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the USAN adopted name listed in *USAN and the USP Dictionary of Drug Names*. . . .⁴

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(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.

Beyond-use dating information must be provided by the manufacturer in the labeling of all solid oral Pharmacopeial dosage forms intended for dispensing on prescription, unless the dosage form is packaged by the manufacturer in a container that is labeled for dispensing directly to the patient. To meet this requirement, there

must be a recommendation for an appropriate dispensing container (e.g., "tight," "well-closed," "light-resistant") and, for unit-dose packaging, a recommendation for the appropriate class of package (see Class A, B, C, or D under *Results in Containers—Permeation* (671)) and the length of time that is appropriate for a beyond-use date in that type of container or package. Such a beyond-use date may be based on an "open dish" study in which the dosage forms are found to remain stable (i.e., conform to all monograph requirements for the declared beyond-use time period). The open dish study is a study in which the dosage forms are exposed to 60% relative humidity at 25° for 30 days without any container protection: three samples of 30-unit doses from one lot are analyzed at 0 and 30 days. The dosage forms may be protected from light during the study. Beyond-use dating information supported by such "open dish" studies need only indicate that, other than regarding the need for light resistance, any appropriate dispensing container may be used for repackaging the dosage form. Alternatively, studies conducted in containers that are one class below (i.e., more permeable to water vapor) the class being recommended for repackaging the dosage form may be substituted for "open dish" studies. For example, a study conducted in Class C unit-dose containers that demonstrates stability will support a recommendation for use of a Class B, or better, package. Beyond-use dating information may be obtained by any other type of stability study including, but not limited to, accelerated stability studies. Exempt from these requirements are drugs dispensed in a container to be used within a day and drugs in container-closure systems that are known to be equivalent in protection to the marketed container system.

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 $25 \pm 2^\circ$ at $60 \pm 5\%$ relative humidity. Accelerated studies are specified at $40 \pm 2^\circ$ and at $75 \pm 5\%$ 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 defined 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 cal-

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

Table 1. International Climatic Zones.

Climatic Zone	Calculated Data				Derived Data		
	°C*	°C MKT**	% RH	mbar***	°C	% RH	mbar
I. <i>Temperate</i> United Kingdom Northern Europe Canada Russia	20.0	20.0	42	9.9	21	45	11.2
II. <i>Mediterranean, Subtropical</i> United States Japan Southern Europe (Portugal-Greece)	21.6	22.0	52	13.5	25	60	19.0
III. <i>Hot, Dry</i> Iran Iraq Sudan	26.4	27.9	35	11.9	30	35	15.0
IV. <i>Hot, Humid</i> 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.

culated 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):

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

in which T_k is the mean kinetic temperature; ΔH is the heat of activation, 83.144 kJ·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 n th 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). These products may be fitted with valves enabling either continuous or metered-dose delivery; hence, the terms "[DRUG] Metered Topical Aerosols," "[DRUG] Metered Nasal Aerosols," etc.

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 must be carefully controlled and the average size of the particles should be under 5 μm. These products are also known as metered-dose inhalers (MDIs). Other aerosol sprays may contain particles up to several hundred micrometers in diameter.

The basic components of an aerosol system are the container, the propellant, the concentrate containing the active ingredient(s), the valve, and the actuator. The nature of these components determines such characteristics as particle size distribution, uniformity of dose

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.

for metered valves, delivery rate, wetness and temperature of the spray, spray pattern and velocity or plume geometry, foam density, and fluid viscosity.

Types of Aerosols

Aerosols consist of two-phase (gas and liquid) or three-phase (gas, liquid, and solid or liquid) systems. The two-phase aerosol consists of a solution of active ingredients in liquefied propellant and the vaporized propellant. The solvent is composed of the propellant or a mixture of the propellant and co-solvents such as alcohol, propylene glycol, and polyethylene glycols, which are often used to enhance the solubility of the active ingredients.

Three-phase systems consist of a suspension or emulsion of the active ingredient(s) in addition to the vaporized propellants. A suspension consists of the active ingredient(s) that may be dispersed in the propellant system with the aid of suitable excipients such as wetting agents and / or solid carriers such as talc or colloidal silicas.

A foam aerosol is an emulsion containing one or more active ingredients, surfactants, aqueous or nonaqueous liquids, and the propellants. If the propellant is in the internal (discontinuous) phase (i.e., of the oil-in-water type), a stable foam is discharged; and if the propellant is in the external (continuous) phase (i.e., of the water-in-oil type), a spray or a quick-breaking foam is discharged.

Propellants

The propellant supplies the necessary pressure within an aerosol system to expel material from the container and, in combination with other components, to convert the material into the desired physical form. Propellants may be broadly classified as liquefied or compressed gases having vapor pressures generally exceeding atmospheric pressure. Propellants within this definition include various hydrocarbons, especially halogenated derivatives of methane, ethane, and propane, low molecular weight hydrocarbons such as the butanes and pentanes, and compressed gases such as carbon dioxide, nitrogen, and nitrous oxide. Mixtures of propellants are frequently used to obtain desirable pressure, delivery, and spray characteristics. A good propellant system should have the proper vapor pressure characteristics consistent with the other aerosol components.

Valves

The primary function of the valve is to regulate the flow of the therapeutic agent and propellant from the container. The spray characteristics of the aerosol are influenced by orifice dimension, number, and location. Most aerosol valves provide for continuous spray operation and are used on most topical products. However, pharmaceutical products for oral or nasal inhalation often utilize metered-dose valves that must deliver a uniform quantity of spray upon each valve activation. The accuracy and reproducibility of the doses delivered from metering valves are generally good, comparing favorably to the uniformity of solid dosage forms such as tablets and capsules. However, when aerosol packages are stored improperly, or when they have not been used for long periods of time, valves must be primed before use. Materials used for the manufacture of valves should be inert to the formulations used. Plastic, rubber, aluminum, and stainless steel valve components are commonly used. Metered-dose valves must deliver an accurate dose within specified tolerances.

Actuators

An actuator is the fitting attached to an aerosol valve stem, which when depressed or moved, opens the valve, and directs the spray containing the drug preparation to the desired area. The actuator usually indicates the direction in which the preparation is dispensed and protects the hand or finger from the refrigerant effects of the propellant. Actuators incorporate an orifice which may vary widely in size and shape. The size of this orifice, the expansion chamber design, and the nature of the propellant and formulation influence the delivered dose as well as the physical characteristics of the spray, foam, or stream of solid particles dispensed. For inhalation aerosols, an actuator capable of delivering the medication in the proper particle size range and with the appropriate spray pattern and plume geometry is utilized.

Containers

Aerosol containers usually are made of glass, plastic, or metal, or a combination of these materials. Glass containers must be precisely engineered to provide the maximum in pressure safety and impact resistance. Plastics may be employed to coat glass containers for improved safety characteristics, or to coat metal containers to improve corrosion resistance and enhance stability of the formulation. Suitable metals include stainless steel, aluminum, and tin-plated steel. Extractables or leachables (e.g., drawing oils, cleaning agents, etc.) and particulates on the internal surfaces of containers should be controlled.

Manufacture

Aerosols are usually prepared by one of two general processes. In the "cold-fill" process, the concentrate (generally cooled to a temperature below 0°) and the refrigerated propellant are measured into open containers (usually chilled). The valve-actuator assembly is then crimped onto the container to form a pressure-tight seal. During the interval between propellant addition and crimping, sufficient volatilization of propellant occurs to displace air from the container. In the "pressure-fill" method, the concentrate is placed in the container, and either the propellant is forced under pressure through the valve orifice after the valve is sealed, or the propellant is allowed to flow under the valve cap and then the valve assembly is sealed ("under-the-cap" filling). In both cases of the "pressure-fill" method, provision must be made for evacuation of air by means of vacuum or displacement with a small amount of propellant vapor. Manufacturing process controls usually include monitoring of proper formulation and propellant fill weight and pressure testing, leak testing, and valve function testing of the finished aerosol. Microbiological attributes should also be controlled.

Extractable Substances

Since pressurized inhalers and aerosols are normally formulated with organic solvents as the propellant or the vehicle, leaching of extractables from the elastomeric and plastic components into the formulation is a potentially serious problem. Thus, the composition and the quality of materials used in the manufacture of the valve components (e.g., stem, gaskets, housing, etc.) must be carefully selected and controlled. Their compatibility with formulation components should be well established so as to prevent distortion of the valve components and to minimize changes in the medication delivery, leak rate, and impurity profile of the drug product over time. The extractable profiles of a representative sample of each of the elastomeric and plastic components of the valve should be established under specified conditions and should be correlated to the extractable profile of the aged drug product or placebo, to ensure reproducible quality and purity of the drug product. Extractables, which may include polynuclear aromatics, nitrosamines, vulcanization accelerators, antioxidants, plasticizers, monomers, etc., should be identified and minimized wherever possible.

Specifications and limits for individual and total extractables from different valve components may require the use of different analytical methods. In addition, the standard USP biological testing (see the general test chapters *Biological Reactivity Tests, In Vitro* (87) and *Biological Reactivity Tests, In Vivo* (88)) as well as other safety data may be needed.

Labeling

Medicinal aerosols should contain at least the following warning information on the label as in accordance with appropriate regulations.

Warning—Avoid inhaling. Avoid spraying into eyes or onto other mucous membranes.

NOTE—The statement "Avoid inhaling" is not necessary for preparations specifically designed for use by inhalation. The phrase "or other mucous membranes" is not necessary for preparations specifically designed for use on mucous membranes.

Warning—Contents under pressure. Do not puncture or incinerate container. Do not expose to heat or store at temperatures above 120° F (49° C). Keep out of reach of children.

In addition to the aforementioned warnings, the label of a drug packaged in an aerosol container in which the propellant consists

in whole or in part of a halocarbon or hydrocarbon shall, where required under regulations of the FDA, bear either of the following warnings:

Warning—Do not inhale directly; deliberate inhalation of contents can cause death.

Warning—Use only as directed; intentional misuse by deliberately concentrating and inhaling the contents can be harmful or fatal.

BOLUSES

Boluses are large elongated tablets intended for administration to animals (see *Tablets*).

CAPSULES

Capsules are solid dosage forms in which the drug is enclosed within either a hard or soft soluble container or "shell." The shells are usually formed from gelatin; however, they also may be made from starch or other suitable substances. Hard shell capsule sizes range from No. 5, the smallest, to No. 000, which is the largest, except for veterinary sizes. However, size No. 00 generally is the largest size acceptable to patients. Size 0 hard gelatin capsules having an elongated body (known as size OE) also are available, which provide greater fill capacity without an increase in diameter. Hard gelatin capsules consist of two, telescoping cap and body pieces. Generally, there are unique grooves or indentations molded into the cap and body portions to provide a positive closure when fully engaged, which helps prevent the accidental separation of the filled capsules during shipping and handling. Positive closure also may be affected by spot fusion ("welding") of the cap and body pieces together through direct thermal means or by application of ultrasonic energy. Factory-filled hard gelatin capsules may be completely sealed by banding, a process in which one or more layers of gelatin are applied over the seam of the cap and body, or by a liquid fusion process wherein the filled capsules are wetted with a hydroalcoholic solution that penetrates into the space where the cap overlaps the body, and then dried. Hard shell capsules made from starch consist of two, fitted cap and body pieces. Since the two pieces do not telescope or interlock positively, they are sealed together at the time of filling to prevent their separation. Starch capsules are sealed by the application of a hydroalcoholic solution to the recessed section of the cap immediately prior to its being placed onto the body.

The banding of hard shell gelatin capsules or the liquid sealing of hard shell starch capsules enhances consumer safety by making the capsules difficult to open without causing visible, obvious damage, and may improve the stability of contents by limiting O₂ penetration. Industrially filled hard shell capsules also are often of distinctive color and shape or are otherwise marked to identify them with the manufacturer. Additionally, such capsules may be printed axially or radially with strengths, product codes, etc. Pharmaceutical grade printing inks are usually based on shellac and employ FDA-approved pigments and lake dyes.

