ⟨1000⟩ to ⟨1999⟩, and chapters pertaining to *nutritional supplements* are numbered above ⟨2000⟩.

The use of the general chapter numbers is encouraged for the identification and rapid access to general tests and information. It is especially helpful where monograph section headings and chapter names are not the same (e.g., *Ultraviolet absorption* ⟨197U⟩ in a monograph refers to method ⟨197U⟩ under general tests chapter ⟨197⟩ *Spectrophotometric Identification Tests; Specific rotation* ⟨781S⟩ in a monograph refers to method ⟨781S⟩ under general tests chapter ⟨781⟩ *Optical Rotation;* and *Calcium* ⟨191⟩ in a monograph refers to the tests for *Calcium* under general tests chapter ⟨191⟩ *Identification Tests—General*).

PHARMACOPEIAL FORUM

Pharmacopeial Forum (*PF*) is the USP journal of standards development and official compendia revision. *Pharmacopeial Forum* is the working document of the USP Committee of Revision. It is intended to provide public portions of communications within the General Committee of Revision and public notice of proposed new and revised standards of the *USP* and *NF* and to afford opportunity for comment thereon. The organization of *PF* includes, but is not limited to, the following sections. Subsections occur where needed for Drugs and Pharmaceutic Ingredients and for Nutritional Supplements.

Pharmacopeial Previews—Possible revisions that are considered to be in a preliminary stage of development.

In-process Revision—New or revised monographs or chapters that are proposed for adoption as official USP or NF standards.

Stimuli to the Revision Process—Reports, statements, articles, or commentaries relating to compendial issues.

Nomenclature—Articles and announcements relevant to compendial nomenclature issues and listings of proposed and new United States Adopted Names (USAN) and International Nonproprietary Names (INN).

Interim Revision Announcement (if present)—Official revisions and their effective dates, announcement of the availability of new USP Reference Standards, and announcement of assays or tests that are held in abeyance pending availability of required USP Reference Standards.

Official Reference Standards—Catalog of current lots of USP Reference Standards with ordering information and names and addresses of worldwide suppliers.

REAGENT STANDARDS

The proper conduct of the Pharmacopeial tests and assays and the reliability of the results depend, in part, upon the quality of the reagents used in the performance of the procedures. Unless otherwise specified, reagents are to be used that conform to the specifications set forth in the current edition of *Reagent Chemicals* published by the American Chemical Society. Where such ACS reagent specifications are not available or where for various reasons the required purity differs, compendial specifications for reagents of acceptable quality are provided. (See *Reagents, Indicators, and Solutions.*) Listing of these reagents, including the indicators and solutions employed as reagents, in no way implies that they have therapeutic utility; furthermore, any reference to USP or NF in their labeling shall include also the term "reagent" or "reagent grade."

USP REFERENCE STANDARDS

USP Reference Standards are authentic specimens that have been approved by the USP Reference Standards Committee as suitable for use as comparison standards in USP or NF tests and assays. (See *USP Reference Standards* ⟨11⟩.) Currently official lots of USP Reference Standards are published in *Pharmacopeial Forum.*

Where a USP Reference Standard is referred to in a monograph or chapter, the words "Reference Standard" are abbreviated to "RS" (see *USP Reference Standards* ⟨11⟩).

Where a test or an assay calls for the use of a compendial article rather than for a USP Reference Standard as a material standard of reference, a substance meeting all of the compendial monograph requirements for that article is to be used.

The requirements for any new USP or NF standards, tests, or assays for which a new USP Reference Standard is specified are not in effect until the specified USP Reference Standard is available. The availability of new USP Reference Standards and the official dates of the USP or NF standards, tests, or assays requiring their use are announced via *Supplements* or *Interim Revision Announcements*.

UNITS OF POTENCY

For substances that cannot be completely characterized by chemical and physical means, it may be necessary to express quantities of activity in biological units of potency, each defined by an authoritative, designated reference standard.

Units of biological potency defined by the World Health Organization (WHO) for International Biological Standards and International Biological Reference Preparations are termed International Units (IU). Units defined by USP Reference Standards are USP Units, and the individual monographs refer to these. Unless otherwise indicated, USP Units are equivalent to the corresponding International Units, where such exist. Such equivalence is usually established on the basis solely of the compendial assay for the substance.

For antibiotics (see *Antibiotics—Microbial Assays* ⟨81⟩), USP Units are defined by the corresponding USP Reference Standards in terms of the units of activity established by the FDA. Each unit is established through the corresponding antibiotic master standard, which in many instances is the basis also for the definition of the WHO International Unit. For most antibiotics, however, biological units of potency are not necessary, and their activity is expressed in metric units (micrograms or milligrams) in terms of the chemically defined substances described in the individual monographs.

For biological products, whether or not International Units or USP Units do exist (see *Biologics* ⟨1041⟩), units of potency are defined by the corresponding US Standard established by the FDA.

INGREDIENTS AND PROCESSES

Official preparations are prepared from ingredients that meet the requirements of the compendial monographs for those individual ingredients for which monographs are provided (see also *NF 18*).

Official substances are prepared according to recognized principles of good manufacturing practice and from ingredients complying with specifications designed to assure that the resultant substances meet the requirements of the compendial monographs (see also *Foreign Substances and Impurities* under *Tests and Assays*).

Preparations for which a complete composition is given in this Pharmacopeia, unless specifically exempted herein or in the individual monograph, are to contain only the ingredients named in the formulas. However, there may be deviation from the specified processes or methods of compounding, though not from the ingredients or proportions thereof, provided the finished preparation conforms to the relevant standards laid down herein and to preparations produced by following the specified process.

Where a monograph on a preparation calls for an ingredient in an amount expressed on the dried basis, the ingredient need not be dried prior to use if due allowance is made for the water or other volatile substances present in the quantity taken.

Unless specifically exempted elsewhere in this Pharmacopeia, the identity, strength, quality, and purity of an official article are determined by the definition, physical properties, tests, assays, and other specifications relating to the article, whether incorporated in the monograph itself, in the *General Notices*, or in the section *General Chapters*.

Water—Water used as an ingredient of official preparations meets the requirements for *Purified Water*, for *Water for Injection*, or for one of the sterile forms of water covered by a monograph in this Pharmacopeia.

Potable water meeting the requirements for drinking water as set forth in the regulations of the federal Environmental Protection Agency may be used in the preparation of official substances.

Alcohol—All statements of percentages of alcohol, such as under the heading *Alcohol content* refer to percentage, by volume, of C_2H_5OH at 15.56°. Where reference is made to "C_2H_5OH," the chemical entity possessing absolute (100 percent) strength is intended.

Alcohol—Where "alcohol" is called for in formulas, tests, and assays, the monograph article *Alcohol* is to be used.

Dehydrated Alcohol—Where "dehydrated alcohol" (absolute alcohol) is called for in tests and assays, the monograph article *Dehydrated Alcohol* is to be used.

Denatured Alcohol—Specially denatured alcohol formulas are available for use in accordance with federal statutes and regulations of the Internal Revenue Service. A suitable formula of specially denatured alcohol may be substituted for Alcohol in the manufacture of Pharmacopeial preparations intended for internal or topical use, provided that the denaturant is volatile and does not remain in the finished product. A finished product that is intended for topical application to the skin may contain specially denatured alcohol, provided that the denaturant is either a normal ingredient or a permissible added substance; in either case the denaturant must be identified on the label of the topical preparation. Where a process is

given in the individual monograph, the preparation so made must be identical with that prepared by the given process.

Added Substances—An official substance, as distinguished from an official preparation, contains no added substances except where specifically permitted in the individual monograph. Where such addition is permitted, the label indicates the name(s) and amount(s) of any added substance(s).

Unless otherwise specified in the individual monograph, or elsewhere in the *General Notices*, suitable substances such as antimicrobial agents, bases, carriers, coatings, colors, flavors, preservatives, stabilizers, and vehicles may be added to an official preparation to enhance its stability, usefulness, or elegance or to facilitate its preparation. Such substances are regarded as unsuitable and are prohibited unless (a) they are harmless in the amounts used, (b) they do not exceed the minimum quantity required to provide their intended effect, (c) their presence does not impair the bioavailability or the therapeutic efficacy or safety of the official preparation, and (d) they do not interfere with the assays and tests prescribed for determining compliance with the Pharmacopeial standards.

Nutritional Supplements—Unless otherwise specified in the individual monograph, or elsewhere in the *General Notices*, consistent with applicable regulatory requirements, suitable added substances such as bases, carriers, coatings, colors, flavors, preservatives, and stabilizers may be added to a nutritional supplement preparation to enhance its stability, usefulness, or elegance, or to facilitate its preparation. Such added substances shall be regarded suitable and shall be permitted unless they interfere with the assays and tests prescribed for determining compliance with Pharmacopeial standards.

Additional Ingredients—Additional ingredients, including excipients, may be added to nutritional supplement preparations containing *recognized nutrients*, consistent with applicable regulatory requirements, provided that (a) they do not interfere with the assays and tests prescribed for determining compliance with Pharmacopeial standards, and (b) that such additional ingredients are listed separately on the label from those ingredients recognized in the definition of the USP article.

Inert Headspace Gases—The air in a container of an article for parenteral use may be evacuated or be replaced by carbon dioxide, helium, or nitrogen, or by a mixture of these gases, which fact need not be declared in the labeling.

Colors—Added substances employed solely to impart color may be incorporated into official preparations, except those intended for parenteral or ophthalmic use, in accordance with the regulations pertaining to the use of colors issued by the FDA provided such added substances are otherwise appropriate in all respects. (See also *Added Substances* under *Injections* ⟨1⟩.)

Ointments and Suppositories—In the preparation of ointments and suppositories, the proportions of the substances constituting the base may be varied to maintain a suitable consistency under different climatic conditions, provided the concentrations of active ingredients are not varied.

TESTS AND ASSAYS

Apparatus—A specification for a definite size or type of container or apparatus in a test or assay is given solely as a recommendation. Where volumetric flasks or other exact measuring, weighing, or sorting devices are specified, this or other equipment of at least equivalent accuracy shall be employed. (See also *Thermometers* ⟨21⟩, *Volumetric Apparatus* ⟨31⟩, and *Weights and Balances* ⟨41⟩). Where low-actinic or light-resistant containers are specified, clear containers that have been rendered opaque by application of a suitable coating or wrapping may be used.

Where an instrument for physical measurement, such as a spectrophotometer, is specified in a test or assay by its distinctive name, another instrument of equivalent or greater sensitivity and accuracy may be used. In order to obtain solutions having concentrations that are adaptable to the working range of the instrument being used, solutions of proportionately higher or lower concentrations may be prepared according to the solvents and proportions thereof that are specified for the procedure.

Where a particular brand or source of a material, instrument, or piece of equipment, or the name and address of a manufacturer or distributor, is mentioned (ordinarily in a footnote), this identification is furnished solely for informational purposes as a matter of convenience, without implication of approval, endorsement, or certification. Items capable of equal or better performance may be used if these characteristics have been validated.

Where the use of a centrifuge is indicated, unless otherwise specified, the directions are predicated upon the use of apparatus having an effective radius of about 20 cm (8 inches) and driven at a speed sufficient to clarify the supernatant layer within 15 minutes.

Unless otherwise specified, for chromatographic tubes and columns the diameter specified refers to internal diameter (ID); for other types of tubes and tubing the diameter specified refers to outside diameter (OD).

Steam Bath—Where the use of a steam bath is directed, exposure to actively flowing steam or to another form of regulated heat, corresponding in temperature to that of flowing steam, may be used.

Water Bath—Where the use of a water bath is directed without qualification with respect to temperature, a bath of vigorously boiling water is intended.

Foreign Substances and Impurities—Tests for the presence of foreign substances and impurities are provided to limit such substances to amounts that are unobjectionable under conditions in which the article is customarily employed (see also *Impurities in Official Articles* ⟨1086⟩).

While one of the primary objectives of the Pharmacopeia is to assure the user of official articles of their identity, strength, quality, and purity, it is manifestly impossible to include in each monograph a test for every impurity, contaminant, or adulterant that might be present, including microbial contamination. These may arise from a change in the source of material or from a change in the processing, or may be introduced from extraneous sources. Tests suitable for detecting such occurrences, the presence of which is inconsistent with applicable manufacturing practice or good pharmaceutical practice, should be employed in addition to the tests provided in the individual monograph.

Procedures—Assay and test procedures are provided for determining compliance with the Pharmacopeial standards of identity, strength, quality, and purity.

In performing the assay or test procedures in this Pharmacopeia, it is expected that safe laboratory practices will be followed. This includes the utilization of precautionary measures, protective equipment, and work practices consistent with the chemicals and procedures utilized. Prior to undertaking any assay or procedure described in this Pharmacopeia, the individual should be aware of the hazards associated with the chemicals and the procedures and means of protecting against them. This Pharmacopeia is not designed to describe such hazards or protective measures.

Every compendial article in commerce shall be so constituted that when examined in accordance with these assay and test procedures, it meets all of the requirements in the monograph defining it. However, it is not to be inferred that application of every analytical procedure in the monograph to samples from every production batch is necessarily a prerequisite for assuring compliance with Pharmacopeial standards before the batch is released for distribution. Data derived from manufacturing *process validation* studies and from *in-process controls* may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from an examination of finished units drawn from that batch. On the basis of such assurances, the analytical procedures in the monograph may be omitted by the manufacturer in judging compliance of the batch with the Pharmacopeial standards.

Automated procedures employing the same basic chemistry as those assay and test procedures given in the monograph are recognized as being equivalent in their suitability for determining compliance. Conversely, where an automated procedure is given in the monograph, manual procedures employing the same basic chemistry are recognized as being equivalent in their suitability for determining compliance. Compliance may be determined also by the use of alternative methods, chosen for advantages in accuracy, sensitivity, precision, selectivity, or adaptability to automation or computerized data reduction or in other special circumstances. Such alternative or automated procedures or methods shall be validated. However, Pharmacopeial standards and procedures are interrelated; therefore, where a difference appears or in the event of dispute, only the result obtained by the procedure given in this Pharmacopeia is conclusive.

In the performance of assay or test procedures, not less than the specified number of dosage units should be taken for analysis. Proportionately larger or smaller quantities than the specified weights and volumes of assay or test substances and Reference Standards may be taken, provided the measurement is made with at least equivalent accuracy and provided that any subsequent steps, such as dilutions, are adjusted accordingly to yield concentrations equivalent to those specified and are made in such manner as to provide at least equivalent accuracy.

Where it is directed in an assay or a test that a certain quantity of substance or a counted number of dosage units is to be examined, the specified quantity or number is a minimal figure (the singlet determination) chosen only for convenience of analytical manipulation; it is not intended to restrict the total quantity of substance or number of units that may be subjected to the assay or test or that should be tested in accordance with good manufacturing practices.

Where it is directed in the assay of Tablets to "weigh and finely powder not less than" a given number, usually 20, of the Tablets, it is intended that a counted number of Tablets shall be weighed and reduced to a powder. The portion of the powdered tablets taken for assay is representative of the whole Tablets and is, in turn, weighed accurately. The result of the assay is then related to the amount of active ingredient per Tablet by multiplying this result by the average Tablet weight and dividing by the weight of the portion taken for the assay.

Similarly, where it is directed in the assay of Capsules to remove, as completely as possible, the contents of not less than a given number, usually 20, of the Capsules, it is intended that a counted number of Capsules should be carefully opened and the contents quantitatively removed, combined, mixed, and weighed accurately. The portion of mixed Capsules contents taken for the assay is representative of the contents of the Capsules and is, in turn, weighed accurately. The result of the assay is then related to the amount of active ingredient per Capsule by multiplying this result by the average weight of Capsule content and dividing by the weight of the portion taken for the assay.

Where the definition in a monograph states the tolerances as being "calculated on the dried (or anhydrous or ignited) basis," the directions for drying or igniting the sample prior to assaying are generally omitted from the *Assay* procedure. Assay and test procedures may be performed on the undried or unignited substance and the results calculated on the dried, anhydrous, or ignited basis, provided a test for *Loss on drying*, or *Water*, or *Loss on ignition*, respectively, is given in the monograph. Where the presence of moisture or other volatile material may interfere with the procedure, previous drying of the substance is specified in the individual monograph and is obligatory.

Throughout a monograph that includes a test for *Loss on drying* or *Water*, the expression "previously dried" without qualification signifies that the substance is to be dried as directed under *Loss on drying* or *Water* (gravimetric determination).

Unless otherwise directed in the test or assay in the individual monograph or in a general chapter, USP Reference Standards are to be dried before use, or used without prior drying, specifically in accordance with the instructions given in the chapter *USP Reference Standards* ⟨11⟩, and on the label of the Reference Standard. Where the label instructions differ in detail from those in the chapter, the label text is determinative.

In stating the appropriate quantities to be taken for assays and tests, the use of the word "about" indicates a quantity within 10% of the specified weight or volume. However, the weight or volume taken is accurately determined and the calculated result is based upon the exact amount taken. The same tolerance applies to specified dimensions.

Where the use of a pipet is directed for measuring a specimen or an aliquot in conducting a test or an assay, the pipet conforms to the standards set forth under *Volumetric Apparatus* ⟨31⟩, and is to be used in such manner that the error does not exceed the limit stated for a pipet of its size. Where a pipet is specified, a suitable buret, conforming to the standards set forth under *Volumetric Apparatus* ⟨31⟩, may be substituted. Where a "to contain" pipet is specified, a suitable volumetric flask may be substituted.

Expressions such as "25.0 mL" and "25.0 mg," used with respect to volumetric or gravimetric measurements, indicate that the quantity is to be "accurately measured" or "accurately weighed" within the limits stated under *Volumetric Apparatus* ⟨31⟩ or under *Weights and Balances* ⟨41⟩.

The term "transfer" is used generally to specify a quantitative manipulation.

The term "concomitantly," used in such expressions as "concomitantly determine" or "concomitantly measured," in directions for assays and tests, is intended to denote that the determinations or measurements are to be performed in immediate succession. See also *Use of Reference Standards* under *Spectrophotometry and Light-scattering* ⟨851⟩.

Blank Determination—Where it is directed that "any necessary correction" be made by a blank determination, the determination is to be conducted using the same quantities of the same reagents treated in the same manner as the solution or mixture containing the portion of the substance under assay or test, but with the substance itself omitted.

Desiccator—The expression "in a desiccator" specifies the use of a tightly closed container of suitable size and design that maintains an atmosphere of low moisture content by means of silica gel or other suitable desiccant.

A "vacuum desiccator" is one that maintains the low-moisture atmosphere at a reduced pressure of not more than 20 mm of mercury or at the pressure designated in the individual monograph.

Dilution—Where it is directed that a solution be diluted "quantitatively and stepwise," an accurately measured portion is to be diluted by adding water or other solvent, in the proportion indicated, in one or more steps. The choice of apparatus to be used should take into account the relatively larger errors generally associated with using small-volume volumetric apparatus (see *Volumetric Apparatus* ⟨31⟩).

Drying to Constant Weight—The specification "dried to constant weight" means that the drying shall be continued until two consecutive weighings do not differ by more than 0.50 mg per g of substance taken, the second weighing following an additional hour of drying.

Filtration—Where it is directed to "filter," without further qualification, the intent is that the liquid be filtered through suitable filter paper or equivalent device until the filtrate is clear.

Identification Tests—The Pharmacopeial tests headed *Identification* are provided as an aid in verifying the identity of articles as they are purported to be, such as those taken from labeled containers. Such tests, however specific, are not necessarily sufficient to establish proof of identity; but failure of an article taken from a labeled container to meet the requirements of a prescribed identification test indicates that the article may be mislabeled. Other tests and specifications in the monograph often contribute to establishing or confirming the identity of the article under examination.

Ignition to Constant Weight—The specification "ignite to constant weight" means that the ignition shall be continued, at 800 ± 25° unless otherwise indicated, until two consecutive weighings do not differ by more than 0.50 mg per g of substance taken, the second weighing following an additional 15-minute ignition period.

Indicators—Where the use of a test solution ("TS") as an indicator is specified in a test or an assay, approximately 0.2 mL, or 3 drops, of the solution shall be added, unless otherwise directed.

Logarithms—Logarithms used in the assays are to the base 10.

Microbial Strains—Where a microbial strain is cited and identified by its ATCC catalog number, the specified strain shall be used directly or, if subcultured, shall be used not more than five passages removed from the original strain.

Negligible—This term indicates a quantity not exceeding 0.50 mg.

Odor—Terms such as "odorless," "practically odorless," "a faint characteristic odor," or variations thereof, apply to examination, after exposure to the air for 15 minutes, of either a freshly opened package of the article (for packages containing not more than 25 g) or (for larger packages) of a portion of about 25 g of the article that has been removed from its package to an open evaporating dish of about 100-mL capacity. An odor designation is descriptive only

and is not to be regarded as a standard of purity for a particular lot of an article.

Pressure Measurements—The term "mm of mercury" used with respect to measurements of blood pressure, pressure within an apparatus, or atmospheric pressure refers to the use of a suitable manometer or barometer calibrated in terms of the pressure exerted by a column of mercury of the stated height.

Solutions—Unless otherwise specified in the individual monograph, all solutions called for in tests and assays are prepared with *Purified Water.*

An expression such as "(1 in 10)" means that 1 part *by volume* of a liquid is to be diluted with, or 1 part *by weight* of a solid is to be dissolved in, sufficient of the diluent or solvent to make the volume of the finished solution 10 parts *by volume.*

An expression such as "(20:5:2)" means that the respective numbers of parts, by volume, of the designated liquids are to be mixed, unless otherwise indicated.

The notation "VS" after a specified volumetric solution indicates that such solution is standardized in accordance with directions given in the individual monograph or under *Volumetric Solutions* in the section *Reagents, Indicators, and Solutions,* and is thus differentiated from solutions of approximate normality or molarity.

Where a standardized solution of a specific concentration is called for in a test or an assay, a solution of other normality or molarity may be used, provided allowance is made for the difference in concentration and provided the error of measurement is not increased thereby.

Specific Gravity—Unless otherwise stated, the specific gravity basis is 25°/25°, i.e., the ratio of the weight of a substance in air at 25° to the weight of an equal volume of water at the same temperature.

Temperatures—Unless otherwise specified, all temperatures in this Pharmacopeia are expressed in centigrade (Celsius) degrees, and all measurements are made at 25°. See *Storage Temperature* under *Preservation, Packaging, Storage, and Labeling* for other definitions.

