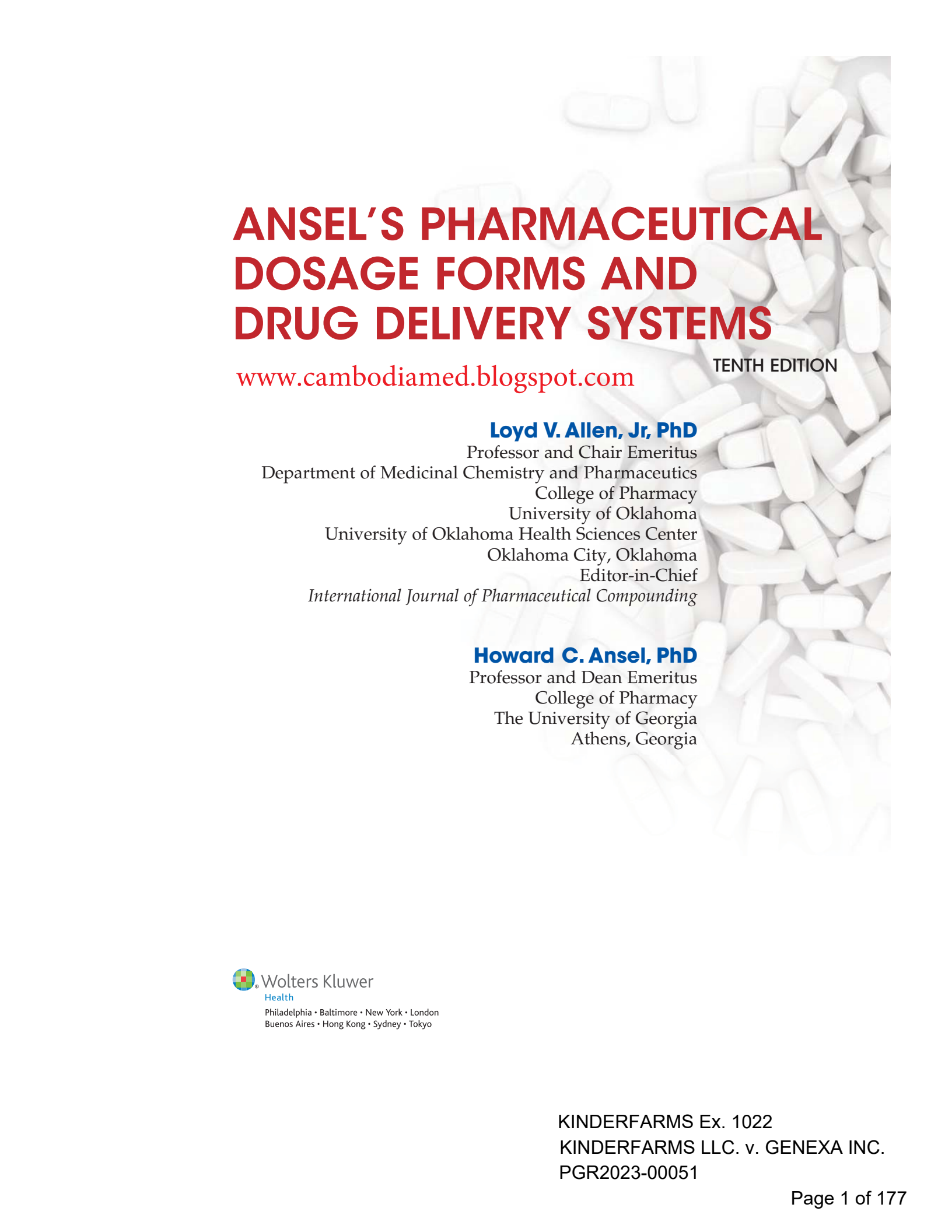




ANSEL'S PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS

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TENTH EDITION

Loyd V. Allen, Jr, PhD

Professor and Chair Emeritus
Department of Medicinal Chemistry and Pharmaceutics
College of Pharmacy
University of Oklahoma
University of Oklahoma Health Sciences Center
Oklahoma City, Oklahoma
Editor-in-Chief
International Journal of Pharmaceutical Compounding

Howard C. Ansel, PhD

Professor and Dean Emeritus
College of Pharmacy
The University of Georgia
Athens, Georgia



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Baltimore, MD 21201 2001 Market Street
Philadelphia, PA 19103

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4 Dosage Form Design: Pharmaceutical and Formulation Considerations

OBJECTIVES

After reading this chapter, the student will be able to:

1. List reasons for the incorporation of drugs into various dosage forms
2. Compare and contrast the advantages/disadvantages of various drug dosage forms
3. Describe the information needed in preformulation studies to characterize a drug substance for possible inclusion into a dosage form
4. Describe the mechanisms of drug degradation and provide examples of each
5. Describe the five types of drug instability of concern to the practicing pharmacist
6. Describe the purpose and general protocol for accelerated stability studies
7. Summarize approaches employed to stabilize drugs in pharmaceutical dosage forms
8. Calculate rate reactions for various liquid dosage forms
9. Categorize various pharmaceutical ingredients and excipients

Drug substances are seldom administered alone; rather they are given as part of a formulation in combination with one or more nonmedicinal agents that serve varied and specialized pharmaceutical functions. Selective use of these nonmedicinal agents, referred to as pharmaceutical ingredients or excipients, produces dosage forms of various types. The pharmaceutical ingredients solubilize, suspend, thicken, dilute, emulsify, stabilize, preserve, color, flavor, and fashion medicinal agents into efficacious and appealing dosage forms. Each type of dosage form is unique in its physical and pharmaceutical characteristics. These varied preparations provide the manufacturing and compounding pharmacist with the

challenges of formulation and the physician with the choice of drug and delivery system to prescribe. The general area of study concerned with the formulation, manufacture, stability, and effectiveness of pharmaceutical dosage forms is termed pharmaceuticals.

The proper design and formulation of a dosage form require consideration of the physical, chemical, and biologic characteristics of all of the drug substances and pharmaceutical ingredients to be used in fabricating the product. The drug and pharmaceutical materials must be compatible with one another to produce a drug product that is stable, efficacious, attractive, easy to administer, and safe. The product should be manufactured with appropriate measures

of quality control and packaged in containers that keep the product stable. The product should be labeled to promote correct use and be stored under conditions that contribute to maximum shelf life.

Methods for the preparation of specific types of dosage forms and drug delivery systems are described in subsequent chapters. This chapter presents some general considerations regarding physical pharmacy, drug product formulation, and pharmaceutical ingredients.

THE NEED FOR DOSAGE FORMS

The potent nature and low dosage of most of the drugs in use today preclude any expectation that the general public could safely obtain the appropriate dose of a drug from the bulk material. Most drug substances are administered in milligram quantities, much too small to be weighed on anything but a sensitive prescription or electronic analytical balance. For instance, how could the lay person accurately obtain from a bulk supply the 325 mg of aspirin found in the common tablet? Not possible. Yet compared with many other drugs, the dose of aspirin is formidable (Table 4.1). For example, the dose of ethinyl estradiol, 0.05 mg, is 1/6,500 the amount of aspirin in an aspirin tablet. To put it another way, 6,500 ethinyl estradiol tablets, each containing 0.05 mg of drug, could be made from an amount of ethinyl estradiol equal to the amount of aspirin in just one standard tablet. When the dose of the drug is minute, as with ethinyl estradiol, solid dosage forms such as tablets and capsules must be prepared with fillers or diluents so that the dosage unit is large enough to pick up with the fingertips. Table 4.1 presents some examples of drugs with low dosage that are formulated and manufactured into capsules and tablets for oral administration.

Besides providing the mechanism for the safe and convenient delivery of accurate dosage, dosage forms are needed for additional reasons:

- To protect the drug substance from the destructive influences of atmospheric oxygen or humidity (coated tablets, sealed ampuls)

Table 4.1 EXAMPLES OF LOW-DOSAGE DRUGS MANUFACTURED INTO CAPSULE OR TABLET DOSAGE FORMS^a

DRUG CONTENT PER CAPSULE OR TABLET	INDICATION OR CATEGORY
Donepezil hydrochloride 5 mg	Dementia
Lisinopril 5 mg	Antihypertensive
Trandolapril 2 mg	Antihypertensive
Rivastigmine tartrate 1.5 mg	Dementia
Colchicine 0.6 mg	Gout
Rasagiline mesylate 0.5 mg	Parkinson disease
Nitroglycerine 0.3 mg	Angina pectoris
Everolimus 0.25 mg	Organ rejection (transplant)
Digoxin 0.125 mg (125 µg)	Heart failure; atrial fibrillation
Fentanyl 0.100 mg (100 µg)	Pain (severe)
Levothyroxine sodium 0.025 mg (25 µg)	Hypothyroidism
Lubiprostone 0.008 mg (8 µg)	Irritable bowel syndrome
Paricalcitol 0.002 mg (2 µg)	Hyperparathyroidism

^aExamples are of the lowest strength capsule or tablet commercially available for each listed drug.

- To protect the drug substance from the destructive influence of gastric acid after oral administration (enteric-coated tablets)
- To conceal the bitter, salty, or offensive taste or odor of a drug substance (capsules, coated tablets, flavored syrups)
- To provide liquid preparations of drug substances, either as dispersions (suspensions) or as clear preparations (solutions)
- To provide rate-controlled drug action (various controlled-release tablets, capsules, and suspensions)
- To provide optimal drug action from topical administration sites (ointments, creams, transdermal patches, and ophthalmic, ear, and nasal preparations)
- To provide for insertion of a drug into one of the body's orifices (rectal or vaginal suppositories)

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- To provide for placement of drugs directly in the bloodstream or body tissues (injections)
- To provide for optimal drug action through inhalation therapy (inhalants and inhalation aerosols)

GENERAL CONSIDERATIONS IN DOSAGE FORM DESIGN

Before formulating a drug substance into a dosage form, the desired product type must be determined insofar as possible to establish the framework for product development. Then, various initial formulations of the product are developed and examined for desired features (e.g., drug release profile, bioavailability, clinical effectiveness) and for pilot plant studies and production scale-up. The formulation that best meets the goals for the product is selected to be its *master formula*. Each batch of product subsequently prepared must meet the specifications established in the master formula.

There are many different forms into which a medicinal agent may be placed for the convenient and efficacious treatment of disease. Most commonly, a manufacturer prepares a drug substance in several dosage forms and strengths for the efficacious and convenient treatment of disease (Fig. 4.1). Before a medicinal agent is formulated into one or more dosage forms, among the factors considered are the physical and chemical properties of the drug substance (discussed later in this chapter) and various therapeutic considerations.

If the medication is intended for systemic use and oral administration is desired, tablets and/or capsules are usually prepared because they are easily handled by the patient and are most convenient in the self-administration of medication. If a drug substance has application in an emergency in which the patient may be comatose or unable to take oral medication, an injectable form of the medication may also be prepared. Many other examples of therapeutic situations affecting dosage form design could be cited, including motion sickness, nausea, and



FIGURE 4.1 Various forms of a drug substance marketed by a pharmaceutical company to meet the special requirements of the patient.

vomiting, for which tablets and skin patches are used for prevention and suppositories and injections for treatment.

The age of the intended patient also plays a role in dosage form design. For infants and children younger than 5 years of age, pharmaceutical liquids rather than solid forms are preferred for oral administration. These liquids, which are flavored aqueous solutions, syrups, or suspensions, are usually administered directly into the infant's or child's mouth by drop, spoon, or oral dispenser (Fig. 4.2) or incorporated into the child's food. The palatability of some commercial products may not be acceptable to some patients so different flavoring additives may be indicated to enhance compliance; an example would be the FLAVORx flavoring system. A single liquid pediatric preparation may be used for infants and children of all ages, with the dose of the drug varied by the volume administered. When a young patient has a productive cough or is vomiting, gagging, or simply rebellious, there may be some question as to how much of the medicine administered is actually swallowed and how much is expectorated. In such instances, injections may be required. Infant-size rectal suppositories may also be employed, although drug absorption from the rectum is often erratic.



FIGURE 4.2 Oral dosage devices to assist in measuring doses for children.

During childhood and even adulthood, a person may have difficulty in swallowing solid dosage forms, especially uncoated tablets. For this reason, some medications are formulated as chewable tablets. Many of these tablets are comparable in texture to an after-dinner mint and break down into a pleasant-tasting creamy material. Newly available tablets dissolve in the mouth in about 10 to 15 seconds; this allows the patient to take a tablet but actually swallow a liquid. Capsules have been found by many to be more easily swallowed than whole tablets. If a capsule is moistened in the mouth before it is swallowed, it becomes slippery and readily slides down the throat with water. Also, a teaspoonful of gelatin dessert, liquid candy, or syrup placed in the mouth and partially swallowed before placing the solid dosage form in the mouth aids in swallowing them. Also, if a person has difficulty in swallowing a capsule, the contents may be emptied into a spoon, mixed with jam, honey, or other similar food to mask

the taste of the medication and swallowed. There is also a device called the Pill Glide that can be used to help swallow solid dosage forms. Medications intended for the elderly are commonly formulated into oral liquids or may be extemporaneously prepared into an oral liquid by the pharmacist. In many patient-care facilities, as nursing homes, tablet-crushing devices are utilized by the nursing staff preparatory to mixing with food (as applesauce) for administration. However, certain tablets and capsules that are designed for controlled release should not be crushed or chewed, because that would interfere with their integrity and intended performance.

Many patients, particularly the elderly, take multiple medications daily. The more distinctive the size, shape, and color of solid dosage forms, the easier is proper identification of the medications. Errors in taking medications among the elderly occur frequently because of their multiple drug therapy and impaired eyesight. Dosage forms that allow reduced frequency of administration without sacrifice of efficiency are particularly advantageous.

In dealing with the problem of formulating a drug substance into a proper dosage form, research pharmacists employ knowledge gained through experience with other chemically similar drugs and through the proper use of the physical, chemical, biologic, and pharmaceutical sciences. The early stages of any new formulation include studies to collect basic information on the physical and chemical characteristics of the drug substance. These basic studies are the *preformulation* work needed before actual product formulation begins.

Preformulation Studies

Before the formulation of a drug substance into a dosage form, it is essential that it be chemically and physically characterized. The following *preformulation studies* (1) and others provide the type of information needed to define the nature of the drug substance. This information provides the framework for the drug's combination with pharmaceutical

ingredients in the fabrication of a dosage form.

Physical Description

It is important to understand the physical description of a drug substance prior to dosage form development. Most drug substances in use today are solid materials, pure chemical compounds of either crystalline or amorphous constitution. The purity of the chemical substance is essential for its identification and for evaluation of its chemical, physical, and biologic properties. Chemical properties include structure, form, and reactivity. Physical properties include such characteristics as its physical description, particle size, crystalline structure, melting point, and solubility. Biologic properties relate to its ability to get to a site of action and elicit a biologic response.

Drugs can be used therapeutically as solids, liquids, and gases. Liquid drugs are used to a much lesser extent than solid drugs, gases even less frequently.

Liquid drugs pose an interesting problem in the design of dosage forms and delivery systems. Many liquids are volatile and must be physically sealed from the atmosphere to prevent evaporation loss. Amyl nitrite, for example, is a clear yellowish liquid that is volatile even at low temperatures and is also highly flammable. It is kept for medicinal purposes in small sealed glass cylinders wrapped with gauze or another suitable material. When amyl nitrite is administered, the glass is broken between the fingertips, and the liquid wets the gauze covering, producing vapors that are inhaled by the patient requiring vasodilation. Propylhexedrine is another volatile liquid that must be contained in a closed system. This drug is used as a nasal inhalant for its vasoconstrictor action. A cylindrical roll of fibrous material is impregnated with propylhexedrine, and the saturated cylinder is placed in a suitable, usually plastic, sealed nasal inhaler. The inhaler's cap must be securely tightened each time it is used. Even then, the inhaler maintains its effectiveness for only a limited time because of the volatility of the drug.

Another problem associated with liquid drugs is that those intended for oral administration cannot generally be formulated into tablet form, the most popular form of oral medication, without chemical modification. An exception to this is the liquid drug nitroglycerin, which is formulated into sublingual tablets that disintegrate within seconds after placement under the tongue. However, because the drug is volatile, it has a tendency to escape from the tablets during storage, and it is critical that the tablets be stored in a tightly sealed glass container. For the most part, when a liquid drug is to be administered orally and a solid dosage form is desired, one of two approaches is used. First, the liquid substance may be sealed in a soft gelatin capsule. Vitamins A, D, and E, and ergoloid mesylates are liquids commercially available in capsule form. Second, the liquid drug may be developed into a solid ester or salt form that will be suitable for tablets or drug capsules. For instance, scopolamine hydrobromide is a solid salt of the liquid drug scopolamine and is easily pressed into tablets. Another approach to formulate liquids into solids is by mixing the drug with a solid or melted semisolid material, such as a high molecular weight polyethylene glycol. The melted mixture is poured into hard gelatin capsules to harden, and the capsules are sealed.

For certain liquid drugs, especially those taken orally in large doses or applied topically, their liquid nature may have some advantage in therapy. For example, 15-mL doses of mineral oil may be administered conveniently as such. Also, the liquid nature of undecylenic acid certainly does not hinder but rather enhances its use topically in the treatment of fungus infections of the skin. However, for the most part, pharmacists prefer solid materials in formulation work because they can easily form them into tablets and capsules.

Formulation and stability difficulties arise less frequently with solid dosage forms than with liquid preparations, and for this reason, many new drugs first reach the market as tablets or dry-filled capsules. Later, when the pharmaceutical problems are resolved, a

liquid form of the same drug may be marketed. This procedure is doubly advantageous, because for the most part, physicians and patients alike prefer small, generally tasteless, accurately dosed tablets or capsules to the analogous liquid forms. Therefore, marketing a drug in solid form first is more practical for the manufacturer and suits most patients. It is estimated that tablets and capsules constitute the dosage form dispensed 70% of the time by community pharmacists, with tablets dispensed twice as frequently as capsules.

Microscopic Examination

Microscopic examination of the raw drug substance is an important step in preformulation work. It gives an indication of particle size and size range of the raw material along with the crystal structure. Photomicrographs of the initial and subsequent batch lots of the drug substance can provide important information in case of problems in formulation processing attributable to changes in particle or crystal characteristics of the drug. During some processing procedures, the solid drug powders must flow freely and not become entangled. Spherical and oval powders flow more easily than needle-shaped powders and make processing easier.

Heat of Vaporization

The use of vapor pressure is important in the operation of implantable pumps delivering medications as well as in aerosol dosage forms. Another application is the use of nasal inhalants (propylhexedrine with menthol and lavender oil—Benzedrex) for treating nasal congestion. In this latter dosage form, the quantity of drug required for effectiveness and a reasonable estimate of time of usefulness can be determined. Also, in the case of spills in inaccessible places, the time to evaporation of a substance can also be calculated. Some volatile drugs can even migrate within a tablet dosage form so the distribution may not be uniform any longer. This may have an impact in tablets that are scored for dosing where the drug in one portion may be higher or lower than in the other portion.

Exposure of personnel to hazardous drugs due to handling, spilling, or aerosolizing of drugs that may vaporize (oncology agents) is another application as the increase in mobility of the hazardous drug molecules may be related to temperature of the environment. Some drugs, such as carmustine, experience greater vapor pressures with increased temperature as compared to cyclophosphamide, etoposide, cisplatin, and 5-fluorouracil, as illustrated in Physical Pharmacy Capsule 4.1, Heat of Vaporization.