In extemporaneous prescription practice, hard shell capsules may be hand-filled; this permits the prescriber a latitude of choice in selecting either a single drug or a combination of drugs at the exact dosage level considered best for the individual patient. This flexibility gives hard shell capsules an advantage over compressed tablets and soft shell capsules as a dosage form. Hard shell capsules are usually formed from gelatins having relatively high gel strength. Either type may be used, but blends of pork skin and bone gelatin are often used to optimize shell clarity and toughness. Hard shell capsules also may be formed from starch or other suitable substances. Hard shell capsules may also contain colorants, such as D&C and FD&C dyes or the various iron oxides, opaquing agents such as titanium dioxide, dispersing agents, hardening agents such as sucrose, and preservatives. They normally contain between 10% and 15% water.

Hard gelatin capsules are made by a process that involves dipping shaped pins into gelatin solutions, after which the gelatin films are dried, trimmed, and removed from the pins, and the body and cap pieces are joined. Starch capsules are made by injection molding a mixture of starch and water, after which the capsules are dried. A separate mold is used for caps and bodies, and the two parts are

supplied separately. The empty capsules should be stored in tight containers until they are filled. Since gelatin is of animal origin and starch is of vegetable origin, capsules made with these materials should be protected from potential sources or microbial contamination.

Hard shell capsules typically are filled with powder, beads, or granules. Inert sugar beads (nonpareils) may be coated with active ingredients and coating compositions that provide extended-release profiles or enteric properties. Alternatively, larger dose active ingredients themselves may be suitably formed into pellets and then coated. Semisolids or liquids also may be filled into hard shell capsules; however, when the latter are encapsulated, one of the sealing techniques must be employed to prevent leakage.

In hard gelatin capsule filling operations, the body and cap of the shell are separated prior to dosing. In hard starch shell filling operations, the bodies and caps are supplied separately and are fed into separate hoppers of the filling machine. Machines employing various dosing principles may be employed to fill powders into hard shell capsules; however, most fully automatic machines form powder plugs by compression and eject them into empty capsule bodies. Accessories to these machines generally are available for the other types of fills. Powder formulations often require adding fillers, lubricants, and glidants to the active ingredients to facilitate encapsulation. The formulation, as well as the method of filling, particularly the degree of compaction, may influence the rate of drug release. The addition of wetting agents to the powder mass is common where the active ingredient is hydrophobic. Disintegrants also may be included in powder formulations to facilitate deaggregation and dispersal of capsule plugs in the gut. Powder formulations often may be produced by dry blending; however, bulky formulations may require densification by roll compaction or other suitable granulation techniques.

Powder mixtures that tend to liquefy may be dispensed in hard shell capsules if an absorbent such as magnesium carbonate, colloidal silicon dioxide, or other suitable substance is used. Potent drugs are often mixed with an inert diluent before being filled into capsules. Where two mutually incompatible drugs are prescribed together, it is sometimes possible to place one in a small capsule and then enclose it with the second drug in a larger capsule. Incompatible drugs also can be separated by placing coated pellets or tablets, or soft shell capsules of one drug into the capsule shell before adding the second drug.

Thixotropic semisolids may be formed by gelling liquid drugs or vehicles with colloidal silicas or powdered high molecular weight polyethylene glycols. Various waxy or fatty compounds may be used to prepare semisolid matrices by fusion.

Soft shell capsules made from gelatin (sometimes called softgels) or other suitable material require large-scale production methods. The soft gelatin shell is somewhat thicker than that of hard shell capsules and may be plasticized by the addition of a polyol such as sorbitol or glycerin. The ratio of dry plasticizer to dry gelatin determines the "hardness" of the shell and may be varied to accommodate environmental conditions as well as the nature of the contents. Like hard shells, the shell composition may include approved dyes and pigments, opaquing agents such as titanium dioxide, and preservatives. Flavors may be added and up to 5% sucrose may be included for its sweetness and to produce a chewable shell. Soft gelatin shells normally contain 6% to 13% water. Soft shell capsules also may be printed with a product code, strength, etc. In most cases, soft shell capsules are filled with liquid contents. Typically, active ingredients are dissolved or suspended in a liquid vehicle. Classically, an oleaginous vehicle such as a vegetable oil was used; however, nonaqueous, water-miscible liquid vehicles such as the lower molecular weight polyethylene glycols are more common today due to fewer bioavailability problems.

Available in a wide variety of sizes and shapes, soft shell capsules are both formed, filled, and sealed in the same machine; typically, this is a rotary die process, although a plate process or reciprocating die process also may be employed. Soft shell capsules also may be manufactured in a bubble process that forms seamless spherical capsules. With suitable equipment, powders and other dry solids also may be filled into soft shell capsules.

Liquid-filled capsules of either type involve similar formulation technology and offer similar advantages and limitations. For instance, both may offer advantages over dry-filled capsules and tablets in content uniformity and drug dissolution. Greater homogeneity is possible in liquid systems, and liquids can be metered more

accurately. Drug dissolution may benefit because the drug may already be in solution or at least suspended in a hydrophilic vehicle. However, the contact between the hard or soft shell and its liquid content is more intimate than exists with dry-filled capsules, and this may enhance the chances for undesired interactions. The liquid nature of capsule contents presents different technological problems than dry-filled capsules in regard to disintegration and dissolution testing. From formulation, technological, and biopharmaceutical points of view, liquid-filled capsules of either type have more in common than liquid-filled and dry-filled capsules having the same shell composition. Thus, for compendial purposes, standards and methods should be established based on capsule contents rather than on whether the contents are filled into hard or soft shell capsules.

DELAYED-RELEASE CAPSULES

Capsules may be coated, or, more commonly, encapsulated granules may be coated to resist releasing the drug in the gastric fluid of the stomach where a delay is important to alleviate potential problems of drug inactivation or gastric mucosal irritation. The term "delayed-release" is used for Pharmacopeial monographs on enteric coated capsules that are intended to delay the release of medicament until the capsule has passed through the stomach, and the individual monographs include tests and specifications for *Drug release* (see *Drug Release* (724)) or *Disintegration* (see *Disintegration* (701)).

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.

CONCENTRATE FOR DIP

Concentrate for Dip is a preparation containing one or more active ingredients usually in the form of a paste or solution. It is used to prepare a diluted suspension, emulsion, or solution of the active ingredient(s) for the prevention and treatment of ectoparasitic infestations of animals. The diluted preparation (Dip) is applied by complete immersion of the animal or, where appropriate, by spraying. Concentrate for Dip may contain suitable antimicrobial preservatives.

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 Sulfate 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., *Ben-*

tonite 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 liquefied 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 μ L (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

An Injection is a preparation intended for parenteral administration or for constituting or diluting a parenteral article prior to administration (see *Injections* (1)).

Each container of an Injection is filled with a volume in slight excess of the labeled "size" or that volume that is to be withdrawn. The excess volumes recommended in the accompanying table are

usually sufficient to permit withdrawal and administration of the labeled volumes.

Labeled Size	Recommended Excess Volume	
	For Mobile Liquids	For Viscous Liquids
0.5 mL	0.10 mL	0.12 mL
1.0 mL	0.10 mL	0.15 mL
2.0 mL	0.15 mL	0.25 mL
5.0 mL	0.30 mL	0.50 mL
10.0 mL	0.50 mL	0.70 mL
20.0 mL	0.60 mL	0.90 mL
30.0 mL	0.80 mL	1.20 mL
50.0 mL or more	2%	3%

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, that 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

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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*). Some paste preparations intended for administration to animals are applied orally. The paste is squeezed into the mouth of the animal, generally at the back of the tongue, or is spread inside the mouth.

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 com-

pacted 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.

Granules for veterinary use may be administered by sprinkling the dry powder on animal feed or by mixing it with animal food.

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)).

PREMIXES

Premixes are mixtures of one or more drug substances with suitable vehicles. Premixes are intended for admixture to animal feed-stuffs before administration. They are used to facilitate dilution of the active drug components with animal feed. Premixes should be as homogeneous as possible. It is essential that materials of suitable fineness be used and that thorough mixing be achieved at all stages of premix preparation. Premixes may be prepared as powder, pellets, or in granulated form. The granulated form is free-flowing and free from aggregates.

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, that contain alcohol as a cosolvent, have been traditionally designated as Elixirs. However, many others 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 un-ionized 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 cat-

egories 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 (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 formulated and manufactured so that they may 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.

DELAYED-RELEASE 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)) or *Disintegration* (see *Disintegration* (701)).

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.

<1161> PHARMACY COMPOUNDING PRACTICES

Compounding is an integral part of pharmacy practice and is essential to the provision of health care. The purpose of this chapter and applicable monographs on formulation is to provide general information to enhance the pharmacist's ability in the pharmacy to extemporaneously compound preparations that are of acceptable strength, quality, and purity.

Compounding is different from manufacturing, which is guided by GMPs (see *Good Manufacturing Practices* (1077)). Some of the characteristics or criteria that differentiate compounding from manufacturing include the existence of specific practitioner-patient-pharmacist relationships; the quantity of medication prepared in anticipation of receiving a prescription or a prescription order; and the conditions of sale, which are limited to specific prescription orders.

The pharmacist's responsibilities in compounding drug preparations are to dispense the finished preparation in accordance with a prescription or a prescriber's order or intent and to dispense those preparations in compliance with requirements established by Boards of Pharmacy and other regulatory agencies. Pharmacists must be familiar with statutes and regulations that govern compounding because these requirements vary from state to state.

The pharmacist is responsible for compounding preparations of acceptable strength, quality, and purity with appropriate packaging and labeling in accordance with good pharmacy practices, official

standards, and relevant scientific data and information. Pharmacists engaging in compounding should continually expand their compounding knowledge by participating in seminars, studying appropriate literature, and consulting colleagues.

COMPOUNDING ENVIRONMENT

Facilities

Pharmacy areas designated for compounding should have adequate space for the orderly placement of equipment and materials to prevent mixups between ingredients, containers, labels, in-process materials, and finished preparations. The compounding area should also be designed, arranged, used, and maintained to prevent adventitious cross-contamination. Areas used for sterile preparations should be separate and distinct from the nonsterile compounding area (see *Sterile Drug Products for Home Use* (1206)). The entire compounding area should be well lighted. Heating, ventilation, and air conditioning systems should be controlled to avoid decomposition of chemicals (see *Storage Temperature* under *Preservation, Packaging, Storage, and Labeling* in the *General Notices* and the manufacturers' labeled storage conditions). Storage areas should provide an environment suitably controlled to ensure quality and stability of bulk chemicals and finished preparations.

Potable water should be supplied for hand and equipment washing. This water should meet the standards prescribed in the Environmental Protection Agency's National Primary Drinking Water Regulations (40 CFR Part 141). *Purified Water* must be used for compounding nonsterile drug preparations when formulations indicate the inclusion of water. *Purified Water* must also be used for rinsing equipment and utensils. In those cases when a water is used to prepare a sterile preparation, *Water for Injection*, *Sterile Water for Injection*, or *Bacteriostatic Water for Injection* must be used (see *Water for Pharmaceutical Purposes* (1231) and *Sterile Drug Products for Home Use* (1206)).

Compounding areas should be maintained in a clean and sanitary condition. Adequate washing facilities should be provided, including hot and cold water, soap or detergent, and air driers or single-service towels. Sewage, trash, and other refuse in the compounding area should be disposed of in a safe, sanitary, and timely manner. Equipment should be thoroughly cleaned promptly after use to avoid cross-contamination of ingredients and preparations. Special precautions should be taken to clean equipment and compounding areas meticulously after compounding preparations that contain allergenic ingredients (e.g., sulfonamides or penicillins).