Time Limit—In the conduct of tests and assays, 5 minutes shall be allowed for the reaction to take place unless otherwise specified.

Vacuum—The term "in vacuum" denotes exposure to a pressure of less than 20 mm of mercury unless otherwise indicated.

Where drying in vacuum over a desiccant is directed in the individual monograph, a vacuum desiccator or a vacuum drying pistol, or other suitable vacuum drying apparatus, is to be used.

Water—Where water is called for in tests and assays, *Purified Water* is to be used unless otherwise specified. For special kinds of water such as "carbon dioxide–free water," see the introduction to the section *Reagents, Indicators, and Solutions.* For *High-purity Water* see *Containers* ⟨661⟩.

Water and *Loss on Drying*—Where the water of hydration or adsorbed water of a Pharmacopeial article is determined by the titrimetric method, the test is generally given under the heading *Water.* Monograph limits expressed as a percentage are figured on a weight/weight basis unless otherwise specified. Where the determination is made by drying under specified conditions, the test is generally given under the heading *Loss on drying.* However, *Loss on drying* is most often given as the heading where the loss in weight is known to represent residual volatile constituents including organic solvents as well as water.

Test Results, Statistics, and Standards—Interpretation of results from official tests and assays requires an understanding of the nature and style of compendial standards, in addition to an understanding of the scientific and mathematical aspects of laboratory analysis and quality assurance for analytical laboratories.

Confusion of compendial standards with release tests and with statistical sampling plans occasionally occurs. Compendial standards define what is an acceptable article and give test procedures that demonstrate that the article is in compliance. These standards apply at any time in the life of the article from production to consumption. The manufacturer's release specifications, and compliance with good manufacturing practices generally, are developed and followed to assure that the article will indeed comply with compendial standards until its expiration date, when stored as directed. Thus, when tested from the viewpoint of commercial or regulatory compliance, any specimen tested as directed in the monograph for that article shall comply (see *Test and Assays* under *General Notices*).

Tests and assays in this Pharmacopeia prescribe operation on a single specimen, that is, the singlet determination, which is the minimum sample on which the attributes of a compendial article should be measured. Some tests, such as those for *Dissolution* and *Uniformity of dosage units,* require multiple dosage units in conjunction with a decision scheme. These tests, albeit using a number of dosage units, are in fact the singlet determinations of those particular attributes of the specimen. These procedures should not be confused with statistical sampling plans. The compendial procedures demonstrate compliance of the attributes of an article with compendial standards for a specimen (of one or more dosage units) that is subjected to analysis. Repeats, replicates, statistical rejection of outliers, or extrapolations of results to larger populations are neither specified nor proscribed by the compendia; such decisions are dependent on the objectives of the testing. Commercial or regulatory compliance testing, or manufacturer's release testing, may or may not require examination of additional specimens, in accordance with predetermined guidelines or sampling strategies. Treatments of data handling are available from organizations such as ISO, IUPAC, and AOAC.

Description—Information on the "description" pertaining to an article, which is relatively general in

nature, is provided in the reference table *Description and Relative Solubility of USP and NF Articles* in this Pharmacopeia for those who use, prepare, and dispense drugs and/or related articles, solely to indicate properties of an article complying with monograph standards. The properties are not in themselves standards or tests for purity even though they may indirectly assist in the preliminary evaluation of an article.

Solubility—The statements concerning solubilities given in the reference table *Description and Relative Solubility of USP and NF Articles* for Pharmacopeial articles are not standards or tests for purity but are provided primarily as information for those who use, prepare, and dispense drugs and/or related articles. Only where a quantitative solubility test is given, and is designated as such, is it a test for purity.

The approximate solubilities of Pharmacopeial substances are indicated by the descriptive terms in the accompanying table.

Descriptive Term	Parts of Solvent Required for 1 Part of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble, or Insoluble	10,000 and over

Soluble Pharmacopeial articles, when brought into solution, may show traces of physical impurities, such as minute fragments of filter paper, fibers, and other particulate matter, unless limited or excluded by definite tests or other specifications in the individual monographs.

PRESCRIBING AND DISPENSING

Prescriptions for compendial articles shall be written to state the quantity and/or strength desired in metric units unless otherwise indicated in the individual monograph (see also *Units of Potency* in these *General Notices*). If an amount is prescribed by any other system of measurement, only an amount that is the metric equivalent of the prescribed amount shall be dispensed.

PRESERVATION, PACKAGING, STORAGE, AND LABELING

Containers—The *container* is that which holds the article and is or may be in direct contact with the article. The *immediate container* is that which is in direct contact with the article at all times. The *closure* is a part of the container.

Prior to its being filled, the container should be clean. Special precautions and cleaning procedures may be necessary to ensure that each container is clean and that extraneous matter is not introduced into or onto the article.

The container does not interact physically or chemically with the article placed in it so as to alter the strength, quality, or purity of the article beyond the official requirements.

The Pharmacopeial requirements for the use of specified containers apply also to articles as packaged by the pharmacist or other dispenser, unless otherwise indicated in the individual monograph.

Tamper-resistant Packaging—The container or individual carton of a sterile article intended for ophthalmic or otic use, except where extemporaneously compounded for immediate dispensing on prescription, shall be so sealed that the contents cannot be used without obvious destruction of the seal.

Articles intended for sale without prescription are also required to comply with the tamper-resistant packaging and labeling requirements of the FDA where applicable.

Preferably, the immediate container and/or the outer container or protective packaging utilized by a manufacturer or distributor for all dosage forms that are not specifically exempt is designed so as to show evidence of any tampering with the contents.

Light-resistant Container (see *Light Transmission* under *Containers* ⟨661⟩)—A light-resistant container protects the contents from the effects of light by virtue of the specific properties of the material of which it is composed, including any coating applied to it. Alternatively, a clear and colorless or a translucent container may be made light-resistant by means of an opaque covering, in which case the label of the container bears a statement that the opaque covering is needed until the contents are to be used or administered. Where it is directed to "protect from light" in an individual monograph, preservation in a light-resistant container is intended.

Where an article is required to be packaged in a light-resistant container, and if the container is made light-resistant by means of an opaque covering, a single-use, unit-dose container or mnemonic pack for dispensing may not be removed from the outer opaque covering prior to dispensing.

Well-closed Container—A well-closed container protects the contents from extraneous solids and from loss of the article under the ordinary or customary conditions of handling, shipment, storage, and distribution.

Tight Container—A tight container protects the contents from contamination by extraneous liquids, solids, or vapors, from loss of the article, and from efflorescence, deliquescence, or evaporation under the ordinary or customary conditions of handling, shipment, storage, and distribution, and is capable of tight re-closure. Where a tight container is specified, it may be replaced by a hermetic container for a single dose of an article.

A gas cylinder is a metallic container designed to hold a gas under pressure. As a safety measure, for carbon dioxide, cyclopropane, helium, nitrous oxide,

and oxygen, the Pin-index Safety System of matched fittings is recommended for cylinders of Size E or smaller.

NOTE—Where packaging and storage in a *tight container* or a *well-closed container* is specified in the individual monograph, the container utilized for an article when dispensed on prescription meets the requirements under *Containers—Permeation* ⟨671⟩.

Hermetic Container—A hermetic container is impervious to air or any other gas under the ordinary or customary conditions of handling, shipment, storage, and distribution.

Single-unit Container—A single-unit container is one that is designed to hold a quantity of drug product intended for administration as a single dose or a single finished device intended for use promptly after the container is opened. Preferably, the immediate container and/or the outer container or protective packaging shall be so designed as to show evidence of any tampering with the contents. Each single-unit container shall be labeled to indicate the identity, quantity and/or strength, name of the manufacturer, lot number, and expiration date of the article.

Single-dose Container (see also *Containers for Injections* under *Injections* ⟨1⟩)—A single-dose container is a single-unit container for articles intended for parenteral administration only. A single-dose container is labeled as such. Examples of single-dose containers include pre-filled syringes, cartridges, fusion-sealed containers, and closure-sealed containers when so labeled.

Unit-dose Container—A unit-dose container is a single-unit container for articles intended for administration by other than the parenteral route as a single dose, direct from the container.

Multiple-unit Container—A multiple-unit container is a container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion.

Multiple-dose Container (see also *Containers for Injections* under *Injections* ⟨1⟩)—A multiple-dose container is a multiple-unit container for articles intended for parenteral administration only.

Storage Temperature—Specific directions are stated in some monographs with respect to the temperatures at which Pharmacopeial articles shall be stored, when stability data indicate that storage at a lower or a higher temperature produces undesirable results. Such directions apply except where the label on an article states a different storage temperature on the basis of stability studies of that particular formulation. The conditions are defined by the following terms.

Freezer—A place in which the temperature is maintained thermostatically between −20° and −10° (−4° and 14°F).

Cold—Any temperature not exceeding 8° (46°F). A *refrigerator* is a cold place in which the temperature is maintained thermostatically between 2° and 8° (36° and 46°F).

Cool—Any temperature between 8° and 15° (46° and 59°F). An article for which storage in a *cool place* is directed may, alternatively, be stored in a *refrigerator*, unless otherwise specified by the individual monograph.

Room Temperature—The temperature prevailing in a working area.

Controlled Room Temperature—A temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25° (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°; and that allows for excursions between 15° and 30° (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses. Articles may be labeled for storage at "controlled room temperature" or at "up to 25°", or other wording based on the same mean kinetic temperature. The mean kinetic temperature is a calculated value that may be used as an isothermal storage temperature that simulates the nonisothermal effects of storage temperature variations. (See also *Stability* under *Pharmaceutical Dosage Forms* ⟨1151⟩.)

An article for which storage at *Controlled room temperature* is directed may, alternatively, be stored in a *cool place*, unless otherwise specified in the individual monograph or on the label.

Warm—Any temperature between 30° and 40° (86° and 104°F).

Excessive Heat—Any temperature above 40° (104°F).

Protection from Freezing—Where, in addition to the risk of breakage of the container, freezing subjects an article to loss of strength or potency, or to destructive alteration of its characteristics, the container label bears an appropriate instruction to protect the article from freezing.

Storage under Nonspecific Conditions—For articles, regardless of quantity, where no specific storage directions or limitations are provided in the individual monograph, it is to be understood that conditions of storage and distribution include protection from moisture, freezing, and excessive heat.

Labeling—The term "labeling" designates all labels and other written, printed, or graphic matter upon an immediate container of an article or upon, or in, any package or wrapper in which it is enclosed, except any outer shipping container. The term "label" designates that part of the labeling upon the immediate container.

A shipping container, unless such container is also essentially the immediate container or the outside of the consumer package, is exempt from the labeling requirements of this Pharmacopeia.

Articles in this Pharmacopeia are subject to compliance with such labeling requirements as may be promulgated by governmental bodies in addition to the Pharmacopeial requirements set forth for the articles.

Amount of Ingredient per Dosage Unit—The strength of a drug product is expressed on the con-

tainer label in terms of micrograms or milligrams or grams or percentage of the therapeutically active moiety or drug substance, whichever form is used in the title. Both the active moiety and drug substance names and their equivalent amounts are then provided in the labeling.

Pharmacopeial articles in capsule, tablet, or other unit dosage form shall be labeled to express the quantity of each active ingredient or recognized nutrient contained in each such unit. Pharmacopeial drug products not in unit dosage form shall be labeled to express the quantity of each active ingredient in each milliliter or in each gram, or to express the percentage of each such ingredient (see *Percentage Measurements*), except that oral liquids or solids intended to be constituted to yield oral liquids may, alternatively, be labeled in terms of each 5-milliliter portion of the liquid or resulting liquid. Unless otherwise indicated in a monograph or chapter, such declarations of strength or quantity shall be stated only in metric units (see also *Units of Potency* in these *General Notices*.

In order to help minimize the possibility of errors in the dispensing and administration of drugs, the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero (e.g., express as 4 mg [not 4.0 mg]). The quantity of active ingredient when expressed as a decimal number smaller than one shall be shown with a zero preceding the decimal point (e.g., express as 0.2 mg [not .2 mg]).

Labeling of Salts of Drugs—It is an established principle that Pharmacopeial articles shall have only one official name. For purposes of saving space on labels, and because chemical symbols for the most common inorganic salts of drugs are well known to practitioners as synonymous with the written forms, the following alternatives are permitted in labeling official articles that are salts: HCl for hydrochloride; HBr for hydrobromide; Na for sodium; and K for potassium. The symbols Na and K are intended for use in abbreviating names of the salts of organic acids; but these symbols are not used where the word Sodium or Potassium appears at the beginning of an official title (e.g., Phenobarbital Na is acceptable, but Na Salicylate is not to be written).

Labeling Vitamin-containing Products—The vitamin content of Pharmacopeial preparations shall be stated on the label in metric units per dosage unit. The amounts of vitamins A, D, and E may be stated also in USP Units. Quantities of vitamin A declared in metric units refer to the equivalent amounts of retinol (vitamin A alcohol). The label of a nutritional supplement shall bear an identifying lot number, control number, or batch number.

Labeling Parenteral and Topical Preparations—The label of a preparation intended for parenteral or topical use states the names of all added substances (see *Added Substances* in these General Notices, and see *Labeling* under *Injections* ⟨1⟩), and, in the case of parenteral preparations, also their amounts or proportions, except that for substances added for adjustment of pH or to achieve isotonicity, the label may indicate only their presence and the reason for their addition.

Labeling Electrolytes—The concentration and dosage of electrolytes for replacement therapy (e.g., sodium chloride or potassium chloride) shall be stated on the label in milliequivalents (mEq). The label of the product shall indicate also the quantity of ingredient(s) in terms of weight or percentage concentration.

Labeling Alcohol—The content of alcohol in a liquid preparation shall be stated on the label as a percentage (v/v) of C_2H_5OH.

Special Capsules and Tablets—The label of any form of Capsule or Tablet intended for administration other than by swallowing intact bears a prominent indication of the manner in which it is to be used.

Expiration Date—The label of an official drug product or nutritional supplement shall bear an expiration date. All articles shall display the expiration date so that it can be read by an ordinary individual under customary conditions of purchase and use. The expiration date shall be prominently displayed in high contrast to the background or sharply embossed, and easily understood (e.g., "EXP 6/89," "Exp. June 89," "Expires 6/89"). [NOTE—For additional information and guidance, refer to the Nonprescription Drug Manufacturers Association's *Voluntary Codes and Guidelines of the OTC Medicines Industry.*]

The monographs for some preparations state how the expiration date that shall appear on the label is to be determined. In the absence of a specific requirement in the individual monograph for a drug product or nutritional supplement, the label shall bear an expiration date assigned for the particular formulation and package of the article, with the following exception: the label need not show an expiration date in the case of a drug product or nutritional supplement packaged in a container that is intended for sale without prescription and the labeling of which states no dosage limitations, and which is stable for not less than 3 years when stored under the prescribed conditions.

Where an official article is required to bear an expiration date, such article shall be dispensed solely in, or from, a container labeled with an expiration date, and the date on which the article is dispensed shall be within the labeled expiry period. The expiration date identifies the time during which the article may be expected to meet the requirements of the Pharmacopeial monograph provided it is kept under the prescribed storage conditions. The expiration date limits the time during which the article may be dispensed or used. Where an expiration date is stated only in terms of the month and the year, it is a representation that the intended expiration date is the last day of the stated month.

For articles requiring constitution prior to use, a suitable beyond-use date for the constituted product shall be identified in the labeling.

In determining an appropriate period of time during which a prescription drug may be retained by a patient after its dispensing, the dispenser shall take into account, in addition to any other relevant factors, the nature of the drug; the container in which it was packaged by the manufacturer and the expiration date thereon; the characteristics of the patient's container, if the article is repackaged for dispensing; the expected storage conditions to which the article may be exposed; and the expected length of time of the course of therapy. Unless otherwise required, the dispenser may, on taking into account the foregoing, place on the label of a multiple-unit container a suitable beyond-use date to limit the patient's use of the article. Unless otherwise specified in the individual monograph, such beyond-use date shall be not later than (a) the expiration date on the manufacturer's container, or (b) one year from the date the drug is dispensed, whichever is earlier.

VEGETABLE AND ANIMAL SUBSTANCES

The requirements for vegetable and animal substances apply to the articles as they enter commerce; however, lots of such substances intended solely for the manufacture or isolation of volatile oils, alkaloids, glycosides, or other active principles may depart from such requirements.

Statements of the distinctive microscopic structural elements in powdered substances of animal or vegetable origin may be included in the individual monograph as a means of determining identity, quality, or purity.

Foreign Matter—Vegetable and animal substances are to be free from pathogenic organisms (see *Microbiological Attributes of Nonsterile Pharmaceutical Products* ⟨1111⟩), and are to be as free as reasonably practicable from microorganisms, insects, and other animal contamination, including animal excreta. They shall show no abnormal discoloration, abnormal odor, sliminess, or other evidence of deterioration.

The amount of foreign inorganic matter in vegetable or animal substances, estimated as *Acid-insoluble ash*, shall not exceed 2 percent of the weight of the substance, unless otherwise specified in the individual monograph.

Before vegetable substances are ground or powdered, stones, dust, lumps of soil, and other foreign inorganic matter are to be removed by mechanical or other suitable means.

In commerce it is seldom possible to obtain vegetable substances that are without some adherent or admixed, innocuous, foreign matter, which usually is not detrimental. No poisonous, dangerous, or otherwise noxious foreign matter or residues may be present. Foreign matter includes any part of the plant not specified as constituting the substance.

Preservation—Vegetable or animal substances may be protected from insect infestation or microbiological contamination by means of suitable agents or processes that leave no harmful residues.

WEIGHTS AND MEASURES

The International System of Units (SI) is used in this Pharmacopeia. The SI metric and other units, and the symbols commonly employed, are as follows.

Ci = curie	Eq = gram-equivalent weight (equivalent)
mCi = millicurie	mEq = milliequivalent
μCi = microcurie	mol = gram-molecular weight (mole)
nCi = nanocurie	Da = dalton (relative molecular mass)
Mrad = megarad	mmol = millimole
m = meter	Osmol = osmole
dm = decimeter	mOsmol = milliosmole
cm = centimeter	Hz = hertz
mm = millimeter	kHz = kilohertz
μm = micrometer (0.001 mm)	MHz = megahertz
nm = nanometer*	MeV = million electron volts
kg = kilogram	keV = kilo-electron volt
g = gram **	mV = millivolt
mg = milligram	psi = pounds per square inch
μg; mcg = microgram†	Pa = pascal
ng = nanogram	kPa = kilopascal
pg = picogram	*g* = gravity (in centrifugation)
dL = deciliter	
L = liter	
mL = milliliter; ‡	
μL = microliter	

* Formerly the symbol mμ (for millimicron) was used.

** The gram is the unit of mass that is used to measure quantities of materials. Weight, which is a measure of the gravitational force acting on the mass of a material, is proportional to, and may differ slightly from, its mass due to the effects of factors such as gravity, temperature, latitude, and altitude. The difference between mass and weight is considered to be insignificant for compendial assays and tests, and the term "weight" is used throughout *USP* and *NF*.

† Formerly the abbreviation mcg was used in the Pharmacopeial monographs; however, the symbol μg now is more widely accepted and thus is used in this Pharmacopeia. The term "gamma," symbolized by γ, is frequently used for microgram in biochemical literature.

NOTE—The abbreviation mcg is still commonly employed to denote microgram(s) in labeling and in prescription writing. Therefore, for purposes of labeling, "mcg" may be used to denote microgram(s).

‡ One milliliter (mL) is used herein as the equivalent of 1 cubic centimeter (cc).

The International System of Units (SI) is also used in all radiopharmaceutical monographs. The symbols commonly employed are as follows.

Bq = becquerel	GBq = gigabecquerel
kBq = kilobecquerel	Gy = gray
MBq = megabecquerel	mGy = milligray

CONCENTRATIONS

Molal, molar, and normal solution concentrations are indicated throughout this Pharmacopeia for most chemical assay and test procedures (see also *Volumetric Solutions* in the section, *Reagents, Indicators, and Solutions*). Molality is designated by the symbol *m* preceded by a number that is the number of moles of the designated solute contained in one kilogram of

the designated solvent. Molarity is designated by the symbol *M* preceded by a number that is the number of moles of the designated solute contained in an amount of the designated solvent that is sufficient to prepare one liter of solution. Normality is designated by the symbol *N* preceded by a number that is the number of equivalents of the designated solute contained in an amount of the designated solvent that is sufficient to prepare one liter of solution.

Percentage Measurements—Percentage concentrations are expressed as follows:

Percent weight in weight—(w/w) expresses the number of g of a constituent in 100 g of solution or mixture.

Percent weight in volume—(w/v) expresses the number of g of a constituent in 100 mL of solution, and is used regardless of whether water or another liquid is the solvent.

Percent volume in volume—(v/v) expresses the number of mL of a constituent in 100 mL of solution.

The term *percent* used without qualification means, for mixtures of solids and semisolids, percent weight in weight; for solutions or suspensions of solids in liquids, percent weight in volume; for solutions of liquids in liquids, percent volume in volume; and for solutions of gases in liquids, percent weight in volume. For example, a 1 percent solution is prepared by dissolving 1 g of a solid or semisolid, or 1 mL of a liquid, in sufficient solvent to make 100 mL of the solution.

In the dispensing of prescription medications, slight changes in volume owing to variations in room temperatures may be disregarded.

Apparatus

The apparatus[1] consists of a basket-rack assembly, a 1000-mL, ...form beaker for the immersion fluid, a thermostatic arrange... for heating the fluid between 35° and 39°, and a device ...sing and lowering the basket in the immersion fluid at a ...stant frequency rate between 29 and 32 cycles per minute ...ugh a distance of not less than 5.3 cm and not more than 5.7 ... The volume of the fluid in the vessel is such that at the ...est point of the upward stroke the wire mesh remains at least ... below the surface of the fluid and descends to not less ... 2.5 cm from the bottom of the vessel on the downward stroke. ...e time required for the upward stroke is equal to the time ...uired for the downward stroke, and the change in stroke di...tion is a smooth transition, rather than an abrupt reversal of ...tion. The basket-rack assembly moves vertically along its axis. ...re is no appreciable horizontal motion or movement of the ... from the vertical.