PHYSICAL PHARMACY CAPSULE 4.1

Heat of Vaporization

The amount of heat absorbed when 1 g of a liquid vaporizes is known as the heat of vaporization of that liquid and is measured in calories. The heat of vaporization of water at 100°C is 540 cal/g or about 9.720 cal/mole. This is the same quantity of heat energy that is released when 1 g of steam condenses to water at 100°C. This energy exchange is important in processes like steam sterilization as it is this energy transfer that results in death of microorganisms.

The movement of molecules varies with temperature. In liquids, this results in a tendency of the molecules to escape the liquid environment into a gaseous environment and possibly loss of the liquid. In the case of solids that sublime, the movement of the molecules is from the solid state to the vapor state. As an example, if one looks at an older bottle containing aspirin, there may be crystals of aspirin on the inside walls of the container. With ibuprofen, the walls of the container may become cloudy as the ibuprofen sublimates.

PHYSICAL PHARMACY CAPSULE 4.1 CONT.

The use of vapor pressure is important in the operation of implantable pumps delivering medications as well as in aerosol dosage forms. Exposure of personnel to hazardous drugs due to handling, spilling, or aerosolizing of drugs that may vaporize (oncology agents) is another application as the increase in mobility of the hazardous drug molecules may be related to temperature of the environment. Some drugs, such as carmustine, experience greater vapor pressures with increased temperature as compared to cyclophosphamide, etoposide, cisplatin, and 5-fluorouracil, as illustrated in the table below. Particle size affects vapor pressure; the smaller the particle size, the greater the vapor pressure. This demonstrates the importance of personnel protection with working with micronized hazardous powders. The time to evaporation of a substance can also be calculated.

The variation of vapor pressure with temperature is described by the form of the Clausius-Clapeyron equation, as follows:

$$\frac{d \ln P}{dT} = \frac{\Delta H_{\text{vap}}}{RT^2}$$

assuming that ΔH_{vap} is constant, integration of the equation gives:

$$\log P = \frac{-\Delta H_{\text{vap}}}{2.303 RT} + \text{constant}$$

A plot of the log of the vapor pressure versus $1/T$ should be linear and the slope will be equal $-\Delta H_{\text{vap}}/2.303R$ from which the enthalpy of vaporization can be calculated. With data obtained from Kiffmeyer et al. (2002), the following table can be constructed:

COMPOUND	MEASURED VAPOR PRESSURE (PA)	
	20°C	40°C
Carmustine	0.019	0.530
Cisplatin	0.0018	0.0031
Cyclophosphamide	0.0033	0.0090
Etoposide	0.0026	0.0038
Fluorouracil	0.0014	0.0039

Source: Kiffmeyer TK, Kube C, Opiolka S, et al. Vapour pressures, evaporation behaviour and airborne concentrations of hazardous drugs: implications for occupational safety. Pharm J. 2002;68:331–337.

Melting Point Depression

A characteristic of a pure substance is a defined melting point or melting range. If not pure, the substance will exhibit a change in melting point. This phenomenon is commonly used to determine the purity of a drug substance and in some cases, the compatibility of various substances before inclusion in the same dosage form. This characteristic is further described in Physical Pharmacy Capsule 4.2, Melting Point Depression.

The Phase Rule

Phase diagrams are often constructed to provide a visual picture of the existence and extent of the presence of solid and liquid phases in binary, ternary, and other mixtures. Phase diagrams are normally two-component (binary) representations, as shown in Physical Pharmacy Capsule 4.3, The Phase Rule, but can also be three-component representations, as shown in Physical Pharmacy Capsule 4.4, Triangular Phase Diagram.



PHYSICAL PHARMACY CAPSULE 4.2

Melting Point Depression

The *melting point*, or *freezing point*, of a pure crystalline solid is defined as the temperature at which the pure liquid and solid exist in equilibrium. Drugs with a low melting point may soften during a processing step in which heat is generated, such as particle size reduction, compression, sintering, and so on. Also, the melting point or range of a drug can be used as an indicator of purity of chemical substances (a pure substance is ordinarily characterized by a very sharp melting peak). An altered peak or a peak at a different temperature may indicate an adulterated or impure drug. This is explained as follows.

The *latent heat of fusion* is the quantity of heat absorbed when 1 g of a solid melts; the molar heat of fusion (ΔH_f) is the quantity of heat absorbed when 1 mole of a solid melts. High-melting-point substances have high heat of fusion, and low-melting-point substances have low heat of fusion. These characteristics are related to the types of bonding in the specific substance. For example, ionic materials have high heats of fusion (NaCl melts at 801 °C with a heat of fusion of 124 cal/g), and those with weaker van der Waals forces have low heats of fusion (paraffin melts at 52 °C with a heat of fusion of 35.1 cal/g). Ice, with weaker hydrogen bonding, has a melting point of 0 °C and a heat of fusion of 80 cal/g.

The addition of a second component to a pure compound (A), resulting in a mixture, will result in a melting point that is lower than that of the pure compound. The degree to which the melting point is lowered is proportional to the mole fraction (N_A) of the second component that is added. This can be expressed thus:

$$\Delta T = \frac{2.303 RT_0}{\Delta H_f} \log N_A$$

where

ΔH_f is the molar heat of fusion,
 T is the absolute equilibrium temperature,
 T_0 is the melting point of pure A, and
 R is the gas constant.

Two noteworthy things contribute to the extent of lowering of the melting point:

1. Evident from this relationship is the inverse proportion between the melting point and the heat of fusion. When a second ingredient is added to a compound with a low molar heat of fusion, a large lowering of the melting point is observed; substances with a high molar heat of fusion will show little change in melting point with the addition of a second component.
2. The extent of lowering of the melting point is also related to the melting point itself. Compounds with low melting points are affected to a greater extent than compounds with high melting points upon the addition of a second component (i.e., low-melting-point compounds will result in a greater lowering of the melting point than those with high melting points).

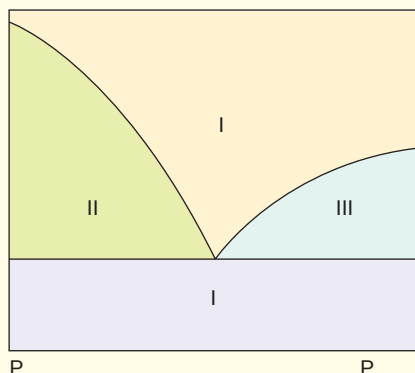


PHYSICAL PHARMACY CAPSULE 4.3

The Phase Rule

A phase diagram, or temperature–composition diagram, represents the melting point as a function of composition of two or three component systems. The figure is an example of such a representation for a two-component mixture.

This phase diagram depicts a two-component mixture in which the components are completely miscible in the molten state and no solid solution or addition compound is formed in the solid state. As is evident, starting from the extremes of either pure component A or pure component B, as the second component is added, the melting point of the pure component decreases. There is a point on this phase diagram at which a minimum melting point occurs (i.e., the eutectic point). As is evident, four regions, or phases, in this diagram, represent the following:



- I. Solid A + solid B
- II. Solid A + melt
- III. Solid B + melt
- IV. Melt

Each phase is a homogenous part of the system, physically separated by distinct boundaries.

A description of the conditions under which these phases can exist is called the *Phase Rule*, which can be presented thus:

$$F = C - P + X$$

where

F is the number of degrees of freedom,

C is the number of components,

P is the number of phases, and

X is a variable dependent upon selected considerations of the phase diagram (1, 2, or 3).

C describes the minimum number of chemical components to be specified to define the phases. F is the number of independent variables that must be specified to define the complete system (e.g., temperature, pressure, concentration).

EXAMPLE 1

In a mixture of menthol and thymol, a phase diagram similar to that illustrated can be obtained. To describe the number of degrees of freedom in the part of the graph moving from the curved line starting at pure A, progressing downward to the eutectic point, and then following an increasing melting point to pure B, it is evident from this presentation that either temperature or composition will describe this system since it is assumed in this instance that pressure is constant. Therefore, the number of degrees of freedom to describe this portion of the phase diagram is given thus:

$$F = 2 - 2 + 1 = 1$$

In other words, along this line either temperature or composition will describe the system.

EXAMPLE 2

When in the area of a single phase of the diagram, such as the melt (IV), the system can be described thus:

PHYSICAL PHARMACY CAPSULE 4.3 CONT.

$$F = 2 - 1 + 1 = 2$$

In this portion of the phase diagram, two factors, temperature and composition, can be varied without a change in the number of phases in the system.

EXAMPLE 3

At the eutectic point,

$$F = 2 - 3 + 1 = 0$$

and any change in the concentration or temperature may cause disappearance of one of the two solid phases or the liquid phase.

Phase diagrams are valuable for interpreting interactions between two or more components, relating not only to melting point depression and possible liquefaction at room temperature but also to the formation of solid solutions, coprecipitates, and other solid-state interactions.



PHYSICAL PHARMACY CAPSULE 4.4

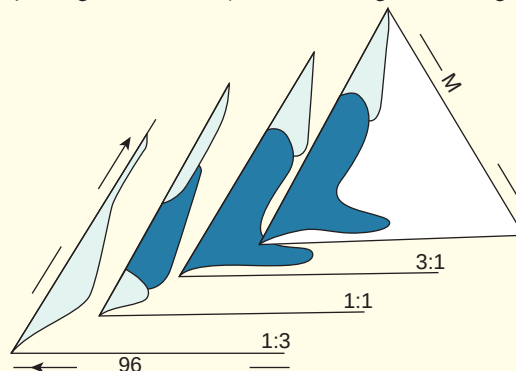
Triangular (Three-Component) Phase Diagram

A three-component phase diagram has four degrees of freedom: $F = 3 - 1 + 2 = 4$. In this case, temperature and pressure are two of the conditions and the concentrations of two of the three components make up the rest. Only two concentrations are required because the third will be the difference between 100% and the sum of the other two components.

These systems are used for determining miscibility/solubility, coacervation regions, gel-forming regions for multicomponent mixtures, etc. To read a three-phase diagram, each of the three corners of the triangle represent 100% by weight of one of the components (A, B, C) and 0% by weight of the other two (A, B, C). The lines joining the corner points forming the triangle each represent two component mixtures of the three possible combinations (AB, BC, and CA). If two of the components are known, the third is known by difference. Any combination of the three components is described by a single point on the diagram. Combining different proportions of the three components and observing for an end point (solubility, gel formation, haziness, etc.), the phase differences can be visualized, as follows.

The following is a stack of four separate pseudoternary phase diagrams for a quaternary system composed of Brij 96, glycerin, mineral oil, and water. The Brij 96:glycerin ratio is noted on the diagram and is considered one of the three components. The shaded regions represent gel systems while the clear regions represent fluid systems.

In addition to observing the phase changes in a single plane, the use of stacked ternary phase diagrams enables one to visualize the change using different ratios of one of the components (in this case, the Brij 96:glycerin ratios). Constructions like this enable a pharmaceutical scientist to select the best ratios and combinations of components for a formulation.



Particle Size

Certain physical and chemical properties of drug substances, including dissolution rate, bioavailability, content uniformity, taste, texture, color, and stability, are affected by the particle size distribution. In addition, flow characteristics and sedimentation rates, among other properties, are important factors related to particle size. It is essential to establish as early as possible how the particle size of the drug substance may affect formulation and efficacy. Of special interest is the effect of particle size on absorption. Particle size significantly influences the oral absorption profiles of certain drugs, including griseofulvin, nitrofurantoin, spironolactone, and procaine penicillin. Also, satisfactory content uniformity in solid dosage forms depends to a large degree on particle size and the equal distribution of the active ingredient throughout the formulation. Particle size is discussed further in Chapter 6. Figure 4.3 shows a particle size analyzer.

Polymorphism

An important factor on formulation is the crystal or amorphous form of the drug substance. Polymorphic forms usually exhibit different physicochemical properties, including melting point and solubility. Polymorphic forms in drugs are relatively common. It has been estimated that at least one third of all organic compounds exhibit polymorphism.



FIGURE 4.3 Mastersizer 2000E particle size analyzer. (Courtesy of Malvern Instruments Ltd.)

In addition to polymorphic forms, compounds may occur in noncrystalline or amorphous forms. The energy required for a molecule of drug to escape from a crystal is much greater than is required to escape from an amorphous powder. Therefore, the amorphous form of a compound is always more soluble than a corresponding crystal form.

Evaluation of crystal structure, polymorphism, and solvate form is an important preformulation activity. The changes in crystal characteristics can influence bioavailability and chemical and physical stability and can have important implications in dosage form process functions. For example, it can be a significant factor relating to tablet formation because of flow and compaction behaviors, among others. Various techniques are used to determine crystal properties. The most widely used methods are hot stage microscopy, thermal analysis, infrared spectroscopy, and x-ray diffraction.

Solubility

An important physicochemical property of a drug substance is solubility, especially aqueous system solubility. A drug must possess some aqueous solubility for therapeutic efficacy. For a drug to enter the systemic circulation and exert a therapeutic effect, it must first be in solution. Relatively insoluble compounds often exhibit incomplete or erratic absorption. If the solubility of the drug substance is less than desirable, consideration must be given to improve its solubility. The methods to accomplish this depend on the chemical nature of the drug and the type of drug product under consideration. Chemical modification of the drug into salt or ester forms is frequently used to increase solubility.

A drug's solubility is usually determined by the equilibrium solubility method, by which an excess of the drug is placed in a solvent and shaken at a constant temperature over a long period until equilibrium is obtained. Chemical analysis of the drug content in solution is performed to determine degree of solubility.



PHYSICAL PHARMACY CAPSULE 4.5

Solubility and Particle Size

The particle size and surface area of a drug exposed to a medium can affect actual solubility within reason, for example, in the following relationship:

$$\log \frac{S}{S_0} = \frac{2\gamma V}{2.303 RT r}$$

where

S is the solubility of the small particles,
 S_0 is the solubility of the large particles,
 γ is the surface tension,
 V is the molar volume,
 R is the gas constant,
 T is the absolute temperature, and
 r is the radius of the small particles.

The equation can be used to estimate the decrease in particle size required to increase solubility. For example, a desired increase in solubility of 5% would require an increase in the S/S_0 ratio to 1.05; that is, the left term in the equation would become $\log 1.05$. If a powder has a surface tension of 125 dynes/cm, molar volume of 45 cm³, and temperature of 27°C, what is the particle size required to obtain the 5% increase in solubility?

$$\log 1.05 = \frac{(2)(125)(45)}{(2.303)(8.314 \times 10^7)(300)r}$$

$$r = 9.238 \times 10^{-6} \text{ cm or } 0.0238 \mu$$

A number of factors are involved in actual solubility enhancement, and this is only an introduction to the general effects of particle size reduction.

Solubility and Particle Size

Although solubility is normally considered a physicochemical constant, small increases in solubility can be accomplished by particle size reduction as described in the Physical Pharmacy Capsule 4.5, Solubility and Particle Size.

Solubility and pH

Another technique, if the drug is to be formulated into a liquid product, is adjustment of the pH of the solvent to enhance solubility. However, for many drug substances, pH adjustment is not an effective means of

improving solubility. Weak acidic or basic drugs may require extremes in pH that are outside accepted physiologic limits or that may cause stability problems with formulation ingredients. Adjustment of pH usually has little effect on the solubility of substances other than electrolytes. In many cases, it is desirable to use cosolvents or other techniques such as complexation, micronization, or solid dispersion to improve aqueous solubility. A review of pH is provided in Physical Pharmacy Capsule 4.6, Principles of pH. The effect of pH on solubility is illustrated in Physical Pharmacy Capsule 4.7, Solubility and pH.



PHYSICAL PHARMACY CAPSULE 4.6

Principles of pH

pH is a critical variable in pharmaceuticals, and a basic understanding of its principles and measurement is important. Let's begin with a definition of the term pH. The p comes from the word power. The H, of course, is the symbol for hydrogen. Together, the term pH means the hydrogen ion exponent.

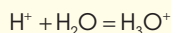
The pH of a substance is a measure of its acidity, just as a degree is a measure of temperature. A specific pH value tells the exact acidity. Rather than stating general ideas, such as cherry syrup is acidic or the water is hot, a specific pH value gives the same relative point of reference, thus providing more exact communication. "The cherry juice has a pH of 3.5" or "the water is at 80°C" provides an exact common language.

pH is defined in terms of the hydrogen ion activity:

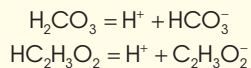
$$\text{pH} = -\log_{10} a_{\text{H}^+} \text{ or } 10^{-\text{pH}} = a_{\text{H}^+}$$

pH equals the negative logarithm of the hydrogen ion activity or the activity of the hydrogen ion is 10 raised to the exponent $-\text{pH}$. The latter expression renders the use of the p exponent more obvious. The activity is the effective concentration of the hydrogen ion in solution. The difference between effective and actual concentration decreases as one moves toward more dilute solutions, in which ionic interaction becomes progressively less important.

Normally, reference is made to the hydrogen ion when reference should be made to the hydronium ion (H_3O^+). It is a matter of convenience and brevity that only the hydrogen ion is mentioned, even though it is normally in its solvated form:



The complexing of the hydrogen ion by water affects activity and applies to other ions, which partially complex or establish an equilibrium with the hydrogen ion. In other words, equilibrium such as



complexes the hydrogen ion so that it is not sensed by the pH measuring system. This is why an acid-base titration is performed if the total concentration of acid (H^+) is needed. These effects on hydrogen ion activity are obvious, but other more subtle effects are involved in the correlation of activity and concentration.

The activity of the hydrogen ion can be defined by its relation to concentration (C_{H^+} , molality) and the activity coefficient f_{H^+} :

$$a_{\text{H}^+} = f_{\text{H}^+} + C_{\text{H}^+}$$

If the activity coefficient is unity, activity is equal to concentration. This is nearly the case in dilute solutions, whose ionic strength is low. Since the objective of most pH measurements is to find a stable and reproducible reading that can be correlated with the results of some process, it is important to know what influences the activity coefficient and therefore the pH measurement.

The factors that affect the activity coefficient are the temperature (T), the ionic strength (μ), the dielectric constant (ϵ), the ion charge (Z), the size of the ion in angstroms ($\text{\AA}$), and the density of the solvent (d). All of these factors are characteristics of the solution that relate the activity to the concentration by two main effects: the salt effect and the medium effect; the latter relates the influence that the solvent can have on the hydrogen ion activity. Thus, hydrogen activity is

PHYSICAL PHARMACY CAPSULE 4.6 CONT.

related to concentration through a salt effect and a solvent effect. Because of these influences, a sample pH value cannot be extrapolated to another temperature or dilution. If the pH value of a particular solution is known at 40°C, it is not automatically known at 25°C.

THE pH SCALE

In pure water, hydrogen and hydroxyl ion concentrations are equal at 10^{-7} M at 25°C. This is a neutral solution. Since most samples encountered have less than 1 M H^+ or OH^- , the extremes of pH 0 for acids and pH 14 for bases are established. Of course, with strong acids or bases, pH values below 0 and above 14 are possible but infrequently measured.

MEASUREMENT OF pH

The activity of the hydrogen ion in solution is measured with a glass electrode, a reference electrode, and a pH meter.

COMBINATION ELECTRODES

A combination electrode is a combination of the glass and reference electrodes into a single probe. The main advantage in using a combination electrode is with the measurement of small volume samples or samples in limited-access containers.

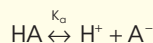


PHYSICAL PHARMACY CAPSULE 4.7

Solubility and pH

pH is one of the most important factors in the formulation process. Two areas of critical importance are the effects of pH on solubility and stability. The effect of pH on solubility is critical in the formulation of liquid dosage forms, from oral and topical solutions to intravenous solutions and admixtures.