Equipment

Equipment should be of appropriate design and size for compounding and suitable for the intended uses. The types and sizes of equipment will depend on the dosage forms and the quantities compounded (see *Weights and Balances* (41), *Prescription Balances and Volumetric Apparatus* (1176), and equipment manufacturers' instruction manuals). All equipment should be constructed so that surfaces that contact pharmaceutical components, in-process materials, or finished preparations are not reactive, additive, or adsorptive to avoid altering the safety, identity, strength, quality, or purity of the preparation. Equipment and accessories used in compounding should be inspected, maintained, and cleaned at appropriate intervals to ensure the accuracy and reliability of their performance.

STABILITY OF COMPOUNDED PREPARATIONS

Stability is defined as the extent to which a preparation retains, within specified limits, and throughout its period of storage and use, the same properties and characteristics that it possessed at the time of compounding. See the table *Criteria for Acceptable Levels of Stability* under *Stability Considerations in Dispensing Practices* (1191).

The compounding pharmacist must avoid formulation ingredients and processing conditions that would result in a potentially toxic or ineffective preparation. The pharmacist's knowledge of the chemical reactions by which drugs degrade provides a means for establishing conditions under which the rate of degradation is minimized. The factors that influence the stability of preparations compounded by pharmacists are generally the same as those for man-

ufactured drug products (see *Factors Affecting Product Stability and Responsibility of the Pharmacist* under *Stability Considerations in Dispensing Practice* (1191)).

Primary Packaging

Compounded preparations should be packaged in containers meeting USP standards (see *Containers* under *Preservation, Packaging, Storage, and Labeling* in the *General Notices*, *Containers* (661), and *Containers—Permeation* (671)). The container used depends on the physical and chemical properties of the compounded preparation. Container-drug interaction should be considered with substances such as phenolic compounds and sorptive materials (e.g., polypeptides and proteins).

Sterility

Assurance of sterility in a compounded sterile preparation is mandatory. Compounding and packaging of sterile drugs, such as ophthalmic solutions, will require strict adherence to guidelines presented in the general information chapter *Sterile Drug Products for Home Use* (1206) and in the manufacturers' labeling instructions.

Stability Criteria and Beyond-use Dating

The beyond-use date is the date after which a compounded preparation should not be used. Because compounded preparations are intended for administration immediately or following short-term storage, their beyond-use dates may be assigned based on criteria different from those applied to assigning expiration dates to manufactured drug products.

Pharmacists should consult and apply drug-specific and general stability documentation and literature when available, and should consider the nature of the drug and its degradation mechanism, the container in which it is packaged, the expected storage conditions, and the intended duration of therapy when assigning a beyond-use date (see *Expiration Date* under *Labeling* in the *General Notices*). Beyond-use dates should be assigned conservatively. When using manufactured solid dosage forms to prepare a solution or aqueous suspension, the pharmacist should also consider factors such as hydrolysis and the freeze-thaw property of the final preparation before assigning a beyond-use date. In assigning a beyond-use date for a compounded drug preparation, in addition to using all available stability information, the pharmacist should also use his or her pharmaceutical education and experience.

When a manufactured product is used as the source of active ingredient for a nonsterile compounded preparation, the product expiration date cannot be used to extrapolate directly a beyond-use date for the compounded preparation. However, a pharmacist may refer to the literature or to the manufacturer for stability information. The pharmacist may also refer to applicable publications to obtain stability, compatibility, and degradation information on ingredients. All stability data must be carefully interpreted in relation to the actual compounded formulation.

At all steps in the compounding, dispensing, and storage process, the pharmacist should observe the compounded drug preparation for signs of instability. For more specific details of some of the common physical signs of deterioration, see *Observing Products for Evidence of Instability* under *Stability Considerations in Dispensing Practice* (1191). However, excessive chemical degradation and other drug concentration loss due to reactions may be invisible more often than they are visible.

In the **absence** of stability information that is applicable to a specific drug and preparation, the following maximum beyond-use dates are recommended for nonsterile compounded drug preparations* that are packaged in tight, light-resistant containers and stored at controlled room temperature unless otherwise indicated.

For nonaqueous liquids and solid formulations (Where the manufactured drug product is the source of active ingredient)—The beyond-use date is not later than 25% of the time remaining until the product's expiration date or 6 months, whichever is earlier.

A USP or NF substance is the source of active ingredient—The beyond-use date is not later than 6 months.

* For guidelines applicable to dating sterile compounded preparations, see *Storage and Expiration Dating* under *Sterile Drug Products for Home Use* (1206).

For water-containing formulations (prepared from ingredients in solid form)—The beyond-use date is not later than 14 days when stored at cold temperatures.

For all other formulations—The beyond-use date is not later than the intended duration of therapy or 30 days, whichever is earlier. These beyond-use date limits may be exceeded when there is supporting valid scientific stability information that is directly applicable to the specific preparation (i.e., the *same* drug concentration range, pH, excipients, vehicle, water content, etc.). See also the beyond-use dating information in the *Labeling* section under *Single-unit Containers and Unit-dose Containers for Nonsterile Solid and Liquid Dosage Forms* in the general test chapter *Containers* <661>.

BEYOND-USE LABELING

Federal law requires that manufactured drug products be labeled with an expiration date. Some state laws may require a beyond-use date. The label on the container or package of an official compounded preparation must bear a beyond-use date. Good pharmacy practice dictates beyond-use labeling for all compounded preparations.

INGREDIENT SELECTION AND CALCULATIONS

Ingredients

Active Ingredient(s)—An *active ingredient* in this *Pharmacopeia* means an official substance. The term active ingredients usually refers to chemicals, substances, or other components of articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases in humans or other animals or for use as nutritional supplements.

Added Substances—*Added substances* in this *Pharmacopeia* mean ingredients that are necessary to prepare the dosage form but are not intended or expected to cause a human pharmacologic response if administered alone in the amount or concentration contained in a single dose of the compounded dosage form. The term added substances is usually used synonymously with the terms *inactive ingredients*, *excipients*, and *pharmaceutical ingredients*.

Sources

A USP or an NF grade drug substance is the preferred source of ingredients for compounding all drug preparations. If that is not available, or when food, cosmetics, or other substances are used, then the use of another high quality source, such as analytical reagent (AR), certified American Chemical Society (ACS), or Food Chemicals Codex (FCC) grade, is an option for professional judgment. For any drug substance used in compounding that is not official in the USP or NF, the pharmacist shall establish purity and safety by reasonable means, which may include lot analysis, manufacturer reputation, or reliability of source.

A manufactured drug product may be a source of active ingredient. Only manufactured drugs from containers labeled with a batch control number and a future expiration date are acceptable as a potential source of active ingredients. When compounding with manufactured drug products, the pharmacist must consider all ingredients present in the drug product relative to the intended use of the compounded preparation.

Calculations

The pharmacist must be able to calculate the amount or concentration of drug substances in each unit or dosage portion of a compounded preparation at the time it is dispensed. Pharmacists must perform calculations and measurements to obtain, theoretically, 100% of the amount of each ingredient in compounded formulations. Calculations must account for the active ingredient, or active moiety, and water content of drug substances, which includes that in the chemical formulas of hydrates. Official drug substances and added substances must meet the requirements under *Loss on Drying* <731>, which must be included in the calculations of amounts and concentrations of ingredients. The pharmacist should consider the effect of ambient humidity on the gain or loss of water from drugs and added substances in containers subjected to intermittent opening over prolonged storage. Each container should be opened for

the shortest duration necessary and then closed tightly immediately after use.

The nature of the drug substance that is to be weighed and used in compounding a prescription must be known exactly. If the substance is a hydrate, its anhydrous equivalent weight may need to be calculated. On the other hand, if there is adsorbed moisture present that is either specified on a certificate of analysis or that is determined in the pharmacy immediately before the drug substance is used by the procedure under *Loss on Drying* <731>, this information must be used when calculating the amount of drug substance that is to be weighed in order to determine the exact amount of anhydrous drug substance required.

There are cases in which the required amount of a dose is specified in terms of a cation [e.g., Li(+), netilmicin (n+)], an anion [e.g., F(-)], or a molecule (e.g., theophylline in aminophylline). In these instances, the drug substance weighed is a salt or complex, a portion of which represents the pharmacologically active moiety. Thus, the exact amount of such substances weighed must be calculated on the basis of the required quantity of the pharmacological moiety.

The following formula may be used to calculate the exact theoretical weight of an ingredient in a compounded preparation:

$$W = ab/de,$$

in which W is the actual weighed amount; a is the prescribed or pharmacist-determined weight of the active or functional moiety of drug or added substance; b is the chemical formula weight of the ingredient, including waters of hydration for hydrous ingredients; d is the fraction of dry weight when the percent by weight of adsorbed moisture content is known from the loss on drying procedure (see *Loss on Drying* <731>); and e is the formula weight of the active or functional moiety of a drug or added substance that is provided in the formula weight of the weighed ingredient.

Example 1: Triturate Morphine Sulfate USP and Lactose NF to obtain 10 g in which there are 30 mg of Morphine Sulfate USP for each 200 mg of the morphine-lactose mixture. [NOTE—Clinical dosages of morphine mean Morphine Sulfate USP, which is the pentahydrate.]

Equation Factor	Numerical Value
W	weight, in g, of Morphine Sulfate USP
a	1.5 g of morphine sulfate pentahydrate in the prescription
b	759 g/mole
d	1.0
e	759 g/mole

$$W = \frac{1.5 \text{ g (759 g/mole)}}{1.0 \text{ (759 g/mole)}} = 1.5 \text{ g.}$$

Example 2: Accurately weigh an amount of Aminophylline USP to obtain 250 mg of anhydrous theophylline. [NOTE—The powdered aminophylline dihydrate weighed contains 0.4% w/w adsorbed moisture as stated in the Certificate of Analysis.]

Equation Factor	Numerical Value
W	weight, in mg, of Aminophylline USP (dihydrate)
a	250 mg of theophylline
b	456 g/mole
d	0.996
e	360 g/mole

$$W = \frac{250 \text{ mg (456 g/mole)}}{0.996 \text{ (360 g/mole)}} = 318 \text{ mg.}$$

Example 3: Accurately weigh an amount of Lithium Citrate USP (containing 2.5% moisture as stated in the Certificate of Analysis) to obtain 200 mEq of lithium (Li+). [NOTE—One mEq of Li+ is equivalent to 0.00694 g of Li+.]

Equation Factor	Numerical Value
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W	weight, in g, of Lithium Citrate USP (tetrahydrate)
a	200 mEq of Li ⁺ or 1.39 g of Li ⁺
b	282 g/mole
d	0.975
e	3 × 6.94 g/mole or 20.8 g/mole

$$W = \frac{1.39 \text{ g (282 g/mole)}}{0.975 (20.8 \text{ g/mole})} = 19.3 \text{ g.}$$

Example 4: Accurately weigh an amount of Netilmicin Sulfate USP, equivalent to 2.5 g of netilmicin. [NOTE—Using the procedure under *Loss on Drying* (731), the Netilmicin Sulfate USP that was weighed lost 12% of its weight.]

Equation Factor	Numerical Value
W	weight, in g, of Netilmicin Sulfate USP
a	2.5 g
b	1442 g/mole
d	0.88
e	951 g/mole

$$W = \frac{2.5 \text{ g (1442 g/mole)}}{0.88 (951 \text{ g/mole})} = 4.31 \text{ g.}$$

CHECKLIST FOR ACCEPTABLE STRENGTH, QUALITY, AND PURITY

The following questions should be considered carefully before compounding:

- (1) Have the physical and chemical properties and medicinal and pharmaceutical uses of the drug substances been reviewed?
- (2) Is the quantity and quality of each active ingredient identifiable?
- (3) Will the active ingredients be effectively absorbed, locally or systemically according to the prescribed purpose, from the preparation and route of administration?
- (4) Are there added substances (confirmed or potentially present) from manufactured products that may be expected to cause an allergic reaction, irritation, toxicity, or undesirable organoleptic response from the patient? Are there added substances (confirmed or potentially present) that may be unfavorable (e.g., unsuitable pH or inadequate solubility)?
- (5) Were all calculations and measurements confirmed to ensure that the preparation will be compounded accurately?