Basket-rack Assembly—The basket-rack assembly consists of ... open-ended transparent tubes, each 7.75 ± 0.25 cm long and ...ving an inside diameter of approximately 21.5 mm and a wall ...ximately 2 mm thick; the tubes are held in a vertical position ...two plastic plates, each about 9 cm in diameter and 6 mm in ...kness, with six holes, each about 24 mm in diameter, equi...ced from the center of the plate and equally spaced from one ...other. Attached to the under surface of the lower plate is 10-...h No. 23 (0.025-inch) W. and M. gauge woven stainless-steel ...re cloth having a plain square weave. The parts of the appa...tus are assembled and rigidly held by means of three bolts ...sing through the two plastic plates. A suitable means is pro...ed to suspend the basket-rack assembly from the raising and ...ering device using a point on its axis.

The design of the basket-rack assembly may be varied some...what provided the specifications for the glass tubes and the screen ...sh size are maintained.

Disks[2]—The use of disks is permitted only where specified in ...e monograph. If specified in the individual monograph, each ...e is provided with a slotted and perforated cylindrical disk ...1 ± 0.15 mm thick and 20.7 ± 0.15 mm in diameter. The ...k is made of a suitable, transparent plastic material having a ...ecific gravity of between 1.18 and 1.20. Five 2-mm holes ex...nd between the ends of the cylinder, one of the holes being ...ough the cylinder axis and the others parallel with it equally ...ced on a 6-mm radius from it. Equally spaced on the sides ...f the cylinder are four notches that form V-shaped planes that ...e perpendicular to the ends of the cylinder. The dimensions of ...ch notch are such that the openings on the bottom of the cyl...der are 1.60 mm square and those on the top are 9.5 mm wide ...d 2.55 mm deep. All surfaces of the disk are smooth. If the ...e of disks is specified in the individual monograph, add a disk ...each tube, and operate the apparatus as directed under *Pro...dure*.

Procedure

Uncoated Tablets—Place 1 tablet in each of the six tubes of ...e basket and operate the apparatus, using water maintained at ...7° as the immersion fluid unless otherwise specified in the ...ividual monograph. At the end of the time limit specified in ...e monograph, lift the basket from the fluid, and observe the ...ets: all of the tablets have disintegrated completely. If 1 or ...ablets fail to disintegrate completely, repeat the test on 12 ...itional tablets: not less than 16 of the total of 18 tablets tested ...disintegrate completely.

Plain Coated Tablets—Apply the test for *Uncoated Tablets*, ...rating the apparatus for the time specified in the individual ...graph.

Enteric-coated Tablets—Place 1 tablet in each of the six tubes ...the basket and, if the tablet has a soluble external coating, ...erse the basket in water at room temperature for 5 minutes. ...n operate the apparatus using simulated gastric fluid TS maintained at 37 ± 2° as the immersion fluid. After 1 hour of operation in simulated gastric fluid TS, lift the basket from the fluid, and observe the tablets: the tablets show no evidence of disintegration, cracking, or softening. Operate the apparatus, using simulated intestinal fluid TS maintained at 37 ± 2° as the immersion fluid, for the time specified in the monograph. Lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Buccal Tablets—Apply the test for *Uncoated Tablets*. After 4 hours, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Sublingual Tablets—Apply the test for *Uncoated Tablets*. Observe the tablets within the time limit specified in the individual monograph: all of the tablets have disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Hard Gelatin Capsules—Apply the test for *Uncoated Tablets*. Attach a removable 10-mesh wire cloth,[3] as described under *Basket-rack Assembly*, to the surface of the upper plate of the basket-rack assembly. Observe the capsules within the time limit specified in the individual monograph: all of the capsules have disintegrated except for fragments from the capsule shell. If 1 or 2 capsules fail to disintegrate completely, repeat the test on 12 additional capsules: not less than 16 of the total of 18 capsules tested disintegrate completely.

Soft Gelatin Capsules—Proceed as directed under *Hard Gelatin Capsules*.

[1] A suitable apparatus, meeting these specifications, is available from laboratory supply houses, from Van-Kel Industries, ... 36 Meridian Rd., Edison, NJ 08820, or from Hanson Re... Corp., P. O. Box 35, Northridge, CA 91324. ... meeting these specifications are obtainable from Van... Industries, Inc.

[3] A suitable wire cloth cover is available as Van-Kel Industries Part TT-1030.

⟨711⟩ DISSOLUTION

This test is provided to determine compliance with the dissolution requirements where stated in the individual monograph for a tablet or capsule dosage form, except where the label states that the tablets are to be chewed unless otherwise directed in the monograph. Where the label states that an article is enteric-coated, and a dissolution or disintegration test that does not specifically state that it is to be applied to enteric-coated articles is included in the individual monograph, the test for *Delayed-release Articles* under *Drug Release* ⟨724⟩ is applied unless otherwise specified in the individual monograph. Of the types of apparatus described herein, use the one specified in the individual monograph.

USP Reference Standards ⟨11⟩—*USP Prednisone Tablets RS* (*Dissolution Calibrator, Nondisintegrating*). *USP Salicylic Acid Tablets RS* (*Dissolution Calibrator, Nondisintegrating*).

Apparatus 1—The assembly consists of the following: a covered vessel made of glass or other inert, transparent material[1]; a motor; a metallic drive shaft; and a cylindrical basket. The vessel is partially immersed in a suitable water bath of any convenient size that permits holding the temperature inside the vessel at 37 ± 0.5° during the test and keeping the bath fluid in constant, smooth motion. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smoothly rotating stirring element. Apparatus that permits observation of the specimen and stirring element during the test is preferable. The vessel is cylindrical, with a hemispherical bottom. It is 160 to 175 mm high, its inside diameter is 98 to 106 mm, and its nominal capacity is 1000 mL. Its sides are flanged at the top. A fitted cover may be used to retard evaporation.[2] The shaft is

[1] The materials should not sorb, react, or interfere with the specimen being tested.

[2] If a cover is used, it provides sufficient openings to allow ready insertion of the thermometer and withdrawal of specimens.

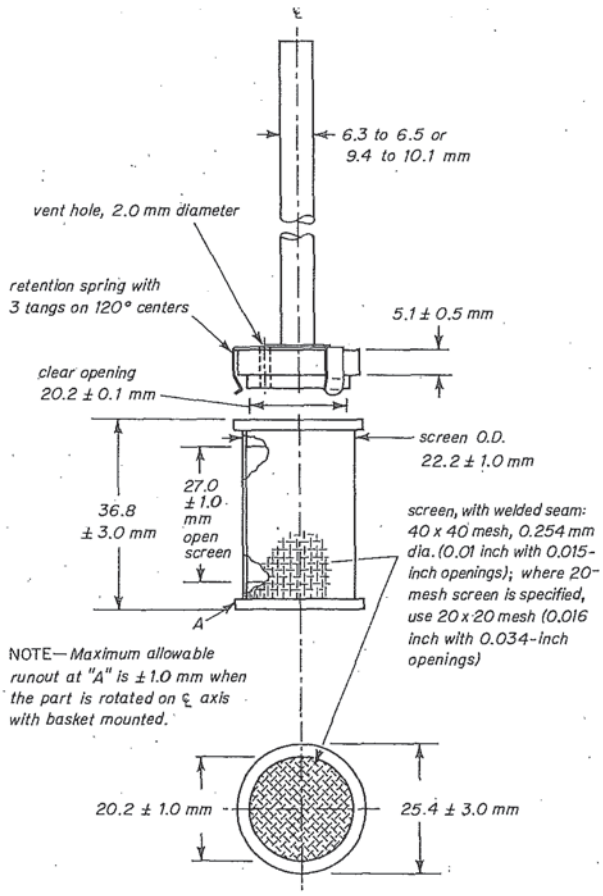


Fig. 1. Basket Stirring Element.

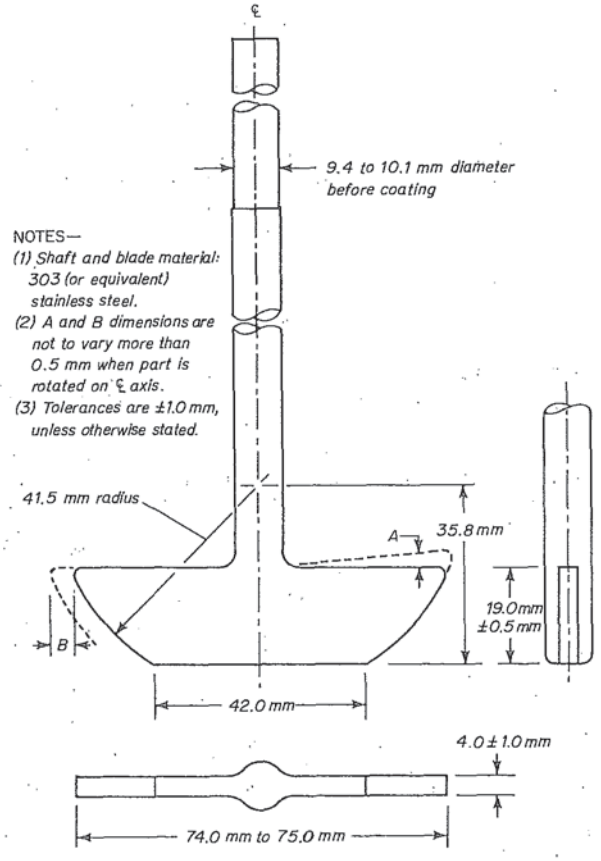


Fig. 2. Paddle Stirring Element.

positioned so that its axis is not more than 2 mm at any poi from the vertical axis of the vessel and rotates smoothly an without significant wobble. A speed-regulating device is use that allows the shaft rotation speed to be selected and maintaine at the rate specified in the individual monograph, within ±4%

Shaft and basket components of the stirring element are fa ricated of stainless steel, type 316 or equivalent, to the specif cations shown in Figure 1. Unless otherwise specified in the i dividual monograph, use 40-mesh cloth. A basket having a gol coating 0.0001 inch (2.5 μm) thick may be used. The dosag unit is placed in a dry basket at the beginning of each test. Th distance between the inside bottom of the vessel and the baske is maintained at 25 ± 2 mm during the test.

Apparatus 2—Use the assembly from *Apparatus 1*, except tha a paddle formed from a blade and a shaft is used as the stirrin element. The shaft is positioned so that its axis is not more tha 2 mm at any point from the vertical axis of the vessel, and rotate smoothly without significant wobble. The blade passes throug the diameter of the shaft so that the bottom of the blade is flus with the bottom of the shaft. The paddle conforms to the spec ifications shown in Figure 2. The distance of 25 ± 2 mm betwee the blade and the inside bottom of the vessel is maintained durin the test. The metallic blade and shaft comprise a single entit that may be coated with a suitable inert coating. The dosag unit is allowed to sink to the bottom of the vessel before rotatio of the blade is started. A small, loose piece of nonreactive ma terial such as not more than a few turns of wire helix may b attached to dosage units that would otherwise float.

Apparatus Suitability Test—Individually test 1 tablet of th *USP Dissolution Calibrator, Disintegrating Type* and 1 table of *USP Dissolution Calibrator, Nondisintegrating Type*, accord ing to the operating conditions specified. The apparatus is suit able if the results obtained are within the acceptable range state in the certificate for that calibrator in the apparatus tested.

Dissolution Medium—Use the solvent specified in the individ ual monograph. If the *Dissolution Medium* is a buffered solution, adjust the solution so that its pH is within 0.05 unit of the pH specified in the individual monograph. [NOTE—Dissolved gases can cause bubbles to form, which may change the results of the test. In such cases, dissolved gases should be removed prior to testing.[3]]

Time—Where a single time specification is given, the test may be concluded in a shorter period if the requirement for minimum amount dissolved is met. If two or more times are specified, specimens are to be withdrawn only at the stated times, within a tolerance of ±2%.

Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets—Place the stated volume of the *Dissolution Medium* in the vessel of the apparatus specified in the individual monograph, assemble the apparatus, equilibrate the *Dissolution Medium* to 37 ± 0.5°, and remove the thermometer. Place 1 tablet or 1 capsule in the apparatus, taking care to exclude air bubbles from the surface of the dosage-form unit, and immediately operate the apparatus at the rate specified in the individual monograph. Within the time interval specified, or at each of the times stated, withdraw a specimen from a zone midway between the surface of the *Dissolution Medium* and the top of the rotating basket or blade, not less than 1 cm from the vessel wall. [NOTE—Replace the aliquots withdrawn for analysis with equal volumes of fresh *Dissolution Medium* at 37° or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered for the duration of the test, and verify the temperature of the mixture under test at suitable times.] Perform the analysis as directed in the individual monograph.[4] Repeat the test with additional dosage form units.

[3] One method of deaeration is as follows: Heat the medium, while stirring gently, to about 45°, immediately filter under vacuum using a filter having a porosity of 0.45 μm or less, with vigorous stirring, and continue stirring under vacuum for about 5 minutes. Other validated deaeration techniques for removal of dissolved gases may be used.

[4] If test specimens are filtered, use an inert filter that does not cause adsorption of the active ingredient or contain extractable substances that would interfere with the analysis.

USP 23

Where capsule shells interfere with the analysis, remove the contents of not less than 6 capsules as completely as possible, and dissolve the empty capsule shells in the specified volume of *Dissolution Medium*. Perform the analysis as directed in the individual monograph. Make any necessary correction. Correction factors greater than 25% of the labeled content are unacceptable.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to the accompanying acceptance table. Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, Q, is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content; both the 5% and 15% values in the acceptance table are percentages of the labeled content so that these values and Q are in the same terms.

Acceptance Table

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is not less than $Q + 5\%$.
S_2	6	Average of 12 units ($S_1 + S_2$) is equal to or greater than Q, and no unit is less than $Q - 15\%$.
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is equal to or greater than Q, not more than 2 units are less than $Q - 15\%$, and no unit is less than $Q - 25\%$.

⟨721⟩ DISTILLING RANGE

To determine the range of temperatures within which an official liquid distils, or the percentage of the material that distils between two specified temperatures, use Method I or Method II as directed in the individual monograph. The *lower limit* of the range is the temperature indicated by the thermometer when the first drop of condensate leaves the tip of the condenser, and the *upper limit* is the Dry Point, i.e., the temperature at which the last drop of liquid evaporates from the lowest point in the distillation flask, without regard to any liquid remaining on the side of the flask, or the temperature observed when the proportion specified in the individual monograph has been collected.

[NOTE—Cool all liquids that distil below 80° to between 10° and 15° before measuring the sample to be distilled.]

METHOD I

Apparatus—Use apparatus similar to that specified for *Method II*, except that the distilling flask is of 50- to 60-mL capacity, and the neck of the flask is 10 to 12 cm long and 14 to 16 mm in internal diameter. The perforation in the upper asbestos board, if one is used, should be such that when the flask is set into it, the portion of the flask below the upper surface of the asbestos has a capacity of 3 to 4 mL.

Procedure—Proceed as directed for *Method II*, but place in the flask only 25 mL of the liquid to be tested.

METHOD II

Apparatus—Use an apparatus consisting of the following parts:

Distilling Flask—A round-bottom distilling flask, of heat-resistant glass, of 200-mL capacity, and having a total length of 17 to 19 cm and an inside neck diameter of 20 to 22 mm. Attached about midway on the neck, approximately 12 cm from the bottom of the flask, is a side-arm 10 to 12 cm long and 5 mm in internal diameter, which forms an angle of 70° to 75° with the lower portion of the neck.

Condenser—A straight glass condenser 55 to 60 cm in length with a water jacket about 40 cm in length, or a condenser of other design having equivalent condensing capacity. The lower end of the condenser may be bent to provide a delivery tube, or it may be connected to a bent adapter that serves as a delivery tube.

Asbestos Boards—Two pieces of asbestos board, 5 to 7 mm thick and 14 to 16 cm square, suitable for confining the heat to the lower part of the flask. Each board has a hole in its center, and the two boards differ only with respect to the diameter of the hole, i.e., the diameters are 4 and 10 cm, respectively. In use, the boards are placed one upon the other, and resting on a tripod or other suitable support, with the board having the larger hole on top.

Receiver—A 100-mL cylinder graduated in 1-mL subdivisions.

Thermometer—In order to avoid the necessity for an emergent stem correction, an accurately standardized, partial-immersion thermometer having the smallest practical subdivisions (not greater than 0.2°) is recommended. Suitable thermometers are available as the ASTM E-1 series 37C through 41C, and 102C through 107C (see *Thermometers* ⟨21⟩). When placed in position, the stem is located in the center of the neck and the top of the contraction chamber (or bulb, if 37C or 38C is used) is level with the bottom of the outlet to the side-arm.

Heat Source—A small Bunsen burner or an electric heater or mantle capable of adjustment comparable to that possible with a Bunsen burner.

Procedure—Assemble the apparatus, and place in the flask 100 mL of the liquid to be tested, taking care not to allow any of the liquid to enter the side-arm. Insert the thermometer, shield the entire burner and flask assembly from external air currents, and apply heat, regulating it so that between 5 and 10 minutes elapse before the first drop of distillate falls from the condenser. Continue the distillation at a rate of 4 to 5 mL of distillate per minute, collecting the distillate in the receiver. Note the temperature when the first drop of distillate falls from the condenser, and again when the last drop of liquid evaporates from the bottom of the flask or when the specified percentage has distilled over. Correct the observed temperature readings for any variation in the barometric pressure from the normal (760 mm), adding if the pressure is lower or subtracting if the pressure is higher than 760 mm, and apply the emergent stem correction where necessary. Unless otherwise specified in the individual monograph, allow 0.1° for each 2.7 mm (0.037° per mm) of variation.

⟨724⟩ DRUG RELEASE

This test is provided to determine compliance with drug-release requirements where specified in individual monographs. Use the apparatus specified in the individual monograph.

Apparatus 1 and Apparatus 2—

APPARATUS 1 AND APPARATUS 2—Proceed as directed under *Dissolution* ⟨711⟩.

Apparatus Suitability Test, Dissolution Medium, and Procedure—Proceed as directed under *Dissolution* ⟨711⟩. [NOTE—Replace the aliquots withdrawn for analysis with equal volumes of fresh *Dissolution Medium* at 37° or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered for the duration of the test, and verify the temperature of the mixture under test at suitable times.]

Extended-release Articles—General Drug Release Standard

Apparatus 3—

APPARATUS—The assembly consists of a set of cylindrical, flat-bottomed glass vessels; a set of glass reciprocating cylinders; stainless steel fittings (type 316 or equivalent) and polypropylene screens that are designed to fit the tops and bottoms of the reciprocating cylinders; and a motor and drive assembly to reciprocate the cylinders vertically inside the vessels and, if desired, index the reciprocating cylinders horizontally to a different row of vessels. The vessels are partially immersed in a suitable water bath of any convenient size that permits holding the temperature at 37 ± 0.5° during the test. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smooth, vertically reciprocating cylinder. An apparatus that permits observation of the specimens and reciprocating cylinders is

preferable. The components conform to the dimensions shown in Figure 1 unless otherwise specified in the individual monograph.

Dissolution Medium—Proceed as directed under *Dissolution* ⟨711⟩.

Procedure—Place the stated volume of the *Dissolution Medium* in each vessel of the apparatus, assemble the apparatus, equilibrate the *Dissolution Medium* to 37 ± 0.5°, and remove the thermometer. Place 1 dosage-form unit in each of the six reciprocating cylinders, taking care to exclude air bubbles from the surface of each dosage-form unit, and immediately operate the apparatus as specified in the individual monograph. During the upward and downward stroke, the reciprocating cylinder, moves through a total distance of 9.9 to 10.1 cm. Within the time interval specified, or at each of the times stated, raise the reciprocating cylinders and withdraw a portion of the solution under test from a zone midway between the surface of the *Dissolution Medium* and the bottom of each vessel. Perform the analysis as directed in the individual monograph. If necessary, repeat the test with additional dosage-form units.

Where capsule shells interfere with the analysis, remove the contents of not less than 6 capsules as completely as possible, and dissolve the empty capsule shells in the specified volume of *Dissolution Medium*. Perform the analysis as directed in the individual monograph. Make any necessary correction. Correction factors greater than 25% of the labeled content are unacceptable.

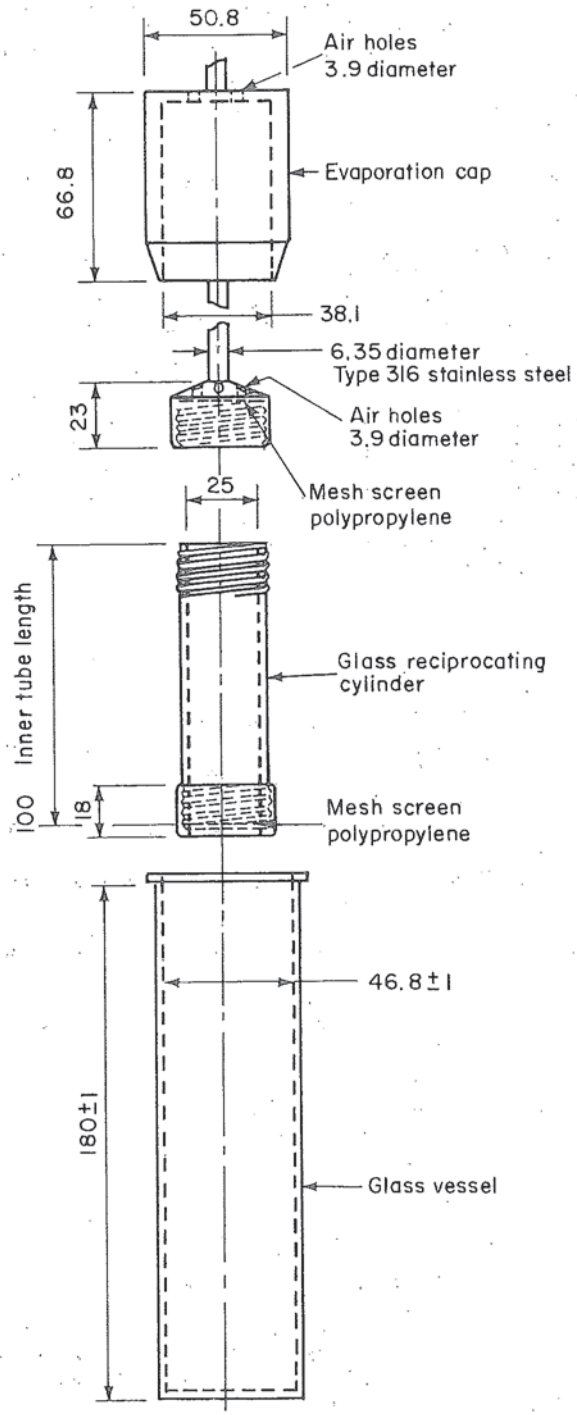


Fig. 1. Apparatus 3.
(All measurements are expressed in mm unless noted otherwise.)