The solubility of a weak acid or base is often pH dependent. The total quantity of a monoprotic weak acid (HA) in solution at a specific pH is the sum of the concentrations of both the free acid and salt (A^-) forms. If excess drug is present, the quantity of free acid in solution is maximized and constant because of its saturation solubility. As the pH of the solution increases, the quantity of drug in solution increases because the water-soluble ionizable salt is formed. The expression is



where K_a is the dissociation constant.

There may be a certain pH level reached where the total solubility (S_T) of the drug solution is saturated with respect to both the salt and acid forms of the drug, that is, the pH_{max} . The solution can be saturated with respect to the salt at pH values higher than this but not with respect to the acid. Also, at pH values less than this, the solution can be saturated with respect to the acid but not to the salt. This is illustrated in the accompanying figure.

To calculate the total quantity of drug that can be maintained in solution at a selected pH, either of two equations can be used, depending on whether the product is to be in a pH region

PHYSICAL PHARMACY CAPSULE 4.7 CONT.

above or below the pH_{max} . The following equation is used when below the pH_{max} :

$$S_T = S_a \left[1 + \frac{K_a}{H^+} \right] \quad (\text{Equation 4.1})$$

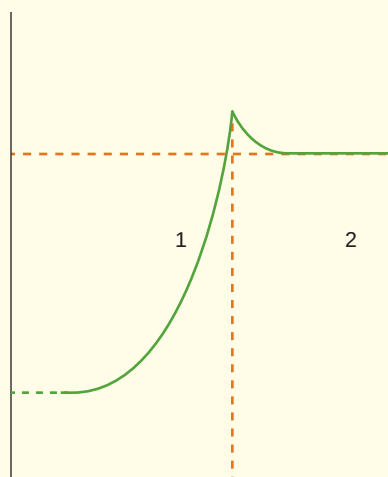
The next equation is used when above the pH_{max} :

$$S_T = S'_a \left[1 + \frac{K_a}{H^+} \right] \quad (\text{Equation 4.2})$$

where

S_a is the saturation solubility of the free acid and

S'_a is the saturation solubility of the salt form.



EXAMPLE

A pharmacist prepares a 3% solution of an antibiotic as an ophthalmic solution and dispenses it to a patient. A few days later, the patient returns the eye drops to the pharmacist because the product contains a precipitate. The pharmacist, checking the pH of the solution and finding it to be 6, reasons that the problem may be pH related. The physicochemical information of interest on the antibiotic includes the following:

Molecular weight	285 (salt) 263 (free acid)
3% solution of the drug	0.1053-M solution
Acid form solubility (S_a)	3.1 mg/mL (0.0118 M)
K_a	5.86×10^{-6}

Using Equation (Equation 4.1, the pharmacist calculates the quantity of the antibiotic in solution at a pH of 6 (Note: pH of 6.0 = $[H^+]$ of 1×10^{-6})

$$S_T = 0.0118 \left[1 + \left(\frac{5.86 \times 10^{-6}}{1 \times 10^{-6}} \right) \right] = 0.0809 \text{ molar}$$

From this, the pharmacist knows that at a pH of 6, a 0.0809-M solution can be prepared. However, the concentration that was to be prepared was a 0.1053-M solution; consequently, the drug will not be in solution at that pH. The pH may have been all right initially but shifted to a lower pH over time, resulting in precipitation of the drug. The question is at what pH (hydrogen ion concentration) the drug will remain in solution. This can be calculated using the same equation and information. The S_T value is 0.1053 M.

$$0.1053 = 0.0118 \left[1 + \frac{5.86 \times 10^{-6}}{H^+} \right]$$

$$[H^+] = 7.333 \times 10^{-7}, \text{ or a pH of } 6.135$$

The pharmacist prepares a solution of the antibiotic, adjusting the pH to above about 6.2, using a suitable buffer system, and dispenses the solution to the patient—with positive results.

An interesting phenomenon concerns the close relationship of pH to solubility. At a pH of 6, only a 0.0809-M solution could be prepared, but at a pH of 6.13, a 0.1053-M solution could be prepared. In other words, a difference of 0.13 pH units resulted in

PHYSICAL PHARMACY CAPSULE 4.7 CONT.

$$\frac{0.1053 - 0.0809}{0.0809} = 30.1\%$$

more drugs going into solution at the higher pH than at the lower pH. In other words, a very small change in pH resulted in about 30% more drugs going into solution. According to the figure, the slope of the curve would be very steep for this example drug, and a small change in pH (x-axis) results in a large change in solubility (y-axis). From this, it can be reasoned that if one observes the pH-solubility profile of a drug, it is possible to predict the magnitude of the pH change on its solubility.

In recent years, more and more physicochemical information on drugs is being made available to pharmacists in routinely used reference books. This type of information is important for pharmacists in different types of practice, especially those involved in compounding and pharmacokinetic monitoring.

In recent years, more and more physicochemical information on drugs is being made available to pharmacists in routinely used reference books. This type of information is important for pharmacists in different types of practice, especially those who compound and do pharmacokinetic monitoring.

Dissolution

Variations in the biologic activity of a drug substance may be brought about by the rate at which it becomes available to the organism. In many instances, dissolution rate, or the time it takes for the drug to dissolve in the fluids at the absorption site, is the rate-limiting step in absorption. This is true for drugs administered orally in solid forms, such as tablets, capsules, or suspensions, and for those administered intramuscularly. When the dissolution rate is the rate-limiting step, anything that affects it will also affect absorption. Consequently, dissolution rate can affect the onset, intensity, and duration of response and control the overall bioavailability of the drug from the dosage form, as discussed in the previous chapter.

The dissolution rate of drugs may be increased by decreasing the drug's particle size. It may also be increased by increasing its solubility in the diffusion layer. The most effective means of obtaining higher dissolution rates is to use a highly water-soluble salt of the parent substance. Although a soluble

salt of a weak acid will precipitate as the free acid in the bulk phase of an acidic solution, such as gastric fluid, it will do so in the form of fine particles with a large surface area.

The dissolution rates of chemical compounds are determined by two methods: the constant surface method, which provides the intrinsic dissolution rate of the agent, and particulate dissolution, in which a suspension of the agent is added to a fixed amount of solvent without exact control of surface area.

The constant surface method uses a compressed disc of known area. This method eliminates surface area and surface electrical charges as dissolution variables. The dissolution rate obtained by this method, the *intrinsic dissolution rate*, is characteristic of each solid compound and a given solvent in the fixed experimental conditions. The value is expressed as milligrams dissolved per minute per square centimeter. It has been suggested that this value is useful in predicting probable absorption problems due to dissolution rate. In particulate dissolution, a weighed amount of powdered sample is added to the dissolution medium in a constant agitation system. This method is frequently used to study the influence of particle size, surface area, and excipients upon the active agent. Occasionally, the surface properties of the drug produce an inverse relationship of particle size to dissolution. In these instances,

surface charge and/or agglomeration results in the reduced particle size form of the drug presenting a lower effective surface area to the solvent due to incomplete wetting or agglomeration. Fick's laws describe the relationship

of diffusion and dissolution of the active drug in the dosage form and when administered in the body, as shown in Physical Pharmacy Capsule 4.8, Fick's Laws of Diffusion and the Noyes-Whitney Equation.



PHYSICAL PHARMACY CAPSULE 4.8

Fick's Laws of Diffusion and the Noyes-Whitney Equation

All drugs must diffuse through various barriers when administered to the body. For example, some drugs must diffuse through the skin, gastric mucosa, or some other barrier to gain access to the interior of the body. Parenteral drugs must diffuse through muscle, connective tissue, and so on, to get to the site of action; even intravenous drugs must diffuse from the blood to the site of action. Drugs must also diffuse through various barriers for metabolism and excretion.

Considering all the diffusion processes that occur in the body (passive, active, and facilitated), it is not surprising that the laws governing diffusion are important to drug delivery systems. In fact, diffusion is important not only in the body but also in some quality control procedures used to determine batch-to-batch uniformity of products (dissolution test for tablets based on the Noyes-Whitney equation, which can be derived from Fick's law).

When individual molecules move within a substance, diffusion is said to occur. This may occur as the result of a concentration gradient or by random molecular motion.

Probably the most widely used laws of diffusion are known as Fick's first and second laws. Fick first law involving steady-state diffusion (where dc/dx does not change) is derived from the following expression for the quantity of material (M) flowing through a cross section of a barrier (S) in unit time (t) expressed as the flux (J):

$$J = dM / (Sdt)$$

Under a concentration gradient (dc/dx), Fick's first law can be expressed thus:

$$J = D[(C_1 - C_2) / h] \text{ or } J = -D(dc/dx)$$

where

J is the flux of a component across a plane of unit area,

C_1 and C_2 are the concentrations in the donor and receptor compartments,

h is the membrane thickness, and

D is the diffusion coefficient (or diffusivity).

The sign is negative, denoting that the flux is in the direction of decreasing concentration. The units of J are grams per square centimeter; C , grams per cubic centimeter; M , grams or moles; S , square centimeters; x , centimeters; and D , square centimeters per second.

D is appropriately called a diffusion coefficient, not a diffusion constant, as it is subject to change. D may change in value with increased concentrations. Also, D can be affected by temperature, pressure, solvent properties, and the chemical nature of the drug itself. To study the rate of change of the drug in the system, one needs an expression that relates the change in concentration with time at a definite location in place of the mass of drug diffusing across a unit area of barrier in unit time; this expression is known as Fick's second law. This law can be summarized as stating that the change in concentration in a particular place with time is proportional to the change in concentration gradient at that particular place in the system.

PHYSICAL PHARMACY CAPSULE 4.8 CONT.

In summary, Fick's first law relates to a steady-state flow, whereas Fick second law relates to a change in concentration of drug with time, at any distance, or an unsteady state of flow.

The diffusion coefficients ($D \times 10^{-6}$) of various compounds in water (25°C) and other media have been determined as follows: ethanol, 12.5 cm²/s; glycine, 10.6 cm²/s; sodium lauryl sulfate, 6.2 cm²/s; glucose, 6.8 cm²/s.

The concentration of drug in the membrane can be calculated using the partition coefficient (K) and the concentration in the donor and receptor compartments.

$$K = (C_1 / C_d) = (C_2 / C_r)$$

where

C_1 and C_d are the concentrations in the donor compartment (g/cm³)
and C_2 and C_r are the concentrations in the receptor compartment (g/cm³).

K is the partition coefficient of the drug between the solution and the membrane. It can be estimated using the oil solubility of the drug versus the water solubility of the drug. Usually, the higher the partition coefficient, the more the drug will be soluble in a lipophilic substance. We can now write the expression:

$$dM/dt = [DSK(C_d - C_r)] / h$$

or in sink conditions,

$$dM / dt = DSKC_d / h = PSC_d$$

The permeability coefficient (centimeters per second) can be obtained by rearranging to:

$$P = DK / h$$

EXAMPLE 1

A drug passing through a 1-mm-thick membrane has a diffusion coefficient of 4.23×10^{-7} cm²/s and an oil-water partition coefficient of 2.03. The radius of the area exposed to the solution is 2 cm, and the concentration of the drug in the donor compartment is 0.5 mg/mL. Calculate the permeability and the diffusion rate of the drug.

$$h = 1 \text{ mm} = 0.1 \text{ cm}$$

$$D = 4.23 \times 10^{-7} \text{ cm}^2/\text{s}$$

$$K = 2.03$$

$$r = 2 \text{ cm}, S = \pi(2 \text{ cm})^2 = 12.57 \text{ cm}^2$$

$$C_d = 0.5 \text{ mg/mL}$$

$$P = [(4.23 \times 10^{-7} \text{ cm}^2/\text{s}) (2.03)] / 0.1 \text{ cm} = 8.59 \times 10^{-6} \text{ cm/s}$$

$$dM/dt = (8.59 \times 10^{-6} \text{ cm/s}) (12.57 \text{ cm}^2) (0.5 \text{ mg/mL}) = 5.40 \times 10^{-5} \text{ mg/s}$$

$$(5.40 \times 10^{-5} \text{ mg/s})(3,600 \text{ s/h}) = 0.19 \text{ mg/h}$$

In the dissolution of particles of drug, the dissolved molecules diffuse away from the individual particle body. An expression to describe this, derived from Fick equations, is known as the Noyes and Whitney expression, proposed in 1897. It can be written as follows:

$$dC / dt = (DS / Vh)(C_s - C)$$

where

C is the concentration of drug dissolved at time t ,

D is the diffusion coefficient of the solute in solution,

PHYSICAL PHARMACY CAPSULE 4.8 CONT.

S is the surface area of the exposed solid,

V is the volume of solution,

h is the thickness of the diffusion layer,

C_s is the saturation solubility of the drug, and

C is the concentration of solute in the bulk phase at a specific time, t .

It is common practice to use sink conditions in which C does not exceed about 20% of the solubility of the drug being investigated. Under these conditions, the expression simplifies to

$$dC/dt = (DSC_s/Vh)$$

and incorporating the volume of solution (V), the thickness of the diffusion layer (h), and the diffusivity coefficient (D) into a coefficient k (to take into account the various factors in the system), the expression becomes

$$dC/dt = kSC_s$$

As the factors are held constant, it becomes apparent that the dissolution rate of a drug can be proportional to the surface area exposed to the dissolution medium. A number of other expressions have been derived for specific application to various situations and conditions.

These relationships expressed as Fick first and second laws, and the Noyes-Whitney equation have great importance and relevance in pharmaceutical systems.

EXAMPLE 2

The following information was obtained using the USP 32-NF 27 dissolution apparatus I. The drug is soluble at 1 g in 3 mL of water, so sink conditions were maintained; the surface area of the tablet exposed was 1.5 cm² (obtained by placing the tablet in a special holder exposing only one side to the dissolution medium); and the dosage form studied was a 16-mg sustained-release tablet; the release pattern should be zero order. What is the rate of release of drug?

TIME (HOURS)	DRUG CONCENTRATION (MG/900 ML OF SOLUTION)	GRAPH OF RELEASE PROFILE
0.0	0.0	
0.5	1.0	
1.0	1.9	
2.0	4.1	
4.0	8.0	
6.0	11.8	
8.0	15.9	

In this problem, since the surface area (S) was maintained constant at 1.5 cm² and the solubility (C_s) of the drug is constant at 1 g in 3 mL of water, the plot of concentration versus time (t) yields a slope with a value of kSC_s , or k_d , expressing the rate of release of the drug as

$$dC/dt = kSC_s$$

$$\begin{aligned} \text{The slope of the line} &= \Delta y / \Delta x = (y_2 - y_1) / (x_2 - x_1) \\ &= (15.9 \text{ mg} - 0 \text{ mg}) / (8.0 \text{ h} - 0 \text{ h}) \\ &= 15.9 / 8 = 1.99 \text{ mg/h} \end{aligned}$$

Therefore, the rate of release of the sustained-release preparation is 1.99 or approximately 2 mg/hour. From this, the quantity of drug released at any time (t) can be calculated.

Early formulation studies should include the effects of pharmaceutical ingredients on the dissolution characteristics of the drug substance.

Membrane Permeability

Modern preformulation studies include an early assessment of passage of drug molecules across biologic membranes. To produce a biologic response, the drug molecule must first cross a biologic membrane. The biologic membrane acts as a lipid barrier to most drugs and permits the absorption of lipid-soluble substances by passive diffusion, while lipid-insoluble substances can diffuse across the barrier only with considerable difficulty if at all. The interrelationship of the dissociation constant, lipid solubility, and pH at the absorption site with the absorption characteristics of various drugs are the basis of the pH partition theory.

Data obtained from the basic physicochemical studies, specifically, pK_a , solubility, and dissolution rate, provide an indication of absorption. To enhance these data, a technique using the everted intestinal sac may be used to evaluate absorption characteristics of drug substances. In this method, a piece of the intestine is removed from an intact animal, is everted, and is filled with a solution of the drug substance, and the degree and rate of passage of the drug through the membrane sac are determined. This method

allows evaluation of both passive and active transport.

In the latter stages of preformulation testing or early formulation studies, animals and humans must be studied to assess the absorption efficiency and pharmacokinetic parameters and to establish possible in vitro and in vivo correlation for dissolution and bioavailability.

Partition Coefficient

The use of the partition coefficient is described in some detail in Physical Pharmacy Capsule 4.9, Partition Coefficient. Inherent in this procedure is the selection of appropriate extraction solvents, drug stability, use of salting-out additives, and environmental concerns. The octanol–water partition coefficient is commonly used in formulation development. Following the illustrations provided earlier, it is defined as

$$P = \frac{(\text{Concentration of drug in octanol})}{(\text{Concentration of drug in water})}$$

P depends on the drug concentration only if the drug molecules have a tendency to associate in solution. For an ionizable drug, the following equation is applicable:

$$P = \frac{(\text{Concentration of drug in octanol})}{[1 - \alpha](\text{Concentration of drug in water})}$$

where α equals the degree of ionization.



PHYSICAL PHARMACY CAPSULE 4.9

Partition Coefficient

The oil–water partition coefficient is a measure of a molecule's lipophilic character; that is, its preference for the hydrophilic or lipophilic phase. If a solute is added to a mixture of two immiscible liquids, it will distribute between the two phases and reach an equilibrium at a constant temperature. The distribution of the solute (unaggregated and undissociated) between the two immiscible layers can be described thus:

$$K = C_u / C_L$$

where

K is the distribution constant or partition constant,

PHYSICAL PHARMACY CAPSULE 4.9 CONT.

C_U is the concentration of the drug in the upper phase, and
 C_L is the concentration of the drug in the lower phase.

This information can be effectively used in the

1. Extraction of crude drugs
2. Recovery of antibiotics from fermentation broth
3. Recovery of biotechnology-derived drugs from bacterial cultures
4. Extraction of drugs from biologic fluids for therapeutic drug monitoring
5. Absorption of drugs from dosage forms (ointments, suppositories, and transdermal patches)
6. Study of the distribution of flavoring oil between oil and water phases of emulsions
7. In other applications

This basic relationship can be used to calculate the quantity of drug extracted from or remaining behind in a given layer and to calculate the number of extractions required to remove a drug from a mixture.

The concentration of drug found in the upper layer (U) of the two immiscible layers is given thus:

$$U = Kr / (Kr + 1)$$

where

K is the distribution partition constant and
 r is V_U/V_L or the ratio of the volume of upper and lower phases.

The concentration of drug remaining in the lower layer (L) is given thus:

$$L = 1 / (Kr + 1)$$

If the lower phase is successively extracted again with n equal volumes of the upper layer, each upper phase (U_n) contains the following fraction of the drug:

$$U_n = Kr / (Kr + 1)^n$$

where

U_n is the fraction contained in the n th extraction and
 n is the n th successive volume.

The fraction of solute remaining in the lower layer (L_n) is given thus:

$$L_n = 1 / (Kr + 1)^n$$

More efficient extractions are obtained using successive small volumes of the extraction solvent than single larger volumes. This can be calculated as follows when the same volume of extracting solvent is used in divided portions. For example, the fraction L_n remaining after the n th extraction:

$$L_n = \frac{1}{\left(\frac{Kr}{n} + 1\right)^n}$$

EXAMPLE 1

At 25°C and pH 6.8, the K for a second-generation cephalosporin is 0.7 between equal volumes of butanol and the fermentation broth. Calculate the U, L, and L_n (using the same volume divided into fourths).

PHYSICAL PHARMACY CAPSULE 4.9 CONT.

$U = 0.7 / (0.7 + 1) = 0.41$, the fraction of drug extracted into the upper layer

$L = 1 / (0.7 + 1) = 0.59$, the fraction of drug remaining in the lower layer

The total of the fractions in the U and L = $0.41 + 0.59 = 1$.