COMPOUNDED DOSAGE FORMS

The terms *compounded dosage forms*, *compounded drugs*, *compounded formulations*, and *compounded preparations* mean finished dosage forms that are prepared by or under the direct supervision of a licensed pharmacist. **When controlled substances are used, check with state and federal authorities concerning their policies.** Compounded dosage forms include, but are not restricted to, the following pharmaceutical dosage forms described under *Pharmaceutical Dosage Forms* (1151).

Capsules, Powders, Lozenges, and Tablets

When compounding these dosage forms, the pharmacist should prepare an amount of the total formulation sufficient to allow the prescribed amount or quantity to be accurately dispensed. Selected practices and precautions for compounding these dosage forms include the following:

- Reducing solid ingredients to the smallest reasonable particle size.
- Implementing appropriate checks to ensure that all ingredients are blended to achieve a homogeneous mixture.
- Monitoring humidity if moisture might cause hydrolysis, dosage form adhesion to containers, or softening or partial dissolution of capsule shells.

- Accurately performing weighings to ensure that each unit shall be not less than 90% and not more than 110% of the theoretically calculated weight for each unit.
- Packaging dosage units according to container specifications for capsules and tablets of the specific active ingredient unless specified otherwise in individual monographs (see *Containers* (661)).

Emulsions, Solutions, and Suspensions

When compounding these dosage forms, the pharmacist should prepare a 2% to 3% excess amount of the total formulation to allow the prescribed amount to be accurately dispensed. Selected practices and precautions for compounding these dosage forms include the following:

- For single-unit containers, the weight of each filled container, corrected for tare weight, shall be the equivalent of not less than 100% and not more than 110% of the labeled volume.
- Aqueous suspensions should be prepared by levigating the powder mixture to a smooth paste with an appropriate wetting agent. This paste is converted to a free-flowing fluid by adding adequate vehicle. Successive portions of the vehicle are used to wash the mortar, or other vessel, to transfer the suspension quantitatively to a calibrated dispensing bottle or graduate. The preparation may be homogenized to ensure a uniform final dispersion.
- Reducing solid ingredients to the smallest reasonable particle size.
- Solutions shall contain no visible undissolved matter when dispensed. [NOTE—An exception may occur with supersaturated solutions such as *Potassium Iodide Oral Solution*.]
- Emulsions and suspensions should be labeled, "Shake well before using."

Suppositories

When compounding suppositories, the pharmacist should prepare an excess amount of total formulation to allow the prescribed quantity to be accurately dispensed. Selected practices and precautions for compounding these dosage forms include the following:

- Not using ingredients that are caustic or irritating, and thoroughly comminute solids that are abrasive to the mucous membranes.
- Selecting a base that allows active ingredients to provide the intended local or systemic therapeutic effect.
- Reducing solid ingredients to the smallest reasonable particle size.
- Weighing a representative number of suppositories to ensure that each is not less than 90% and not more than 110% of the average weight of all suppositories in the batch.

Creams, Topical Gels, Ointments, and Pastes

When compounding semisolid dosage forms, the pharmacist should prepare an excess amount of total formulation to allow the prescribed quantity to be accurately dispensed. Selected practices and precautions for compounding these dosage forms include the following:

- Not using ingredients that are caustic, irritating, or allergenic to the skin or other application sites unless they are necessary for a treatment.
- Selecting a base or vehicle that allows active ingredients to provide the intended local or systemic therapeutic effect.
- Reducing solid ingredients to the smallest reasonable particle size.
- Geometrically incorporating the active ingredients with the added substances to achieve a uniform liquid or solid dispersion in the dosage form.
- Observing the uniformity of the dispersion by spreading a thin film of finished formulation on a flat transparent surface (e.g., clear glass ointment slab).

COMPOUNDING PROCESS

The pharmacists should consider using the following steps to minimize error and maximize the prescriber's intent:

- (1) Judge the suitability of the prescription to be compounded in terms of its safety and intended use.

- (2) Perform necessary calculations to establish the amounts of ingredients needed.
- (3) Identify equipment needed.
- (4) Don the proper attire and wash hands.
- (5) Clean the compounding area and needed equipment.
- (6) Only one prescription should be compounded at one time in a specified compounding area.
- (7) Assemble all necessary materials to compound the prescription.
- (8) Compound the preparation following the formulation record or prescription (see *Compounding Records and Documents* below), according to the art and science of pharmacy.
- (9) Assess weight variation, adequacy of mixing, clarity, odor, color, consistency, and pH as appropriate.
- (10) Annotate the compounding log and describe the appearance of the formulation.
- (11) Label the prescription containers to include the following items: a) the name of the preparation; b) the date of compounding; c) the internal identification number; d) the beyond-use date (see *Beyond-use Labeling*); e) the initials of the pharmacist who prepared the label; and f) any storage requirements.
- (12) Sign and date the prescription affirming that all procedures were carried out to ensure uniformity, identity, strength, quantity, and purity.
- (13) Thoroughly and promptly clean all equipment and store properly.

COMPOUNDING RECORDS AND DOCUMENTS

All pharmacists who dispense prescriptions must comply with the record keeping requirements of their individual states. If the pharmacist compounds a preparation according to the manufacturer's labeling instructions, then further documentation is not required. All other compounded preparations require further documentation. Such compounding documents should list the ingredients and the quantity of each in the order of the compounding process.

The objective of the documentation is to allow another pharmacist to reproduce the identical prescription at a future date. The formulation record provides a consistent source document for preparing the preparation (recipe), and the compounding record documents the actual ingredients in the preparation and the person responsible for the compounding activity. These records should be retained for the same period of time that is required for any prescription under state law. The record may be a copy of the prescription in written or machine readable form that includes a formulation record, a compounding record, and a Material Safety Data Sheets (MSDS) file.

Formulation Record

The formulation record is a file of individually compounded preparations. This record must list the name, strength, and dosage form of the preparation compounded, all ingredients and their quantities, equipment needed to prepare the preparation, when appropriate, and mixing instructions. Mixing instructions should include the order of mixing, mixing temperatures or other environmental controls, such as the duration of mixing, and other factors pertinent to the replication of the preparation as compounded. The formulation record must include an assigned beyond-use date, the container used in dispensing, the storage requirements, and any quality control procedures.

Compounding Record

The compounding record contains documentation of the name and strength of the compounded preparation, the formulation record reference for the preparation, and the sources and lot numbers of ingredients. The compounding record also should include information on the total number of dosage units compounded, the name of the person who prepared the preparation and the name of the pharmacist who approved the preparation, the date of preparation, the assigned internal identification number or the prescription number and an assigned beyond-use date, and the prescription number. For all compounded preparations, results of quality control procedures should be recorded (e.g., weight range of filled capsules).

MSDS File

The MSDS File contains the Material Safety Data Sheets for any drug substance or bulk chemical located on the pharmacy premises not in a solid dosage form. The MSDS should be requested from the supplier of each substance and kept on file in the pharmacy. Employees should be instructed as to the location of the file and its content.

QUALITY CONTROL

The safety, quality, and performance of compounded preparations depend on correct ingredients and calculations, accurate and precise measurements, appropriate formulation conditions and procedures, and prudent pharmaceutical judgment. As a final check, the pharmacist should review each procedure in the compounding process. To ensure accuracy and completeness, the pharmacist should observe the finished preparation to ensure that it appears as expected and should investigate any discrepancies and take appropriate corrective action before the prescription is dispensed to the patient (see the *Checklist for Acceptable Strength, Quality, and Purity*, the appropriate pharmaceutical dosage form under *Compounded Dosage Forms*, and the steps under *Compounding Process*).

PATIENT COUNSELING

The patient or the patient's agent should be counseled about proper use, storage, and evidence of instability in the compounded preparation at the time of dispensing (see *Responsibility of the Pharmacist under Stability Considerations in Dispensing Practice* (1191)).

(1171) PHASE-SOLUBILITY ANALYSIS

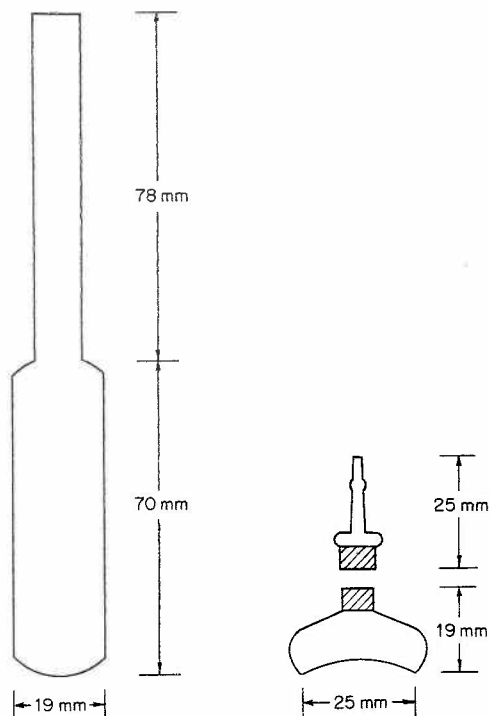
Phase-solubility analysis is the quantitative determination of the purity of a substance through the application of precise solubility measurements. At a given temperature, a definite amount of a pure substance is soluble in a definite quantity of solvent. The resulting solution is saturated with respect 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.

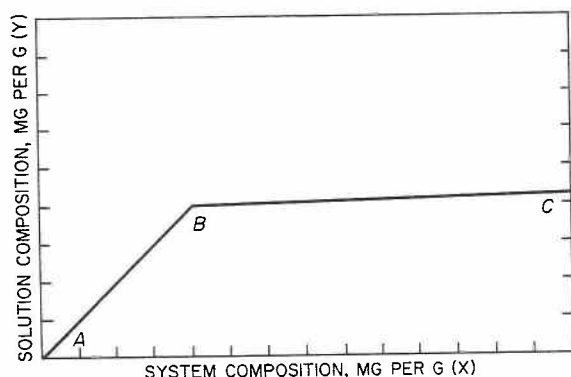
The standard solubility method consists of six distinct steps: (1) mixing, in a series of separate systems, increasing quantities of material with measured, fixed amounts of a solvent; (2) establishment of equilibrium for each system at identical constant temperature and pressure; (3) separation of the 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



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



Typical Phase-solubility Diagram

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 $\pm 0.1^\circ$ 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.

Procedure

NOTE—Make all weighings within $\pm 10 \mu\text{g}$.

System Composition—Weigh accurately, in g, not less than 7 scrupulously cleaned 15-mL ampuls. Weigh accurately, in g, increasingly larger amounts of the test substance into each of the ampuls. The weight of the test substance is selected so that the first ampul contains slightly less material than will go into solution in 5 mL of the selected solvent, the second ampul contains slightly more material, and each subsequent ampul contains increasingly more material than meets the indicated solubility. Transfer 5.0 mL of the solvent to each of the ampuls, cool in a dry ice-acetone mixture, and seal, using a double-jet air-gas burner and taking care to save all glass. Allow the ampuls and their contents to come to room temperature, and weigh the individual sealed ampuls with the corresponding glass fragments. Calculate the system composition, in mg per g, for each ampul by the formula:

$$1000(W_2 - W_1)/(W_3 - W_2),$$

in which W_2 is the weight of the ampul plus test substance, W_1 is the weight of the empty ampul, and W_3 is the weight of ampul plus test substance, solvent, and separated glass.

Equilibration—The time required for equilibration varies with the substance, the method of mixing (rotation or vibration), and the temperature. Normally, equilibrium is obtained more rapidly by the vibration method (1 to 7 days) than by the rotational method (7 to 14 days). In order to determine whether equilibration has been effected, 1 ampul, i.e., the next to the last in the series, may be warmed to 40° to produce a super-saturated solution. Equilibration is assured if the solubility obtained on the super-saturated solution falls in line with the test specimens that approach equilibrium from an undersaturated solution.