Apparatus 4—

APPARATUS—The assembly consists of a reservoir and a pump for the *Dissolution Medium;* a flow-through cell; a water bath that maintains the *Dissolution Medium* at 37 ± 0.5° (see Figures 2 and 3). The cell size is specified in the individual monograph

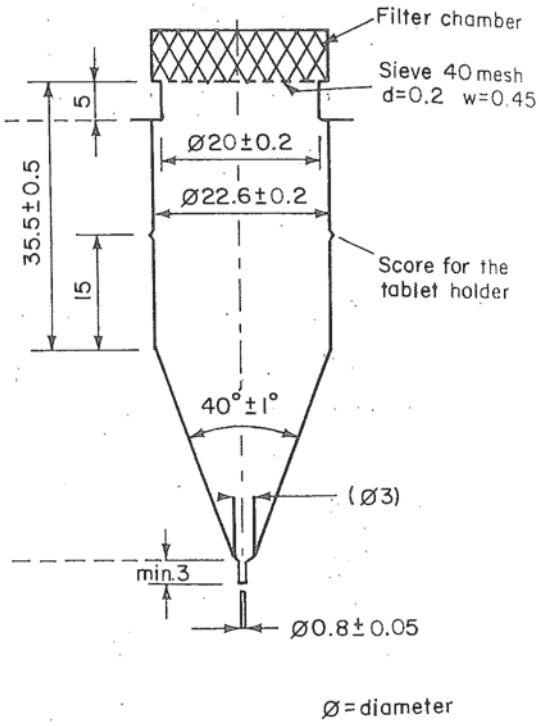


Fig. 2. Large cell for tablets and capsules.
(All measurements are expressed in mm unless noted otherwise.)

The pump forces the *Dissolution Medium* upwards through the flow-through cell. The pump has a delivery range between 240 and 960 mL per hour, with standard flow rates of 4, 8, and 16 mL per minute. It must be volumetric to deliver constant flow independent of flow resistance in the filter device; the flow profile is sinusoidal with a pulsation of 120 ± 10 pulses per minute.

The flow-through cell (see Figures 2 and 3), of transparent and inert material, is mounted vertically with a filter system (specified in the individual monograph) that prevents escape of undissolved particles from the top of the cell; standard cell diameters are 12 and 22.6 mm; the bottom cone is usually filled with small glass beads of about 1-mm diameter with one bead of about 5 mm positioned at the apex to protect the fluid entry tube; a tablet holder (see Figures 2a and 3a) is available for positioning of special dosage forms, for example, inlay tablets. The cell is immersed in a water bath and the temperature is maintained at 37 ± 0.5°.

The apparatus uses a clamp mechanism and two O-rings for the fixation of the cell assembly. The pump is separated from the dissolution unit in order to shield the latter against any vibrations originating from the pump. The position of the pump

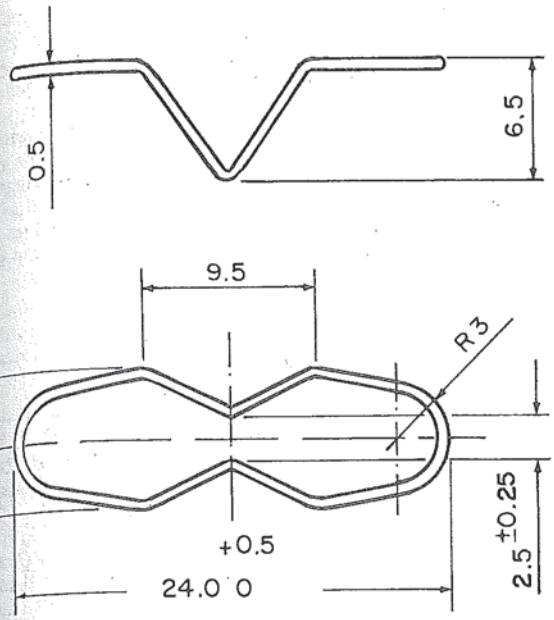


Fig. 2a. Tablet holder for the large cell. (All measurements are expressed in mm unless noted otherwise.)

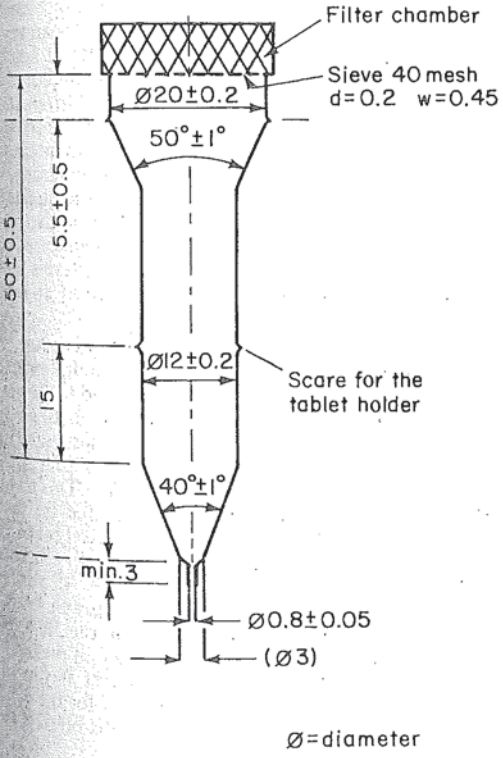


Fig. 3. Small cell for tablets and capsules. (All measurements are expressed in mm unless noted otherwise.)

uld not be on a level higher than the reservoir flasks. Tube nnections are as short as possible. Use polytef tubing with a 6mm inner diameter and chemically inert flanged-end con-ctions.

Apparatus Suitability Test and Dissolution Medium—Proceed directed under *Dissolution* ⟨711⟩.

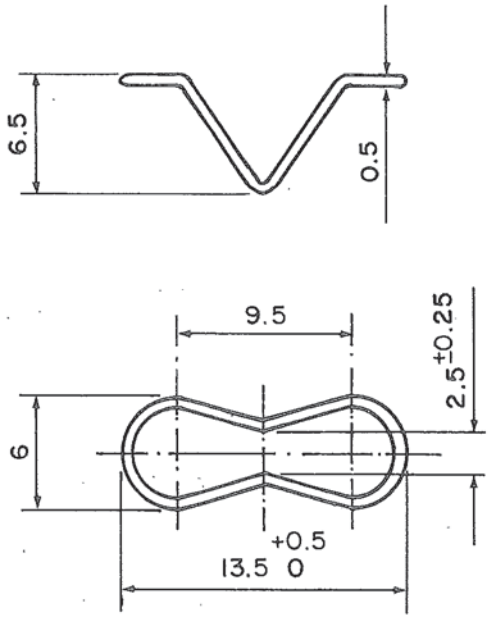


Fig. 3a. Tablet holder for the small cell. (All measurements are expressed in mm unless noted otherwise.)

Procedure—Place the glass beads into the cell specified in the monograph. Place 1 dosage-form unit on top of the beads or, if specified in the monograph, on a wire carrier. Assemble the filter head and fix the parts together by means of a suitable clamping device. Introduce by the pump the *Dissolution Medium* warmed to 37 ± 0.5° through the bottom of the cell to obtain the flow rate specified in the individual monograph and measured with an accuracy of 5%. Collect the eluate by fractions at each of the times stated. Perform the analysis as directed in the individual monograph. Repeat the test with additional dosage-form units.

Where capsule shells interfere with the analysis, remove the contents of not less than 6 capsules as completely as possible, and dissolve the empty capsule shells in the specified volume of *Dissolution Medium*. Perform the analysis as directed in the individual monograph. Make any necessary correction. Correction factors greater than 25% of the labeled content are unacceptable.

Time—The test-time points, generally three, are expressed in hours. Specimens are to be withdrawn within a tolerance of ±2% of the stated time.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to *Acceptance Table 1*. Continue testing through the three levels unless the results conform at either L_1 or L_2. Limits on the amounts of active ingredient dissolved are expressed in terms of the percentage of labeled content. The limits embrace each value of Q_i, the amount dissolved at each specified fractional dosing interval.

Delayed-release (Enteric-coated) Articles—General Drug Release Standard

Use *Method A* or *Method B* and the apparatus specified in the individual monograph. Conduct the *Apparatus Suitability Test* as directed under *Dissolution* ⟨711⟩. All test times stated are to be observed within a tolerance of ±2%, unless otherwise specified.

Method A:

Procedure (unless otherwise directed in the individual monograph)—

Acid Stage—Place 750 mL of 0.1 *N* hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5°. Place 1 tablet or 1 capsule in the apparatus, cover the vessel, and operate the apparatus for 2 hours at the rate specified in the monograph.

Acceptance Table 1

Level	Number Tested	Criteria
L_1	6	No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.
L_2	6	The average value of the 12 units ($L_1 + L_2$) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10% of labeled content outside each of the stated ranges; and none is more than 10% of labeled content below the stated amount at the final test time.
L_3	12	The average value of the 24 units ($L_1 + L_2 + L_3$) lies within each of the stated ranges, and is not less than the stated amount at the final test time; not more than 2 of the 24 units are more than 10% of labeled content outside each of the stated ranges; not more than 2 of the 24 units are more than 10% of labeled content below the stated amount at the final test time; and none of the units is more than 20% of labeled content outside each of the stated ranges or more than 20% of labeled content below the stated amount at the final test time.

After 2 hours of operation in 0.1 *N* hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed under *Buffer Stage*.

Perform an analysis of the aliquot using the *Procedure* specified in the test for *Drug release* in the individual monograph.

Unless otherwise specified in the individual monograph, the requirements of this portion of the test are met if the quantities, based on the percentage of the labeled content, of active ingredient dissolved from the units tested conform to *Acceptance Table 2*. Continue testing through all levels unless the results of both acid and buffer stages conform at an earlier level.

Acceptance Table 2

Level	Number Tested	Criteria
A_1	6	No individual value exceeds 10% dissolved.
A_2	6	Average of the 12 units ($A_1 + A_2$) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.
A_3	12	Average of the 24 units ($A_1 + A_2 + A_3$) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.

Buffer Stage—[NOTE—Complete the operations of adding the buffer, and adjusting the pH within 5 minutes.] With the apparatus operating at the rate specified in the monograph, add to the fluid in the vessel 250 mL of 0.20 *M* tribasic sodium phosphate that has been equilibrated to 37 ± 0.5°. Adjust, if necessary, with 2 *N* hydrochloric acid or 2 *N* sodium hydroxide to a pH of 6.8 ± 0.05. Continue to operate the apparatus for 45 minutes, or for the time specified in the individual monograph. At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis using the *Procedure* specified in the test for *Drug release* in the individual monograph. The test may be concluded in a shorter time period than that specified for the *Buffer Stage* if the requirement for minimum amount dissolved is met at an earlier time.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to *Acceptance Table 3*. Continue testing through the three levels unless the results of both stages conform at an earlier level. The value of *Q* in *Acceptance Table 3* is 75% dissolved unless otherwise specified in the individual monograph. The quantity, *Q*, specified in the individual monograph, is the total amount of active ingredient dissolved in both the acid and buffer stages, expressed as a percentage of the labeled content. The 5% and 15% values in *Acceptance Table 3* are percentages of the labeled content so that these values and *Q* are in the same terms.

Acceptance Table 3

Level	Number Tested	Criteria
B_1	6	Each unit is not less than $Q + 5\%$.
B_2	6	Average of 12 units ($B_1 + B_2$) is equal to or greater than *Q*, and no unit is less than $Q - 15\%$.
B_3	12	Average of 24 units ($B_1 + B_2 + B_3$) is equal to or greater than *Q*, not more than 2 units are less than $Q - 15\%$, and no unit is less than $Q - 25\%$.

Method B:

Procedure (unless otherwise directed in the individual monograph)—

Acid Stage—Place 1000 mL of 0.1 *N* hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5°. Place 1 tablet or 1 capsule in the apparatus, cover the vessel, and operate the apparatus for 2 hours at the rate specified in the monograph. After 2 hours of operation in 0.1 *N* hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed under *Buffer Stage*.

Perform an analysis of the aliquot using the *Procedure* specified in the test for *Drug release* in the individual monograph.

Unless otherwise specified in the individual monograph, the requirements of this portion of the test are met if the quantities, based on the percentage of the labeled content, of active ingredient dissolved from the units tested conform to *Acceptance Table 2* under *Method A*. Continue testing through all levels unless the results of both acid and buffer stages conform at an earlier level.

Buffer Stage—[NOTE—For this stage of the procedure, use buffer that previously has been equilibrated to a temperature of 37 ± 0.5°.] Drain the acid from the vessel, and add to the vessel 1000 mL of pH 6.8 phosphate buffer, prepared by mixing 0.1 *N* hydrochloric acid with 0.20 *M* tribasic sodium phosphate (3:1) and adjusting, if necessary, with 2 *N* hydrochloric acid or 2 *N* sodium hydroxide to a pH of 6.8 ± 0.05. [NOTE—This may be accomplished also by removing from the apparatus the vessel containing the acid and replacing it with another vessel containing the buffer and transferring the dosage unit to the vessel containing the buffer.] Continue to operate the apparatus for 45 minutes, or for the time specified in the individual monograph. At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis using the *Procedure* specified in the test for *Drug release* in the individual monograph. The test may be concluded in a shorter time period than that specified for the *Buffer stage* if the requirement for minimum amount dissolved is met at an earlier time.

Interpretation—Proceed as directed for *Interpretation* under *Method A*.

Transdermal Delivery Systems—General Drug Release Standards

Time—The test-time points, generally three, are expressed in terms of the labeled dosing interval, *D*, expressed in hours. Specimens are to be withdrawn within a tolerance of ±15 minutes or ±2% of the stated time, the tolerance that results in the narrowest time interval being selected.

Apparatus 5—

PADDLE OVER DISK—

APPARATUS—Use the paddle and vessel assembly from *Apparatus 2* as described under *Dissolution* ⟨711⟩, with the addition of a stainless steel disk assembly[1] designed for holding the transdermal system at the bottom of the vessel. The temperature is maintained at 32 ± 0.5°. A distance of 25 ± 2 mm between the paddle blade and the surface of the disk assembly is maintained during the test. The vessel may be covered during the test to minimize evaporation. The disk assembly for holding the transdermal system is designed to minimize any "dead" volume between the disk assembly and the bottom of the vessel. The disk assembly holds the system flat and is positioned such that the release surface is parallel with the bottom of the paddle blade (see Figure 4).

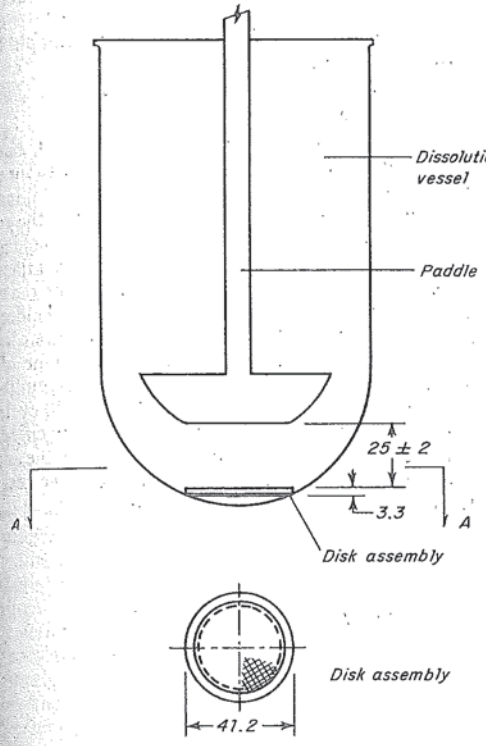


Fig. 4. Paddle Over Disk.
(All measurements are expressed in mm unless noted otherwise.)

Apparatus Suitability Test and Dissolution Medium—Proceed as directed for *Apparatus 2* under *Dissolution* ⟨711⟩.

Procedure—Place the stated volume of the *Dissolution Medium* in the vessel, assemble the apparatus without the disk assembly, and equilibrate the medium to 32 ± 0.5°. Apply the transdermal system to the disk assembly, assuring that the release surface of the system is as flat as possible. The system may be attached to the disk by applying a suitable adhesive[2] to the disk assembly. Dry for 1 minute. Press the system, release surface up, onto the adhesive-coated side of the disk assembly. If a membrane[3] is used to support the system, it is applied so that no air bubbles occur between the membrane and the release surface. Place the disk assembly flat at the bottom of the vessel with the release surface facing up and parallel to the edge of the paddle blade and surface of the *Dissolution Medium*. The bottom edge of the paddle is 25 ± 2 mm from the surface of the disk assembly. Immediately operate the apparatus at the rate specified in the monograph. At each sampling time interval, withdraw a specimen from a zone midway between the surface of the *Dissolution Medium* and the top of the blade, not less than 1 cm from the vessel wall. Perform the analysis on each sampled aliquot as directed in the individual monograph, correcting for any volume losses, as necessary. Repeat the test with additional transdermal systems.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient released from the system conform to *Acceptance Table 4* for transdermal drug delivery systems. Continue testing through the three levels unless the results conform at either L_1 or L_2.

Acceptance Table 4

Level	Number Tested	Criteria
L_1	6	No individual value lies outside the stated range.
L_2	6	The average value of the 12 units (L_1 + L_2) lies within the stated range. No individual value is outside the stated range by more than 10% of the average of the stated range.
L_3	12	The average value of the 24 units (L_1 + L_2 + L_3) lies within the stated range. Not more than 2 of the 24 units are outside the stated range by more than 10% of the average of the stated range; and none of the units is outside the stated range by more than 20% of the average of the stated range.

Apparatus 6—Cylinder—

APPARATUS—Use the vessel assembly from *Apparatus 1* as described under *Dissolution* ⟨711⟩, except to replace the basket and shaft with a stainless steel cylinder stirring element and to maintain the temperature at 32 ± 0.5° during the test. The shaft and cylinder components of the stirring element are fabricated of stainless steel to the specifications shown in Figure 5. The dosage unit is placed on the cylinder at the beginning of each test. The distance between the inside bottom of the vessel and the cylinder is maintained at 25 ± 2 mm during the test.

Dissolution Medium—Use the medium specified in the individual monograph (see *Dissolution* ⟨711⟩).

Procedure—Place the stated volume of the *Dissolution Medium* in the vessel of the apparatus specified in the individual monograph, assemble the apparatus, and equilibrate the *Dissolution Medium* to 32 ± 0.5°. Unless otherwise directed in the individual monograph, prepare the test system prior to test as follows. Remove the protective liner from the system, and place the adhesive side on a piece of Cuprophan[3] that is not less than 1 cm larger on all sides than the system. Place the system, Cuprophan covered side down, on a clean surface, and apply a suitable adhesive[2] to the exposed Cuprophan borders. If necessary, apply additional adhesive to the back of the system. Dry for 1 minute. Carefully apply the adhesive-coated side of the system to the exterior of the cylinder such that the long axis of the system fits around the circumference of the cylinder. Press the Cuprophan covering to remove trapped air bubbles. Place the cylinder in the apparatus, and immediately rotate at the rate specified in the individual monograph. Within the time interval specified, or at each of the times stated, withdraw a quantity of *Dissolution Medium* for analysis from a zone midway between the surface of the *Dissolution Medium* and the top of the rotating cylinder, not less than 1 cm from the vessel wall. Perform the analysis as directed in the individual monograph, correcting for any volume losses as necessary. Repeat the test with additional transdermal drug delivery systems.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient released from the system conform to *Acceptance Table*

[1] Disk assembly (stainless support disk) may be obtained from Hanson Corp., Ashley Rd., Bedford, MA 01730. Other appropriate devices may be used, provided they do not react with, or interfere with the specimen being tested.

[2] Use Dow Corning, 355 Medical Adhesive 18.5% in Freon or the equivalent.

[3] Use Cuprophan, Type 150 pm, 11 ± 0.5-μm thick, an inert, porous cellulosic material, which is available from ENKA AG, or Castle Cove Circle, Corona DelMar, CA 92625, or LifeMed 2107 Delano Blvd., Compton, CA 90220.

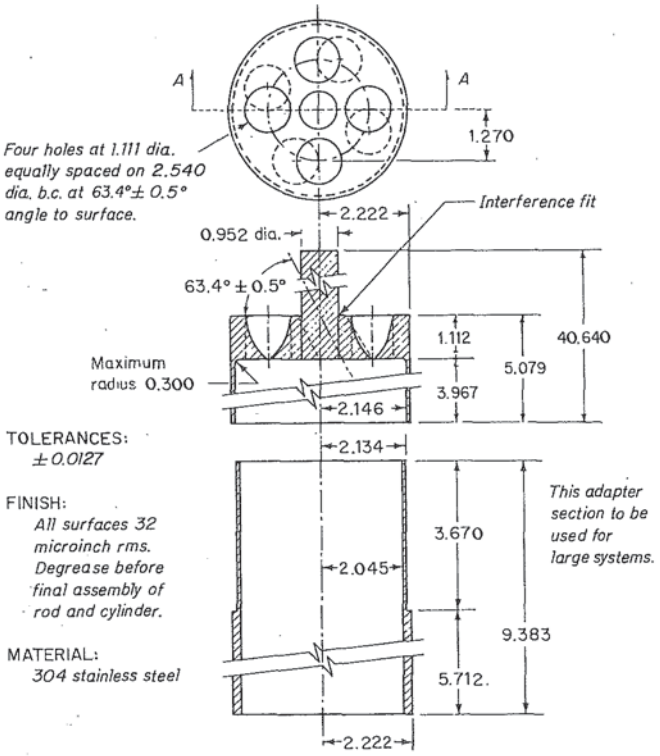


Fig. 5. Cylinder Stirring Element.[4]
(All measurements are expressed in cm unless noted otherwise.)

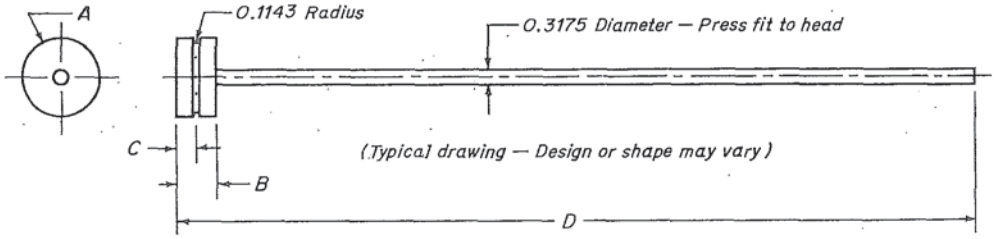
4 for transdermal drug delivery systems. Continue testing through the three levels unless the results conform at either L_1 or L_2.