If the fermentation broth is extracted with four successive extractions accomplished by dividing the quantity of butanol used into fourths, the quantity of drug remaining after the fourth extraction is

$$L_{4th} = \frac{1}{\left(\frac{0.7 \times 1}{4} + 1\right)^4} = 0.525$$

From this, the quantity remaining after a single volume, single extraction is 0.59, but when the single volume is divided into fourths and four successive extractions are done, the quantity remaining is 0.525; therefore, more was extracted using divided portions of the extracting solvent. Inherent in this procedure is the selection of appropriate extraction solvents, drug stability, use of salting-out additives, and environmental concerns.

pK_a /Dissociation Constants

Among the physicochemical characteristics of interest is the extent of dissociation or ionization of drug substances. This is important because the extent of ionization has an important effect on the formulation and pharmacokinetic parameters of the drug. The extent of dissociation or ionization in many cases is highly dependent on the pH of the medium containing the drug. In formulation, often the vehicle is adjusted to a certain pH to obtain a certain level of ionization of

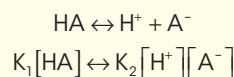
the drug for solubility and stability. In the pharmacokinetic area, the extent of ionization of a drug has a strong effect on its extent of absorption, distribution, and elimination. The dissociation constant, or pK_a , is usually determined by potentiometric titration. For the practicing pharmacist, it is important in predicting precipitation in admixtures and in calculating the solubility of drugs at certain pH values. Physical Pharmacy Capsule 4.10, pK_a /Dissociation Constants, presents a brief summary of dissociation and ionization concepts.



PHYSICAL PHARMACY CAPSULE 4.10

pK_a /Dissociation Constants

The dissociation of a weak acid in water is given by this expression:



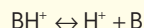
At equilibrium, the reaction rate constants K_1 and K_2 are equal. This can be rearranged, and the dissociation constant is defined as

$$K_a = \frac{K_1}{K_2} = \frac{[H^+][A^-]}{[HA]}$$

PHYSICAL PHARMACY CAPSULE 4.10 CONT.

where K_a is the acid dissociation constant.

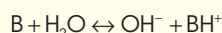
For the dissociation of a weak base that does not contain a hydroxyl group, the following relationship can be used:



The dissociation constant is described by

$$K_a = \frac{[H^+][B]}{[BH^+]}$$

The dissociation of a hydroxyl-containing weak base,



The dissociation constant is described by

$$K_b = \frac{[OH^-][BH^+]}{B}$$

The hydrogen ion concentrations can be calculated for the solution of a weak acid using

$$[H^+] = \sqrt{K_a C}$$

Similarly, the hydroxyl ion concentration for a solution of a weak base is approximated by

$$[OH^-] = \sqrt{K_b C}$$

Some practical applications of these equations are as follows.

EXAMPLE 1

The K_a of lactic acid is 1.387×10^{-4} at 25°C . What is the hydrogen ion concentration of a 0.02 M solution?

$$[H^+] = \sqrt{1.387 \times 10^{-4} \times 0.02} = 1.665 \times 10^{-3} \text{ G- ion / L}$$

EXAMPLE 2

The K_b of morphine is 7.4×10^{-7} . What is the hydroxyl ion concentration of a 0.02 M solution?

$$[OH^-] = \sqrt{7.4 \times 10^{-7} \times 0.02} = 1.216 \times 10^{-4} \text{ G- ion / L}$$

Hydrates and Solvates

Many active pharmaceutical agents exist as hydrates or solvates; some are hygroscopic, deliquescent, and/or efflorescent. Hygroscopic powders are those that will tend to absorb moisture from the air. Deliquescent powders are those that will absorb moisture from the air and even liquefy. Efflorescent powders are those that may give up their water of crystallization and may even become

damp and pasty. When working with these powders, extra care must be taken. Generally, the USP description of a powder will state whether it has hygroscopic, deliquescent, or efflorescent properties.

One other factor is that if a hygroscopic or deliquescent powder is being weighed on a balance, the powder may absorb moisture from the air and weigh heavier than it should. Therefore, weighings should be

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PHYSICAL PHARMACY CAPSULE 4.11

Hydrates and Solvates

When a substance is a hydrate and water is present in the molecule, more of the chemical must be weighed to obtain the actual active drug. As a drug example that is available with different amounts of water, let us look at different forms of dexamethasone.

- Dexamethasone contains less than 0.5% of its weight in water.
- Dexamethasone acetate has one molecule of water of hydration and contains between 3.5% and 4.5% of water; the anhydrous form contains less than 0.4% water.
- Dexamethasone sodium phosphate contains a sum of water and alcohol that may be up to 16%

Another example is lidocaine hydrochloride. Lidocaine hydrochloride occurs as a monohydrate and as the anhydrous form. The water content may be between 5% and 7%

CALCULATIONS

How much adjustment should be made if using lidocaine hydrochloride monohydrate in place of lidocaine hydrochloride anhydrous for a compounded prescription?

Lidocaine HCl monohydrate $C_{14}H_{22}N_2O \cdot HCl \cdot H_2O$ MW 288.81

Lidocaine HCl anhydrous $C_{14}H_{22}N_2O \cdot HCl$ MW 270.80

A comparison of the molecular weights reveals a factor of 1.066 can be used for the adjustment:

$$(288.81) / (270.80) = 1.066$$

EXAMPLE:

If a prescription for lidocaine hydrochloride 2% gel (100 g) is to be made, then 2 g of anhydrous lidocaine HCl could be used, OR:

$$2 \text{ g} \times 1.066 = 2.132 \text{ g of lidocaine HCl monohydrate.}$$

Also, a direct comparison of the molecular weights and the physical quantity required can be used, as follows:

$$\frac{\text{MW hydrate}}{\text{MW anhydrous}} = \frac{\text{weight of hydrated form}}{\text{weight of anhydrous form}}$$

$$\frac{288.81}{270.80} = \frac{X}{2\text{g}}$$

$$X = 2.133 \text{ g}$$

Further, the USP monograph for lidocaine hydrochloride Jelly, USP states "It contains not less than 95% and not more than 105.09% of the labeled amount of lidocaine hydrochloride ($C_{14}H_{22}N_2O \cdot HCl$)."

Note that this is the anhydrous form. It is important to also check the C of A for the lidocaine hydrochloride being used to determine the water content. Fortunately, most pure powders (anhydrous) generally only contain 0.2% to 0.5% moisture, which can be insignificant but need to be checked, nevertheless.

made quickly after opening the bulk chemical containers and then resealing them.

Solvates and hydrates must be packaged in "tight" containers to prevent the loss or gain of moisture. In fact, it is best to have all chemicals stored in "tight" containers and to keep them thoroughly closed at all times

except for the short time when a weighing step is involved. Storage at the indicated temperatures is also important and to minimize any exposure to very high humidity levels. More on hydrates and solvates is presented in Physical Pharmacy Capsule 4.11, Hydrates and Solvates.

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Organic Salt Considerations

Because many drugs are either weak acids or weak bases and have limited water solubility, they are often used as their “salts” to increase their aqueous solubility. For example, sodium salts are often made from weak acids (sodium salicylate is the salt of the weak acid, salicylic acid, and a strong base, sodium hydroxide). Also, a salt such as ephedrine hydrochloride can be prepared between a weak base, ephedrine, and a strong acid, hydrochloric acid. Third, the combination of a weak base, codeine, and a weak acid, phosphoric acid, can be used, as in codeine phosphate.

When salts are placed in an aqueous environment, they will dissolve to some extent, based upon their solubility in the aqueous media and the pH of the media. There will be a portion of the drug that is dissolved and some may remain undissolved. Of the dissolved portion, there will be a part that is “ionized” and the remainder will be “unionized,” depending upon the pH of the media. Generally, it is the “unionized” portion of the drug in solution that will be absorbed for systemic effect. This is described by the “dissociation constant” or “ pK_a ” of the drug.

Since the bulk substance or active pharmaceutical ingredient (API) in a salt form is not 100% active drug, it is important to know whether or not the dose of the drug is based upon the drug salt or drug base form. Many drugs are “salts,” and the dose may be based on the “total salt” form or just the “base” form of the drug.

Sources of information that can be used to determine the “form” of the drug (base, salt, or ester) include the wording of commercial products (package inserts) and the USP/NF. For example, Albuterol Sulfate Tablets USP are based on the “albuterol” content (present as the sulfate form). The USP states “Albuterol Tablets USP contain an amount of albuterol sulfate equivalent to not less than 90% and not more than 110% of the labeled amount of albuterol ($C_{13}H_{21}NO_3$).” In other words, sufficient albuterol sulfate is present to provide the labeled amount of the albuterol base.

In another scenario, the dose of Diphenhydramine Hydrochloride Capsules USP

is based on the total molecule, that is, diphenhydramine hydrochloride. The USP states “Diphenhydramine Hydrochloride Capsules USP contain not less than 90% and not more than 110% of the labeled amount of diphenhydramine hydrochloride ($C_{17}H_{21}NO \cdot HCl$).” As one can see, the weight of the “HCl” is considered in the dose of the drug.

The purpose of the “salt” form is usually to enhance the solubility of the drug; but it may also enhance the stability and change other attributes of the drug that make it easier to handle and manipulate for producing dosage forms. Also, it is the “unionized” portion of the drug that will ultimately exert its effect in the body, as the remainder of the salt molecule may no longer follow the base, or unionized, form of the drug into the body.

Why do we have some drugs that are dosed on the “base” form of the drug and some drugs that are dosed on the total weight of the “salt” form of the drug? In reviewing the USP revisions, it appears that this has always been an issue for many years with no apparent basis for which way the salts are dosed. However, both the official monographs and the U.S. Food and Drug Administration (FDA)–approved drug products appear to be inconsistent in how they determine how a drug is dosed. It is the responsibility of the pharmacist to know whether or not the base/acid of the salt form of the drug is to be used in the calculations for the amount of API to actually be used, if compounding.

The new “Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Medications” (USP General Chapter <1121> Nomenclature) states the following:

“The titles of USP monographs for drug products and compounded preparations formulated with a salt of an acid or base use the name of the active moiety, as defined below. The strength of the product or preparation also is expressed in terms of the active moiety.

An active moiety is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt



PHYSICAL PHARMACY CAPSULE 4.12

Organic Salts

It is important to know whether or not a drug is “dosed” on the base or the salt form. Consider that the fentanyl dose is calculated on the “base” form but the “salt” is the form that is used in the dosage form. For example:

A prescription calls for 10 mL of fentanyl 50 µg/0.1 mL (as the citrate) topical gel. How much fentanyl citrate will be required?

1. $50\text{ }\mu\text{g}/0.1\text{ mL} = X\text{ }\mu\text{g}/10\text{ mL}$, $X = 5\text{ mg}$
2. Fentanyl MW = 336.47
Fentanyl citrate MW = 528.59
3. $336.47/5\text{ mg} = 528.59/X$, $X = 7.85\text{ mg}$
4. Each mg of fentanyl equals $528.59/336.47 = 1.57\text{ mg}$ fentanyl citrate

In a different example, Diphenhydramine Hydrochloride Capsules USP are based on the total molecule, that is, diphenhydramine hydrochloride. The USP states “Diphenhydramine Hydrochloride Capsules USP contain not less than 90% and not more than 110% of the labeled amount of diphenhydramine hydrochloride ($\text{C}_{17}\text{H}_{21}\text{NO} \cdot \text{HCl}$).” As one can see, the weight of the “HCl” is considered in the dose of the drug. For example:

A prescription calls for 30 capsules of diphenhydramine hydrochloride 35 mg each. How much diphenhydramine hydrochloride will be required?

1. Since the total salt molecule is part of the dose:
2. $30 \times 35\text{ mg} = 1.05\text{ g}$ of diphenhydramine hydrochloride is required.

USP XII (1942) lists about 20 tablet monographs that are all based on the “salt” form of the drug, for example, Morphine Sulfate Tablets USP contain not less than 93% and not more than 107% of the labeled amount of morphine sulfate [$(\text{C}_{17}\text{H}_{19}\text{O}_3\text{N})_2 \cdot \text{H}_2\text{SO}_4 \cdot 5\text{H}_2\text{O}$]. The names of the monographed items in this time period were quite clear as the salt names were a part of the official name if it was to be used. For example, Barbitol Tablets USP are based on the labeled amount of barbitol ($\text{C}_8\text{H}_{12}\text{N}_2\text{O}_3$), but Barbitol Sodium Tablets were based on the labeled amount of barbitol sodium ($\text{C}_8\text{H}_{11}\text{N}_2\text{O}_3\text{Na}$).

USP XVI (1960) monograph for Amodiaquine Hydrochloride Tablets USP states “Amodiaquine Hydrochloride Tablets contain an amount of amodiaquine hydrochloride ($\text{C}_{20}\text{H}_{22}\text{ClN}_3\text{O} \cdot 2\text{HCl} \cdot 2\text{H}_2\text{O}$) equivalent to not less than 93% and not more than 107% of the labeled amount of amodiaquine base ($\text{C}_{20}\text{H}_{22}\text{ClN}_3\text{O}$).” It is evident in this monograph that the dose is calculated on the “base” form of the drug.

It is the responsibility of the formulator to determine whether or not the base/acid of the salt form of the drug is to be used in the calculations for the amount of API to actually be used.

with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance without regard to the actual charged state of the molecule in vivo.

For example, the active moiety of a hydrochloride salt of a base will be the free base and not the protonated form of the base. The active moiety of a metal acid salt will be the free acid.

This Policy is followed by USP in naming drug products and compounded preparations that are newly recognized in the USP. Revising existing monographs to conform to this Policy is not intended, except where the USP Council of Experts determines that, for reasons such as safety, a nomenclature change is warranted.”

See example organic salt considerations in Physical Pharmacy Capsule 4.12, Organic Salts.

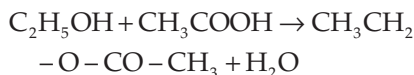
Organic Ester Considerations

Many drugs are available as the base form or as an “ester,” and the dose may be based on the total ester form or just the base form of the drug. If a number of factors are not considered, a final manufactured product or compounded preparation may not fall within the strength requirements, for example, 90% to 110% for compounded preparations or the USP monographs.

Some drugs are esters by virtue of their internal chemical structure (atropine, cocaine, many local anesthetics, etc.), and others are esters by the addition of a moiety that will form an ester for certain purposes. It is only the latter that are discussed here; those that are esters because of their basic molecular structure are not included.

An ester is a compound of the general formula $R-C-O-R_1$ where R and R_1 may be the same or different and may be either aliphatic or aromatic. The term “aliphatic” refers to an acyclic or cyclic, saturated or unsaturated carbon compounds excluding aromatic compounds; the term “aromatic” was originally used to describe compounds that “smelled” but were later found to contain either benzene or a fused benzene rings in the structure. The term has been generalized to include aromatic heterocyclic structures.

The dehydration of a molecule of an alcohol and a molecule of an organic acid can form an ester. For example, ethanol reacts with acetic acid to form ethyl acetate, an ester:



Following salts, esters are the most important acid derivatives used in pharmacy. Esters can be prepared for a number of reasons, including solubility, stability, resistance to degradation after administration, use as prodrugs, etc.

Some drugs are very soluble but tend to degrade rapidly when in solution. One approach to increase their stability, and shelf-life, is to prepare esters that are poorly soluble. This results in a “suspension” dosage form in place of a “solution” dosage form. A drug in a suspension dosage form degrades at a much slower rate than one in solution. After oral administration, the ester is cleaved and the active drug moiety released for absorption, etc.

Some drugs may cause pain at the site of injection, especially if they precipitate and damage the surrounding tissue. This can be overcome by preparing a drug with increased solubility. Chloramphenicol has low water solubility, but the succinate ester is formed to increase the water solubility of the drug and facilitate parenteral administration. This succinate ester is inactive but is hydrolyzed to release the active chloramphenicol moiety.

Esters are an important means of preparing prodrugs due to the number of esterases present in various parts of the body that will cleave the ester linkage, releasing the active moiety. Carboxylic acid esters are common in pharmacy and are neutral liquids or solids, which can be hydrolyzed slowly by water and rapidly by acids or alkalis into their components. Some of the simple esters are soluble in water, but those with more than four carbon atoms are practically insoluble in water. See examples in Physical Pharmacy Capsule 4.13, Organic Esters.



PHYSICAL PHARMACY CAPSULE 4.13

Organic Esters

Esters are quite interesting because one cannot simply look at the title and determine whether or not the drug is a salt or an ester. For example, “*acetate salts*” include calcium acetate, chlorhexidine acetate, desmopressin acetate, flecainide acetate, gonadorelin acetate, guanabenz acetate, leuprolide acetate, lysine acetate, mafenide acetate, and zinc acetate, and “*acetate esters*” include cortisone acetate, desoxycorticosterone acetate, dexamethasone

PHYSICAL PHARMACY CAPSULE 4.13 CONT.

acetate, fludrocortisone acetate, fluorometholone acetate, hydrocortisone acetate, isoflupredone acetate, medroxyprogesterone acetate, megestrol acetate, melengestrol acetate, methylprednisolone acetate, norethindrone acetate, paramethasone acetate, prednisolone acetate, trenbolone acetate, and betamethasone acetate.

Further, “*succinate salts*” include sumatriptan succinate, doxylamine succinate, loxapine succinate, and metoprolol succinate, and “*succinate esters*” include chloramphenicol sodium succinate, hydrocortisone sodium succinate, hypromellose acetate succinate, methylprednisolone sodium succinate, and prednisolone sodium succinate.

Let’s look at cefuroxime axetil as an example of an ester that is dosed on the base form.

1. Cefuroxime axetil is $C_{20}H_{22}N_4O_{10}S$, with a molecular weight of 510.47. Cefuroxime axetil is described as a mixture of the diastereoisomers of cefuroxime axetil and contains the equivalent of not less than 745 μg and not more than 875 μg of cefuroxime ($C_{16}H_{16}N_4O_8S$) per mg, calculated on the anhydrous basis.
2. Cefuroxime Axetil Tablets USP contain the equivalent of not less than 90% and not more than 110% of the labeled amount of cefuroxime ($C_{16}H_{16}N_4O_8S$).
3. Ceftin Tablets (cefuroxime axetil tablets) provide the equivalent of 250 or 500 mg of cefuroxime as cefuroxime axetil.
4. Ceftin for Oral Suspension (cefuroxime axetil powder for oral suspension) provides the equivalent of 125 or 250 mg of cefuroxime as cefuroxime axetil per 5 mL of suspension.
5. After oral administration, cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolyzed by nonspecific esterases in the intestinal mucosa and blood to cefuroxime; the axetil moiety is metabolized to acetaldehyde and acetic acid.
6. The molecular weight of cefuroxime axetil is 510.47. The molecular weight of cefuroxime is 424.39. Therefore, 1 mg of cefuroxime is contained in $510.47/424.39 = 1.2$ mg of cefuroxime axetil. A 250 mg of cefuroxime tablet will contain $250 \times 1.2 = 300$ mg of cefuroxime axetil.
7. Therefore, if using a commercial product to prepare a dosage form, no conversion should be required. However, if using a bulk active ingredient, then the required amount of cefuroxime axetil that is equivalent to the desired dosage of cefuroxime must be calculated.

Dexamethasone-labeled strengths pose an interesting problem as they are not consistent in naming either the base or the ester form, for example

“Dexamethasone” dosage form monographs are based on the labeled amount of “dexamethasone.”

“Dexamethasone acetate” dosage form monograph is based on the labeled amount of “dexamethasone.”

“Dexamethasone sodium phosphate” dosage form monographs are based upon the labeled amount of “dexamethasone phosphate,” not “dexamethasone.”

An example of a drug that occurs both as salt and ester forms is the drug erythromycin: Erythromycin estolate is a salt; erythromycin ethylsuccinate is an ester; erythromycin gluceptate is a salt; erythromycin lactobionate is a salt; and erythromycin stearate is a salt.