Solution Composition—After equilibration, place the ampuls vertically in a rack in the constant-temperature bath, with the necks of the ampuls above the water level, and allow the contents to settle. Open the ampuls, and remove a portion greater than 2 mL from each by means of a pipet equipped with a small pledget of cotton membrane or other suitable filter. Transfer a 2.0-mL aliquot of clear solution from each ampul to a marked, tared solubility flask, and weigh each flask plus its solution to obtain the weight of the solution. Cool the flasks in a dry ice-acetone bath, and then evaporate the solvent in vacuum. Gradually increase the temperature to a temperature consistent with the stability of the compound, and dry the residue to constant weight. Calculate the solution composition, in mg per g, by the formula:

$$1000(F_3 - F_1)/(F_2 - F_3),$$

in which F_3 is the weight of the flask plus residue, F_1 is the weight of the solubility flask, and F_2 is the weight of the flask plus solution.

Calculation

For each portion of the test substance taken, plot the solution composition as the ordinate and the system composition as the abscissa. As shown in the accompanying diagram, the points for those containers, frequently only one, that represent a true solution fall on a straight line (AB) with a slope of 1, passing through the origin; the points corresponding to saturated solutions fall on another straight line (BC), the slope, S , of which represents the weight fraction of impurity or impurities present in the test substance. Failure of points to fall on a straight line indicates that equilibrium has not been achieved. A curve indicates the material under test may be a solid solution. Calculate the percentage purity of the test substance by the formula:

$$100 - 100S.$$

The slope, S , may be calculated graphically or by least-squares treatment for best fit of the experimental values to a straight line.

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

The solubility of the main component is obtained by extending the solubility line (BC) through the y-axis. The point of interception on the y-axis is the extrapolated solubility, in mg per g, and is a constant for a given compound.

Purification Technique

Since the solvent phase in all combinations of solvent and solute that are used to construct segment BC of a phase-solubility diagram contains essentially all of the impurities originally present in the substance under analysis, while the solid phase is essentially free from impurities, phase-solubility analysis can be used to prepare pure reference specimens of desired compounds as well as concentrates of impurities from substances otherwise considered pure. A simple modification of this technique can be used to accomplish these purposes with considerably less effort than is usually required for rigorous phase-solubility analysis.

In practice, a weighed amount of test specimen is suspended in a nonreactive solvent of suitable composition and amount so that about 10% of the material is dissolved at equilibrium. The suspension is sealed (a screw-cap vial is usually adequate) and shaken at room temperature until equilibrium is attained (usually 24 hours is sufficient for this purpose). The mother liquor is then drawn off and evaporated at or near room temperature to dryness. Since the mother liquor contained essentially all of the impurities that were present in the specimen, the residue has been concentrated with respect to the impurities roughly in proportion to the ratio of the weight of specimen taken to the weight of solids dissolved in the volume of solvent used.

The undissolved crystals remaining after withdrawal of the mother liquor are usually sufficiently pure to be used as a reference standard after appropriate rinsing and drying.

(1176) PRESCRIPTION BALANCES AND VOLUMETRIC APPARATUS

Prescription Balances

NOTE—Balances other than the type described herein may be used provided these afford equivalent or better accuracy. This includes micro-, semimicro-, or electronic single-pan balances (see *Weights and Balances* (41)). Some balances offer digital or direct-reading features. All balances should be calibrated and tested frequently using appropriate test weights, both singly and in combination.

Description—A prescription balance is a scale or balance adapted to weighing medicinal and other substances required in prescriptions or in other pharmaceutical compounding. It is constructed so as to support its full capacity without developing undue stresses, and its adjustment is not altered by repeated weighings of the capacity load. The removable pans or weighing vessels should be of equal weight. The balance should have leveling feet or screws. The balance may feature dial-in weights and also a precision spring and dial instead of a weighbeam. A balance that has a graduated weighbeam must have a stop that halts the rider or poise at the "zero" reading. The reading edge of the rider is parallel to the graduations on the weighbeam. The distance from the face of the index plate to the indicator pointer or pointers should be not more than 1.0 mm, the points should be sharp, and when there are two, their ends should be separated by not more than 1.0 mm when the scale is in balance. The indicating elements and the lever system should be protected against drafts, and the balance lid should permit free movement of the loaded weighing pans when the lid is closed. The balance must have a mechanical arresting device.

Definitions—

Capacity—Maximum weight, including the weight of tares, to be placed on one pan. The *N.B.S. Handbook 44*, 4th ed., states: "In the absence of information to the contrary, the nominal capacity of a Class A balance shall be assumed to be 155 g ($\frac{1}{2}$ apothecaries'

ounce)." Most of the commercially available Class A balances have a capacity of 120 g and bear a statement to that effect.

Weighbeam or Beam—A graduated bar equipped with a movable poise or rider. Metric graduations are in 0.01-g increments up to a maximum of 1.0 g.

Tare Bar—An auxiliary ungraduated weighbeam bar with a movable poise. This can be used to correct for variations in weighing-glasses or papers.

Balance Indicator—A combination of elements, one or both of which will oscillate with respect to the other, to indicate the equilibrium state of the balance during weighing.

Rest Point—The point on the index plate at which the indicator or pointer stops when the oscillations of the balance cease; or the index plate position of the indicator or pointer calculated from recorded consecutive oscillations in both directions past the "zero" of the index plate scale. If the balance has a two-pointer indicating mechanism, the position or the oscillations of only one of the pointers need be recorded or used to determine the rest point.

Sensitivity Requirements (SR)—The maximum change in load that will cause a specified change, one subdivision on the index plate, in the position of rest of the indicating element or elements of the balance.

Class A Prescription Balance—A balance that meets the tests for this type of balance has a sensitivity requirement of 6 mg or less with no load and with a load of 10 g on each pan. The Class A balance should be used for all of the weighing operations required in prescription compounding.

In order to avoid errors of 5 percent or more that might be due to the limit of sensitivity of the Class A prescription balance, do not weigh less than 120 mg of any material. If a smaller weight of dry material is required, mix a larger known weight of the ingredient with a known weight of dry diluent, and weigh an aliquot portion of the mixture for use.

Testing the Prescription Balance—A Class A prescription balance meets the following four basic tests. Use a set of test weights, and keep the rider on the weighbeam at zero unless directed to change its position.

1. **Sensitivity Requirement**—Level the balance, determine the rest point, and place a 6-mg weight on one of the empty pans. Repeat the operation with a 10-g weight in the center of each pan. The rest point is shifted not less than one division on the index plate each time the 6-mg weight is added.

2. **Arm Ratio Test**—This test is designed to check the equality of length of both arms of the balance. Determine the rest point of the balance with no weight on the pans. Place in the center of each pan a 30-g test weight, and determine the rest point. If the second rest point is not the same as the first, place a 20-mg weight on the lighter side; the rest point should move back to the original place on the index plate scale or farther.

3. **Shift Tests**—These tests are designed to check the arm and lever components of the balance.

- A. Determine the rest point of the indicator without any weights on the pans.

- B. Place one of the 10-g weights in the center of the left pan, and place the other 10-g weight successively toward the right, left, front, and back of the right pan, noting the rest point in each case. If in any case the rest point differs from the rest point determined in Step A, add a 10-mg weight to the lighter side; this should cause the rest point to shift back to the rest point determined in Step A or farther.

- C. Place a 10-g weight in the center of the right pan, and place a 10-g weight successively toward the right, left, front, and back of the left pan, noting the rest point in each case. If in any case the rest point is different from that obtained with no weights on the pans, this difference should be overcome by addition of the 10-mg weight to the lighter side.

- D. Make a series of observations in which both weights are simultaneously shifted to off-center positions on their pans, both toward the outside, both toward the inside, one toward the outside, and the other toward the inside, both toward the back, and so on until all combinations have been checked. If in any case the rest point differs from that obtained with no weights on the pan, the addition of the 10-mg weight to the lighter side should overcome this difference.

A balance that does not meet the requirements of these tests must be adjusted.

4. **Rider and Graduated Beam Tests**—Determine the rest point for the balance with no weight on the pans. Place on the left pan the 500-mg test weight, move the rider to the 500-mg point on the beam, and determine the rest point. If it is different from the zero rest point, add a 6-mg weight to the lighter side. This should bring the rest point back to its original position or farther. Repeat this test, using the 1-g test weight and moving the rider to the 1-g division on the beam. If the rest point is different, it should be brought back at least to the zero rest point position by addition of 6 mg to the lighter pan. If the balance does not meet this test, the weighbeam graduations or the rider must be corrected.

Metric or apothecaries' weights for use with a prescription balance should be kept in a special rigid and compartmentalized box and handled with plastic or plastic-tipped forceps to prevent scratching or soiling. For prescription use, analytical weights (Class P or better) are recommended. However, Class Q weights have tolerances well within the limits of accuracy of the prescription balance, and they retain their accuracy for a long time with proper care. Coin-type (or disk-shaped) weights should not be used.

Test weights consisting of two 20-g or two 30-g, two 10-g, one 1-g, one 500-mg, one 20-mg, one 10-mg, and one 6-mg (or suitable combination totaling 6 mg) weights, adjusted to N.B.S. tolerances for analytical weights (Class P or better) should be used for testing the prescription balances. These weights should be kept in a tightly closed box and should be handled only with plastic or plastic-tipped forceps. The set of test weights should be used only for testing the balance or constantly used weights. If properly cared for, the set lasts indefinitely.

Volumetric Apparatus

Pharmaceutical devices for measuring volumes of liquids, including burets, pipets, and cylinders graduated either in metric or apothecary units meet the standard specifications for glass volumetric apparatus described in NTIS COM-73-10504 of the National Technical Information Service.¹ Conical graduates meet the standard specifications described in N.B.S. *Handbook 44*, 4th Edition, of the National Institute of Standards and Technology.² Graduated medicine droppers meet the specifications (see *Medicine Dropper* (1101)). An acceptable ungraduated medicine dropper has a delivery end 3 mm in external diameter and delivers 20 drops of water, weighing 1 g at a temperature of 15°. A tolerance of $\pm 10\%$ of the delivery specification is reasonable.

Selection and Use of Graduates

Capacity—The capacity of a graduate is the designated volume, at the maximum graduation, that the graduate will contain, or deliver, as indicated, at the specified temperature.

Cylindrical and Conical Graduates—The error in a measured volume caused by a deviation of ± 1 mm, in reading the lower meniscus in a graduated cylinder remains constant along the height of the uniform column. The same deviation of ± 1 mm causes a progressively larger error in a conical graduate, the extent of the error being further dependent upon the angle of the flared sides to the perpendicular of the upright graduate. A deviation of ± 1 mm in the meniscus reading causes an error of approximately 0.5 mL in the measured volume at any mark on the uniform 100-mL cylinder graduate. The same deviation of ± 1 mm can cause an error of 1.8 mL at the 100-mL mark on an acceptable conical graduate marked for 125 mL.

A general rule for selection of a graduate for use is to use the graduate with a capacity equal to or just exceeding the volume to be measured. Measurement of small volumes in large graduates tends to increase errors, because the larger diameter increases the volume error in a deviation of ± 1 mm from the mark. The relation of the volume error to the internal diameters of graduated cylinders is based upon the equation $V = \pi r^2 h$. An acceptable 10-mL cylinder having an internal diameter of 1.18 cm holds 109 μ L in 1 mm of the column. Reading 4.5 mL in this graduate with a deviation of ± 1 mm from the mark causes an error of about $\pm 2.5\%$,

while the same deviation in a volume of 2.2 mL in the same graduate causes an error of about $\pm 5\%$. Minimum volumes that can be measured within certain limits of error in graduated cylinders of different capacities are incorporated in the design details of graduates in N.B.S. *Handbook 44*, 4th ed., of the National Institute of Standards and Technology. Conical graduates having a capacity of less than 25 mL should not be used in prescription compounding.