Apparatus 7—Reciprocating Disk—[NOTE—This apparatus may also be specified for use with solid oral dosage forms.]

APPARATUS—The assembly consists of a set of volumetrically calibrated or tared solution containers made of glass or other suitable inert material,[5] a motor and drive assembly to reciprocate the system vertically and to index the system horizontally to a different row of vessels automatically if desired, and a set of disk-shaped sample holders (see Figure 6). The solution containers are partially immersed in a suitable water bath of any convenient size that permits maintaining the temperature inside the containers at 32 ± 0.5° during the test. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smooth, vertically reciprocating sample holder. Apparatus that permits observation of the system and holder during the test is preferable. Use the size container and sample holder as specified in the individual monograph.

Dissolution Medium—Use the *Dissolution Medium* specified in the individual monograph (see *Dissolution* ⟨711⟩).

Procedure—Remove the transdermal system from its backing. Press the system onto a dry, unused piece of Cuprophan[3] or equivalent with the adhesive side against the Cuprophan, taking care to eliminate air bubbles between the Cuprophan and the release surface. Attach the system to a suitable size sample holder with a suitable O-ring such that the back of the system is adjacent to and centered on the bottom of the sample holder. Trim the excess Cuprophan with a sharp blade. Suspend each sample holder from a vertically reciprocating shaker such that each system is continuously immersed in an accurately measured volume of *Dissolution Medium* within a calibrated container pre-equilibrated to 32 ± 0.5°. Reciprocate at a frequency of about 30 cycles per minute with an amplitude of about 1.9 cm for the specified time in the medium specified for each time point. Perform the analysis as directed in the individual monograph. Repeat the test with additional transdermal drug delivery systems.



Dimensions are in centimeters.

System[a]	HEAD				ROD		O-RING
	A (Diameter)	*B*	*C*	Material[b]	*D*	Material[c]	*(not shown)*
1.6 cm²	1.428	0.9525	0.4750	SS/VT	30.48	SS/P	Parker 2-113-V884-75
2.5 cm²	1.778	0.9525	0.4750	SS/VT	30.48	SS/P	Parker 2-016-V884-75
5 cm²	2.6924	0.7620	0.3810	SS/VT	8.890	SS/P	Parker 2-022-V884-75
7 cm²	3.1750	0.7620	0.3810	SS/VT	30.48	SS/P	Parker 2-124-V884-75
10 cm²	5.0292	0.6350	0.3505	SS/VT	31.01	SS/P	Parker 2-225-V884-75

[a] Typical system sizes.
[b] SS/VT = Either stainless steel or virgin Teflon.
[c] SS/P = Either stainless steel or Plexiglas.

Fig. 6. Reciprocating Disk Sample Holder.[6]

[4] The cylinder stirring element is available from Accurate Tool, Inc., 25 Diaz St., Stamford, CT 06907, or from Van-Kel Industries, Inc., 36 Meridian Rd., Edison, NJ 08820.

[5] The materials should not sorb, react with, or interfere with the specimen being tested.

[6] The reciprocating disk sample holder may be purchased from ALZA Corp., 950 Page Mill Rd., Palo Alto, CA 94304 or Van-Kel Industries, Inc.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient released from the system conform to *Acceptance Table 1* for transdermal drug delivery systems. Continue testing through the three levels unless the results conform at either L_1 or L_2.

⟨726⟩ ELECTROPHORESIS

Electrophoresis refers to the migration of electrically charged proteins, colloids, molecules, or other particles when dissolved or suspended in an electrolyte through which an electric current is passed.

Based upon the type of apparatus used, electrophoretic methods may be divided into two categories, one called *free solution* or moving boundary electrophoresis and the other called *zone electrophoresis*.

In the *free solution* method, a buffered solution of proteins in a U-shaped cell is subjected to an electric current which causes the proteins to form a series of layers in order of decreasing mobility, which are separated by boundaries. Only a part of the fastest moving protein is physically separated from the other proteins, but examination of the moving boundaries using a schlieren optical system provides data for calculation of mobilities and information on the qualitative and quantitative composition of the protein mixture.

In *zone electrophoresis*, the sample is introduced as a narrow zone or spot in a column, slab, or film of buffer. Migration of the components as narrow zones permits their complete separation. Remixing of the separated zones by thermal convection is prevented by stabilizing the electrolyte in a porous matrix such as a powdered solid, or a fibrous material such as paper, or a gel such as starch, agar, or polyacrylamide.

Various methods of zone electrophoresis are widely employed. *Gel electrophoresis*, particularly the variant called *disk electrophoresis*, is especially useful for protein separation because of its high resolving power.

Gel electrophoresis, which is employed by the compendium, is discussed in more detail following the presentation of some theoretical principles and methodological practices, which are shared to varying degrees by all electrophoretic methods.

The electrophoretic migration observed for particles of a particular substance depends on characteristics of the particle, primarily its electrical charge, its size or molecular weight, and its shape, as well as characteristics and operating parameters of the system. These latter include the pH, ionic strength, viscosity and temperature of the electrolyte, density or cross-linking of any stabilizing matrix such as gel, and the voltage gradient employed.

Effect of Charge, Particle Size, Electrolyte Viscosity, and Voltage Gradient—Electrically charged particles migrate toward the electrode of opposite charge, and molecules with both positive and negative charges move in a direction dependent on the net charge. The rate of migration is directly related to the magnitude of the net charge on the particle and is inversely related to the size of the particle, which in turn is directly related to its molecular weight.

Very large spherical particles, for which Stokes' law is valid, exhibit an electrophoretic mobility, u_0, which is inversely related to the first power of the radius as depicted in the equation:

$$u_0 = \frac{v}{E} = \frac{Q}{6\pi r\eta},$$

where v is the velocity of the particle, E is the voltage gradient imposed on the electrolyte, Q is the charge on the particle, r is the particle radius, and η is the viscosity of the electrolyte. This idealized expression is strictly valid only at infinite dilution and in the absence of a stabilizing matrix such as paper or a gel.

Ions, and peptides up to molecular weights of at least 5000, particularly in the presence of stabilizing media, do not obey Stokes' law, and their electrophoretic behavior is best described by an equation of the type:

$$u_0 = \frac{Q}{A\pi r^2\eta},$$

where A is a shape factor generally in the range of 4 to 6, which shows an inverse dependence of the mobility on the square of the radius. In terms of molecular weight, this implies an inverse dependence of mobility on the ⅔ power of the molecular weight.

Effect of pH—The direction and rate of migration of molecules containing a variety of ionizable functional groups, such as amino acids and proteins, depends upon the pH of the electrolyte. For instance, the mobility of a simple amino acid such as glycine varies with pH approximately as shown in Figure 1. The pK_a values of 2.2 and 9.9 coincide with the inflection points of the sigmoid portions of the plot. Since the respective functional groups are 50% ionized at the pH values where pH = pK_a, the electrophoretic mobilities at these points are half of the value observed for the fully ionized cation and anion obtained at very low and very high pH, respectively. The zwitterion that exists at the intermediate pH range is electrically neutral and has zero mobility.

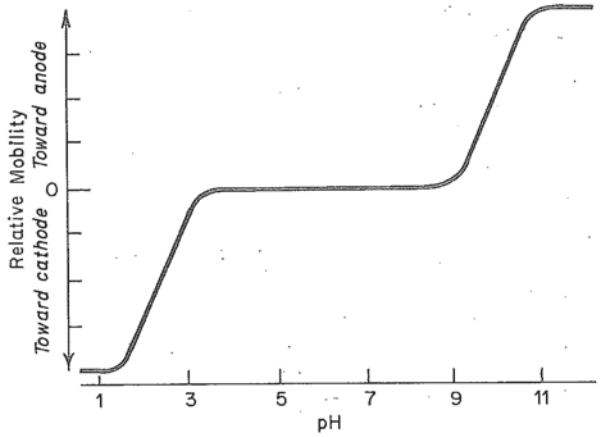


Fig. 1.

Effect of Ionic Strength and Temperature—Electrophoretic mobility decreases with increasing ionic strength of the supporting electrolyte. Ionic strength, μ, is defined as:

$$\mu = 0.5\Sigma C_i Z_i^2,$$

where C_i is the concentration of an ion in moles per liter and Z_i is its valence, and the sum is calculated for all ions in the solution. For buffers in which both the anion and cation are univalent, ionic strength is identical with molarity.

Ionic strengths of electrolytes employed in electrophoresis commonly range from about 0.01 to 0.10. A suitable strength is somewhat dependent on the sample composition, since the buffer capacity must be great enough to maintain a constant pH over the area of the component zones. Zones become sharper or more compact as ionic strength is increased.

Temperature affects mobility indirectly, since the viscosity, η, of the supporting electrolyte is temperature-dependent. The viscosity of water decreases at a rate of about 3% per °C in the range of 0° to 5° and at a slightly lower rate in the vicinity of room temperature. Mobility, therefore, increases with increasing electrolyte temperature.

Considerable heat is evolved as a result of current passing through the supporting electrolyte. This heat increases with the applied voltage and with increasing ionic strength. Particularly in larger apparatus, despite the circulation of a coolant, this heat produces a temperature gradient across the bed which may lead to distortion of the separated zones. Therefore, practical considerations and the design of the particular apparatus dictate the choice of ionic strength and operating voltage.

Effect of a Stabilizing Medium, Electroosmosis—When an electrical current is passed through an electrolyte contained in a glass tube or contained between plates of glass or plastic, a bulk flow of the electrolyte toward one of the electrodes is observed. This flow is called electroosmosis. It results from the surface charge on the walls of the apparatus, which arises either from ionizable functional groups inherent in the structural material or from ions adsorbed on the cell walls from the electrolyte contacting them. The effect is usually increased when the cell is

and uniformity in drug nomenclature. In support of the U. S. Adopted Names program (see *Preface*), of which the U. S. Pharmacopeial Convention is a co-sponsor, the USP Committee of Revision gives consideration to the adoption of the U. S. Adopted Name, if any, as the official title for any compound that attains compendial recognition.

A compilation of the U. S. Adopted Names (USAN) published from the start of the USAN program in 1961, as well as other names for drugs, both current and retrospective, is provided in *USAN and the USP Dictionary of Drug Names*. This publication is intended to serve as a book of names useful for identifying and distinguishing all kinds of names for drugs, whether public or proprietary or chemical or code-designated names.[2]

A nonproprietary name of a drug serves numerous and varied purposes, its principal function being to identify the substance to which it applies by means of a designation that may be used by the professional and lay public free from the restrictions associated with registered trademarks. Teaching in pharmacy and medicine requires a common designation, especially for a drug that is available from several sources or is incorporated into a combination drug product; nonproprietary names facilitate communication among physicians; nonproprietary names must be used as the titles of the articles recognized by official drug compendia; a nonproprietary name is essential to the pharmaceutical manufacturer as a means of protecting trademark rights in the brand name for the article concerned; and, finally, the manufacturer is obligated by federal law to include the established nonproprietary name in advertising and labeling.

Under the terms of the Drug Amendments of 1962 to the Federal Food, Drug, and Cosmetic Act, which became law October 10, 1962, the Secretary of Health and Human Services is authorized to designate an official name for any drug wherever deemed "necessary or desirable in the interest of usefulness and simplicity."[3]

The Commissioner of Food and Drugs and the Secretary of Health and Human Services published in the *Federal Register* regulations effective November 26, 1984, which state, in part:

Sec. 299.4 Established names of drugs.

(e) "The Food and Drug Administration will not routinely designate official names under section 508 of the act. As a result, the established name under section 502(e) of the act will ordinarily be either the compendial name of the drug or, if there is no compendial name, the common or usual name of the drug. Interested persons, in the absence of the designation by the Food and Drug Administration of an official name, may rely on as the established name for any drug the current compendial name or the USAN adopted name listed in *USAN and the USP Dictionary of Drug Names*. . . ."[4]

It will be noted that the monographs on the biologics, which are produced under licenses issued by the Secretary of the U. S. Department of Health and Human Services, represent a special case. Although efforts continue toward achieving uniformity, there may be a difference between the respective title required by federal law and the USP title. Such differences are fewer than in past revisions of the Pharmacopeia. The USP title, where different from the FDA Bureau of Biologics title, does not constitute a synonym for labeling purposes; the conditions of licensing the biologic concerned require that each such article be designated by the name appearing in the product license issued to the manufacturer. Where a USP title differs from the title in the federal regulations, the former has been adopted with a view to usefulness and simplicity and conformity with the principles governing the selection of monograph titles generally.

[2] *USAN and the USP Dictionary of Drug Names* is obtainable on order from the USAN Division, USP Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852.

[3] F.D.&C. Act, Sec. 508 [358].

[4] 53 Fed. Reg. 5369 (1988) amending 21 CFR § 299.4.

⟨1151⟩ PHARMACEUTICAL DOSAGE FORMS

Dosage forms are provided for most of the Pharmacopeial drug substances, but the processes for the preparation of many of them are, in general, beyond the scope of the Pharmacopeia. In addition to defining the dosage forms, this section presents the general principles involved in the manufacture of some of them, particularly on a small scale. Other information that is given bears on the use of the Pharmacopeial substances in extemporaneous compounding of dosage forms.

BIOAVAILABILITY

Bioavailability, or the extent to which the therapeutic constituent of a pharmaceutical dosage form intended for oral or topical use is available for absorption is influenced by a variety of factors. Among the inherent factors known to affect absorption are the method of manufacture or method of compounding; the particle size and crystal form or polymorph of the drug substance; and the diluents and excipients used in formulating the dosage form, including fillers, binders, disintegrating agents, lubricants, coatings, solvents, suspending agents, and dyes. Lubricants and coatings are foremost among these. The maintenance of a demonstrably high degree of bioavailability requires particular attention to all aspects of production and quality control that may affect the nature of the finished dosage form.

STABILITY

The term "stability," with respect to a drug dosage form, refers to the chemical and physical integrity of the dosage unit, and, when appropriate, the ability of the dosage unit to maintain protection against microbiological contamination. The shelf life of the dosage form is the time lapse from initial preparation to the specified expiration date. The monograph specifications of identity, strength, quality, and purity apply throughout the shelf life of the product.

The stability parameters of a drug dosage form can be influenced by environmental conditions of storage (temperature, light, air, and humidity), as well as the package components. Pharmacopeial articles should include required storage conditions on their labeling. These are the conditions under which the expiration date shall apply. The storage requirements specified in the labeling for the article must be observed throughout the distribution of the article (i.e., beyond the time it leaves the manufacturer up to and including its handling by the dispenser or seller of the article to the consumer). Although labeling for the consumer should indicate proper storage conditions, it is recognized that control beyond the dispenser or seller is difficult.

Stability Protocols—Stability of manufactured dosage forms must be demonstrated by the manufacturer by the use of methods adequate for the purpose. Monograph assays may be used for stability testing if they are stability-indicating (i.e., if they accurately differentiate between the intact drug molecules and their degradation products). Stability considerations should include not only the specific compendial requirements, but also changes in physical appearance of the product that would warn users that the product's continued integrity is questionable.

Stability studies on active substances and packaged dosage forms are conducted by means of "real-time," long-term tests at specific temperatures and relative humidities representing storage conditions experienced in the distribution chain of the climatic zone(s) of the country or region of the world concerned. Labeling of the packaged active substance or dosage form should reflect the effects of temperature, relative humidity, air, and light on its stability. Label temperature storage warnings will reflect both the results of the real-time storage tests and also allow for expected seasonal excursions of temperature.

Controlled room temperature (see the *Storage Temperature* section under *General Notices and Requirements—Preservation, Packaging, Storage, and Labeling*) delineates the allowable tolerance in storage circumstances at any location in the chain of distribution (e.g., pharmacies, hospitals, and warehouses). This terminology also allows patients or consumers to be counseled as to appropriate storage for the product. Products may be labeled either to store at "Controlled room temperature" or to store at temperatures "up to 25°" where labeling is supported by long-term stability studies at the designated storage condition of 25°. *Controlled room temperature* limits the permissible excursions to those consistent with the maintenance of a mean kinetic temperature calculated to be not more than 25°. See *Mean Kinetic Temperature*. The common international guideline for long-term stability studies specifies 25° at 60% relative humidity

Accelerated studies are specified at 40 ± 2° and at 75 ± 5% relative humidity. Accelerated studies also allow the interpretation of data and information on short-term spikes in storage conditions in addition to the excursions allowed for by controlled room temperature.

The term "room temperature" is used in different ways in different countries, and it is usually preferable for product labeling for products to be shipped outside the continental U.S. to refer to a maximum storage temperature or temperature range in degrees Celsius.

Mean Kinetic Temperature—Mean kinetic temperature is described as a single calculated temperature at which the degradation of an article would be equivalent to the actual degradation that would result from temperature fluctuations during the storage period. It is not a simple arithmetic mean. The mean kinetic temperature is calculated from average storage temperatures recorded over a one-year period, with a minimum of twelve equally spaced average storage temperature observations being recorded. Average temperature may be determined using automated recording devices or as the arithmetic mean of the highest and lowest temperatures attained during the observation period as measured on a high-low thermometer. The mean kinetic temperature is calculated by the following equation (derived from the Arrhenius equation):

$$T_k = \frac{\Delta H/R}{-ln\left(\frac{e^{-\Delta H/RT_1} + e^{-\Delta H/RT_2} + \ldots + e^{-\Delta H/RT_n}}{n}\right)},$$

in which T_k is the mean kinetic temperature; ΔH is the heat of activation, 83.144kJ·mole^{-1} (unless more accurate information is available from experimental studies); R is the universal gas constant, 8.3144×10^{-3} kJ·mole^{-1}·degree^{-1}; T_1 is the average storage temperature during the first time period (e.g., month); T_2 is the average storage temperature during the second time period; T_n is the average storage temperature during the nth time period, n being the total number of average storage temperatures recorded (minimum of twelve) during the observation period; and all temperatures (T) being absolute temperatures in degrees Kelvin (°K).

Climatic Zones—For convenience in planning for packaging and storage, and for stability studies, international practice identifies four climatic zones, which are described in Table 1. The United States, Europe, and Japan are characterized by zones I and II. The values in Table 1 are based on observed temperatures and relative humidities, both outside and in rooms, from which mean kinetic temperatures and average humidity values are calculated.[1] Derived values are based on inspection of data from individual cities and on allowances for a margin of safety in assignment of these specified conditions.

A discussion of aspects of drug product stability that are of primary concern to the pharmacist in the dispensing of medications may be found under *Stability Considerations in Dispensing Practice* ⟨1191⟩.

Inasmuch as this chapter is for purposes of general information only, no statement herein is intended to modify or supplant any of the specific requirements pertinent to pharmaceutical preparations, which are given elsewhere in this Pharmacopeia.

TERMINOLOGY

Occasionally it is necessary to add solvent to the contents of a container just prior to use, usually because of instability of some drugs in the diluted form. Thus, a solid diluted to yield a suspension is called [*DRUG*] *for Suspension;* a solid dissolved and diluted to yield a solution is called [*DRUG*] *for Solution;* and a solution or suspension diluted to yield a more dilute form of the drug is called [*DRUG*] *Oral Concentrate.* After dilution, it is important that the drug be homogeneously dispersed before administration.

AEROSOLS

Pharmaceutical aerosols are products that are packaged under pressure and contain therapeutically active ingredients that are released upon activation of an appropriate valve system. They are intended for topical application to the skin as well as local application into the nose (nasal aerosols), mouth (lingual aerosols), or lungs (inhalation aerosols).

The term "aerosol" refers to the fine mist of spray that results from most pressurized systems. However, the term has been broadly misapplied to all self-contained pressurized products, some of which deliver foams or semisolid fluids. In the case of *Inhalation Aerosols*, the particle size of the delivered medication

[1] The source of the data and information in Table 1 is the International Conference on Harmonization sponsored by the International Federation of Pharmaceutical Manufacturers Associations.

Table 1. International Climatic Zones.

Climatic Zone	Calculated Data °C*	°C MKT**	%	mbar***	Derived Data °C	%	mbar
I. *Temperate* United Kingdom Northern Europe Canada Russia	20.0	20.0	42	9.9	21	45	11.2
II *Mediterranean, Subtropical* United States Japan Southern Europe (Portugal-Greece)	21.6	22.0	52	13.5	25	60	19.0
III. *Hot, Dry* Iran Iraq Sudan	26.4	27.9	35	11.9	30	35	15.0
IV. *Hot, Humid* Brazil Ghana Indonesia Nicaragua Philippines	26.7	27.4	76	26.6	30	70	30.0

*Data recorded as <19° calculated as 19°.
**Calculated mean kinetic temperature.
***Partial pressure of water vapor.

EXTENDED-RELEASE CAPSULES

Extended-release capsules are formulated in such manner as to make the contained medicament available over an extended period of time following ingestion. Expressions such as "prolonged-action," "repeat-action," and "sustained-release" have also been used to describe such dosage forms. However, the term "extended-release" is used for Pharmacopeial purposes and requirements for *Drug release* (see *Drug Release* ⟨724⟩) typically are specified in the individual monographs.

CREAMS

Creams are semisolid dosage forms containing one or more drug substances dissolved or dispersed in a suitable base. This term has traditionally been applied to semisolids that possess a relatively fluid consistency formulated as either water-in-oil (e.g., *Cold Cream*) or oil-in-water (e.g., *Fluocinolone Acetonide Cream*) emulsions. However, more recently the term has been restricted to products consisting of oil-in-water emulsions or aqueous microcrystalline dispersions of long chain fatty acids or alcohols that are water washable and more cosmetically and aesthetically acceptable. Creams can be used for administering drugs via the vaginal route (e.g., *Triple Sulfa Vaginal Cream*).

ELIXIRS

See *Solutions*.

EMULSIONS

Emulsions are two-phase systems in which one liquid is dispersed throughout another liquid in the form of small droplets. Where oil is the dispersed phase and an aqueous solution is the continuous phase, the system is designated as an oil-in-water emulsion. Conversely, where water or an aqueous solution is the dispersed phase and oil or oleaginous material is the continuous phase, the system is designated as a water-in-oil emulsion. Emulsions are stabilized by emulsifying agents that prevent coalescence, the merging of small droplets into larger droplets and, ultimately, into a single separated phase. Emulsifying agents (surfactants) do this by concentrating in the interface between the droplet and external phase and by providing a physical barrier around the particle to coalescence. Surfactants also reduce the interfacial tension between the phases, thus increasing the ease of emulsification upon mixing.