Potency-Designated Active Pharmaceutical Ingredients

In the case of “potency-designated drugs,” the bulk substance, or API, is not 100% active drug in all cases. It is important to know the assayed potency designation of the ingredient so that appropriate allowances can be made to obtain the correct amount. This

may be on the label or on the Certificate of Analysis.

Some APIs, including some antibiotics, endocrine products, biotechnology-derived products, biologics, etc., have potencies that are based on “activity” and are expressed in terms of “units of activity,” “micrograms per milligram,” or other standard terms of

measurements. These are described for each API in the USP.

Regarding biologicals, the following is found in the General Notices of the USP:

“5.50.10 Units of Potency (Biological)”

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

Units of biological potency defined by the World Health Organization (WHO) for International Biological Standards and International Biological Reference Preparations are termed International Units (IU). Monographs refer to the units defined by USP Reference Standards as “USP Units.” For biological products, units of potency are defined by the corresponding U.S. Standard established by FDA, whether or not

International Units or USP Units have been defined.

There is no relationship between the units of potency of one drug with that of another different drug.

In the case of potency-designated drugs, there must be a “reference standard” for comparison. In actual usage, the potency specifications often include a range or “not less than ___” and “not more than ___.” In some cases, only a lower range is given, and in a few cases, there is no upper limit.

The determinations of potency are generally done on the “dried or anhydrous basis.” In the case of hygroscopic APIs, one must exercise precautions to maintain the substance in a dried state in tight containers. In some cases, there is a designation of specified solvent-free conditions.

See examples in Physical Pharmacy Capsule 4.14, Potency-Designated Active Pharmaceutical Ingredients.



PHYSICAL PHARMACY CAPSULE 4.14

Potency-Designated Active Pharmaceutical Ingredients

For those APIs, including some antibiotics, endocrine products, biotechnology-derived products, biologics, etc., that have potencies that are based on “activity” and are expressed in terms of “units of activity,” “micrograms per milligram,” or other standard terms of measurements, calculations must be made to ensure that the correct quantity of active drug is used.

In the case of dihydrostreptomycin, there are different potencies depending upon the use of the API. The potency may be not less than 450, 650, or 725 μg , depending upon its form or usage (route of administration).

In some cases, as in erythromycin ethylsuccinate and erythromycin stearate, the potency is based on the sum of the percentages of three different erythromycins that make up the API. Generally, the potency designation is determined on the “base” of the drug, but in few instances, the salt or ester form is used.

The potency of antibiotics is commonly expressed as “ μg of activity per mg of substance.” Obviously, there will be different equivalents for the base versus the salt forms of the drug. Tobramycin has not less than 900 μg of tobramycin per mg, and tobramycin sulfate has a potency of not less than 634 μg of tobramycin per mg, all on the anhydrous basis. As another example, ampicillin contains not less than 900 μg and not more than 1,050 μg of ampicillin per mg, and ampicillin sodium contains not less than 845 μg and not more than 988 μg of ampicillin per mg, both calculated on the anhydrous basis. So, one can tell that it is extremely important to check the labels accompanying each batch of each API for the necessary values to be used in calculations.

PHYSICAL PHARMACY CAPSULE 4.14 CONT.

In some drugs, the actual dose may be expressed in units instead of mg. Examples of this include heparin and insulin. Other examples include enzymes (pancreatin, pancrelipase, papain) and antibiotics.

Each container must be labeled with the actual potency, and this information is to be used in calculations involving dosing prior to compounding activities. These calculations must be done and checked and documented, as different lots of the same API may have different potencies. An example of a calculation follows.

EXAMPLE

A formula calls for 500 mg of neomycin sulfate. The label on the API shows 650 µg of neomycin activity per mg of powder. How much of this powder is required to provide the 500 mg of neomycin sulfate?

$$\frac{650 \mu\text{g}}{1000 \mu\text{g}} = \frac{500 \text{ mg}}{X}$$

X = 769 mg of the powder is required to provide 500 mg of actual neomycin sulfate.

Complex Organic Molecules

Most complex molecules and biotechnology products are proteins; however, some may be smaller peptide-like molecules. Proteins are inherently unstable molecules and require special handling; also, their degradation profiles can be quite complex. Pharmacists involved in working with or handling biologically active proteins must be interested in their stabilization, formulation, and delivery to the site of action.

In working with complex molecules, one must be cognizant of both the active drug constituent and the total drug formulation in which it is contained. This is true when

converting a commercial product into a compounded preparation. Protein drugs are very potent and are generally used in quite low concentrations. The bulk of many manufactured products and compounded preparations may be the excipients. These excipients include the vehicle, buffers, stabilizers, and others that are often incorporated in these products. A number of different stabilizers can be used from different chemical classes and include surfactants, amino acids, polyhydric alcohols, fatty acids, proteins, antioxidants, reducing agents, and metal ions. See Physical Pharmacy Capsule 4.15, Complex Organic Molecules for further considerations.

**PHYSICAL PHARMACY CAPSULE 4.15****Complex Organic Molecules**

Most complex molecules and biotechnology products are proteins; however, some may be smaller peptide-like molecules. Proteins are inherently unstable molecules and require special handling; also, their degradation profiles can be quite complex. Pharmacists involved in compounding with biologically active proteins must be interested in their stabilization, formulation, and delivery to the site of action.

Protein drugs are potent and are generally used in low concentrations; consequently, the bulk of many manufactured products and compounded preparations may be the excipients,

PHYSICAL PHARMACY CAPSULE 4.15 CONT.

including the vehicle, buffers, stabilizers, and others that are often incorporated in these products.

FACTORS

pH: pH is one of the key important factors in formulating a stable preparation. The optimal pH range can be achieved through the selection of appropriate physiologic buffers, usually in buffer concentration ranges of 0.01 to 0.1 M. In general, an increase in the buffer concentration means an increase in pain on injection so is generally kept as low as reasonable.

Chelating agents: Chelating agents are incorporated to bind trace metals such as copper, iron, calcium, and manganese and minimize rates of degradation. Ethylenediaminetetraacetic acid (EDTA) is commonly used at a concentration of about 0.01% to 0.05%.

Antioxidants: Antioxidants are often used since oxidation is one of the major factors in protein degradation. Examples include ascorbic acid, sodium disulfide, monothioglycerol, and α -tocopherol are frequently used at a concentration of about 0.05% to 0.1%.

Preservatives: Preservatives are used, especially if multiple dose vials are indicated. Examples include phenol (0.3% to 0.5%), chlorobutanol (0.3% to 0.5%), and benzyl alcohol (1% to 3%).

Others: Others may include the polyols, which are good stabilizers and are commonly used in concentrations from 1% to 10%, and tonicity-adjusting agents, which include sodium chloride and dextrose in concentrations necessary to achieve isotonicity of approximately 290 mOsm/L.

The use of filters in manipulating biotechnology products can result in "sorption" or the loss of some of the drug available to the patient. Sorption is "sticking" either by "absorption" into the filter or by "adsorption" onto the surface of the filter. Special filters have been prepared to minimize this problem. For example, muromonab-CD3 (Orthoclone OKT3) injection should be filtered with a low-protein-binding filter of 0.2 to 0.22 μ m. Many biotechnology products should not be filtered at all. If a filtration device is part of the IV administration apparatus, large molecule drugs should generally be administered distal to the site of the filter. Filters that have been shown to minimize protein adsorption are those made from polyvinylidene difluoride, polycarbonate, polysulfone, and regenerated cellulose. As a precaution, low-protein-binding filters should be used.

Sorption of proteins to containers (glass or plastic) can result in drug loss. This loss can be minimized either by the use of albumin or by siliconization. Adding about 0.1% albumin to the product can decrease the sorption of proteins to containers. If glass containers are used, the albumin solution should be added and manipulated to coat the interior surface before adding the drug. If siliconization is used, one can prepare a silicon solution or emulsion and soak or rinse the glass vials in it. The drained vials should then be placed in an oven at about 250°C for 5 to 6 hours. This procedure will minimize protein adsorption to the glass; it can be used for both the preparation equipment and the packaging containers.

Specific issues relevant to large molecule drugs include the following:

- effect of agitation and/or frothing on a preparation's stability;
- high molecular weight and potential for aggregation (i.e., a small change in structure can result in a change in activity);
- assignment of potency to the reference standards (when traditional pharmaceuticals are about 98% pure, these materials may be only 0.1% to 1% active, with their activity assigned by potentially variable assays);
- use of micropipets, which can require frequent calibration;
- stability may be less than lyophilized preparations;
- interaction of the product with the inner wall of the glass vial and with the elastomeric closure;
- effectiveness of the preservative if a multidose product is mixed with other products; and

PHYSICAL PHARMACY CAPSULE 4.15 CONT.

- immunogenic potential, because some are produced by a fermentation-type process and proteins can copurify with proteins.

Sorption is a problem with colony-stimulating factors and with aldesleukin (Proleukin) at low concentrations. To minimize “sticking” of the protein to the glass, the addition of about 0.1% albumin to the product to occupy the potential binding sites in the container is often helpful. Pharmacists must consider this problem before making any changes in packaging.

Agitation resulting in frothing can create difficulties in two ways. First, frothing can cause difficulties in using a syringe to withdraw the required amount of drug from a vial. To avoid this problem, the formulator should mix the product by rolling the vial in the hands or gently swirling it. Second, excessive agitation can cause changes in a protein’s quaternary structure that often reduce or eliminate a drug’s therapeutic activity. Some products, such as filgrastim (Neupogen) and sargramostim (Leukine), are reconstituted by directing a soft stream of diluent against the inside of the container wall. Others, such as recombinant tissue plasminogen activator (tPA; alteplase), are reconstituted by directing a stream of diluent directly into the product at the bottom of the vial.

Storage: The recommended storage temperature depends on the specific preparation and may include room temperature (15°C to 25°C), refrigerator temperature (2°C to 8°C), frozen (–20°C), or ultra frozen temperature (down to –80°C). Freezing does affect the activity of certain products; for instance, the activity of filgrastim decreases if it is frozen. Some products can retain potency at room temperature after reconstitution. Sargramostim retains potency for up to 30 days at 25°C. However, most manufacturers recommend refrigeration at 2°C to 8°C, regardless of the product’s potency at room temperature.

The short shelf life of these products after reconstitution can be due to chemical, physical, or microbiological instability. The manufacturer’s recommendations or those validated by the published literature should be followed for products after they are reconstituted and manipulated. One example is tPA, which has been used in treating intraocular fibrin formation after a vitrectomy and in managing subconjunctival hemorrhage after glaucoma filtration surgery. The prepared solution is stable in a pH range of 5 to 7.5 and is incompatible with bacteriostatic agents. To prepare a compounded preparation, the commercial product is reconstituted according to the manufacturer’s directions, using sterile water for injection without preservatives to yield a concentration of 1 mg/mL. This solution is further diluted with 0.9% sodium chloride injection to yield a concentration of 25 µg/100 µL. Aliquots of 0.3 mL are withdrawn into 1-mL tuberculin syringes and capped. The syringes are stored in an ultra freezer at –70°C. This product has been shown, by both bioassay and clinical use, to retain its activity for at least 1 year. This type of specific product information is not included in the manufacturer’s label information and is usually obtained from the literature or by asking the manufacturer directly.

Physical stability: This can involve degradation by aggregation, denaturation, and precipitation. *Aggregation* can be the result of covalent or noncovalent processes and can be either physical or chemical in nature. Aggregate formation can actually begin when primary particles are formed from protein molecules as a result of Brownian movement.

Denaturation can result from heat, cold, extreme pH values, organic solvents, hydrophilic surfaces, shear, agitation, mixing, filtering, shaking, freeze–thaw cycles, ionic strength, and other factors. Denaturation can be quite complex and can be either reversible or irreversible.

Precipitation can result from shaking, heating, filtration, pH, and chemical interactions. The first step in a precipitation process is generally aggregation. When the aggregates gain a sufficient size, they precipitate out of solution and are clearly evident. Precipitation can occur on membrane filters, in equipment, in tubing, and in contact with other equipment and supplies.

Drug and Drug Product Stability

One of the most important activities of preformulation work is evaluation of the physical and chemical stability of the pure drug substance. It is essential that these initial studies be conducted using drug samples of known purity. The presence of impurities can lead to erroneous conclusions in such evaluations. Stability studies conducted in the preformulation phase include solid-state stability of the drug alone, solution-phase stability, and stability in the presence of expected excipients. Initial investigation begins with knowledge of the drug's chemical structure, which allows the preformulation scientist to anticipate the possible degradation reactions.

Drug Stability: Mechanisms of Degradation

Chemical instability of medicinal agents may take many forms because the drugs in use today are of such diverse chemical constitution. Chemically, drug substances are alcohols, phenols, aldehydes, ketones, esters, ethers, acids, salts, alkaloids, glycosides, and others, each with reactive chemical groups having different susceptibilities to chemical instability. Chemically, the most frequently encountered destructive processes are hydrolysis and oxidation.

Hydrolysis is a solvolysis process in which (drug) molecules interact with water molecules to yield breakdown products. For example, aspirin, or acetylsalicylic acid, combines with a water molecule and hydrolyzes into one molecule of salicylic acid and one molecule of acetic acid.

Hydrolysis is probably the most important single cause of drug decomposition, mainly because a great number of medicinal agents are esters or contain such other groupings as substituted amides, lactones, and lactams, which are susceptible to the hydrolytic process (2).

Another destructive process is oxidation, which destroys many drug types, including aldehydes, alcohols, phenols, sugars, alkaloids, and unsaturated fats and oils. Chemically, oxidation is loss of electrons from an atom or a molecule. Each electron

lost is accepted by some other atom or molecule, reducing the recipient. In inorganic chemistry, oxidation is accompanied by an increase in the positive valence of an element, for example, ferrous (+2) oxidizing to ferric (+3). In organic chemistry, oxidation is frequently considered synonymous with the loss of hydrogen (dehydrogenation) from a molecule. Oxidation frequently involves free chemical radicals, which are molecules or atoms containing one or more unpaired electrons, such as molecular (atmospheric) oxygen ($\bullet\text{O}-\text{O}\bullet$) and free hydroxyl ($\bullet\text{OH}$). These radicals tend to take electrons from other chemicals, thereby oxidizing the donor.

Many of the oxidative changes in pharmaceutical preparations have the character of autoxidations. Autoxidations occur spontaneously under the initial influence of atmospheric oxygen and proceed slowly at first and then more rapidly. The process has been described as a type of chain reaction commencing with the union of oxygen with the drug molecule and continuing with a free radical of this oxidized molecule participating in the destruction of other drug molecules and so forth.

In drug product formulation work, steps are taken to reduce or prevent deterioration due to hydrolysis, oxidation, and other processes. These techniques are discussed later.

Drug and Drug Product Stability: Kinetics and Shelf Life

Stability is 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 concern pharmacists:

1. *Chemical*: Each active ingredient retains its chemical integrity and labeled potency within the specified limits.
2. *Physical*: The original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability, are retained.
3. *Microbiologic*: Sterility or resistance to microbial growth is retained according to

the specified requirements. Antimicrobial agents retain effectiveness within specified limits.

4. *Therapeutic*: The therapeutic effect remains unchanged.
5. *Toxicologic*: No significant increase in toxicity occurs.

Chemical stability is important for selecting storage conditions (temperature, light, humidity), selecting the proper container for dispensing (glass versus plastic, clear versus amber or opaque, cap liners), and anticipating interactions when mixing drugs and dosage forms. Stability and expiration dating are based on reaction kinetics, that is, the study of the rate of chemical change and the way this rate is influenced by concentration of reactants, products, and other chemical

species and by factors such as solvent, pressure, and temperature.

In considering chemical stability of a pharmaceutical, one must know the reaction order and reaction rate. The reaction order may be the overall order (the sum of the exponents of the concentration terms of the rate expression) or the order with respect to each reactant (the exponent of the individual concentration term in the rate expression).

Rate Reactions

The reaction rate is a description of the drug concentration with respect to time. Most commonly, zero-order and first-order reactions are encountered in pharmacy. These are presented in Physical Pharmacy Capsule 4.16, Rate Reactions, along with some appropriate examples.



PHYSICAL PHARMACY CAPSULE 4.16

Rate Reactions

ZERO-ORDER RATE REACTIONS

If the loss of drug is independent of the concentration of the reactants and constant with respect to time (i.e., 1 mg/mL/h), the rate is called zero order. The mathematical expression is

$$\frac{-dC}{dt} = k_0$$

where k_0 is the zero-order rate constant [concentration (C)/time (t)].

The integrated and more useful form of the equation:

$$C = -k_0 t + C_0$$

where C_0 is the initial concentration of the drug.

The units for a zero rate constant k_0 are concentration per unit time, such as moles per liter-second or milligrams per milliliter per minute.

It is meaningless to attempt to describe the time required for *all* material in a reaction to decompose, that is, infinity. Therefore, reaction rates are commonly described by k or by their half-life, $t_{1/2}$.

The half-life equation for a zero-order reaction:

$$t_{1/2} = (1/2)(C_0 / k_0)$$

If the C_0 changes, the $t_{1/2}$ changes. There is an inverse relationship between the $t_{1/2}$ and k .

EXAMPLE 1

A drug suspension (125 mg/mL) decays by zero-order kinetics with a reaction rate constant of 0.5 mg/mL/h. What is the concentration of intact drug remaining after 3 days (72 hours), and what is its $t_{1/2}$?

PHYSICAL PHARMACY CAPSULE 4.16 CONT.

$$C = -(0.5 \text{ mg/mL/h})(72 \text{ h}) + 125 \text{ mg/mL}$$

$$C = 89 \text{ mg/mL after 3 d}$$

$$t_{1/2} = 1/2(125 \text{ mg/mL} - 0.5 \text{ mg/mL/h})$$

$$t_{1/2} = 125 \text{ h}$$

EXAMPLE 2

How long will it take for the suspension to reach 90% of its original concentration?

$$90\% \times 125 \text{ mg/mL} = 112.5 \text{ mg/mL}$$

$$t = \frac{C - C_0}{-k_0} = \frac{112.5 \text{ mg/mL} - 125 \text{ mg/mL}}{-0.5 \text{ mg/mL/h}} = 25 \text{ h}$$

Drug suspensions are examples of pharmaceuticals that ordinarily follow zero-order kinetics for degradation.

FIRST-ORDER RATE REACTIONS

If the loss of drug is directly proportional to the concentration remaining with respect to time, it is called a first-order reaction and has the units of reciprocal time, that is, time^{-1} . The mathematical expression is

$$\frac{-dC}{dt} = kC$$

where

C is the concentration of intact drug remaining,
 t is time,
 (dC/dt) is the rate at which the intact drug degrades, and
 k is the specific reaction rate constant.

The integrated and more useful form of the equation:

$$\log C = \frac{-kt}{2.303} + \log C_0$$

where C_0 is the initial concentration of the drug.

In natural log form, the equation is

$$\ln C = -kt + \ln C_0$$

The units of k for a first-order reaction are per unit of time, such as per second.

The half-life equation for a first-order reaction is

$$t_{1/2} = 0.693 / k$$

and can be easily derived from the first-order equation by substituting values of $C = 50\%$ and $C_0 = 100\%$, representing a decrease in concentration by 50%.

EXAMPLE 3

An ophthalmic solution of a mydriatic drug at 5 mg/mL exhibits first-order degradation with a rate of 0.0005/day. How much drug will remain after 120 days, and what is its half-life?