(1181) SCANNING ELECTRON MICROSCOPY

Scanning electron microscopy (SEM) is an electron optical imaging technique that yields both topographic images and elemental information when used in conjunction with energy-dispersive X-ray analysis (EDX) or wavelength-dispersive X-ray spectrometry (WDS). SEM is useful for characterizing the size and morphology of microscopic specimens. Together, image and X-ray analyses are important for the identification of small particles. Elemental analyses using SEM/EDX or SEM/WDS are useful for qualitative and semiquantitative determination of elemental content. Accurate quantitation is possible only for bulk samples with smooth surfaces and thus is not practical for particle specimens.

Typically, SEM analysis requires a small amount— 10^{-10} to 10^{-12} g—of a solid specimen that is coated with a conductive substance to inhibit sample charging. The sample is placed in an evacuated chamber and scanned in a controlled raster pattern by an electron beam. Interaction of the electron beam with the specimen produces a variety of physical phenomena that, when detected, are used to form images and provide elemental information about the specimen. These phenomena include (1) emission of secondary electrons (SE), (2) reflection of backscattered electrons (BSE), (3) characteristic X-ray emission, (4) emission of Auger electrons, (5) cathodoluminescence (CL), (6) conduction of current, (7) charging from induced voltages (IV) or adsorbed electrons (AE), (8) electron transmission, (9) heat generation, and (10) electromotive forces (see Figure 1). Of these, SE and BSE are the most important for constructing SEM images, and X-ray emission analyses are the most common methods for detecting the presence of particular elements. Use of ancillary instrumentation to detect the variety of phenomena other than (1), (2), or (3) above greatly increases the cost and complexity of the SEM system and will not be addressed here.

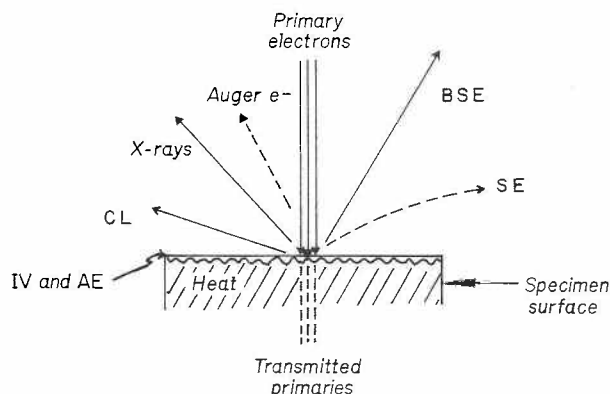


Fig. 1. Interaction Diagram.

Electron Beam/Sample Interaction

Imaging—Images are formed in a SEM system by detection and manipulation of electrons. SE are emitted from a specimen surface as the result of inelastic collisions between primary (incident) electrons (PE) and electrons within a specimen. When the energy imparted to a specimen electron exceeds the work function of a sample, that electron is emitted as an SE. Most SE have energies of 5 to 20 eV; electrons in this low-energy range can be efficiently col-

¹ NTIS COM-73-10504 is for sale by the National Technical Information Service, Springfield, VA 22151.

² N.B.S. *Handbook 44*, 4th ed. (1971) is for sale by the Superintendent of Documents, U. S. Government Printing Office, Washington, DC 20402.

lected, yielding high signal/noise images. Because such low-energy electrons can penetrate only short distances through the specimen, SE originate from within 2 to 30 nm of the surface and generate highly resolved images. The actual PE penetration depth is dependent on PE accelerating voltage, specimen elemental composition, specimen density, and specimen mounting angle. Excitation volumes of 0.5 to 5 μm in diameter are common.

Backscattered electrons are PE that have been reflected from the sample. The PE can undergo multiple collisions prior to exiting from the specimen; therefore, BSE have energies over a broad range and emerge from relatively deep penetration (≈ 0.1 to 5 μm) (see Figure 2). These high-energy (15 to 25 keV) BSE are collected less efficiently than SE, and they yield images with poorer resolution. The efficiency of BSE reflection is a function of the atomic number (Z) of the specimen atoms; thus, the contrast of BSE images depends on elemental composition. The penetration depth of all electrons is affected by elemental composition, specimen density, specimen tilt, and incident beam energy (accelerating voltage). For example, the SE images of sodium phosphate and zinc phosphate crystals are quite similar. However, the heavier nuclei of the zinc species produce more efficient BSE reflection and BSE images with higher contrast. BSE images of heavy- versus light-element phases, or mixtures of species, show dramatic contrast differences that are representative of elemental heterogeneity.

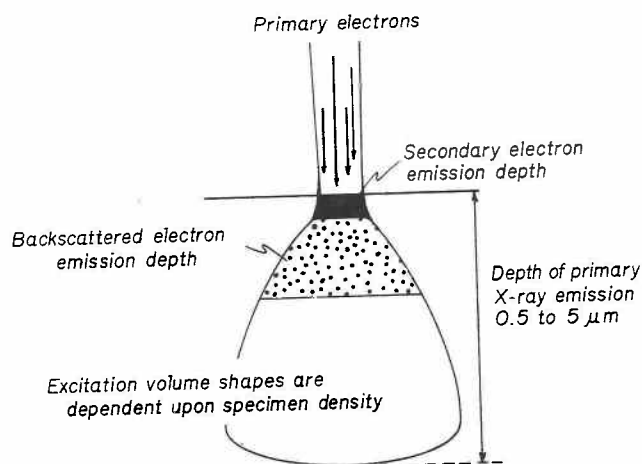


Fig. 2. Bulk Penetration.

While single-angstrom resolution is possible, practical SEM image resolution is limited to $\geq 100 \text{ \AA}$ ($\geq 0.1 \mu\text{m}$ for X-ray images). These limits depend not only on instrument performance but also on operator acuity. Resolution is optimized under the following conditions: minimum working distance, high accelerating voltage, excellent grounding, excellent mechanical alignment, excellent electronic alignment, minimum incident spot diameter, minimum final aperture diameter, and cleanest column conditions. Sample preparations can be viewed in a variety of orientations and detector modes. Often the examination of a specimen at an oblique angle reveals features unobserved by an electron beam normal to the surface. This is especially true of specimens that have flat, featureless surfaces or that are poor conductors, e.g., glass surfaces. The PE accelerating voltage can be varied to change the PE penetration depth. This procedure is useful for characterizing specimens that are laminated or otherwise heterogeneous between surface and bulk content.

Coating a sample allows observation of a specimen's topography, undisturbed by flare and distortion caused by thermal effects and insufficient grounding. Coatings such as gold, gold-palladium, and carbon are often used because they are highly conductive, easy to apply, and relatively inert. Either evaporation or sputter-coating systems can be used to apply metal films; carbon films must be evaporated. Metal coatings give superior resolution, although their fluorescence can interfere with elemental analysis. Specimen charging affects not only image quality but also X-ray fluorescence yield.

X-ray Emission, Analysis—When a PE encounters an orbital electron in an atom, the resultant collision can either promote that orbital electron to a higher energy level or ionize the atom. Stabilization of an atom by relaxation of a higher energy electron to fill a vacancy results in the emission of an X-ray photon. These X-ray energies are discrete and element-specific; they equal the differences between the shell electron energies for the various shells of a given element. For instance, an ejected K -shell electron can be stabilized by a higher energy L -shell electron, yielding a net energy ($E_L - E_K$), which is specific for the X-ray photon energy of the elemental K line. X-ray emission lines are classified according to the electron shell in which the vacancy existed, e.g., K , L , M , etc. The lines are further categorized according to the shell from which the relaxing electron originates. Thus, a $K\alpha$ X-ray line arises from a vacancy in a K -shell that is filled from an L -shell; a $K\beta$ X-ray line arises from a K -shell vacancy filled from an M -shell, and so on (see Figure 3). Since each shell above K possesses a number of energy levels, electron transitions yield a number of lines, such as $K\alpha_1$, $K\alpha_2$, $K\beta_1$, $K\beta_2$, etc. The existence of several X-ray emission lines for each element (a few for $Z \leq 11$ and many for $Z \geq 11$) is useful in overcoming detection problems due to (1) interelement spectral interferences, e.g., titanium $K\alpha$ and barium $L\alpha$; (2) sample matrix effects on energy or intensity; and (3) insufficient PE energy to excite some elemental lines, e.g., lead, K lines.

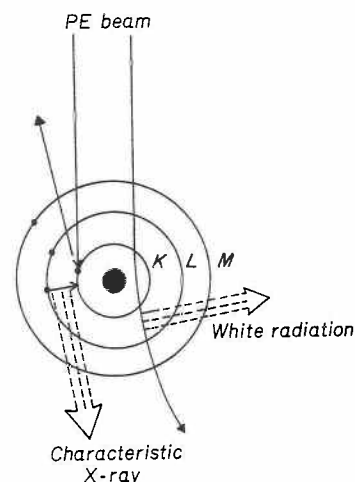


Fig. 3. Atom Model.

The energies normally encountered in a SEM/EDX (or WDS) analysis range from 0.28 keV ($\approx 447 \text{ nm}$) for carbon $K\alpha$ to the upper end of the instrument accelerating voltage, typically $\leq 40 \text{ keV}$ ($\leq 1 \text{ nm}$). The natural line width, which is inversely proportional to the lifetime of the upper electronic state, is governed primarily by the transition probabilities for X-ray emission and Auger electron emission. Interaction of X-ray photons with electrons within the specimen can result in Compton scattering to produce a broadened line shifted to lower energy. X-ray photons are also emitted as a result of inelastic acceleration of electrons by atomic nuclei within a specimen. These X-ray photons, termed bremsstrahlung or white radiation, have a broad continuous energy distribution; and their characteristic lines are superimposed on this background signal.

For lighter elements, $Z \leq 11$, the low-energy X-ray photons originating from K -shell transitions can be detected only with wavelength-dispersive spectrometers or specially configured energy-dispersive detectors. All other elements emit easily detectable X-ray photons. Heavier elements, $Z \geq 16$ emit 2 or more detectable lines corresponding to K - and L -shell transitions; and $Z > 57$ emit 3 or more detectable lines corresponding to K -, L -, and M -shell transitions. For a given element, X-ray intensities generally vary as follows: $K\alpha > K\beta > L\alpha > L\beta$, etc. (see Figure 4).

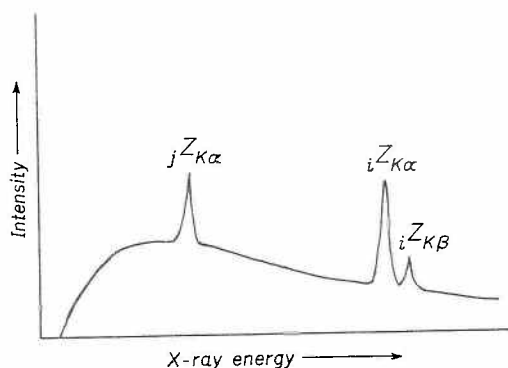


Fig. 4. X-ray Spectrum.

The elemental content of a sample has a bearing on the selection of conditions for analysis. The most useful range of accelerating voltage is ≈ 3 to 20 kV; most elements of interest can be ionized by electrons with energies in this range. The energy required to excite X-ray emission from a given line is termed its critical excitation potential. The critical excitation potential for a K line can be approximated by the sum of the primary line energies ($K\alpha + L\alpha + M\alpha$). Selection of an accelerating voltage equal to 1.5 times this sum is usually sufficient for semiquantitative analyses. For example, copper has $K\alpha$ at 8.05 keV + $L\alpha$ at 0.93 keV = 8.98 keV: $1.5 \times 8.98 \text{ keV} = 13.47 \text{ keV}$. Selection of 15 kV accelerating voltage yields sufficient energy to ionize the K -shell of copper atoms and generate a useful analytical signal.