Natural, semisynthetic, and synthetic hydrophilic polymers may be used in conjunction with surfactants in oil-in-water emulsions as they accumulate at interfaces and also increase the viscosity of the aqueous phase, thereby decreasing the rate of formation of aggregates of droplets. Aggregation is generally accompanied by a relatively rapid separation of an emulsion into a droplet-rich and droplet-poor phase. Normally the density of an oil is lower than that of water, in which case the oil droplets and droplet aggregates rise, a process referred to as creaming. The greater the rate of aggregation, the greater the droplet size and the greater the rate of creaming. The water droplets in a water-in-oil emulsion generally sediment because of their greater density.

The consistency of emulsions varies widely, ranging from easily pourable liquids to semisolid creams. Generally oil-in-water creams are prepared at high temperature, where they are fluid, and cooled to room temperature, whereupon they solidify as a result of solidification of the internal phase. When this is the case, a high internal-phase volume to external-phase volume ratio is not necessary for semisolid character, and, for example, stearic acid creams or vanishing creams are semisolid with as little as 15% internal phase. Any semisolid character with water-in-oil emulsions generally is attributable to a semisolid external phase.

All emulsions require an antimicrobial agent because the aqueous phase is favorable to the growth of microorganisms. The presence of a preservative is particularly critical in oil-in-water emulsions where contamination of the external phase occurs readily. Since fungi and yeasts are found with greater frequency than bacteria, fungistatic as well as bacteriostatic properties are desirable. Bacteria have been shown to degrade nonionic and anionic emulsifying agents, glycerin, and many natural stabilizers such as tragacanth and guar gum.

Complications arise in preserving emulsion systems, as a result of partitioning of the antimicrobial agent out of the aqueous phase where it is most needed, or of complexation with emulsion ingredients that reduce effectiveness. Therefore, the effectiveness of the preservative system should always be tested in the final product. Preservatives commonly used in emulsions include methyl-, ethyl-, propyl-, and butyl-parabens, benzoic acid, and quaternary ammonium compounds.

See also *Creams* and *Ointments*.

EXTRACTS AND FLUIDEXTRACTS

Extracts are concentrated preparations of vegetable or animal drugs obtained by removal of the active constituents of the respective drugs with suitable menstrua, by evaporation of all or nearly all of the solvent, and by adjustment of the residual masses or powders to the prescribed standards.

In the manufacture of most extracts, the drugs are extracted by percolation. The entire percolates are concentrated, generally by distillation under reduced pressure in order to subject the drug principles to as little heat as possible.

Fluidextracts are liquid preparations of vegetable drugs, containing alcohol as a solvent or as a preservative, or both, and so made that, unless otherwise specified in an individual monograph, each mL contains the therapeutic constituents of 1 g of the standard drug that it represents.

A fluidextract that tends to deposit sediment may be aged and filtered or the clear portion decanted, provided the resulting clear liquid conforms to the Pharmacopeial standards.

Fluidextracts may be prepared from suitable extracts.

GELS

Gels (sometimes called Jellies) are semisolid systems consisting of either suspensions made up of small inorganic particles or large organic molecules interpenetrated by a liquid. Where the gel mass consists of a network of small discrete particles, the gel is classified as a two-phase system (e.g., *Aluminum Hydroxide Gel*). In a two-phase system, if the particle size of the dispersed phase is relatively large, the gel mass is sometimes referred to as a magma (e.g., *Bentonite Magma*). Both gels and magmas may be thixotropic, forming semisolids on standing and becoming liquid on agitation. They should be shaken before use to ensure homogeneity and should be labeled to that effect. (See *Suspensions*.)

Single-phase gels consist of organic macromolecules uniformly distributed throughout a liquid in such a manner that no apparent boundaries exist between the dispersed macromolecules and the liquid. Single-phase gels may be made from synthetic macromolecules (e.g., *Carbomer*) or from natural gums (e.g., *Tragacanth*). The latter preparations are also called mucilages. Although these gels are commonly aqueous, alcohols and oils may be used as the continuous phase. For example, mineral oil can be combined with a polyethylene resin to form an oleaginous ointment base.

Gels can be used to administer drugs topically or into body cavities (e.g., *Phenylephrine Hydrochloride Nasal Jelly*).

IMPLANTS (PELLETS)

Implants or pellets are small sterile solid masses consisting of a highly purified drug (with or without excipients) made by compression or molding. They are intended for implantation in the body (usually subcutaneously) for the purpose of providing continuous release of the drug over long periods of time. Implants are administered by means of a suitable special injector or surgical incision. This dosage form has been used to administer hormones such as testosterone or estradiol. They are packaged individually in sterile vials or foil strips.

INFUSIONS, INTRAMAMMARY

Intramammary infusions are suspensions of drugs in suitable oil vehicles. These preparations are intended for veterinary use only, and are administered by instillation via the teat canals into the udders of milk-producing animals.

INHALATIONS

Inhalations are drugs or solutions or suspensions of one or more drug substances administered by the nasal or oral respiratory route for local or systemic effect.

Solutions of drug substances in sterile water for inhalation or in sodium chloride inhalation solution may be nebulized by use of inert gases. Nebulizers are suitable for the administration of inhalation solutions only if they give droplets sufficiently fine and uniform in size so that the mist reaches the bronchioles. Nebulized solutions may be breathed directly from the nebulizer or the nebulizer may be attached to a plastic face mask, tent, or intermittent positive pressure breathing (IPPB) machine.

Another group of products, also known as metered-dose inhalers (MDIs) are propellant driven drug suspensions or solutions in liquified gas propellant with or without a cosolvent and are intended for delivering metered doses of the drug to the respiratory tract. An MDI contains multiple doses, often exceeding several hundred. The most common single-dose volumes delivered are from 25 to 100 μL (also expressed as mg) per actuation. Examples of MDIs containing drug solutions and suspensions in this pharmacopeia are *Epinephrine Inhalation Aerosol* and *Isoproterenol Hydrochloride and Phenylephrine Bitartrate Inhalation Aerosol*, respectively.

Powders may also be administered by mechanical devices that require manually produced pressure or a deep inhalation by the patient (e.g., *Cromolyn Sodium for Inhalation*).

A special class of inhalations termed inhalants consists of drugs or combination of drugs, that by virtue of their high vapor pressure, can be carried by an air current into the nasal passage where they exert their effect. The container from which the inhalant generally is administered is known as an inhaler.

INJECTIONS

See *Injections* ⟨1⟩.

IRRIGATIONS

Irrigations are sterile solutions intended to bathe or flush open wounds or body cavities. They are used topically, never parenterally. They are labeled to indicate that they are not intended for injection.

LOTIONS

See *Solutions* or *Suspensions*.

LOZENGES

Lozenges are solid preparations, which are intended to dissolve or disintegrate slowly in the mouth. They contain one or more medicaments, usually in a flavored, sweetened base. They can be prepared by molding (gelatin and/or fused sucrose or sorbitol base) or by compression of sugar based tablets. Molded lozenges are sometimes referred to as pastilles while compressed lozenges are often referred to as troches. They are usually intended for treatment of local irritation or infections of the mouth or throat but may contain active ingredients intended for systemic absorption after swallowing.

OINTMENTS

Ointments are semisolid preparations intended for external application to the skin or mucous membranes.

Ointment bases recognized for use as vehicles fall into four general classes: the hydrocarbon bases, the absorption bases, the water-removable bases, and the water-soluble bases. Each therapeutic ointment possesses as its base a representative of one of these four general classes.

Hydrocarbon Bases

These bases, which are known also as "oleaginous ointment bases," are represented by *White Petrolatum* and *White Ointment*. Only small amounts of an aqueous component can be incorporated into them. They serve to keep medicaments in prolonged contact with the skin and act as occlusive dressings. Hydrocarbon bases are used chiefly for their emollient effects, and are difficult to wash off. They do not "dry out" or change noticeably on aging.

Absorption Bases

This class of bases may be divided into two groups: the first group consisting of bases that permit the incorporation of aqueous solutions with the formation of a water-in-oil emulsion (*Hydrophilic Petrolatum* and *Lanolin*), and the second group consisting of water-in-oil emulsions that permit the incorporation of additional quantities of aqueous solutions (*Lanolin*). Absorption bases are useful also as emollients.

Water-removable Bases

Such bases are oil-in-water emulsions, e.g., *Hydrophilic Ointment*, and are more correctly called "creams." (See *Creams*.) They are also described as "water-washable," since they may be readily washed from the skin or clothing with water, an attribute that makes them more acceptable for cosmetic reasons. Some medicaments may be more effective in these bases than in hydrocarbon bases. Other advantages of the water-removable bases are that they may be diluted with water and that they favor the absorption of serous discharges in dermatological conditions.

Water-soluble Bases

This group of so-called "greaseless ointment bases" is comprised of water-soluble constituents. *Polyethylene Glycol Ointment* is the only Pharmacopeial preparation in this group. Bases of this type offer many of the advantages of the water-removable bases and, in addition, contain no water-insoluble substances such as petrolatum, anhydrous lanolin, or waxes. They are more correctly called "Gels." (See *Gels*.)

Choice of Base—The choice of an ointment base depends upon many factors, such as the action desired, the nature of the medicament to be incorporated and its bioavailability and stability, and the requisite shelf-life of the finished product. In some cases, it is necessary to use a base that is less than ideal in order to achieve the stability required. Drugs that hydrolyze rapidly, for example, are more stable in hydrocarbon bases than in bases containing water, even though they may be more effective in the latter.

OPHTHALMIC PREPARATIONS

Drugs are administered to the eyes in a wide variety of dosage forms, some of which require special consideration. They are discussed in the following paragraphs.

Ointments

Ophthalmic ointments are ointments for application to the eye. Special precautions must be taken in the preparation of ophthalmic ointments. They are manufactured from sterilized ingredients under rigidly aseptic conditions and meet the requirements under *Sterility Tests* ⟨71⟩. If the specific ingredients used in the formulation do not lend themselves to routine sterilization techniques, ingredients that meet the sterility requirements described under *Sterility Tests* ⟨71⟩, along with aseptic manufacture, may be employed. Ophthalmic ointments must contain a suitable substance or mixture of substances to prevent growth of, or to destroy, microorganisms accidentally introduced when the container is opened during use, unless otherwise directed in the individual monograph, or unless the formula itself is bacteriostatic (see *Added Substances* under *Ophthalmic Ointments* ⟨771⟩). The medicinal agent is added to the ointment base either as a solution or as a micronized powder. The finished ointment must be free from large particles and must meet the requirements for *Leakage* and for *Metal Particles* under *Ophthalmic Ointments* ⟨771⟩. The immediate containers for ophthalmic ointments shall be sterile at the time of filling and closing. It is mandatory that the immediate containers for ophthalmic ointments be sealed and tamper-proof so that sterility is assured at time of first use.

The ointment base that is selected must be nonirritating to the eye, permit diffusion of the drug throughout the secretions bathing the eye, and retain the activity of the medicament for a reasonable period under proper storage conditions.

Petrolatum is mainly used as a base for ophthalmic drugs. Some absorption bases, water-removable bases, and water-soluble

bases may be desirable for water-soluble drugs. Such bases allow for better dispersion of water-soluble medicaments, but they must be nonirritating to the eye.

Solutions

Ophthalmic solutions are sterile solutions, essentially free from foreign particles, suitably compounded and packaged for instillation into the eye. Preparation of an ophthalmic solution requires careful consideration of such factors as the inherent toxicity of the drug itself, isotonicity value, the need for buffering agents, the need for a preservative (and, if needed, its selection), sterilization, and proper packaging. Similar considerations are also made for nasal and otic products.

ISOTONICITY VALUE

Lacrimal fluid is isotonic with blood, having an isotonicity value corresponding to that of a 0.9% sodium chloride solution. Ideally, an ophthalmic solution should have this isotonicity value; but the eye can tolerate isotonicity values as low as that of a 0.6% sodium chloride solution and as high as that of a 2.0% sodium chloride solution without marked discomfort.

Some ophthalmic solutions are necessarily hypertonic in order to enhance absorption and provide a concentration of the active ingredient(s) strong enough to exert a prompt and effective action. Where the amount of such solutions used is small, dilution with lacrimal fluid takes place rapidly so that discomfort from the hypertonicity is only temporary. However, any adjustment toward isotonicity by dilution with tears is negligible where large volumes of hypertonic solutions are used as collyria to wash the eyes; it is therefore important that solutions used for this purpose be approximately isotonic.

BUFFERING

Many drugs, notably alkaloidal salts, are most effective at pH levels that favor the undissociated free bases. At such pH levels, however, the drug may be unstable so that compromise levels must be found and held by means of buffers. One purpose of buffering some ophthalmic solutions is to prevent an increase in pH caused by the slow release of hydroxyl ions by glass. Such a rise in pH can affect both the solubility and the stability of the drug. The decision whether or not buffering agents should be added in preparing an ophthalmic solution must be based on several considerations. Normal tears have a pH of about 7.4 and possess some buffer capacity. The application of a solution to the eye stimulates the flow of tears and the rapid neutralization of any excess hydrogen or hydroxyl ions within the buffer capacity of the tears. Many ophthalmic drugs, such as alkaloidal salts, are weakly acidic and have only weak buffer capacity. Where only 1 or 2 drops of a solution containing them are added to the eye, the buffering action of the tears is usually adequate to raise the pH and prevent marked discomfort. In some cases pH may vary between 3.5 and 8.5. Some drugs, notably pilocarpine hydrochloride and epinephrine bitartrate, are more acid and overtax the buffer capacity of the lacrimal fluid. Ideally, an ophthalmic solution should have the same pH, as well as the same isotonicity value, as lacrimal fluid. This is not usually possible since, at pH 7.4, many drugs are not appreciably soluble in water. Most alkaloidal salts precipitate as the free alkaloid at this pH. Additionally, many drugs are chemically unstable at pH levels approaching 7.4. This instability is more marked at the high temperatures employed in heat sterilization. For this reason, the buffer system should be selected that is nearest to the physiological pH of 7.4 and does not cause precipitation of the drug or its rapid deterioration.

An ophthalmic preparation with a buffer system approaching the physiological pH can be obtained by mixing a sterile solution of the drug with a sterile buffer solution using aseptic technique. Even so, the possibility of a shorter shelf-life at the higher pH must be taken into consideration, and attention must be directed toward the attainment and maintenance of sterility throughout the manipulations.

Many drugs, when buffered to a therapeutically acceptable pH, would not be stable in solution for long periods of time. These products are lyophilized and are intended for reconstitution immediately before use (e.g., *Acetylcholine Chloride for Ophthalmic Solution*).

STERILIZATION

The sterility of solutions applied to an injured eye is of the greatest importance. Sterile preparations in special containers for individual use on one patient should be available in every hospital, office, or other installation where accidentally or surgically traumatized eyes are treated. The method of attaining sterility is determined primarily by the character of the particular product (see *Sterilization and Sterility Assurance of Compendial Articles* ⟨1211⟩).

Whenever possible, sterile membrane filtration under aseptic conditions is the preferred method. If it can be shown that product stability is not adversely affected, sterilization by autoclaving in the final container is also a preferred method.

Buffering certain drugs near the physiological pH range makes them quite unstable at high temperature.

Avoiding the use of heat by employing a bacteria-retaining filter is a valuable technique, provided caution is exercised in the selection, assembly, and use of the equipment. Single-filtration, presterilized disposable units are available and should be utilized wherever possible.

PRESERVATION

Ophthalmic solutions may be packaged in multiple-dose containers when intended for the individual use of one patient and where the ocular surfaces are intact. It is mandatory that the immediate containers for ophthalmic solutions be sealed and tamper-proof so that sterility is assured at time of first use. Each solution must contain a suitable substance or mixture of substances to prevent the growth of, or to destroy, microorganisms accidentally introduced when the container is opened during use.

Where intended for use in surgical procedures, ophthalmic solutions, although they must be sterile, should not contain antibacterial agents, since they may be irritating to the ocular tissues.

THICKENING AGENT

A pharmaceutical grade of methylcellulose (e.g., 1% if the viscosity is 25 centipoises, or 0.25% if 4000 centipoises) or other suitable thickening agents such as hydroxypropyl methylcellulose or polyvinyl alcohol occasionally are added to ophthalmic solutions to increase the viscosity and prolong contact of the drug with the tissue. The thickened ophthalmic solution must be free from visible particles.

Suspensions

Ophthalmic suspensions are sterile liquid preparations containing solid particles dispersed in a liquid vehicle intended for application to the eye (see *Suspensions*). It is imperative that such suspensions contain the drug in a micronized form to prevent irritation and/or scratching of the cornea. Ophthalmic suspensions should never be dispensed if there is evidence of caking or aggregation.

Strips

Fluorescein sodium solution should be dispensed in a sterile, single-use container or in the form of a sterile, impregnated paper strip. The strip releases a sufficient amount of the drug for diagnostic purposes when touched to the eye being examined for a foreign body or a corneal abrasion. Contact of the paper with the eye may be avoided by leaching the drug from the strip onto the eye with the aid of sterile water or sterile sodium chloride solution.

PASTES

Pastes are semisolid dosage forms that contain one or more drug substances intended for topical application. One class is made from a single phase aqueous gel (e.g., *Carboxymethylcellulose Sodium Paste*). The other class, the fatty pastes (e.g., *Zinc Oxide Paste*), consists of thick, stiff ointments that do not ordinarily flow at body temperature, and therefore serve as protective coatings over the areas to which they are applied.

The fatty pastes appear less greasy and more absorptive than ointments by reason of a high proportion of drug substance(s) having an affinity for water. These pastes tend to absorb serous

secretions, and are less penetrating and less macerating than ointments, so that they are preferred for acute lesions that have a tendency towards crusting, vesiculation, or oozing.

A dental paste is intended for adhesion to the mucous membrane for local effect (e.g., *Triamcinolone Acetonide Dental Paste*).

PELLETS

See *Implants*.

POWDERS

Powders are intimate mixtures of dry, finely divided drugs and/or chemicals that may be intended for internal (Oral Powders) or external (Topical Powders) use. Because of their greater specific surface area, powders disperse and dissolve more readily than compacted dosage forms. Children and those adults who experience difficulty in swallowing tablets or capsules may find powders more acceptable. Drugs that are too bulky to be formed into tablets or capsules of convenient size may be administered as powders. Immediately prior to use, oral powders are mixed in a beverage or apple sauce.

Often, stability problems encountered in liquid dosage forms are avoided in powdered dosage forms. Drugs that are unstable in aqueous suspensions or solutions may be prepared in the form of granules or powders. These are intended to be constituted by the pharmacist by the addition of a specified quantity of water just prior to dispensing. Because these constituted products have limited stability, they are required to have a specified expiration date after constitution and may require storage in a refrigerator.

Oral powders may be dispensed in doses premeasured by the pharmacist, i.e., divided powders, or in bulk. Traditionally, divided powders have been wrapped in materials such as bond paper and parchment. However, the pharmacist may provide greater protection from the environment by sealing individual doses in small cellophane or polyethylene envelopes.

Bulk oral powders are limited to relatively nonpotent drugs such as laxatives, antacids, dietary supplements, and certain analgesics that the patient may safely measure by the teaspoonful or capful. Other bulky powders include douche powders, tooth powders, and dusting powders. Bulk powders are best dispensed in tight, wide-mouth glass containers to afford maximum protection from the atmosphere and to prevent the loss of volatile constituents.

Dusting powders are impalpable powders intended for topical application. They may be dispensed in sifter-top containers to facilitate dusting onto the skin. In general, dusting powders should be passed through at least a 100-mesh sieve to assure freedom from grit that could irritate traumatized areas (see *Powder Fineness* ⟨811⟩).

SOLUTIONS

Solutions are liquid preparations that contain one or more chemical substances dissolved, i.e., molecularly dispersed, in a suitable solvent or mixture of mutually miscible solvents. Since molecules in solutions are uniformly dispersed, the use of solutions as dosage forms generally provides for the assurance of uniform dosage upon administration, and good accuracy when diluting or otherwise mixing solutions.

Substances in solutions, however, are more susceptible to chemical instability than the solid state and dose for dose, generally require more bulk and weight in packaging relative to solid dosage forms. For all solutions, but particularly those containing volatile solvents, tight containers, stored away from excessive heat, should be used. Consideration should also be given to the use of light-resistant containers when photolytic chemical degradation is a potential stability problem. Dosage forms categorized as "Solutions" are classified according to route of administration, such as "Oral Solutions" and "Topical Solutions," or by their solute and solvent systems, such as "Spirits," "Tinctures," and "Waters." Solutions intended for parenteral administration are officially entitled "Injections" (see *Injections* ⟨1⟩).

Oral Solutions

Oral Solutions are liquid preparations, intended for oral administration, that contain one or more substances with or without flavoring, sweetening, or coloring agents dissolved in water or cosolvent-water mixtures. Oral Solutions may be formulated for direct oral administration to the patient or they may be dispensed in a more concentrated form that must be diluted prior to administration. It is important to recognize that dilution with water of Oral Solutions containing cosolvents, such as alcohol, could lead to precipitation of some ingredients. Hence, great care must be taken in diluting concentrated solutions when cosolvents are present. Preparations dispensed as soluble solids or soluble mixtures of solids, with the intent of dissolving them in a solvent and administering them orally, are designated "for Oral Solution" (e.g., *Potassium Chloride for Oral Solution*).

Oral Solutions containing high concentrations of sucrose or other sugars traditionally have been designated as Syrups. A near-saturated solution of sucrose in purified water, for example, is known as Syrup or "Simple Syrup." Through common usage the term, syrup, also has been used to include any other liquid dosage form prepared in a sweet and viscid vehicle, including oral suspensions.

In addition to sucrose and other sugars, certain polyols such as sorbitol or glycerin may be present in Oral Solutions to inhibit crystallization and to modify solubility, taste, mouth-feel, and other vehicle properties. Antimicrobial agents to prevent the growth of bacteria, yeasts, and molds are generally also present. Some sugarless Oral Solutions contain sweetening agents such as sorbitol or aspartame, as well as thickening agents such as the cellulose gums. Such viscid sweetened solutions, containing no sugars, are occasionally prepared as vehicles for administration of drugs to diabetic patients.