PHYSICAL PHARMACY CAPSULE 4.16 CONT.

$$\begin{aligned}\ln C &= -(0.0005 / d)(120) + \ln(5 \text{ mg / mL}) \\ \ln C &= -0.06 + 1.609 \\ \ln C &= 1.549 \\ C &= 4.71 \text{ mg / mL} \\ t_{1/2} &= 0.693 / 0.0005 / d \\ t_{1/2} &= 1,386 \text{ d}\end{aligned}$$

EXAMPLE 4

In Example 3, how long will it take for the drug to degrade to 90% of its original concentration?

$$\begin{aligned}90\% \text{ of } 5 \text{ mg / mL} &= 4.5 \text{ mg / mL} \\ \ln 4.5 \text{ mg / mL} &= -(0.0005 / d)t + \ln(5 \text{ mg / mL}) \\ t &= \frac{\ln 4.5 \text{ mg / mL} - \ln 5 \text{ mg / mL}}{-0.0005 / d} \\ t &= 210 \text{ d}\end{aligned}$$

ENERGY OF ACTIVATION: ARRHENIUS EQUATION

Stability projections for shelf life (t_{90} or the time required for 10% of the drug to degrade with 90% of the intact drug remaining) are commonly based on the Arrhenius equation:

$$\log \frac{k_2}{k_1} = \frac{E_a(T_2 - T_1)}{2.3RT_1T_2}$$

which relates the reaction rate constants (k) to temperatures (T) with the gas constant (R) and the energy of activation (E_a).

The relationship of the reaction rate constants at two different temperatures provides the energy of activation for the degradation. By performing the reactions at elevated temperatures instead of allowing the process to proceed slowly at room temperature, the E_a can be calculated and a k value for room temperature determined with the Arrhenius equation.

EXAMPLE 5

The degradation of a new cancer drug follows first-order kinetics and has first-order degradation rate constants of 0.0001 per hour at 60°C and 0.0009 per hour at 80°C. What is its E_a ?

$$\begin{aligned}\log \frac{(0.0009)}{(0.0001)} &= \frac{E_a(353 - 333)}{(2.3)(1.987)(353)(333)} \\ E_a &= 25,651 \text{ kcal / mol}\end{aligned}$$

Q₁₀ Method of Shelf Life Estimation

The Q_{10} method of shelf life estimation lets the pharmacist estimate shelf life for a product that has been stored or is going to be stored under a different set of conditions. It is explained in Physical Pharmacy Capsule 4.19, Q_{10} Method of Shelf Life Estimation.

Enhancing Stability of Drug Products

Many pharmaceutical ingredients may be used to prepare the desired dosage form of a drug substance. Some of these agents may be used to achieve the desired physical and chemical characteristics of the product or to enhance its appearance, odor, and taste.

Other substances may be used to increase the stability of the drug substance, particularly against hydrolysis and oxidation. In each instance, the added pharmaceutical ingredient must be compatible with and must not detract from the stability of the drug substance.

There are several approaches to the stabilization of pharmaceutical preparations containing drugs subject to hydrolysis. Perhaps the most obvious is the reduction or elimination of water from the pharmaceutical system. Even solid dosage forms containing water-labile drugs must be protected from humidity in the atmosphere. This may be accomplished by applying a waterproof protective coating over tablets or by keeping the drug in a tightly closed container. It is fairly common to detect hydrolyzed aspirin by noticing an odor of acetic acid upon opening a bottle of aspirin tablets. In liquid preparations, water can frequently be replaced or reduced in the formulation through the use of substitute liquids such as glycerin, propylene glycol, and alcohol. In certain injectable products, anhydrous vegetable oils may be used as the drug's solvent to reduce the chance of hydrolytic decomposition.

Decomposition by hydrolysis may be prevented in other liquid drugs by suspending

them in a nonaqueous vehicle rather than dissolving them in an aqueous solvent. In still other instances, particularly for certain unstable antibiotic drugs, when an aqueous preparation is desired, the drug may be supplied to the pharmacist in a dry form for *reconstitution* by adding a specified volume of purified water just before dispensing. The dry powder is actually a mixture of the antibiotic, suspending agents, flavorants, and colorants; when reconstituted by the pharmacist, it remains stable for the period over which the preparation is normally consumed. Refrigeration is advisable for most preparations considered subject to hydrolysis. Together with temperature, pH is a major determinant of the stability of a drug prone to hydrolytic decomposition. Hydrolysis of most drugs depends on the relative concentrations of the hydroxyl and hydronium ions, and a pH at which each drug is optimally stable can be easily determined. For most hydrolyzable drugs, optimum stability is on the acid side, somewhere between pH 5 and 6. Therefore, through judicious use of buffering agents, the stability of otherwise unstable compounds can be increased. Buffers are used to maintain a certain pH, as described in Physical Pharmacy Capsule 4.17, Buffer Capacity.



PHYSICAL PHARMACY CAPSULE 4.17

Buffer Capacity

pH, buffers, and buffer capacity are especially important in drug product formulation, since they affect the drug's solubility, activity, absorption, and stability and the patient's comfort.

A buffer is a system, usually an aqueous solution, that can resist changes in pH upon addition of an acid or a base. Buffers are composed of a weak acid and its conjugate base or a weak base and its conjugate acid. Buffers are prepared by one of these processes:

1. Mixing a weak acid and its conjugate base or a weak base and its conjugate acid
2. Mixing a weak acid and a strong base to form the conjugate base or a weak base and a strong acid to form the conjugate acid

Using the Henderson-Hasselbalch equation:

$$\text{pH} = \text{pK}_a + \log(\text{base} / \text{acid})$$

PHYSICAL PHARMACY CAPSULE 4.17 CONT.

Remember that the acid is the proton donor and the base is the proton acceptor.

EXAMPLE 1

A buffer is prepared by mixing 100 mL of 0.2 M phosphoric acid with 200 mL of 0.08 M sodium phosphate monobasic. What is the pH of this buffer? (K_a of phosphoric acid = 7.5×10^{-3})

Moles acid = $(0.2 \text{ mol}/1,000 \text{ mL}) (100 \text{ mL}) = 0.02 \text{ mol}$; $(0.02 \text{ mol})/(0.3 \text{ L}) = 0.067 \text{ M}$
 Moles base = $(0.08 \text{ mol}/1,000 \text{ mL}) (200 \text{ mL}) = 0.016 \text{ mol}$; $(0.016 \text{ mol})/(0.3 \text{ L}) = 0.053 \text{ M}$
 $\text{pK}_a = -\log 7.5 \times 10^{-3} = 2.125$
 $\text{pH} = 2.125 + \log (0.016 \text{ mol}/0.02 \text{ mol}) = 2.028$

EXAMPLE 2

Determine the pH of the buffer prepared as shown:

Sodium acetate 50 g

Conc. HCl 10 mL

Water qs 2 L

Helpful numbers:

pK_a acetic acid = 4.76

m.w. sodium acetate = 82.08

m.w. acetic acid = 60.05

m.w. HCl = 36.45

Conc. HCl, 44% HCl w/v

$\text{NaAc} + \text{HCl} \rightarrow \text{NaCl} + \text{HAc} + \text{NaAc}$

$(0.609 \text{ mol}) (0.121 \text{ mol}) (0.121 \text{ mol}) (0.121 \text{ mol}) (0.488 \text{ mol})$

$\text{HCl} : \{ (10 \text{ mL}) [(44 \text{ g}) / (100 \text{ mL})] (1 \text{ mol}) / (36.45 \text{ g}) \} = 0.121 \text{ mol}$

$\text{NaAc} : \{ (50 \text{ g}) [(1 \text{ mol}) / (82.08 \text{ g})] \} = 0.609 \text{ mol}$
 $(0.609 \text{ mol}) - (0.121 \text{ mol}) = 0.488 \text{ mol}$

$\text{pH} = 4.76 + \log (0.488 \text{ mol}) / (0.121 \text{ mol}) = 5.367$

The ability of a buffer solution to resist changes in pH upon the addition of an acid or a base is called buffer capacity (β) and is defined thus:

$$\beta = \Delta B / \Delta \text{pH}$$

where

ΔB is molar concentration of acid or base added,

ΔpH is change in pH due to addition of acid or base, and

ΔpH can be determined experimentally or calculated using the Henderson-Hasselbalch equation.

EXAMPLE 3

If 0.2 mole of HCl is added to a 0.015 M solution of ammonium hydroxide and the pH falls from 9.5 to 8.9, what is the buffer capacity?

$$\Delta \text{pH} = 9.5 - 8.9 = 0.6$$

$$\Delta B = 0.2 \text{ mol} / \text{L} = 0.2 \text{ M}$$

$$\beta = 0.2 \text{ M} / 0.6 = 0.33 \text{ M}$$

EXAMPLE 4

If 0.002 mole of HCl is added to the buffer in Example 1, what is its buffer capacity? After adding 0.002 mole HCl:

PHYSICAL PHARMACY CAPSULE 4.17 CONT.

$$\begin{aligned} \text{H}_3\text{PO}_4 &: 0.02 \text{ mol} + 0.002 \text{ mol} = 0.022 \text{ mol} \\ \text{NaH}_2\text{PO}_4 &: 0.016 \text{ mol} - 0.002 \text{ mol} = 0.014 \text{ mol} \\ \text{pH} &= 2.125 + \log(0.014 \text{ mol} / 0.022 \text{ mol}) = 1.929 \\ \Delta\text{pH} &= 2.028 - 1.929 = 0.099 \\ \Delta\text{AB} &= 0.002 \text{ mol} / 0.3 \text{ L} = 0.0067 \text{ M} \\ \beta &= 0.0067 \text{ M} / 0.099 = 0.067 \text{ M} \end{aligned}$$

Another approach to calculating buffer capacity involves the use of Van Slyke equation:

$$\beta = 2.3C\{K_a[H^+] / (K_a[H^+] + 1)\}^2$$

where

C is the sum of the molar concentrations of the acid and base, and $[H^+] = 10^{-\text{pH}}$.

EXAMPLE 5

What is the Van Slyke buffer capacity of the buffer prepared in Example 1?

$$C = 0.0067 \text{ M} + 0.0053 \text{ M} = 0.12 \text{ M}$$

$$K_a = 7.5 \times 10^{-3}$$

$$[H^+] = 10^{-2.028} = 9.38 \times 10^{-3} \text{ M}$$

$$\beta = 2.3(0.12 \text{ M}) \{[(7.5 \times 10^{-3} \text{ M})(9.38 \times 10^{-3} \text{ M})] / [(7.5 \times 10^{-3} \text{ M}) + (9.38 \times 10^{-3} \text{ M})]\}^2 = 0.68 \text{ M}$$

Pharmaceutically, oxidation of a susceptible drug substance is most likely to occur when it is not kept dry in the presence of oxygen or when it is exposed to light or combined with other chemical agents without proper regard to their influence on oxidation. Oxidation of a chemical in a pharmaceutical preparation is usually accompanied by an alteration in the color of that preparation. It may also result in precipitation or a change in odor.

The oxidative process is diverted and the stability of the drug is preserved by agents called *antioxidants*, which react with one or more compounds in the drug to prevent progress of the chain reaction. In general, antioxidants act by providing electrons and easily available hydrogen atoms that are accepted more readily by the free radicals than are those of the drug being protected. Various antioxidants are employed in pharmacy. Among those, most frequently used in aqueous preparations are sodium sulfite (Na_2SO_3 , at high pH values), sodium bisulfite (NaHSO_3 , at intermediate pH values), sodium metabisulfite ($\text{Na}_2\text{S}_2\text{O}_5$, at low pH

values), hypophosphorous acid (H_3PO_2), and ascorbic acid. In oleaginous (oily or unctuous) preparations, alpha-tocopherol, butyl hydroxy anisole, and ascorbyl palmitate find application.

In its labeling regulations for pharmaceutical products containing sulfites, the FDA requires a warning about possible allergic-type reactions, including possible life-threatening anaphylaxis symptoms and/or asthma episodes, in susceptible persons (3). Sulfites are used as preservatives in many injectable drugs, such as antibiotics and local anesthetics. Some inhalants and ophthalmic preparations also contain sulfites, but relatively few oral drugs contain these chemicals. The purpose of the regulation is to protect the estimated 0.2% of the population who are subject to allergic reactions to the chemicals. Many sulfite-sensitive persons have asthma or other allergic conditions. Previous to the regulations dealing with prescription medication, the FDA issued regulations for the use of sulfites in food. Asthmatics and other patients who may be sulfite sensitive should be reminded to read the labels of packaged

foods and medications to check for the presence of these agents. Sulfite agents covered by the regulations are potassium bisulfite, potassium metabisulfite, sodium bisulfite, sodium metabisulfite, sodium sulfite, and sulfur dioxide. The FDA permits the use of sulfites in prescription products, with the proper labeling, because there are no generally suitable substitutes for sulfites to maintain potency in certain medications. Some but not all epinephrine injections contain sulfites.

The proper use of antioxidants permits their specific application only after appropriate biomedical and pharmaceutical studies. In certain instances, other pharmaceutical additives can inactivate a given antioxidant. In other cases, certain antioxidants can react chemically with the drugs they were intended to stabilize without a noticeable change in the appearance of the preparation.

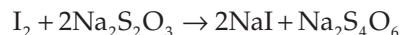
Because oxygen may adversely affect their stability, certain pharmaceuticals require an oxygen-free atmosphere during preparation and storage. Oxygen may be present in pharmaceutical liquids in the airspace within the container or may be dissolved in the liquid vehicle. To avoid these exposures, oxygen-sensitive drugs may be prepared in the dry state and packaged in sealed containers with the air replaced by an inert gas such as nitrogen, as may liquid preparations. This is a common practice in commercial production of vials and ampuls of easily oxidizable preparations intended for parenteral use.

Trace metals originating in the drug, solvent, container, or stopper are a constant source of difficulty in preparing stable solutions of oxidizable drugs. The rate of formation of color in epinephrine solutions, for instance, is greatly increased by the presence of ferric, ferrous, cupric, and chromic ions. Great care must be taken to eliminate these trace metals from labile preparations by thorough purification of the source of the contaminant or by chemically complexing or binding the metal through the use of specialized agents that make it chemically unavailable for participation in the oxidative process. These chelating agents are exemplified by calcium disodium edetate and EDTA.

Light can also act as a catalyst to oxidation reactions, transferring its energy (photons) to drug molecules, making the latter more reactive through increased energy capability. As a precaution against acceleration of oxidation, sensitive preparations are packaged in light-resistant or opaque containers.

Because most drug degradations proceed more rapidly as temperature increases, it is also advisable to maintain oxidizable drugs in a cool place. Another factor that can affect the stability of an oxidizable drug in solution is the pH of the preparation. Each drug must be maintained in solution at the pH most favorable to its stability. This varies from preparation to preparation and must be determined on an individual basis for the drug in question.

Statements in the USP warn of the oxidative decomposition of susceptible drugs and preparations. In some instances, the specific agent to employ as a stabilizer is mentioned in the monograph, and in others, the term "suitable stabilizer" is used. An example in which a particular agent is designated for use is in the monograph for Potassium Iodide Oral Solution, USP. Potassium iodide in solution is prone to photocatalyzed oxidation and the release of free iodine, with a resultant yellow-to-brown discoloration of the solution. The use of light-resistant containers is essential to its stability. As a further precaution against decomposition if the solution is not to be used within a short time, the USP recommends the addition of 0.5 mg of sodium thiosulfate for each gram of potassium iodide. In the event, free iodine is released during storage, and the sodium thiosulfate converts it to colorless and soluble sodium iodide:



In summary, for easily oxidizable drugs, the formulation pharmacist may stabilize the preparation by the selective exclusion from the system of oxygen, oxidizing agents, trace metals, light, heat, and other chemical catalysts to the oxidation process. Antioxidants, chelating agents, and buffering agents may be added to create and maintain a favorable pH.

In addition to oxidation and hydrolysis, destructive processes include polymerization, chemical decarboxylation, and deamination. However, these processes occur less frequently and are peculiar to only small groups of chemical substances.

Stability Testing

FDA's Current Good Manufacturing Practice regulations include sections on stability and stability testing of pharmaceutical components and finished pharmaceutical products (4). In addition, FDA and International Conference on Harmonization guidelines and guidances provide working recommendations to support the regulatory requirements. Among these are the following (5):

- "Stability Testing of New Drug Substances and Products"

- "Quality of Biotechnological Products: Stability Testing of Biotechnology/Biological Drug Products"
- "Photostability Testing of New Drug Substances and Products"
- "Stability Testing of New Dosage Forms"

Drug and drug product stability testing during every stage of development is critical to the quality of the product. Physical Pharmacy Capsule 4.18, Analytical Methods and Standard Curves provides a summary of the procedures required for the analysis of drug substances. Drug stability is important during preclinical testing and in clinical (human) trials to obtain a true and accurate assessment of the product being evaluated. For a marketed drug product, assurance of stability is vital to its safety and effectiveness during the course of its shelf life and use.



PHYSICAL PHARMACY CAPSULE 4.18

Analytical Methods and Standard Curves

Any study involving concentration of a drug requires an analytical method and the development of standard curves. There are numerous analytical methods used in pharmacy. It is important for pharmacists to have a basic understanding of pharmaceutical analysis to ensure that valid results are obtained when tests are being conducted. It is important to know (a) when to test, (b) what to test, (c) what method(s) to use, (d) how to interpret the results, (e) the limits of the test, and (f) the importance of analytical testing in the overall quality program in pharmacy.

The goal in analytical testing is to produce results as accurately, efficiently, and quickly as possible. Any analytical method used should have accuracy, speed, reproducibility, and specificity. No single analytical method is ideally suited for all drugs; each method has its own strengths and weaknesses, and there are a number of factors that determine the validity and reliability of results.

SELECTION OF AN ANALYTICAL METHOD

One general consideration in analytical method selection is the type of information that is needed: quantitative (potency, concentration), semiquantitative (where a "cutoff" level is involved, as in endotoxin levels), or qualitative (yes/no type of testing, including substance identification, sterility). Another consideration involves the physical and chemical characteristics of the analyte, including its solubility, partition coefficient, dissociation constant (pK_a), volatility, binding, and the quantity present.

One must consider the degree of quantitative measurement in the validation process, for example, accuracy, repeatability/reproducibility, and precision are required; generally, the greater the level that is required, the more sophisticated and expensive the analytical methods that must be used. This is also governed by the types of instrumentation that are on hand or available and the standards available for comparison.

PHYSICAL PHARMACY CAPSULE 4.18 CONT.**FACTORS INVOLVED IN METHODS SELECTION**

The ultimate analytical method selected depends upon a number of factors, including sample requirements, sample handling/preparation/purification requirements, type of data needed, and levels of specificity and accuracy required.

SAMPLING REQUIREMENTS

In any analytical method, there may be certain sample requirements that impact one's choice, such as the number of samples needed, the difficulty in obtaining a representative sample, the physical state of the sample (solid, liquid, or gas), the type of container required for collection and storage of the sample (some analytes may sorb to the walls or cap liner of the sample containers), and leaching of the container material into the sample, if a liquid, may occur. All these may cause problems in analysis. In the event of sorption, siliconization of the sample vials may sometimes help.

The storage requirements for the sample after collection must be specified (type of container, material used, UV protection, latex contamination, etc.). The effects of air, such as oxidation of the sample ingredients, the presence of carbon dioxide and the formation of insoluble carbonates, pH changes, free versus bound drug, etc., must be considered. The sample must be stored at the proper temperature (refrigerated, frozen, or controlled room) prior to shipment and during shipment. Procedures to follow if the sample is accidentally frozen or experiences a freeze-thaw cycle should be detailed.