Interelement interferences originate from many effects. High-energy X-rays emitted from heavy atoms can ionize lighter elements to produce secondary X-ray emission from the lighter species. Lower high- Z element fluorescence and higher low- Z element fluorescence can be observed, in contrast to that expected from the PE-induced signal of a pure element. Conversely, X-ray emission from a light element may be absorbed by a heavier matrix to yield a negative bias in the light-element signal. These effects always exist in heterogeneous specimens and must be corrected for during any quantitative analysis. A common algorithm, ZAF, may be used to correct for Z -dependent interferences due to absorption and secondary X-ray emission.

Apparatus

The SEM system consists of three electronic groups: (1) illumination, (2) optics, and (3) scanning control-display (see Figure 5). The image is produced by mapping a specimen with an incident electron beam, rastered in a two-dimensional array. The electron beam is generated by emission from one of three types of sources, listed in order of increasing current density, vacuum requirements, and cost: (1) a tungsten filament cathode, (2) a LaB_6 cathode, or (3) a field emission gun. By far the most common SEM source is the tungsten filament, although the high current density of the LaB_6 source is especially useful where high resolution and/or detection of low- Z elements is required.

The optics consist of condenser and objective lenses, in conjunction with selected apertures. The size of the final aperture controls the beam diameter and, accordingly, the image resolution and total current at a specimen. Selection of an objective aperture is an important choice. Small apertures are required for high resolution and large apertures provide high current for optimal X-ray emission intensity. In many systems, the objective aperture can be adjusted during use with a sliding or rotating holder. Flexibility in trading resolution for specimen current is also important because sample characteristics affect these two criteria differently. This feature is beneficial to users requiring high magnification and elemental detection, especially of $Z \leq 11$ elements.

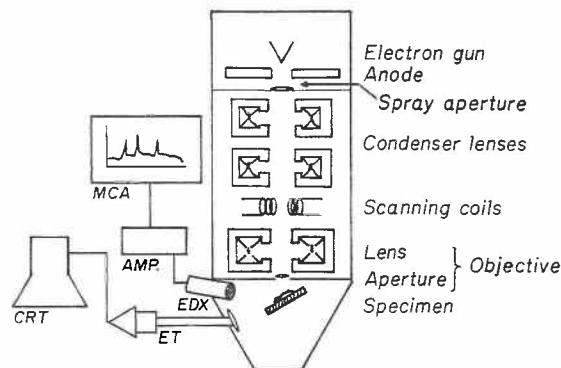


Fig. 5. Optics Diagram.

Image magnification is controlled by altering the area of the electron beam raster; smaller areas yield higher magnification since the cathode-ray tube (CRT) area remains constant. An Everhart-Thornley (ET) detector is used for electron detection; the resultant images are most similar to those of reflected light microscopy. An ET detector consists of a Faraday cage and a scintillator disk connected by a light pipe to a photomultiplier tube. The Faraday cage serves three functions: (1) at positive bias it attracts SE; (2) at negative bias it repels SE to enable the ET to collect BSE signals alone; and (3) it shields the PE beam from the scintillator potential. Various scintillator coatings are used. For example, phosphorus-based coatings yield intense, high-contrast images. Aluminum-based coatings, while less sensitive, can withstand the high SE flux generated during elemental analyses. Solid-state detectors provide up to 10 times greater sensitivity for BSE collection. They can be placed at a variety of positions and distances with respect to a specimen.

Procedure

Preparation—Samples for analysis are easily prepared, especially with an optical aid or a stereomicroscope.

PARTICLES—Place isolated or selected particles onto the SEM sample substrate (e.g., a pyrolytic carbon or metal pedestal). In all cases, the specimen should be attached to an exposed area of the substrate with a suitable liquid cement* (see Figure 6). Use silver or carbon paint to provide a conductive path between the cement surface and the substrate. A single preparation can accommodate from one to several hundred particles, placed in an identifiable pattern.

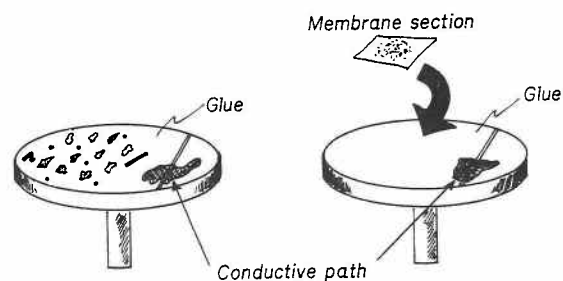


Fig. 6. SEM PEDESTAL MOUNT.

*Any "superglue," copper diallylphthalate, double-sided sticky tape, or other types of mounting resins can be used. The cement with the least residual organic phase will have the longest stability.

Particles isolated from liquid samples by membrane filtration can be examined by placing a filter membrane on a sample substrate, as described above (see Figure 6). This preparation is especially useful for examining a random sample of particles from a liquid. Membrane or film filters rather than depth filters are recommended, since small particles are easily lost in the open pores of a depth filter. Portions of a random isolate can be used for the SEM examination, and the remainder can be saved for other tests. Alternatively, particles can be dispersed in a solvent and concentrated onto a substrate. If a membrane filter is precoated and used to collect particles, a sample can be examined directly without further coating. This procedure alleviates excessive handling of a specimen and lessens exposure of the specimen to coater (sputter or evaporation) environments and to background conductive film signals.

BULK MATERIALS—Scatter a loose powder over double-sided sticky tape on a substrate; excess material can be blown off with a clean air jet. Liquid adhesives can be used instead of tape. However, rapid filming of an adhesive surface can occur and can hinder particle adhesion. Also, particles may sink into an adhesive before it dries. Pack loose powder into small holes cut into the surface of a metal pedestal. This technique is favored for semiquantitative analyses because it produces a relatively flat surface, is, for practical purposes, infinitely thick to the electron beam, provides effective grounding, and requires a minimal amount of sample.

Cement or clamp large materials directly onto the mounting substrate. Nearly any sample that will fit into a vacuum chamber, withstand evacuated conditions, and be effectively grounded is amenable to analysis. For all of the above methods, specimen coating is required. In the absence of coating, a preparation must be viewed at sufficiently low energies, usually ≤ 5 kV, to yield suitable micrograph quality.

Analysis—The method of probing each particle and obtaining a composition is dependent on the level of information required. Several factors must be considered if semiquantitative analysis is desired. The presence of multiple elements, the type of elements contained in the specimen, and the size and surface characteristics of each particle are a few of the considerations.

Any specimen ≥ 10 μm in diameter can be probed quickly and without subsequent data reduction. Particles between 10 μm and 0.2 μm must be considered more carefully, since their size approaches that of the excitation volume of the probe. Elemental characterization of a particle should be conducted on a specimen sufficiently thick that the particle volume is equal to or greater than the volume of X-ray production. Depth of signal excitation (d_x) determines the volume of X-ray production. Conditions such as accelerating voltage, source current, and spot size that are appropriate for analyzing a given specimen volume can be determined empirically, if particles are mounted on a metal substrate from which fluorescence can be detected. Substrate fluorescence indicates that the excitation volume has exceeded the volume of the particle. Quantitatively, d_x depends on particle characteristics and SEM conditions as follows:

$$d_x = 0.033 \frac{A_{\text{ave}}}{dZ_{\text{ave}}} (E_o^{1.69} - E_c^{1.69}),$$

where d_x is the depth of signal excitation, Z_{ave} is the average atomic number, A_{ave} is the average atomic mass, E_o is the energy of incident electrons, E_c is the critical excitation energy of the measured X-ray line, and d is the density of the particle.

Elemental content is estimated directly from elemental line intensities. Use the following procedures.

(1) Mount the specimen(s) by any of the above procedures and ensure good electronic and physical alignment of the SEM.

(2) Tilt or align the specimen toward the detector window at an angle that optimizes collection of the X-rays, i.e., 45° for horizontal detectors.

(3) Select the symmetrical center of the particle and use the raster mode, rather than the point mode, for the analysis. This eliminates topographical variations and generates an average signal for the sample. Choose a magnification at which the raster is $\approx 50\%$ of the particle area to eliminate background signal from the substrate.

(4) Adjust the accelerating voltage to produce adequate signal/noise for detection of the element of choice.

(5) Integrate the signal as long as necessary to achieve statistically significant results. This period can be determined through

analysis of reference materials using the SEM conditions of choice (40 seconds per particle is a good working rule).

(6) Ensure sufficient specimen current. A good working rule is 20% to 40% dead time, as measured by the detector multichannel analyzer (MCA).

(7) Subtract a background spectrum that is representative of the coating, chamber, and handling.

(8) Perform an analysis, using exactly the same conditions as above on a reference standard that contains the element of choice.

(9) Perform an analysis, using exactly the same conditions as above on an internal reference (such as the substrate or other metal), for use in normalizing the analytical conditions.

The weight percent of a given element (E) in the specimen can be calculated as

$$\text{Weight } \% = \frac{(I_E/I_{\text{ref}}) \text{ Sample}}{(I_E/I_{\text{ref}}) \text{ Standard}} \times C^{\text{Std}} \times 100\%,$$

where I_E is the intensity of the element of interest, I_{ref} is the intensity of the internal reference element, and C^{Std} is the concentration of the element of interest in the standard specimen. More accurate quantitative analysis must take into account the effects of matrix type, of interelements, of counting times, and of takeoff angle. The ZAF algorithm used to correct for these effects involves multiplying the measured weight percent by a series of correction factors.

◀1191▶ STABILITY CONSIDERATIONS IN DISPENSING PRACTICE

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

Aspects of drug product stability that are of primary concern to the pharmacist in the dispensing of medications are discussed herein.

Stability is defined as the extent to which a product retains, within specified limits, and throughout its period of storage and use (i.e., its shelf-life), the same properties and characteristics that it possessed at the time of its manufacture. Five types of stability generally recognized are shown in the accompanying table.

Criteria for Acceptable Levels of Stability

Type of Stability	Conditions Maintained Throughout the Shelf-Life of the Drug Product
Chemical	Each active ingredient retains its chemical integrity and labeled potency, within the specified limits.
Physical	The original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability are retained.
Microbiological	Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents that are present retain effectiveness within the specified limits.
Therapeutic	The therapeutic effect remains unchanged.
Toxicological	No significant increase in toxicity occurs.

Factors Affecting Product Stability

Each ingredient, whether therapeutically active or inactive, in a dosage form can affect stability. Environmental factors, such as temperature, radiation, light, air (specifically oxygen, carbon dioxide, and water vapor), and humidity also can affect stability. Similarly, such factors as particle size, pH, the properties of water and

other solvents employed, the nature of the container, and the presence of other chemicals resulting from contamination or from the intentional mixing of different products can influence stability.

Stability Studies in Manufacturing

The scope and design of a stability study vary according to the product and the manufacturer concerned. Ordinarily the formulator of a product first determines the effects of temperature, light, air, pH, moisture, and trace metals, and commonly used excipients or solvents on the active ingredient(s). From this information, one or more formulations of each dosage form are prepared, packaged in suitable containers, and stored under a variety of environmental conditions, both exaggerated and normal. See *Stability under Pharmaceutical Dosage Forms* <1151>. At appropriate time intervals, samples of the product are assayed for potency by use of a stability-indicating method, observed for physical changes, and, where applicable, tested for sterility and/or for resistance to microbial growth and for toxicity and bioavailability. Such a study, in combination with clinical and toxicological results, enables the manufacturer to select the optimum formulation and container and to assign recommended storage conditions and an expiration date for each dosage form in its package.

For solid oral dosage forms, the manufacturer may conduct "open dish" studies to determine what will constitute appropriate labeling information for the pharmacist concerning dispensing container selection and to provide beyond-use date recommendations for the dosage forms. The open dish study is a study in which the dosage forms are exposed to 60% relative humidity at 25° for 30 days without any container protection: three samples of 30-unit doses from one lot are analyzed at 0 and 30 days. Other approaches to obtain this information include, but are not limited to, accelerated stability studies and stability studies in containers that are one class below that being recommended for use in repackaging the dosage form.