Many oral solutions, which contain alcohol as a cosolvent, have been traditionally designated as Elixirs. Many others, however, designated as Oral Solutions, also contain significant amounts of alcohol. Since high concentrations of alcohol can produce a pharmacologic effect when administered orally, other cosolvents, such as glycerin and propylene glycol, should be used to minimize the amount of alcohol required. To be designated as an Elixir, however, the solution must contain alcohol.

Topical Solutions

Topical Solutions are solutions, usually aqueous but often containing other solvents, such as alcohol and polyols, intended for topical application to the skin, or as in the case of Lidocaine Oral Topical Solution, to the oral mucosal surface. The term "lotion" is applied to solutions or suspensions applied topically.

Otic Solutions

Otic Solutions, intended for instillation in the outer ear, are aqueous, or they are solutions prepared with glycerin or other solvents and dispersing agents (e.g., *Antipyrine and Benzocaine Otic Solution* and *Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Solution*).

Ophthalmic Solutions

(See *Ophthalmic Preparations*.)

Spirits

Spirits are alcoholic or hydroalcoholic solutions of volatile substances prepared usually by simple solution or by admixture of the ingredients. Some spirits serve as flavoring agents while others have medicinal value. Reduction of the high alcoholic content of spirits by admixture with aqueous preparations often causes turbidity.

Spirits require storage in tight, light-resistant containers to prevent loss by evaporation and to limit oxidative changes.

Tinctures

Tinctures are alcoholic or hydroalcoholic solutions prepared from vegetable materials or from chemical substances.

The proportion of drug represented in the different chemical tinctures is not uniform but varies according to the established standards for each. Traditionally, tinctures of potent vegetable drugs essentially represent the activity of 10 g of the drug in each 100 mL of tincture, the potency being adjusted following assay. Most other vegetable tinctures represent 20 g of the respective vegetable material in each 100 mL of tincture.

PROCESS P

Carefully mix the ground drug or mixture of drugs with a sufficient quantity of the prescribed solvent or solvent mixture to render it evenly and distinctly damp, allow it to stand for 15 minutes, transfer it to a suitable percolator, and pack the drug firmly. Pour on enough of the prescribed solvent or solvent mixture to saturate the drug, cover the top of the percolator and, when the liquid is about to drip from the percolator, close the lower orifice, and allow the drug to macerate for 24 hours or for the time specified in the monograph. If no assay is directed, allow the percolation to proceed slowly, or at the specified rate, gradually adding sufficient solvent or solvent mixture to produce 1000 mL of tincture, and mix (for definitions of flow rates, see under *Fluidextracts*). If an assay is directed, collect only 950 mL of percolate, mix this, and assay a portion of it as directed. Dilute the remainder with such quantity of the prescribed solvent or solvent mixture as calculation from the assay indicates is necessary to produce a tincture that conforms to the prescribed standard, and mix.

PROCESS M

Macerate the drug with 750 mL of the prescribed solvent or solvent mixture in a container that can be closed, and put in a warm place. Agitate it frequently during 3 days or until the soluble matter is dissolved. Transfer the mixture to a filter, and when most of the liquid has drained away, wash the residue on the filter with a sufficient quantity of the prescribed solvent or solvent mixture, combining the filtrates, to produce 1000 mL of tincture, and mix.

Tinctures require storage in tight, light-resistant containers, away from direct sunlight and excessive heat.

Waters, Aromatic

Aromatic waters are clear, saturated aqueous solutions (unless otherwise specified) of volatile oils or other aromatic or volatile substances. Their odors and tastes are similar, respectively, to those of the drugs or volatile substances from which they are prepared, and they are free from empyreumatic and other foreign odors. Aromatic waters may be prepared by distillation or solution of the aromatic substance, with or without the use of a dispersing agent.

Aromatic waters require protection from intense light and excessive heat.

SUPPOSITORIES

Suppositories are solid bodies of various weights and shapes, adapted for introduction into the rectal, vaginal, or urethral orifice of the human body. They usually melt, soften, or dissolve at body temperature. A suppository may act as a protectant or palliative to the local tissues at the point of introduction or as a carrier of therapeutic agents for systemic or local action. Suppository bases usually employed are cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights, and fatty acid esters of polyethylene glycol.

The suppository base employed has a marked influence on the release of the active ingredient incorporated in it. While cocoa butter melts quickly at body temperature, it is immiscible with body fluids and this inhibits the diffusion of fat-soluble drugs to the affected sites. Polyethylene glycol is a suitable base for some antiseptics. In cases where systemic action is expected, it is preferable to incorporate the ionized rather than the nonionized form of the drug, in order to maximize bioavailability. Although unionized drugs partition more readily out of water-miscible bases such as glycerinated gelatin and polyethylene glycol, the bases themselves tend to dissolve very slowly and thus retard release in this manner. Oleaginous vehicles such as cocoa butter are seldom used in vaginal preparations because of the nonabsorbable residue formed, while glycerinated gelatin is seldom used rectally because of its slow dissolution. Cocoa butter and its substitutes (Hard Fat) are superior for allaying irritation, as in preparations intended for treating internal hemorrhoids.

Cocoa Butter Suppositories

Suppositories having cocoa butter as the base may be made by means of incorporating the finely divided medicinal substance into the solid oil at room temperature and suitably shaping the resulting mass, or by working with the oil in the melted state and allowing the resulting suspension to cool in molds. A suitable quantity of hardening agents may be added to counteract the tendency of some medicaments such as chloral hydrate and phenol to soften the base. It is important that the finished suppository melt at body temperature.

The approximate weights of suppositories prepared with cocoa butter are given below. Suppositories prepared from other bases vary in weight and generally are heavier than the weights indicated here.

Rectal Suppositories for adults are tapered at one or both ends and usually weigh about 2 g each.

Vaginal Suppositories are usually globular or oviform and weigh about 5 g each. They are made from water soluble or water miscible vehicles such as polyethylene glycol or glycerinated gelatin.

Suppositories with cocoa butter base require storage in well-closed containers, preferably at a temperature below 30° (controlled room temperature).

Cocoa Butter Substitutes

Fat-type suppository bases can be produced from a variety of vegetable oils, such as coconut or palm kernel, which are modified by esterification, hydrogenation, and fractionation to obtain products of varying composition and melting temperatures (e.g., *Hydrogenated Vegetable Oil* and *Hard Fat*). These products can be so designed as to reduce rancidity. At the same time, desired characteristics such as narrow intervals between melting and solidification temperatures, and melting ranges to accommodate various formulation and climatic conditions, can be built in.

Glycerinated Gelatin Suppositories

Medicinal substances may be incorporated into glycerinated gelatin bases by addition of the prescribed quantities to a vehicle consisting of about 70 parts of glycerin, 20 parts of gelatin, and 10 parts of water.

Glycerinated gelatin suppositories require storage in tight containers, preferably at a temperature below 35°.

Polyethylene Glycol–Base Suppositories

Several combinations of polyethylene glycols having melting temperatures that are above body temperature have been used as suppository bases. Inasmuch as release from these bases depends on dissolution rather than on melting, there are significantly fewer problems in preparation and storage than exist with melting-type vehicles. However, high concentrations of higher molecular weight polyethylene glycols may lengthen dissolution time, resulting in problems with retention. Labels on polyethylene glycol suppositories should contain directions that they be moistened with water before inserting. Although they can be stored without refrigeration, they should be packaged in tightly closed containers.

Surfactant Suppository Bases

Several nonionic surface-active agents closely related chemically to the polyethylene glycols can be used as suppository vehicles. Examples of such surfactants are polyoxyethylene sorbitan fatty acid esters and the polyoxyethylene stearates. These surfactants are used alone or in combination with other suppository vehicles to yield a wide range of melting temperatures and consistencies. One of the major advantages of such vehicles is their water-dispersibility. However, care must be taken with the use of surfactants, because they may either increase the rate of drug absorption or interact with drug molecules, causing a decrease in therapeutic activity.

Tableted Suppositories or Inserts

Vaginal suppositories occasionally are prepared by the compression of powdered materials into a suitable shape. They are prepared also by encapsulation in soft gelatin

SUSPENSIONS

Suspensions are liquid preparations that consist of solid particles dispersed throughout a liquid phase in which the particles are not soluble. Dosage forms officially categorized as Suspensions are designated as such if they are not included in other more specific categories of suspensions, such as Oral Suspensions, Topical Suspensions, etc. (see these other categories). Some suspensions are prepared and ready for use, while others are prepared as solid mixtures intended for constitution just before use with an appropriate vehicle. Such products are designated "for Oral Suspension," etc. The term, Milk, is sometimes used for suspensions in aqueous vehicles intended for oral administration (e.g., *Milk of Magnesia*). The term, Magma, is often used to describe suspensions of inorganic solids such as clays in water, where there is a tendency for strong hydration and aggregation of the solid, giving rise to gel-like consistency and thixotropic rheological behavior (e.g., *Bentonite Magma*). The term, Lotion, has been used to categorize many topical suspensions and emulsions intended for application to the skin (e.g., *Calamine Lotion*). Some suspensions are prepared in sterile form and are used as Injectables, as well as for ophthalmic and otic administration. These may be of two types, ready to use or intended for constitution with a prescribed amount of Water for Injection or other suitable diluent before use by the designated route. Suspensions should not be injected intravenously or intrathecally.

Suspensions intended for any route of administration should contain suitable antimicrobial agents to protect against bacteria, yeast, and mold contamination (see *Emulsions* for some consideration of antimicrobial preservative properties that apply also to Suspensions). By its very nature, the particular matter in a suspension may settle or sediment to the bottom of the container upon standing. Such sedimentation may also lead to caking and solidification of the sediment with a resulting difficulty in redispersing the suspension upon agitation. To prevent such problems, suitable ingredients that increase viscosity and the gel state of the suspension, such as clays, surfactants, polyols, polymers, or sugars, should be added. It is important that suspensions always be shaken well before use to ensure uniform distribution of the solid in the vehicle, thereby ensuring uniform and proper dosage. Suspensions require storage in tight containers.

Oral Suspensions

Oral Suspensions are liquid preparations containing solid particles dispersed in a liquid vehicle, with suitable flavoring agents, intended for oral administration. Some suspensions labeled as Milks or Magmas fall into this category.

Topical Suspensions

Topical Suspensions are liquid preparations containing solid particles dispersed in a liquid vehicle, intended for application to the skin. Some suspensions labeled as Lotions fall into this category.

Otic Suspensions

Otic Suspensions are liquid preparations containing micronized particles intended for instillation in the outer ear.

Ophthalmic Suspensions

(See *Ophthalmic Preparations*).

SYRUPS

See *Solutions*.

SYSTEMS

In recent years, a number of dosage forms have been developed using modern technology that allows for the uniform release or targeting of drugs to the body. These products are commonly called delivery systems. The most widely used of these are Transdermal Systems.

Transdermal Systems

Transdermal drug delivery systems are self-contained, discrete dosage forms that, when applied to intact skin, are designed to deliver the drug(s) through the skin to the systemic circulation. Systems typically comprise an outer covering (barrier), a drug reservoir, which may have a rate controlling membrane, a contact adhesive applied to some or all parts of the system and the system/skin interface, and a protective liner that is removed before applying the system. The activity of these systems is defined in terms of the release rate of the drug(s) from the system. The total duration of drug release from the system and the system surface area may also be stated.

Transdermal drug delivery systems work by diffusion: the drug diffuses from the drug reservoir, directly or through the rate controlling membrane and/or contact adhesive if present, and then through the skin into the general circulation. Typically, modified-release systems are designed to provide drug delivery at a constant rate, such that a true steady state blood concentration is achieved and maintained until the system is removed. At that time, blood concentration declines at a rate consistent with the pharmacokinetics of the drug.

Transdermal drug delivery systems are applied to body areas consistent with the labeling for the product(s). As long as drug concentration at the system/skin interface remains constant, the amount of drug in the dosage form does not influence plasma concentrations. The functional lifetime of the system is defined by the initial amount of drug in the reservoir and the release rate from the reservoir.

NOTE—Drugs for local rather than systemic effect are commonly applied to the skin embedded in glue on a cloth or plastic backing. These products are defined traditionally as plasters or tapes.

Ocular System

Another type of system is the ocular system, which is intended for placement in the lower conjunctival fornix from which the drug diffuses through a membrane at a constant rate over a seven-day period (e.g., *Pilocarpine Ocular System*).

Intrauterine System

An intrauterine system, based on a similar principle but intended for release of drug over a much longer period of time, i.e., one year, is also available (e.g., *Progesterone Intrauterine Contraceptive System*).

TABLETS

Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. They may be classed, according to the method of manufacture, as compressed tablets or molded tablets .

The vast majority of all tablets manufactured are made by compression, and compressed tablets are the most widely used dosage form in this country. Compressed tablets are prepared by the application of high pressures, utilizing steel punches and dies, to powders or granulations. Tablets can be produced in a wide variety of sizes, shapes, and surface markings, depending upon the design of the punches and dies. Capsule-shaped tablets are commonly referred to as caplets. Boluses are large tablets intended for veterinary use, usually for large animals.

Molded tablets are prepared by forcing dampened powders under low pressure into die cavities. Solidification depends upon crystal bridges built up during the subsequent drying process, and not upon the compaction force.

Tablet triturates are small, usually cylindrical, molded or compressed tablets. Tablet triturates were traditionally used as dispensing tablets in order to provide a convenient, measured quantity of a potent drug for compounding purposes. Such tablets are rarely used today. Hypodermic tablets are molded tablets made from completely and readily water-soluble ingredients and formerly were intended for use in making preparations for hypodermic injection. They are employed orally, or where rapid drug availability is required such as in the case of *Nitroglycerin Tablets*, sublingually.

Buccal tablets are intended to be inserted in the buccal pouch, and sublingual tablets are intended to be inserted beneath the

tongue, where the active ingredient is absorbed directly through the oral mucosa. Few drugs are readily absorbed in this way, but for those that are (such as nitroglycerin and certain steroid hormones), a number of advantages may result.

Soluble, effervescent tablets are prepared by compression and contain, in addition to active ingredients, mixtures of acids (citric acid, tartaric acid) and sodium bicarbonate, which release carbon dioxide when dissolved in water. They are intended to be dissolved or dispersed in water before administration. Effervescent tablets should be stored in tightly closed containers or moisture-proof packs and labeled to indicate that they are not to be swallowed directly.

Chewable Tablets

Chewable tablets are intended to be chewed, producing a pleasant tasting residue in the oral cavity that is easily swallowed and does not leave a bitter or unpleasant after-taste. These tablets have been used in tablet formulations for children, especially multivitamin formulations, and for the administration of antacids and selected antibiotics. Chewable tablets are prepared by compression, usually utilizing mannitol, sorbitol, or sucrose as binders and fillers, and containing colors and flavors to enhance their appearance and taste.

Preparation of Molded Tablets

Molded tablets are prepared from mixtures of medicinal substances and a diluent usually consisting of lactose and powdered sucrose in varying proportions. The powders are dampened with solutions containing high percentages of alcohol. The concentration of alcohol depends upon the solubility of the active ingredients and fillers in the solvent system and the desired degree of hardness of the finished tablets. The dampened powders are pressed into molds, removed, and allowed to dry. Molded tablets are quite friable and care must be taken in packaging and dispensing.

Formulation of Compressed Tablets

Most compressed tablets consist of the active ingredient and a diluent (filler), binder, disintegrating agent, and lubricant. Approved FD&C and D&C dyes or lakes (dyes adsorbed onto insoluble aluminum hydroxide), flavors, and sweetening agents may also be present. Diluents are added where the quantity of active ingredient is small or difficult to compress. Common tablet fillers include lactose, starch, dibasic calcium phosphate, and microcrystalline cellulose. Chewable tablets often contain sucrose, mannitol, or sorbitol as a filler. Where the amount of active ingredient is small, the overall tableting properties are in large measure determined by the filler. Because of problems encountered with bioavailability of hydrophobic drugs of low water-solubility, water-soluble diluents are used as fillers for these tablets.

Binders give adhesiveness to the powder during the preliminary granulation and to the compressed tablet. They add to the cohesive strength already available in the diluent. While binders may be added dry, they are more effective when added out of solution. Common binders include acacia, gelatin, sucrose, povidone, methylcellulose, carboxymethylcellulose, and hydrolyzed starch pastes. The most effective dry binder is microcrystalline cellulose, which is commonly used for this purpose in tablets prepared by direct compression.

A disintegrating agent serves to assist in the fragmentation of the tablet after administration. The most widely used tablet disintegrating agent is starch. Chemically modified starches and cellulose, alginic acid, microcrystalline cellulose, and cross-linked povidone, are also used for this purpose. Effervescent mixtures are used in soluble tablet systems as disintegrating agents. The concentration of the disintegrating agent, method of addition, and degree of compaction play a role in effectiveness.

Lubricants reduce friction during the compression and ejection cycle. In addition, they aid in preventing adherence of tablet material to the dies and punches. Metallic stearates, stearic acid, hydrogenated vegetable oils, and talc are used as lubricants. Because of the nature of this function, most lubricants are hydrophobic, and as such tend to reduce the rates of tablet disintegration and dissolution. Consequently, excessive concentrations of lubricant should be avoided. Polyethylene glycols and some lauryl sulfate salts have been used as soluble lubricants, but such agents generally do not possess optimal lubricating properties, and comparatively high concentrations are usually required.

Glidants are agents that improve powder fluidity, and they are commonly employed in direct compression where no granulation step is involved. The most effective glidants are the colloidal pyrogenic silicas.

Colorants are often added to tablet formulations for esthetic value or for product identification. Both D&C and FD&C dyes and lakes are used. Most dyes are photosensitive and they fade when exposed to light. The federal Food and Drug Administration regulates the colorants employed in drugs.

Manufacturing Methods

Tablets are prepared by three general methods: wet granulation, dry granulation (roll compaction or slugging), and direct compression. The purpose of both wet and dry granulation is to improve flow of the mixture and/or to enhance its compressibility.

Dry granulation (slugging) involves the compaction of powders at high pressures into large, often poorly formed tablet compacts. These compacts are then milled and screened to form a granulation of the desired particle size. The advantage of dry granulation is the elimination of both heat and moisture in the processing. Dry granulations can be produced also by extruding powders between hydraulically operated rollers to produce thin cakes which are subsequently screened or milled to give the desired granule size.

Excipients are available that allow production of tablets at high speeds without prior granulation steps. These directly compressible excipients consist of special physical forms of substances such as lactose, sucrose, dextrose, or cellulose, which possess the desirable properties of fluidity and compressibility. The most widely used direct-compaction fillers are microcrystalline cellulose, anhydrous lactose, spray-dried lactose, compressible sucrose, and some forms of modified starches. Direct compression avoids many of the problems associated with wet and dry granulations. However, the inherent physical properties of the individual filler materials are highly critical, and minor variations can alter flow and compression characteristics so as to make them unsuitable for direct compression.

Physical evidence of poor tablet quality is discussed under *Stability Considerations in Dispensing Practice* ⟨1191⟩.

WEIGHT VARIATION AND CONTENT UNIFORMITY

Tablets are required to meet a weight variation test (see *Uniformity of Dosage Units* ⟨905⟩) where the active ingredient comprises a major portion of the tablet and where control of weight may be presumed to be an adequate control of drug content uniformity. Weight variation is not an adequate indication of content uniformity where the drug substance comprises a relatively minor portion of the tablet, or where the tablet is sugar-coated. Thus, the Pharmacopeia generally requires that coated tablets and tablets containing 50 mg or less of active ingredient, comprising less than 50% by weight of the dosage-form unit, pass a content uniformity test (see *Uniformity of Dosage Units* ⟨905⟩), wherein individual tablets are assayed for actual drug content.

DISINTEGRATION AND DISSOLUTION

Disintegration is an essential attribute of tablets intended for administration by mouth, except those intended to be chewed before being swallowed and except some types of extended-release tablets. A disintegration test is provided (see *Disintegration* ⟨701⟩), and limits on the times in which disintegration is to take place, appropriate for the types of tablets concerned, are given in the individual monographs.

For drugs of limited water-solubility, dissolution may be a more meaningful quality attribute than disintegration. A dissolution test (see *Dissolution* ⟨711⟩) is required in a number of monographs on tablets. In many cases, it is possible to correlate dissolution rates with biological availability of the active ingredient. However, such tests are useful mainly as a means of screening preliminary formulations and as a routine quality-control procedure.

Coatings

Tablets may be coated for a variety of reasons, including protection of the ingredients from air, moisture, or light, masking of

unpleasant tastes and odors, improvement of appearance, and control of the site of drug release in the gastrointestinal tract.

PLAIN COATED TABLETS

Classically, tablets have been coated with sugar applied from aqueous suspensions containing insoluble powders such as starch, calcium carbonate, talc, or titanium dioxide, suspended by means of acacia or gelatin. For purposes of identification and esthetic value, the outside coatings may be colored. The finished coated tablets are polished by application of dilute solutions of wax in solvents such as chloroform or powdered mix. Water-protective coatings consisting of substances such as shellac or cellulose acetate phthalate are often applied out of nonaqueous solvents prior to application of sugar coats. Excessive quantities should be avoided. Drawbacks of sugar coating include the lengthy time necessary for application, the need for waterproofing, which also adversely affects dissolution, and the increased bulk of the finished tablet. These factors have resulted in increased acceptance of film coatings. Film coatings consist of water-soluble or dispersible materials such as hydroxypropyl methylcellulose, methylcellulose, hydroxypropylcellulose, carboxymethylcellulose sodium, and mixtures of cellulose acetate phthalate and polyethylene glycols applied out of nonaqueous or aqueous solvents. Evaporation of the solvents leaves a thin film that adheres directly to the tablet and allows it to retain the original shape, including grooves or identification codes.

ENTERIC-COATED TABLETS

Where the drug may be destroyed or inactivated by the gastric juice or where it may irritate the gastric mucosa, the use of "enteric" coatings is indicated. Such coatings are intended to delay the release of the medication until the tablet has passed through the stomach. The term "delayed-release" is used for Pharmacopeial purposes, and the individual monographs include tests and specifications for *Drug release* (see *Drug Release* ⟨724⟩).

EXTENDED-RELEASE TABLETS

Extended-release tablets are formulated in such manner as to make the contained medicament available over an extended period of time following ingestion. Expressions such as "prolonged-action," "repeat-action," and "sustained-release" have also been used to describe such dosage forms. However, the term "extended-release" is used for Pharmacopeial purposes, and requirements for *Drug release* typically are specified in the individual monographs.