In considering the chemical and physical stability of the sample, the effects of water must also be considered. If the sample must be maintained in a dry environment, including a desiccant, this should be detailed. The stability of the sample during storage, extraction, and preparation must be determined. The potential for enzymatic breakdown, or other adverse effects of pH, temperature, solvents, bacterial growth, etc., must be addressed. If volatile solvents are required, special handling must be implemented to prevent evaporation because if some of the solvent is allowed to evaporate, the resulting concentration may be falsely elevated.

The sample matrix effects must be determined. Any effects caused by sample viscosity (pipetting, aspiration), ionic strength (immunoassays, dialysis), buffers (ionized/unionized ratio can alter the extraction efficiency of an analyte prior to analysis), and vapor pressure, where drug can be lost, must be considered. If any sample pretreatment is required prior to shipment or working in-house, consider any inaccuracies that may occur from pipetting, which is one of the most common sources of analytical errors when working with small volumes.

There must be a consideration of any physical methods of separation and purification that might be used. Most analytical methods require some degree of sample pretreatment to prepare it for analysis. These may include crystallization from solution, distillation, sublimation, solvent extraction, solid-phase extraction, chromatography, and centrifugation; the proper choice of separation and purification depends upon the physical and chemical properties of the sample, including its solubility, volatility, binding, quantity present, etc. The effect of any substances in the formulation that may interfere or alter the results must be known beforehand.

DATA INTERPRETATION REQUIREMENTS

The collection of raw data from the analytical process must be done appropriately. One must ensure that appropriate and valid descriptive statistics are used to analyze the data and that the operating parameters of the analytical instruments are well established. Reference values, if available, should be provided with the analytical results. A description of the analytical controls used by the laboratory is important for documentation, as well as the source of reference standards used to establish standard curves.

PHYSICAL PHARMACY CAPSULE 4.18 CONT.**ANALYTICAL METHODS**

In pharmaceutical analysis, analytical methods can be generally divided into physical testing methods, methods that interact with electromagnetic radiation, conductometric techniques, immunoassay methods, separation techniques, and others.

Nonspecific methods generally include melting, freezing and boiling points, density, refractive index, polarimetry, ultraviolet/visible spectroscopy, and pH. Methods that are somewhat more specific include infrared spectroscopic, mass spectroscopy, ion-selective electrodes, immunoassay methods, and chromatographic methods (high-performance liquid chromatography [HPLC] and gas chromatography [GC]), provided proper standards are used.

Methods that can be routinely used for testing incoming bulk materials, whether active or excipients, include melting, freezing and boiling points, density, refractive index, UV/visible spectroscopy, infrared spectroscopy, polarimetry, pH, and the separation methods. Final products may generally require a method such as HPLC or GC. A classification of analytical methods follows along with suggested analytical methods that can be used for different dosage forms.

CLASSIFICATION OF ANALYTICAL AND MICROBIOLOGICAL METHODS**Physical testing procedures**

- Melting point
- Freezing point
- Boiling point
- Density
- Refractive index
- Optical rotation (polarimetry)
- Thermal analysis
- Color change
- Precipitate formation
- Viscosity change

Interaction of electromagnetic radiation

- Ultraviolet/visible spectroscopy
- Infrared spectroscopy
- Fluorescence/phosphorescence spectroscopy
- Raman spectroscopy
- X-ray spectroscopy
- Flame emission and atomic absorption spectroscopy
- Polarimetry
- Refractometry
- Interferometry

Conductance methods

- pH
- Ion-selective electrodes
- Polarography

Immunoassay

- Radioimmunoassay
- Enzyme-multiplied immunoassay technique
- Enzyme-linked immunosorbent assay
- Fluorescent immunoassay

Separation techniques

- HPLC
- GC
- Thin-layer chromatography

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Paper chromatography
 Column chromatography
 Gravimetric
 Balance
 Others
 Osmolality
 Microbiological methods
 Sterility testing
 Endotoxin testing
 Preservative effectiveness testing

Suggested analytical methods for various dosage forms, depending upon the active drug:

DOSAGE	ANALYTICAL METHOD													
FORM	WT	VOL	PH	OSM	RI	SP	GR	MP	UV/VIS	HPLC	GC	IR	STERIL	ENDO
Bulk substances	—	—	*	—	*	—	*	*	*	*	*	*	—	—
Powders	*	—	—	—	—	—	—	—	—	*	*	—	—	—
Capsules	*	—	—	—	—	—	—	—	—	*	*	—	—	—
Tablets	*	—	—	—	—	—	—	—	—	*	*	—	—	—
Lozenges	*	—	—	—	—	—	—	—	—	*	*	—	—	—
Suppositories	*	—	—	—	—	*	*	—	—	*	*	—	—	—
Sticks	*	—	—	—	—	*	*	—	—	*	*	—	—	—
Solutions	*	*	*	*	*	*	—	—	*	*	*	—	—	—
Suspensions	*	*	*	—	—	*	—	—	—	*	*	—	—	—
Emulsions	*	*	*	—	—	*	—	—	—	*	*	—	—	—
Semisolids	*	—	—	—	—	*	*	—	—	*	*	—	—	—
Gels	*	*	*	—	*	*	—	—	—	*	*	—	—	—
Ophthalmics, Otics, and Nasals	*	*	*	*	*	*	—	—	*	*	*	—	*(Ophthalmic only)	—
Inhalations	*	*	*	*	*	—	—	—	*	*	*	—	*	—
Injections	*	*	*	*	*	*	—	—	*	*	*	—	*	*

CONSTRUCTION OF A STANDARD CURVE

A standard curve is constructed by analyzing samples (standards) of known composition, generally in increasing concentrations. As each standard is analyzed, an instrumental response (absorbance, peak height, peak area, other numerical value) will be obtained. The standard concentrations are plotted as the "x" axis on a graph and the instrumental responses are plotted on the "y" axis. As an example,

The following table represents the results from an HPLC analytical method of methotrexate.

Concentration (µg/mL)	0	10	20	30
Response (Peak Height in units)	0	2,600	5,190	7,780

When plotted on a graph, one obtains the following:

PHYSICAL PHARMACY CAPSULE 4.18 CONT.

The next step involves analyzing the unknown sample to obtain a response from the instrument. For example, if the unknown sample provided an instrumental response of 3,895, checking that value on the y-axis and moving toward the right on the graph until it intersects the plotted line and dropping down to the x-axis, we can read a value of 15 µg/mL of the methotrexate. As an option, the equation of the line can be calculated and the concentration determined by substituting the values of "y" and "b" with the slope of the line to obtain the drug concentration, as follows:

$$m = \Delta y / \Delta x = (7780 - 0) / (30 - 0) = 7780 / 30 = 259.3$$

$$\begin{aligned} y &= mx + b \\ 3,895 &= 259.3x + 0 \\ x &= 15.02 \text{ } \mu\text{g/mL} \end{aligned}$$

The FDA-required demonstration of drug stability is necessarily different for each stage of drug development, such as for a 2-week preclinical study, an early phase I study, a limited phase II trial, a pivotal phase III clinical study, or for a new drug application. As a drug development program progresses, so do the requisite data to demonstrate and document the product's stability profile. Before approval for marketing, a product's stability must be assessed with regard to its formulation; the influence of its pharmaceutical ingredients; the influence of the container and closure; the manufacturing and processing conditions (e.g., heat); packaging components; conditions of storage; anticipated conditions of shipping, temperature, light, and humidity; and anticipated duration and conditions of pharmacy shelf life and patient use. Holding intermediate product components (such as drug granulations for tablets) for long periods before processing into finished pharmaceutical products can affect the stability of both the intermediate component and the finished product. Therefore, in-process stability testing, including retesting of intermediate components, is important.

Product containers, closures, and other packaging features must be considered in stability testing. For instance, tablets or capsules packaged in glass or plastic bottles

require different stability test protocols from those for blister packs or strip packaging. Drugs particularly subject to hydrolysis or oxidative decomposition must be evaluated accordingly. And sterile products must meet sterility test standards to ensure protection against microbial contamination. All preservatives must be tested for effectiveness in the finished product.

As noted elsewhere in this section, drug products must meet stability standards for long-term storage at room temperature and relative humidity. Products are also subjected to accelerated stability studies as an indication of shelf life stability. Drug instability in pharmaceutical formulations may be detected in some instances by a change in the physical appearance, color, odor, taste, or texture of the formulation, whereas in other instances, chemical changes may not be self-evident and may be ascertained only through chemical analysis. Scientific data pertaining to the stability of a formulation can lead to prediction of the expected shelf life of the proposed product, and when necessary to redesign of the drug (e.g., into more stable salt or ester form) and to reformulation of the dosage form. Obviously, the rate at which a drug product degrades is of prime importance. The study of the rate of chemical change and the way it is influenced by such factors as the concentration of the drug or

reactant, the solvent, temperature and pressure, and other chemical agents in the formulation is reaction kinetics.

In general, a kinetic study begins by measuring the concentration of the drug at given intervals under a specific set of conditions, including temperature, pH, ionic strength, light intensity, and drug concentration. The measurement of the drug's concentration at the various times reveals the stability or instability of the drug under the specified conditions with the passage of time. From this starting point, each of the original conditions may be varied to determine the influence of such changes on the drug's stability. For example, the pH of the solution may be changed while the temperature, light intensity, and original drug concentration are held constant.

The findings may be presented graphically, by plotting the drug concentration as a function of time. From the experimental data, the reaction rate may be determined and a rate constant and half-life calculated.

Accelerated Stability Studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and where appropriate, oxidation, light and microbial exposure. Stability testing is also used to establish the shelf life for a drug product and recommended storage conditions (6,7).

Among the definitions applied in stability testing are (7):

Accelerated testing: Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of long-term, intermediate, and accelerated studies. Data from these studies are used to assess degradation that might occur under normal (nonexaggerated) or slight deviations in storage conditions as during shipping and storage. Results allow the development of product labeling with regard to expiration dating and recommended conditions for storage.

Drug product: The dosage form in the final immediate packaging intended for marketing.

Drug substance: The unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form.

Excipient: Anything other than the drug substance in the dosage form.

Expiration date: The date placed on the container label of a drug product designating the time prior to which a batch of the product is expected to remain within the approved shelf life specification, if stored under defined conditions, and after which it must not be used.

Shelf life (also referred to as expiration dating period): The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

Stress testing (drug substance): Studies undertaken to elucidate the intrinsic stability of a drug substance. Such testing is part of the drug development process and is normally carried out under more severe conditions than those used for accelerated testing.

Stress testing (drug product): Studies undertaken to assess the effect of severe conditions on the drug product. Such studies include photostability testing as well as the specific testing of certain product types (e.g., metered dose inhalers, creams, emulsions).

For the drug substance, the testing should evaluate its susceptibility to hydrolysis across a wide range of pH values when in solution or suspension. Photostability testing should be an integral part of stress testing. Data should be obtained from at least three pilot-scale batches of the drug substance, manufactured by the method and procedures that mirror the process to be used for final full-scale production batches. Stability studies also should be conducted on the drug substance packaged in the container closure system that is the same or simulates the packaging proposed for the final product.

For the drug product, the design of the stability studies should be based on knowledge gained from those studies of the drug substance. Stability studies should be conducted

Table 4.2 EXAMPLE PROTOCOL FOR DRUG AND/OR DRUG PRODUCT STABILITY STUDIES^a

STUDY TYPE	STORAGE CONDITION	MINIMUM TIME PERIOD
Long term	25°C ± 2°C @ 60% RH ^a ± 5% RH	12 mo
Intermediate	30°C ± 2°C @ 65% RH ^a ± 5% RH	6 mo
Accelerated	40°C ± 2°C @ 75% RH ^a ± 5% RH	6 mo

^aFor chemical entities. Adapted from Stability and Testing of New Drug Substances and Products. Available at: <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128204.pdf>. (Accessed September 28, 2012).

^aRH, relative humidity.

on at least three batches of the manufactured dosage form, packaged in the container and closure system, including all secondary packaging (e.g., outer carton) proposed for marketing. The studies should include testing of those attributes of the product that are susceptible to change during storage, thereby affecting quality and efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes; preservative content (e.g., antioxidant, antimicrobial preservative); and functionality tests (e.g., metered-dose delivery system).

Table 4.2 presents an example protocol for long-term, intermediate, and accelerated stability studies for a chemical drug entity and dosage form product. Protocols vary for products intended to be maintained under conditions of refrigeration, for those to be frozen, for products known to be destined for geographic areas of temperature extremes, and for biotechnological/biological products, which have separate protocols for stability studies. Physical Pharmacy Capsule 4.19 presents the Q_{10} Method of Shelf Life Estimation.



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Q_{10} Method of Shelf Life Estimation

The Q_{10} approach, based on E_a , which is independent of reaction order, is described as

$$Q_{10} = e^{\left\{ \frac{E_a}{R} \left[\frac{1}{T+10} - \frac{1}{T} \right] \right\}}$$

where

E_a is the energy of activation,

R is the gas constant, and

T is the absolute temperature.

In usable terms, Q_{10} , the ratio of two different reaction rate constants, is defined thus:

$$Q_{10} = \frac{K_{(T+10)}}{K_T}$$

The commonly used Q values of 2, 3, and 4 relate to the energies of activations of the reactions for temperatures around room temperature (25°C). For example, a Q value of 2 corresponds to an E_a (kcal/mol) of 12.2, a Q value of 3 corresponds to an E_a of 19.4, and a Q value of 4 corresponds to an E_a of 24.5. Reasonable estimates can often be made using the value of 3.

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The equation for Q_{10} shelf life estimates is

$$t_{90}(T_2) = \frac{t_{90}(T_1)}{Q_{10}^{(\Delta T/10)}}$$

where

$t_{90}T_2$ is the estimated shelf life,

$t_{90}T_1$ is the given shelf life at a given temperature, and

ΔT is the difference in the temperatures T_1 and T_2 .

As is evident from this relationship, an increase in ΔT will decrease the shelf life and a decrease in ΔT will increase the shelf life. This is the same as saying that storing at a warmer temperature will shorten the life of the drug and storing at a cooler temperature will increase the life of the drug.

EXAMPLE 1

An antibiotic solution has a shelf life of 48 hours in the refrigerator (5°C). What is its estimated shelf life at room temperature (25°C)?

Using a Q value of 3, we set up the relationship as follows:

$$t_{90}(T_2) = \frac{t_{90}(T_1)}{Q_{10}^{(\Delta T/10)}} = \frac{48}{3^{[(25-5)/10]}} = \frac{48}{3^2} = 5.33 \text{ hours}$$

EXAMPLE 2

An ophthalmic solution has a shelf life of 6 hours at room temperature (25°C). What is the estimated shelf life in a refrigerator at 5°C? (*Note:* Since the temperature is decreasing, ΔT will be negative.)

$$t_{90}(T_2) = \frac{6}{3^{[(5-25)/10]}} = \frac{6}{3^{-2}} = 6 \times 3^2 = 54 \text{ hours}$$

These are estimates, and actual energies of activation can often be obtained from the literature for more exact calculations.

Following FDA product approval and initial marketing, pharmaceutical manufacturers retain production samples of drug/drug product for 5 years or longer and continue studies for signs of degradation under various conditions of storage. Pharmacy practitioners should also observe signs of product instability (e.g., color change, distorted capsules, softened tablets, etc.) and report such findings.

Prescriptions requiring extemporaneous compounding by the pharmacist do not require the extended shelf life that

commercially manufactured and distributed products do because they are intended to be used immediately on receipt by the patient and used only during the immediate course of the prescribed treatment. However, these compounded prescriptions must remain stable and efficacious during the course of use, and the compounding pharmacist must employ formulative components and techniques that will result in a stable product (7).

Today, there are a number of literature sources for the pharmacist to utilize in the compounding of high quality and

stable prescriptions. Several of these are listed among the references, including the USP chapters on the compounding of sterile and nonsterile preparations (8–12).

USP guidelines on stability of extemporaneous compounded formulations state that in the absence of stability information applicable to a specific drug and preparation, the following guidelines can be used: nonaqueous liquids and solid formulations in which the manufactured drug is the source of the active ingredient, not later than 25% of the time remaining until the product's expiration date or 6 months, whichever is earlier; nonaqueous liquids and solid formulations in which a USP or National Formulary (NF) substance is the source of active ingredient, a beyond-use date of 6 months; for water-containing formulations prepared from ingredients in solid form, a beyond-use date not later than 14 days in storage at cold temperatures; and for all other formulations, a beyond-use date of the intended duration of therapy or 30 days, whichever is earlier (8). Thus, if an oral aqueous liquid preparation is made from a tablet or capsule formulation, the pharmacist should make up only at most 14 days' supply, and it must be stored in a refrigerator. Furthermore, the pharmacist must dispense the medication in a container conducive to stability and use and must advise the patient of the proper method of use and conditions of storage of the medication.

Finally, when compounding on the basis of extrapolated or less than concrete information, the pharmacist is well advised to keep the formulation simple and not to shortcut but use the necessary pharmaceutical adjuvants to prepare the prescription.

PHARMACEUTICAL INGREDIENTS AND EXCIPIENTS

Definitions and Types

To produce a drug substance in a final dosage form requires pharmaceutical ingredients. For example, in the preparation of solutions, one or more *solvents* are used to dissolve the drug substance, *flavors* and *sweeteners* are

used to make the product more palatable, *colorants* are added to enhance appeal, *preservatives* may be added to prevent microbial growth, and *stabilizers*, such as antioxidants and chelating agents, may be used to prevent decomposition, as previously discussed. In the preparation of tablets, *diluents* or *fillers* are commonly added to increase the bulk of the formulation, *binders* to cause adhesion of the powdered drug and pharmaceutical substances, *antiadherents* or *lubricants* to assist smooth tablet formation, *disintegrating agents* to promote tablet breakup after administration, and coatings to improve stability, control disintegration, or enhance appearance. Ointments, creams, and suppositories acquire their characteristic features from their pharmaceutical bases. Thus, for each dosage form, the pharmaceutical ingredients establish the primary features of the product and contribute to the physical form, texture, stability, taste, and overall appearance.

Table 4.3 presents the principal categories of pharmaceutical ingredients, listing some of the official and commercial agents in use. Additional discussion of many ingredients may be found in the chapters where they are most relevant; for example, pharmaceutical materials used in tablet and capsule formulations are discussed in Chapters 7 and 8, and those used in modified-release solid oral dosage forms and drug delivery systems in Chapter 9.