Responsibility of the Pharmacist

The pharmacist helps to ensure that the products under his supervision meet acceptable criteria of stability by (1) dispensing oldest stock first and observing expiration dates; (2) storing products under the environmental conditions stated in the individual monographs and/or in the labeling; (3) observing products for evidence of instability; (4) properly treating and labeling products that are repackaged, diluted, or mixed with other products; (5) dispensing in the proper container with the proper closure; and (6) informing and educating patients concerning the proper storage and use of the products, including the disposition of outdated or excessively aged prescriptions.

Rotating Stock and Observance of Expiration Dates—Proper rotation of stock is necessary to ensure the dispensing of suitable products. A product that is dispensed on an infrequent basis should be closely monitored so that old stocks are given special attention, particularly with regard to expiration dates. The manufacturer can guarantee the quality of a product up to the time designated as its expiration date only if the product has been stored in the original container under recommended storage conditions.

Storage under Recommended Environmental Conditions—In most instances, the recommended storage conditions are stated on the label, in which case it is imperative to adhere to those conditions. They may include a specified temperature range or a designated storage place or condition (e.g., "refrigerator," or "controlled room temperature") as defined in the *General Notices*. Supplemental instructions, such as a direction to protect the product from light, also should be followed carefully. Where a product is required to be protected from light and is in a clear or translucent container enclosed in an opaque outer covering, such outer covering is not to be removed and discarded until the contents have been used. In the absence of specific instructions, the product should be stored at controlled room temperature (see *Storage Temperature* in the *General Notices*). The product should be stored away from locations where excessive or variable heat, cold, or light prevails, such as near heating pipes or fluorescent lighting.

Observing Products for Evidence of Instability—Loss of potency usually results from a chemical change, the most common

reactions being hydrolysis, oxidation-reduction, and photolysis. Chemical changes may occur also through interaction between ingredients within a product, or rarely between product and container. An apparent loss of potency in the active ingredient(s) may result from diffusion of the drug into or its combination with the surface of the container-closure system. An apparent gain in potency usually is caused by solvent evaporation or by leaching of materials from the container-closure system.

The chemical potency of the active ingredient(s) is required to remain within the limits specified in the monograph definition. Potency is determined by means of an assay procedure that differentiates between the intact molecule and its degradation products. Chemical stability data should be available from the manufacturer. Although chemical degradation ordinarily cannot be detected by the pharmacist, excessive chemical degradation sometimes is accompanied by observable physical changes. In addition, some physical changes not necessarily related to chemical potency, such as change in color and odor, or formation of a precipitate, or clouding of solution, may serve to alert the pharmacist to the possibility of a stability problem. It should be assumed that a product that has undergone a physical change not explained in the labeling may also have undergone a chemical change and such a product is never to be dispensed. Excessive microbial growth and/or contamination also may appear as a physical change. A gross change in a physical characteristic such as color or odor is a sign of instability in any product. Other common physical signs of deterioration of dosage forms include the following.

SOLID DOSAGE FORMS—Many solid dosage forms are designed for storage under low-moisture conditions. They require protection from environmental water, and therefore should be stored in tight containers (see *Containers* in the *General Notices*) or in the container supplied by the manufacturer. The appearance of fog or liquid droplets, or clumping of the product, inside the container signifies improper conditions. The presence of a desiccant inside the manufacturer's container indicates that special care should be taken in dispensing. Some degradation products, for example, salicylic acid from aspirin, may sublime and be deposited as crystals on the outside of the dosage form or on the walls of the container.

Hard and Soft Gelatin Capsules—Since the capsule formulation is encased in a gelatin shell, a change in gross physical appearance or consistency, including hardening or softening of the shell, is the primary evidence of instability. Evidence of release of gas, such as a distended paper seal, is another sign of instability.

Uncoated Tablets—Evidence of physical instability in uncoated tablets may be shown by excessive powder and/or pieces (i.e., crumbling as distinct from breakage) of tablet at the bottom of the container (from abraded, crushed, or broken tablets); cracks or chips in tablet surfaces; swelling; mottling; discoloration; fusion between tablets; or the appearance of crystals that obviously are not part of the tablet itself on the container walls or on the tablets.

Coated Tablets—Evidence of physical instability in coated tablets is shown by cracks, mottling, or tackiness in the coating and the clumping of tablets.

Dry Powders and Granules—Dry powders and granules that are not intended for constitution into a liquid form in the original container may cake into hard masses or change color, which may render them unacceptable.

Powders and Granules Intended for Constitution as Solutions or Suspensions—Dry powders and granules intended for constitution into solutions or suspensions require special attention. Usually such forms are those antibiotics or vitamins that are particularly sensitive to moisture. Since they are always dispensed in the original container, they generally are not subject to contamination by moisture. However, an unusual caked appearance necessitates careful evaluation, and the presence of a fog or liquid droplets inside the container generally renders the preparation unfit for use. Presence of an objectionable odor also may be evidence of instability.

Effervescent Tablets, Granules, and Powders—Effervescent products are particularly sensitive to moisture. Swelling of the mass or development of gas pressure is a specific sign of instability, indicating that some of the effervescent action has occurred prematurely.

LIQUID DOSAGE FORMS—Of primary concern with respect to liquid dosage forms are homogeneity and freedom from excessive microbial contamination and growth. Instability may be indicated by

cloudiness or precipitation in a solution, breaking of an emulsion, nonresuspendable caking of a suspension, or organoleptic changes. Microbial growth may be accompanied by discoloration, turbidity, or gas formation.

Solutions, Elixirs, and Syrups—Precipitation and evidence of microbial or chemical gas formation are the two major signs of instability.

Emulsions—The breaking of an emulsion (i.e., separation of an oil phase that is not easily dispersed) is a characteristic sign of instability; this is not to be confused with creaming, an easily redispersible separation of the oil phase that is a common occurrence with stable emulsions.

Suspensions—A caked solid phase that cannot be resuspended by a reasonable amount of shaking is a primary indication of instability in a suspension. The presence of relatively large particles may mean that excessive crystal growth has occurred.

Tinctures and Fluidextracts—Tinctures, fluidextracts, and similar preparations usually are dark in color because they are concentrated, and thus they should be scrutinized carefully for evidence of precipitation.

Sterile Liquids—Maintenance of sterility is of course critical for sterile liquids. The presence of microbial contamination in sterile liquids usually cannot be detected visually, but any haze, color change, cloudiness, surface film, particulate or flocculent matter, or gas formation is sufficient reason to suspect possible contamination. Clarity of sterile solutions intended for ophthalmic or parenteral use is of utmost importance. Evidence that the integrity of the seal has been violated on such products should make them suspect.

SEMISOLIDS (CREAMS, OINTMENTS, AND SUPPOSITORIES)—For creams, ointments, and suppositories, the primary indication of instability is often either discoloration or a noticeable change in consistency or odor.

Creams—Unlike ointments, creams usually are emulsions containing water and oil. Indications of instability in creams are emulsion breakage, crystal growth, shrinking due to evaporation of water, and gross microbial contamination.

Ointments—Common signs of instability in ointments are a change in consistency and excessive "bleeding" (i.e., separation of excessive amounts of liquid) and formation of granules or grittiness.

Suppositories—Excessive softening is the major indication of instability in suppositories, although some suppositories may dry out and harden or shrivel. Evidence of oil stains on packaging material should warn the pharmacist to examine individual suppositories more closely by removing any foil covering if necessary. As a general rule (although there are exceptions), suppositories should be stored in a refrigerator (see *Storage Temperature* in the *General Notices*).

Proper Treatment of Products Subjected to Additional Manipulations—In repackaging, diluting, or mixing a product with another product, the pharmacist may become responsible for its stability.

REPACKAGING—In general, repackaging is inadvisable. However, if repackaging is necessary, the manufacturer should be consulted concerning potential problems. In the filling of prescriptions, it is essential that suitable containers be used. Appropriate storage conditions and, where appropriate, an expiration date, should be indicated on the label of the prescription container. Single-unit packaging calls for care and judgment, and for strict observance of the following guidelines: (1) use appropriate packaging materials; (2) where stability data on the new package are not available, repackaging at any one time only sufficient stock for a limited time; (3) include on the unit-dose label a lot number and an appropriate expiration date; (4) where a sterile product is repackaged from a multiple-dose vial into unit-dose (disposable) syringes, discard the latter if not used within 24 hours, unless data are available to support longer storage; (5) where quantities are repackaged in advance of immediate needs, maintain suitable repackaging records showing name of manufacturer, lot number, date, and designation of persons responsible for repackaging and for checking; (6) where safety closures are required, use container closure systems that ensure compliance with compendial and regulatory standards for storage.

DILUTION OR MIXING—Where a product is diluted, or where two products are mixed, the pharmacist should observe good professional and scientific procedures to guard against incompatibility and

instability. For example, tinctures such as those of belladonna and digitalis contain high concentrations of alcohol to dissolve the active ingredient(s), and they may develop a precipitate if they are diluted or mixed with aqueous systems. Pertinent technical literature and labeling should be consulted routinely; it should be current literature, because at times formulas are changed by the manufacturer. If a particular combination is commonly used, consultation with the manufacturer(s) is advisable. Since the chemical stability of extemporaneously prepared mixtures is unknown, the use of such combinations should be discouraged; if such a mixture involved an incompatibility, the pharmacist might be responsible. Oral antibiotic preparations constituted from powder into liquid form should never be mixed with other products.

Combining parenteral products necessitates special care, particularly in the case of intravenous solutions, primarily because of the route of administration. This area of practice demands the utmost in care, aseptic technique, judgment, and diligence. Because of potential unobservable problems with respect to sterility and chemical stability, all extemporaneous parenteral preparations should be used within 24 hours unless data are available to support longer storage.

Informing and Educating the Patient—As a final step in meeting responsibility for the stability of drugs dispensed, the pharmacist is obligated to inform the patient regarding the proper storage conditions (for example, in a cool, dry place—not in the bathroom), for both prescription and nonprescription products, and to suggest a reasonable estimate of the time after which the medication should be discarded. Where expiration dates are applied, the pharmacist should emphasize to the patient that the dates are applicable only when proper storage conditions are used. Patients should be encouraged to clean out their drug storage cabinets periodically.

(1206) STERILE DRUG PRODUCTS FOR HOME USE

A home-use sterile drug product (HSD) is a drug product requiring sterility, such as injectables and ophthalmics, that is prepared in and dispensed from a licensed pharmacy for intended administration by the patient or by a family member or other caregiver in a setting other than an organized, professionally staffed health care facility. The residence or other location to which an HSD is delivered typically is not equipped to ensure injectable drug quality as described in this chapter and is not under the *direct supervision* of the dispensing pharmacist.

This chapter explains in detail various procedures necessary to prepare and dispense sterile drug products intended for home use: the validation of sterilization and aseptic processes, the quality and control of environmental conditions for aseptic operations, personnel training, aseptic techniques, finished product release testing, storage and expiration dating, the control of product quality beyond the pharmacy, patient or caregiver training, patient monitoring and complaints, and finally, a quality assurance program. This information is not prescriptive, nor does it exclude alternate practices. However, alternatives when used should be shown on the basis of valid evidence to be at least as suitable, effective, and reliable as the practices provided herein.

RESPONSIBILITY OF THE DISPENSING PHARMACIST

A pharmacist dispensing any HSD is responsible for ensuring that the product has been prepared, labeled, controlled, stored, dispensed, and distributed properly. This includes the responsibility for ensuring that the HSD is kept under appropriate controlled conditions at the location of use and that it is administered properly through adequate labeling and verbal or written instructions. The dispensing pharmacist is also responsible for ensuring that the HSD retains its quality attributes within acceptable limits through a written quality assurance program. This program should ensure that for the entire labeled life of the product, or until manipulated by the