⟨1171⟩ PHASE-SOLUBILITY ANALYSIS

Phase-solubility analysis is the quantitative determination of the purity of a substance through the application of precise solubility measurements. At a given temperature, a definite amount of a pure substance is soluble in a definite quantity of solvent. The resulting solution is saturated with respect to the particular substance, but the solution remains unsaturated with respect to other substances, even though such substances may be closely related in chemical structure and physical properties to the particular substance being tested. Constancy of solubility, just as constancy of melting temperature or other physical properties, indicates that a material is pure or is free from foreign admixture except in the unique case where the percentage composition of the substance under test is in direct ratio to solubilities of the respective components. Conversely, variability of solubility indicates the presence of an impurity or impurities.

Phase-solubility analysis is applicable to all species of compounds that are crystalline solids and that form stable solutions. It is not readily applicable to compounds that form solid solutions with impurities.

The standard solubility method consists of six distinct steps: (1) mixing, in a series of separate systems, increasing quantities of material with measured, fixed amounts of a solvent; (2) establishment of equilibrium for each system at identical constant temperature and pressure; (3) separation of the solid phase from the solutions; (4) determination of the concentration of the material dissolved in the various solutions; (5) plotting the concentration of the dissolved materials per unit of solvent (*y*-axis or solution composition) against the weight of material per unit of solvent (*x*-axis or system composition); and (6) extrapolation and calculation.

Solvents

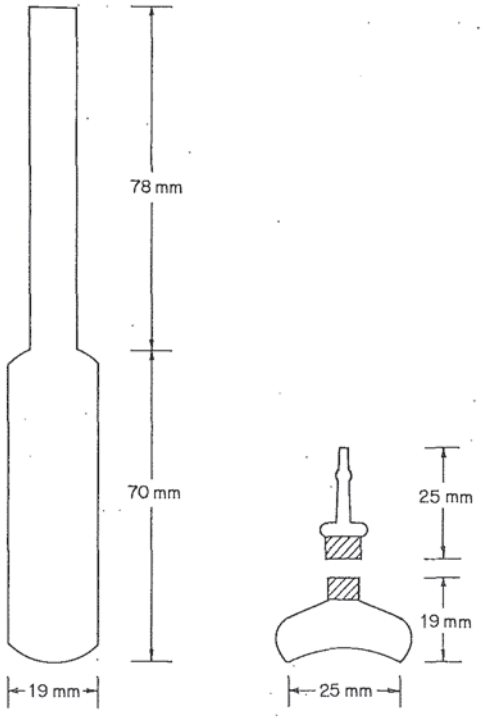
A proper solvent for phase-solubility analysis meets the following criteria: (1) The solvent is of sufficient volatility so that it can be evaporated under vacuum, but is not so volatile that difficulty is experienced in transferring and weighing the solvent and its solutions. Normally, solvents having boiling points between 60° and 150° are suitable. (2) The solvent does not adversely affect the substance being tested. Solvents that cause decomposition or react with the test substance are not to be used. Solvents that solvate or form salts are to be avoided, if possible. (3) The solvent is of known purity and composition. Carefully prepared mixed solvents are permissible. Trace impurities may affect solubility greatly. (4) A solubility of 10 mg to 20 mg per g is optimal, but a wider working range can be utilized.

Apparatus*

Constant-temperature Bath—Use a constant-temperature bath that is capable of maintaining the temperature within ±0.1° and that is equipped with a horizontal shaft capable of rotating at approximately 25 rpm. The shaft is equipped with clamps to hold the *Ampuls*. Alternatively, the bath may contain a suitable vibrator, capable of agitating the ampuls at 100 to 120 vibrations per second, and equipped with a shaft and suitable clamps to hold the ampuls.

Ampuls—Use 15-mL ampuls of the type shown in the accompanying illustration. Other containers may be used provided that they are leakproof and otherwise suitable.

Solubility Flasks—Use solubility flasks of the type shown in the accompanying illustration.



Ampul (left) and Solubility Flask (right) Used in Phase-solubility Analysis

* Available from Hanson Research Corp., 19727 Bahama St., P. O. Box 35, Northridge, CA 91324.

PHARMACEUTIC INGREDIENTS

USP and NF Pharmaceutic Ingredients, Listed by Categories

Acidifying Agent
- Acetic Acid
- Acetic Acid, Glacial
- Citric Acid
- Fumaric Acid
- Hydrochloric Acid
- Hydrochloric Acid, Diluted
- Malic Acid
- Nitric Acid
- Phosphoric Acid
- Phosphoric Acid, Diluted
- Propionic Acid
- Sulfuric Acid
- Tartaric Acid

Aerosol Propellant
- Butane
- Dichlorodifluoromethane
- Dichlorotetrafluoroethane
- Isobutane
- Propane
- Trichloromonofluoromethane

Air Displacement
- Carbon Dioxide
- Nitrogen

Alcohol Denaturant
- Denatonium Benzoate
- Methyl Isobutyl Ketone
- Sucrose Octaacetate

Alkalizing Agent
- Ammonia Solution, Strong
- Ammonium Carbonate
- Diethanolamine
- Potassium Hydroxide
- Sodium Bicarbonate
- Sodium Borate
- Sodium Carbonate
- Sodium Hydroxide
- Trolamine

Anticaking Agent (See *Glidant*)

Antifoaming Agent
- Dimethicone
- Simethicone

Antimicrobial Preservative
- Benzalkonium Chloride
- Benzalkonium Chloride Solution
- Benzethonium Chloride
- Benzoic Acid
- Benzyl Alcohol
- Butylparaben
- Cetylpyridinium Chloride
- Chlorobutanol
- Chlorocresol
- Cresol
- Dehydroacetic Acid
- Ethylparaben
- Methylparaben
- Methylparaben Sodium
- Phenol
- Phenylethyl Alcohol
- Phenylmercuric Acetate
- Phenylmercuric Nitrate
- Potassium Benzoate
- Potassium Sorbate
- Propylparaben
- Propylparaben Sodium
- Sodium Benzoate
- Sodium Dehydroacetate
- Sodium Propionate
- Sorbic Acid
- Thimerosal
- Thymol

Antioxidant
- Ascorbic Acid
- Ascorbyl Palmitate
- Butylated Hydroxyanisole
- Butylated Hydroxytoluene
- Hypophosphorous Acid
- Monothioglycerol
- Potassium Metabisulfite
- Propyl Gallate
- Sodium Formaldehyde Sulfoxylate
- Sodium Metabisulfite
- Sodium Thiosulfate
- Sulfur Dioxide
- Tocopherol
- Tocopherols Excipient

Buffering Agent
- Acetic Acid
- Ammonium Carbonate
- Ammonium Phosphate
- Boric Acid
- Citric Acid
- Lactic Acid
- Phosphoric Acid
- Potassium Citrate
- Potassium Metaphosphate
- Potassium Phosphate, Monobasic
- Sodium Acetate
- Sodium Citrate
- Sodium Lactate Solution
- Sodium Phosphate, Dibasic
- Sodium Phosphate, Monobasic

Bulking Agent for Freeze-Drying
- Creatinine
- Mannitol

Capsule Lubricant (See *Tablet and/or Capsule Lubricant*)

Chelating Agent
- Edetate Disodium
- Edetic Acid

Coating Agent
- Carboxymethylcellulose, Sodium
- Cellulose Acetate
- Cellulose Acetate Phthalate
- Ethylcellulose
- Gelatin
- Glaze, Pharmaceutical
- Hydroxypropyl Cellulose
- Hydroxypropyl Methylcellulose
- Hydroxypropyl Methylcellulose Phthalate
- Methacrylic Acid Copolymer
- Methylcellulose
- Polyethylene Glycol
- Polyvinyl Acetate Phthalate
- Shellac
- Sucrose
- Titanium Dioxide
- Wax, Carnauba
- Wax, Microcrystalline
- Zein

Color
- Caramel
- Ferric Oxide, red
  yellow, black, or blends

Complexing Agent
- Edetate Disodium
- Edetic Acid
- Gentisic Acid Ethanolamide
- Oxyquinoline Sulfate

Desiccant
- Calcium Chloride
- Calcium Sulfate
- Silicon Dioxide

Emulsifying and/or Solubilizing Agent
- Acacia
- Cholesterol
- Diethanolamine (Adjunct)
- Glyceryl Monostearate
- Lanolin Alcohols
- Lecithin
- Mono- and Di-glycerides
- Monoethanolamine (Adjunct)
- Oleic Acid (Adjunct)
- Oleyl Alcohol (Stabilizer)
- Poloxamer
- Polyoxyethylene 50 Stearate
- Polyoxyl 35 Castor Oil
- Polyoxyl 40 Hydrogenated Castor Oil
- Polyoxyl 10 Oleyl Ether
- Polyoxyl 20 Cetostearyl Ether
- Polyoxyl 40 Stearate
- Polysorbate 20
- Polysorbate 40
- Polysorbate 60
- Polysorbate 80
- Propylene Glycol Diacetate
- Propylene Glycol Monostearate
- Sodium Lauryl Sulfate
- Sodium Stearate
- Sorbitan Monolaurate
- Sorbitan Monooleate
- Sorbitan Monopalmitate
- Sorbitan Monostearate
- Stearic Acid
- Trolamine
- Wax, Emulsifying

Filtering Aid
- Cellulose, Powdered
- Siliceous Earth, Purified

Flavors and Perfumes
- Anethole
- Benzaldehyde
- Ethyl Vanillin
- Menthol
- Methyl Salicylate
- Monosodium Glutamate
- Peppermint
- Peppermint Oil
- Peppermint Spirit
- Rose Oil
- Rose Water, Stronger
- Thymol
- Vanillin

Glidant and/or Anticaking Agent
- Calcium Silicate
- Magnesium Silicate
- Silicon Dioxide, Colloidal
- Talc

Humectant
- Glycerin
- Hexylene Glycol
- Propylene Glycol
- Sorbitol

Ointment Base
Lanolin
Ointment, Hydrophilic
Ointment, White
Ointment, Yellow
Polyethylene Glycol Ointment
Petrolatum
Petrolatum, Hydrophilic
Petrolatum, White
Rose Water Ointment
Squalane
Vegetable Oil, Hydrogenated, Type II

Plasticizer
Castor Oil
Diacetylated Monoglycerides
Dibutyl Sebacate
Diethyl Phthalate
Glycerin
Mono- and Di-acetylated Monoglycerides
Polyethylene Glycol
Propylene Glycol
Triacetin
Triethyl Citrate

Polymer Membrane
Cellulose Acetate

Sequestering Agent
Beta Cyclodextrin

Solvent
Acetone
Alcohol
Alcohol, Diluted
Amylene Hydrate
Benzyl Benzoate
Butyl Alcohol
Corn Oil
Cottonseed Oil
Ethyl Acetate
Glycerin
Hexylene Glycol
Isopropyl Alcohol
Methyl Alcohol
Methylene Chloride
Methyl Isobutyl Ketone
Mineral Oil
Peanut Oil
Polyethylene Glycol
Propylene Glycol
Sesame Oil
Water for Injection
Water for Injection, Sterile
Water for Irrigation, Sterile
Water, Purified

Sorbent
Cellulose, Powdered
Charcoal
Siliceous Earth, Purified

Sorbent, Carbon Dioxide
Barium Hydroxide Lime
Soda Lime

Stiffening Agent
Castor Oil, Hydrogenated
Cetostearyl Alcohol
Cetyl Alcohol
Cetyl Esters Wax
Hard Fat
Paraffin
Synthetic Paraffin
Stearyl Alcohol
Wax, Emulsifying
Wax, White
Wax, Yellow

Suppository Base
Cocoa Butter
Hard Fat
Polyethylene Glycol

Suspending and/or Viscosity-increasing Agent
Acacia
Agar
Alginic Acid
Aluminum Monostearate
Attapulgite, Activated
Attapulgite, Colloidal Activated
Bentonite
Bentonite, Purified
Bentonite Magma
Carbomer 910
Carbomer 934
Carbomer 934P
Carbomer 940
Carbomer 941
Carbomer 1342
Carboxymethylcellulose Calcium
Carboxymethylcellulose Sodium
Carboxymethylcellulose Sodium 12
Carrageenan
Cellulose, Microcrystalline, and Carboxymethylcellulose Sodium
Dextrin
Gelatin
Guar Gum
Hydroxyethyl Cellulose
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose
Magnesium Aluminum Silicate
Methylcellulose
Pectin
Polyethylene Oxide
Polyvinyl Alcohol
Povidone
Propylene Glycol Alginate
Silicon Dioxide
Silicon Dioxide, Colloidal
Sodium Alginate
Tragacanth
Xanthan Gum

Sweetening Agent
Aspartame
Dextrates
Dextrose
Dextrose Excipient
Fructose
Mannitol
Saccharin
Saccharin Calcium
Saccharin Sodium
Sorbitol
Sorbitol Solution
Sucrose
Sugar, Compressible
Sugar, Confectioner's
Syrup

Tablet Binder
Acacia
Alginic Acid
Carboxymethylcellulose, Sodium
Cellulose, Microcrystalline
Dextrin
Ethylcellulose
Gelatin
Glucose, Liquid
Guar Gum
Hydroxypropyl Methylcellulose
Methylcellulose
Polyethylene Oxide
Povidone
Starch, Pregelatinized
Syrup

Tablet and/or Capsule Diluent
Calcium Carbonate
Calcium Phosphate, Dibasic
Calcium Phosphate, Tribasic
Calcium Sulfate
Cellulose, Microcrystalline
Cellulose, Powdered
Dextrates
Dextrin
Dextrose Excipient
Fructose
Kaolin
Lactose
Mannitol
Sorbitol
Starch
Starch, Pregelatinized
Sucrose
Sugar, Compressible
Sugar, Confectioner's

Tablet Disintegrant
Alginic Acid
Cellulose, Microcrystalline
Croscarmellose Sodium
Crospovidone
Polacrilin Potassium
Sodium Starch Glycolate
Starch
Starch, Pregelatinized

Tablet and/or Capsule Lubricant
Calcium Stearate
Glyceryl Behenate
Magnesium Stearate
Mineral Oil, Light
Polyethylene Glycol
Sodium Stearyl Fumarate
Stearic Acid
Stearic Acid, Purified
Talc
Vegetable Oil, Hydrogenated, Type I
Zinc Stearate

Tonicity Agent
Dextrose
Glycerin
Mannitol
Potassium Chloride
Sodium Chloride

Vehicle
FLAVORED AND/OR SWEETENED
Aromatic Elixir
Benzaldehyde Elixir, Compound
Peppermint Water
Sorbitol Solution
Syrup

OLEAGINOUS
Almond Oil
Corn Oil
Cottonseed Oil
Ethyl Oleate
Isopropyl Myristate
Isopropyl Palmitate
Mineral Oil
Mineral Oil, Light
Myristyl Alcohol
Octyldodecanol
Olive Oil
Peanut Oil
Safflower Oil
Sesame Oil
Soybean Oil
Squalane

SOLID CARRIER
Sugar Spheres

STERILE
Sodium Chloride Injection, Bacteriostatic
Water for Injection, Bacteriostatic

Viscosity-Increasing (See *Suspending Agent*)

Water Repelling Agent
Cyclomethicone
Dimethicone
Simethicone

Wetting and/or Solubilizing Agent
Benzalkonium Chloride
Benzethonium Chloride
Cetylpyridinium Chloride
Docusate Sodium
Nonoxynol 9
Nonoxynol 10
Octoxynol 9
Poloxamer
Polyoxyl 35 Castor Oil
Polyoxyl 40 Hydrogenated Castor Oil
Polyoxyl 50 Stearate
Polyoxyl 10 Oleyl Ether
Polyoxyl 20 Cetostearyl Ether
Polyoxyl 40 Stearate
Polysorbate 20
Polysorbate 40
Polysorbate 60
Polysorbate 80
Sodium Lauryl Sulfate
Sorbitan Monolaurate
Sorbitan Monooleate
Sorbitan Monopalmitate
Sorbitan Monostearate
Tyloxapol

Calcium ⟨191⟩—To 5 mL of the filtrate add 5 mL of water and 1 mL of ammonium oxalate TS: the solution remains clear for not less than 1 minute.

Sulfate ⟨221⟩—A 25-mL portion of the filtrate shows no more sulfate than corresponds to 0.30 mL of 0.020 *N* sulfuric acid (0.006%).

Heavy metals ⟨231⟩—To 20 mL of the filtrate add 4 mL of water and 1 mL of 0.1 *N* hydrochloric acid: the limit is 5 ppm.

Microbial limits ⟨61⟩—It meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*.

Loss on drying ⟨731⟩—Dry it at 105° for 4 hours: it loses not more than 1.0% of its weight.

Residue on ignition ⟨281⟩: not more than 0.08%.

Sugar Spheres

» Sugar Spheres contain not less than 62.5 percent and not more than 91.5 percent of sucrose ($C_{12}H_{22}O_{11}$), calculated on the dried basis, the remainder consisting chiefly of starch. They consist of approximately spherical particles of a labeled nominal size range. They may contain color additives permitted by the FDA for use in drugs.

Packaging and storage—Preserve in well-closed containers.

Labeling—The label states the nominal particle size range.

Identification and Specific rotation—Transfer about 20 g, accurately weighed, to a 200-mL volumetric flask, add 160 mL of water, shake to dissolve the sucrose, add water to volume, and mix. Separate the solubilized sucrose from the insoluble starch component by vacuum filtration through fine filter paper until the filtrate is clear. Use the insoluble portion for the *Identification* test, and use the freshly prepared, clear filtrate for the *Specific rotation* test.

Identification—A water slurry of the insoluble portion responds to *Identification* test *B* under *Starch*.

Specific rotation ⟨781⟩: not less than +41° and not more than +61°, determined on a portion of the filtrate, corresponding to not less than 62.5% and not more than 91.5% of sucrose ($C_{12}H_{22}O_{11}$), calculated on the dried basis.

Microbial limits ⟨61⟩—The Spheres meet the requirements of the tests for absence of *Salmonella* species, *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*, and the total aerobic microbial count does not exceed 100 per g.

Loss on drying ⟨731⟩—Dry the Spheres at 105° for 4 hours: the material loses not more than 4.0% of its weight.

Residue on ignition ⟨281⟩: not more than 0.25%, determined on a 2.0-g specimen ignited at a temperature of 700 ± 25°.

Particle size (see *Powder Fineness* ⟨811⟩)—Test a portion of the Spheres in accordance with the procedure for coarse powders. Not less than 90.0% of it passes the coarser sieve size stated in the labeling; all of it passes the next coarser sieve size listed in Table 2 of the general chapter. Not more than 10.0% passes the finer sieve size stated in the labeling. [NOTE—Use a mechanical sieve-shaking unit that employs both rotary horizontal motion and tapping, in order to ensure reliability of this test.]

Heavy metals, *Method II* ⟨231⟩: 5 ppm.

Sulfur Dioxide

SO_2 64.07
Sulfur dioxide.
Sulfur dioxide [*7446-09-5*].

» Sulfur Dioxide contains not less than 97.0 percent, by volume, of SO_2.

Caution—Sulfur Dioxide is poisonous.

Packaging and storage—Preserve in cylinders.

NOTE—Sulfur Dioxide is used most in the form of a gas in pharmaceutical applications, and is described herein for such purposes. However, it is usually packaged under pressure, hence the following specifications are designed for testing it in liquid form.

Water, *Method I* ⟨921⟩—Taking precautions to avoid absorption of moisture, transfer 3 g (about 2.1 mL) to a suitable flask, and add 20 mL of anhydrous pyridine: not more than 2.0% is found.

Limit of nonvolatile residue—Transfer 300 g (about 209 mL) to a tared, 250-mL conical flask, and allow the liquid to evaporate spontaneously in a well-ventilated hood. When evaporation appears complete, blow a current of dry, filtered air through the flask until the odor of sulfur dioxide is no longer apparent: the weight of the residue does not exceed 7.5 mg (0.0025%).

Sulfuric acid—To the flask containing the residue obtained in the test for *Nonvolatile residue* add 25 mL of water previously neutralized to methyl red TS. Swirl the flask, and titrate with 0.10 *N* sodium hydroxide: not more than 1.3 mL is required (about 0.002%).

Assay—Collect 100.0 mL of gaseous Sulfur Dioxide over mercury, and note the temperature of the sample and the pressure upon it. Slowly introduce 50.0 mL of 0.1 *N* sodium hydroxide into the air space over the mercury, and absorb the sample in the solution by shaking. When absorption is complete, transfer the solution to a 250-mL conical flask, add 3 mL of starch TS, and titrate with 0.1 *N* iodine VS until the solution is pale blue in color. Each mL of 0.1 *N* iodine is equivalent to 1.094 mL of SO_2 at a temperature of 0° and a pressure of 760 mm of mercury.

Sulfuric Acid

H_2SO_4 98.08
Sulfuric acid.
Sulfuric acid [*7664-93-9*].

» Sulfuric Acid contains not less than 95.0 percent and not more than 98.0 percent, by weight, of H_2SO_4.

Caution—When Sulfuric Acid is to be mixed with other liquids, always add it to the diluent and exercise great caution.

Packaging and storage—Preserve in tight containers.

Identification—It responds to the tests for *Sulfate* ⟨191⟩.

Residue on ignition ⟨281⟩—Evaporate 22 mL (40 g) to dryness, and ignite: not more than 2 mg of residue remains (0.005%).

Chloride ⟨221⟩—A dilution of 1.1 mL (2.0 g) in water shows no more chloride than corresponds to 0.15 mL of 0.020 *N* hydrochloric acid (0.005%).

Arsenic ⟨211⟩—Add 1.6 mL (3.0 g) to 3 mL of nitric acid and 20 mL of water, and evaporate until dense fumes of sulfur trioxide form. Cool, and cautiously wash the solution into an arsine generating flask with 50 mL of water; the resulting solution meets the requirements of the test, the addition of 20 mL of dilute sulfuric acid (1 in 5) specified under *Procedure* being omitted (1 ppm).

Heavy metals ⟨231⟩—Add 2.2 mL (4.0 g) to about 10 mg of sodium carbonate dissolved in 10 mL of water. Heat until almost dry, add 1 mL of nitric acid, evaporate to dryness, add 2 mL of 1 *N* acetic acid to the residue, and dilute with water to 25 mL: the limit is 5 ppm.

Reducing substances—Carefully dilute 4.4 mL (8.0 g) with about 50 mL of ice cold water, keeping the solution cold during the addition. Add 0.10 mL of 0.10 *N* potassium permanganate: the solution remains pink for 5 minutes.