All drug products should be labeled to state the identity of all added substances (excipients). Such listing should be in alphabetical order by name and be distinguished from the identification statement of the active ingredient(s). The name of the inactive ingredient should be taken from the current edition of one of the following references works (in the following order of precedence): (a) the USP or the NF, (b) USAN and the USP Dictionary of Drug Names, (c) CTFA Cosmetic Ingredient Dictionary, and (d) Food Chemicals codes. If not listed in the above, then the reference works should be identified by the common or usual name or, if no common or usual name is available, by its chemical or other technical name. If an ingredient

Table 4.3 EXAMPLES OF PHARMACEUTICAL INGREDIENTS

INGREDIENT TYPE	DEFINITION	EXAMPLES
<i>Acidifying agent</i>	Used in liquid preparations to provide acidic medium for product stability	Citric acid Acetic acid Fumaric acid Hydrochloric acid Nitric acid
<i>Alkalinizing agent</i>	Used in liquid preparations to provide alkaline medium for product stability	Ammonia solution Ammonium carbonate Diethanolamine Monoethanolamine Potassium hydroxide Sodium bicarbonate Sodium borate Sodium carbonate Sodium hydroxide Trolamine
<i>Adsorbent</i>	An agent capable of holding other molecules onto its surface by physical or chemical (chemisorption) means	Powdered cellulose Activated charcoal
<i>Aerosol propellant</i>	Agent responsible for developing the pressure within an aerosol container and expelling the product when the valve is opened	Carbon dioxide Dichlorodifluoromethane Dichlorotetrafluoroethane Trichloromonofluoromethane
<i>Air displacement</i>	Agent employed to displace air in a hermetically sealed container to enhance product stability	Nitrogen Carbon dioxide
<i>Antifungal preservative</i>	Used in liquid and semisolid preparations to prevent growth of fungi. Effectiveness of parabens is usually enhanced by use in combination	Butylparaben Ethylparaben Methylparaben Benzoic acid Propylparaben Sodium benzoate Sodium propionate
<i>Antimicrobial preservative</i>	Used in liquid and semisolid preparations to prevent growth of microorganisms	Benzalkonium chloride
<i>Antioxidant</i>	Used to prevent deterioration of preparations by oxidation	Ascorbic acid Ascorbyl palmitate Butylated hydroxyanisole Butylated hydroxytoluene Hypophosphorous acid Monothioglycerol Propyl gallate Sodium ascorbate Sodium bisulfite Sodium formaldehyde Sulfoxylate Sodium metabisulfite
<i>Buffering agent</i>	Used to resist change in pH upon dilution or addition of acid or alkali	Potassium metaphosphate Potassium phosphate, monobasic Sodium acetate Sodium citrate, anhydrous and dihydrate

(Continued)

Table 4.3 EXAMPLES OF PHARMACEUTICAL INGREDIENTS (Continued)

INGREDIENT TYPE	DEFINITION	EXAMPLES
<i>Chelating agent</i>	Substance that forms stable water-soluble complexes (chelates) with metals; used in some liquid pharmaceuticals as stabilizers to complex heavy metals that might promote instability. In such use, they are also called <i>sequestering agents</i>	Edetic acid Edetate disodium
<i>Colorant</i>	Used to impart color to liquid and solid (e.g., tablets and capsules) preparations	FD&C Red No. 3 FD&C Red No. 20 FD&C Yellow No. 6 FD&C Blue No. 2 D&C Green No. 5 D&C Orange No. 5 D&C Red No. 8 Caramel Ferric oxide, red
<i>Clarifying agent</i>	Used as a filtering aid for its adsorbent qualities	Bentonite
<i>Emulsifying agent</i>	Used to promote and maintain dispersion of finely subdivided particles of liquid in a vehicle in which it is immiscible. End product may be a liquid emulsion or semisolid emulsion (e.g., a cream)	Acacia Cetomacrogol Cetyl alcohol Glyceryl monostearate Sorbitan monooleate Polyoxyethylene 50 stearate
<i>Encapsulating agent</i>	Used to form thin shells to enclose a drug for ease of administration	Gelatin
<i>Flavorant</i>	Used to impart a pleasant flavor and often odor to a preparation. In addition to the natural flavorants listed, many synthetic ones are used	Anise oil Cinnamon oil Cocoa Menthol Orange oil Peppermint oil Vanillin
<i>Humectant</i>	Used to prevent drying of preparations, particularly ointments and creams	Glycerin Propylene glycol Sorbitol
<i>Levigating agent</i>	Liquid used as an intervening agent to reduce the particle size of a powder by grinding, usually in a mortar	Mineral oil Glycerin Propylene glycol
<i>Ointment base</i>	Semisolid vehicle for medicated ointments	Lanolin Hydrophilic ointment Polyethylene glycol ointment Petrolatum Hydrophilic petrolatum White ointment Yellow ointment Rose water ointment
<i>Plasticizer</i>	Component of film-coating solutions to make film more pliable, enhance spread of coat over tablets, beads, and granules	Diethyl phthalate Glycerin

Table 4.3 EXAMPLES OF PHARMACEUTICAL INGREDIENTS (Continued)

INGREDIENT TYPE	DEFINITION	EXAMPLES
<i>Solvent</i>	Used to dissolve another substance in preparation of a solution; may be aqueous or not (e.g., oleaginous). Cosolvents, such as water and alcohol (hydroalcoholic) and water and glycerin, may be used when needed. Sterile solvents are used in certain preparations (e.g., injections)	Alcohol Corn oil Cottonseed oil Glycerin Isopropyl alcohol Mineral oil Oleic acid Peanut oil Purified water Water for injection Sterile water for injection Sterile water for irrigation
<i>Stiffening agent</i>	Used to increase thickness or hardness of a preparation, usually an ointment	Cetyl alcohol Cetyl esters wax Microcrystalline wax Paraffin Stearyl alcohol White wax Yellow wax
<i>Suppository base</i>	Vehicle for suppositories	Cocoa butter Polyethylene glycols (mixtures) PEG 3350
<i>Surfactant (surface active agent)</i>	Substances that absorb to surfaces or interfaces to reduce surface or interfacial tension. May be used as wetting agents, detergents, or emulsifying agents	Benzalkonium chloride Nonoxynol 10 Octoxynol 9 Polysorbate 80 Sodium lauryl sulfate Sorbitan monopalmitate
<i>Suspending agent</i>	Viscosity-increasing agent used to reduce sedimentation rate of particles in a vehicle in which they are not soluble; suspension may be formulated for oral, parenteral, ophthalmic, topical, or other route	Agar Bentonite Carbomer (e.g., Carbopol) Carboxymethylcellulose sodium Hydroxyethyl cellulose Hydroxypropyl cellulose Hydroxypropyl methylcellulose Kaolin Methylcellulose Tragacanth Veegum
<i>Sweetening agent</i>	Used to impart sweetness to a preparation	Aspartame Dextrose Glycerin Mannitol Saccharin sodium Sorbitol Sucrose
<i>Tablet antiadherents</i>	Prevent tablet ingredients from sticking to punches and dies during production	Magnesium stearate

(Continued)

Table 4.3 EXAMPLES OF PHARMACEUTICAL INGREDIENTS (Continued)

INGREDIENT TYPE	DEFINITION	EXAMPLES
<i>Tablet binders</i>	Substances used to cause adhesion of powder particles in tablet granulations	Acacia Alginate acid Carboxymethylcellulose sodium Compressible sugar (e.g., Nu-Tab) Ethylcellulose Gelatin Liquid glucose Methylcellulose Povidone Pregelatinized starch
<i>Tablet and capsule diluent</i>	Inert filler to create desired bulk, flow properties, and compression characteristics of tablets and capsules	Dibasic calcium phosphate Kaolin Lactose Mannitol Microcrystalline cellulose Powdered cellulose Precipitated calcium carbonate Sorbitol Starch
<i>Tablet-coating agent</i>	Used to coat a tablet to protect against decomposition by atmospheric oxygen or humidity, to provide a desired release pattern, to mask taste or odor, or for aesthetic purposes. Coating may be sugar, film, or thick covering around a tablet. Sugar-coated tablets generally start to break up in the stomach. Film forms a thin cover around a formed tablet or bead. Unless it is enteric, film dissolves in the stomach. Enteric coating passes through the stomach to break up in the intestines. Some water-insoluble coatings (e.g., ethylcellulose) are used to slow the release of drug in the gastrointestinal tract	
<i>Sugar coating</i>		Liquid glucose Sucrose
<i>Film coating</i>		Hydroxyethyl cellulose Hydroxypropyl cellulose Hydroxypropyl methylcellulose Methylcellulose (e.g., Methocel) Ethylcellulose (e.g., Ethocel)
<i>Enteric coating</i>		Cellulose acetate phthalate Shellac (35% in alcohol, pharmaceutical glaze)
<i>Tablet direct compression excipient</i>	Used in direct compression tablet formulations	Dibasic calcium phosphate (e.g., Datab)
<i>Tablet disintegrant</i>	Used in solid forms to promote disruption of the mass into smaller particles more readily dispersed or dissolved	Alginate acid Polacrillin potassium (e.g., Amberlite) Sodium alginate Sodium starch glycolate Starch

Table 4.3 EXAMPLES OF PHARMACEUTICAL INGREDIENTS (Continued)

INGREDIENT TYPE	DEFINITION	EXAMPLES
<i>Tablet glidant</i>	Used in tablet and capsule formulations to improve flow properties of the powder mixture	Colloidal silica Cornstarch Talc
<i>Tablet lubricant</i>	Used in tablet formulations to reduce friction during tablet compression	Calcium stearate Magnesium stearate Mineral oil Stearic acid Zinc stearate
<i>Tablet or capsule opaquant</i>	Used to render a coating opaque. May be used alone or with a colorant	Titanium dioxide
<i>Tablet polishing agent</i>	Used to impart an attractive sheen to coated tablets	Carnauba wax White wax
<i>Tonicity agent</i>	Used to render solution similar in osmotic-dextrose characteristics to physiologic fluids, for example, in ophthalmic, parenteral, and irrigation fluids	Sodium chloride
<i>Vehicle</i>	Carrying agent used in formulating a variety of liquids for oral and parenteral administration. Generally, oral liquids are aqueous (e.g., syrups) or hydroalcoholic (e.g., elixirs). Solutions for intravenous use are aqueous, whereas intramuscular injections may be aqueous or oleaginous	
<i>Flavored, sweetened</i>		Acacia syrup Aromatic syrup Aromatic elixir Cherry syrup Cocoa syrup Orange syrup Syrup
<i>Oleaginous</i>		Corn oil Mineral oil Peanut oil Sesame oil
<i>Sterile</i>		Bacteriostatic sodium chloride injection
<i>Viscosity-increasing agent</i>	Used to render preparations more resistant to flow. Used in suspensions to deter sedimentation, in ophthalmic solutions to enhance contact time (e.g., methylcellulose), to thicken topical creams, etc.	Alginic acid Bentonite Carbomer Carboxymethylcellulose Sodium Methylcellulose Povidone Sodium alginate Tragacanth

may or may not be present, it should be qualified by words such as “or” or “may also contain.” If an ingredient is a trade secret, it may be omitted from the list if the list states “and other ingredients.” If an ingredient is

only present in a trace amount and has no functional or technical effect on the product, it does not need to be listed unless it has been shown to cause sensitivity reactions or allergic responses.

Handbook of Pharmaceutical Excipients

The *Handbook of Pharmaceutical Excipients* (10) presents monographs on more than 300 excipients used in dosage form preparation. Each monograph includes such information as nonproprietary, chemical, and commercial names; empirical and chemical formulas and molecular weight; pharmaceutical specifications and chemical and physical properties; incompatibilities and interactions with other excipients and drug substances; regulatory status; safety, stability, and handling information; and applications in pharmaceutical formulation or technology.

Appearance and Palatability

Although most drug substances in use today are unpalatable and unattractive in their natural state, their preparations present them to the patient as colorful, flavorful formulations attractive to the sight, smell, and taste. These qualities, which are the rule rather than the exception, have virtually eliminated the natural reluctance of many patients to take medications because of disagreeable odor or taste. In fact, the inherent attractiveness of today's pharmaceuticals has caused them to acquire the dubious distinction of being a source of accidental poisonings in the home, particularly among children who are lured by their organoleptic appeal.

There is some psychologic basis to drug therapy, and the odor, taste, and color of a pharmaceutical preparation can play a part. An appropriate drug has its most beneficial effect when it is accepted and taken properly by the patient. The proper combination of flavor, fragrance, and color in a pharmaceutical product contributes to its acceptance.

An "electronic tongue" is used to aid in providing a global "taste fingerprint" during formulation development. It provides information on bitterness levels and the stability of flavors in terms of taste (Figure 4.4).

Flavoring Pharmaceuticals

The flavoring of pharmaceuticals applies primarily to liquids intended for oral administration. The 10,000 taste buds on the tongue,



FIGURE 4.4 Electronic tongue to assist in formulation development. (Courtesy of Alpha MOS.)

roof of the mouth, cheeks, and throat have 60 to 100 receptor cells each (13). These receptor cells interact with molecules dissolved in the saliva and produce a positive or negative taste sensation. Medication in liquid form comes into immediate and direct contact with these taste buds. The addition of flavoring agents to liquid medication can mask the disagreeable taste. Drugs placed in capsules or prepared as coated tablets may be easily swallowed with no contact between the drug and the taste buds. Tablets containing drugs that are not especially distasteful may remain uncoated and unflavored. Swallowing them with water usually is sufficient to avoid undesirable taste sensations. However, chewable tablets, such as certain antacid and vitamin products, usually are sweetened and flavored to improve acceptance.

The flavor sensation of a food or pharmaceutical is actually a complex blend of taste and smell, with lesser influences of texture, temperature, and even sight. In flavor-formulating a pharmaceutical product, the pharmacist must give consideration to the color, odor, texture, and taste of the preparation. It would be incongruous, for example, to color a liquid pharmaceutical red and give it a banana taste and a mint odor. The color of a pharmaceutical must have a psychogenic balance with the taste, and the odor must also enhance that taste. Odor greatly affects the flavor of a preparation or foodstuff. If one's sense of smell is impaired, as during a head cold, the usual flavor sensation of food is similarly diminished.

The medicinal chemist and the formulation pharmacist are well acquainted with the taste characteristics of certain chemical types of drugs and strive to mask the unwanted taste through the appropriate use of flavoring agents. Although there are no rules for unerringly predicting the taste sensation of a drug based on its chemical constitution, experience permits the presentation of several observations. For instance, although we recognize and assume the salty taste of sodium chloride, the formulation pharmacist knows that not all salts are salty but that their taste is a function of both cation and anion. Whereas salty tastes are evoked by chlorides of sodium, potassium, and ammonium and by sodium bromide, bromides of potassium and ammonium elicit bitter and salty sensations, and potassium iodide and magnesium sulfate (epsom salt) are predominantly bitter. In general, low molecular weight salts are salty, and high molecular weight salts are bitter.

With organic compounds, an increase in the number of hydroxyl groups (—OH) seems to increase the sweetness of the compound. Sucrose, which has eight hydroxyl groups, is sweeter than glycerin, another pharmaceutical sweetener, which has three hydroxyl groups. In general, the organic esters, alcohols, and aldehydes are pleasant to the taste, and since many of them are volatile, they also contribute to the odor and thus the flavor of preparations in which they are used. Many nitrogen-containing compounds, especially the plant alkaloids (e.g., quinine), are extremely bitter, but certain other nitrogen-containing compounds (e.g., aspartame) are extremely sweet. The medicinal chemist recognizes that even the most simple structural change in an organic compound can alter its taste. D-Glucose is sweet, but L-glucose has a slightly salty taste; saccharin is very sweet, but N-methyl-saccharin is tasteless (14).

Thus, prediction of the taste characteristics of a new drug is only speculative. However, it is soon learned and the formulation pharmacist is then put to the task of increasing the drug's palatability in the environment of other formulative agents. The selection of an

appropriate flavoring agent depends on several factors, primarily the taste of the drug substance itself. Certain flavoring materials are more effective than others in masking or disguising the particular bitter, salty, sour, or otherwise undesirable taste of medicinal agents. Although individuals' tastes and flavor preferences differ, cocoa-flavored vehicles are considered effective for masking the taste of bitter drugs. Fruit or citrus flavors are frequently used to combat sour or acid-tasting drugs, and cinnamon, orange, raspberry, and other flavors have been successfully used to make preparations of salty drugs more palatable.

The age of the intended patient should also be considered in the selection of the flavoring agent, because certain age groups seem to prefer certain flavors. Children prefer sweet candy-like preparations with fruity flavors, but adults seem to prefer less sweet preparations with a tart rather than a fruit flavor.

Flavors can consist of oil- or water-soluble liquids and dry powders; most are diluted in carriers. Oil-soluble carriers include soybean and other edible oils; water-soluble carriers include water, ethanol, propylene glycol, glycerin, and emulsifiers. Dry carriers include maltodextrins, corn syrup solids, modified starches, gum arabic, salt, sugars, and whey protein. Flavors can degrade as a result of exposure to light, temperature, headspace oxygen, water, enzymes, contaminants, and other product components, so they must be carefully selected and checked for stability.

Flavoring agents may be derived from natural sources (e.g., fruit components) or prepared artificially. They may be either water soluble or oil soluble. Their selected use in pharmaceutical products is based on desired flavor, their solubility characteristics, and their chemical and physical compatibility with the active therapeutic agent and other components of the formulation.

Flavoring agents in liquid pharmaceutical products are added to the solvent or vehicle component of the formulation in which it is most soluble or miscible. That is, water-soluble flavorings are added to the aqueous

component of a formulation and oil-soluble flavorings are added to the nonaqueous components. In general, artificial flavors are used in liquid pharmaceutical at levels of 0.1% to 0.2%, whereas natural flavors are used within the 1% to 2% range.

Sweetening Pharmaceuticals

In addition to sucrose, a number of artificial sweetening agents have been used in foods and pharmaceuticals over the years. Some of these, including aspartame, saccharin, and cyclamate, have faced challenges over their safety by the FDA and restrictions to their use and sale.

A review of the history of safety concerns over the use of artificial sweeteners, current scientific findings, and related FDA and legislative actions, may be found at the Web site: <http://www.cancer.gov/cancertopics/factsheet/Risk/artificial-sweeteners>.

At the present time, the following artificial sweeteners are approved by the FDA with, in parenthesis, the number of times (×) each one is sweeter than table sugar:

- Acesulfame potassium (~200 ×)
- Aspartame (~180 to 200 ×)
- Sucralose (~600 ×)
- Saccharin (~300 ×)

Most large pharmaceutical manufacturers have special laboratories for taste-testing proposed formulations of their products. Panels of employees or interested community participants participate in evaluating the various formulations, and their assessments become the basis for the firm's flavoring decisions.

Coloring Pharmaceuticals

Coloring agents are used in pharmaceutical preparations for esthetics. A distinction should be made between agents that have inherent color and those that are employed as colorants. An example of a natural substance with inherent color that is employed as a colorant is red ferric oxide. It is mixed in small proportions with zinc oxide powder to give calamine its characteristic pink color, which is intended to match the skin tone upon application.

Most agents employed today to impart color to foods, drugs, cosmetics, and medical devices are synthetic. Synthetic coloring agents were first prepared in the middle of the 19th century from principles of coal tar. Coal tar (*pix carbonis*), a thick, black viscid liquid, is a by-product of the destructive distillation of coal. Its composition is extremely complex, and many of its constituents may be separated by fractional distillation. Among its products are anthracene, benzene, naphtha, creosote, phenol, and pitch. About 90% of the dyes used in the products FDA regulates are synthesized from a single colorless derivative of benzene called aniline. These aniline dyes are also known as synthetic organic dyes or as coal tar dyes, since aniline was originally obtained from bituminous coal. Aniline dyes today come mainly from petroleum.

Many coal tar dyes were originally used indiscriminately in foods and beverages to enhance their appeal without regard to their toxic potential. It was only after careful scrutiny that some dyes were found to be hazardous to health because of either their own chemical nature or the impurities they carried. As more dyestuffs became available, some expert guidance and regulation were needed to ensure the safety of the public. After passage of the Food and Drug Act in 1906, the U.S. Department of Agriculture established regulations by which a few colorants were *permitted* or *certified* for use in certain products. Today, the FDA regulates the use of color additives in foods, drugs, and cosmetics through the provisions of the Federal Food, Drug, and Cosmetic Act of 1938, as amended in 1960 with the Color Additive Amendments. Lists of color additives *exempt* from certification and those *subject* to certification are codified into law and regulated by the FDA (15). Certified color additives are classified according to their approved use: (a) FD&C color additives, which may be used in foods, drugs, and cosmetics; (b) D&C color additives, some of which are approved for use in drugs, some in cosmetics, and some in medical devices; and (c) external D&C color additives, the use of which is restricted to external parts of the body, not including

the lips or any other body surface covered by mucous membrane. Each certification category has a variety of basic colors and shades for coloring pharmaceuticals. A current list of certified color additives may be found at 21CFR74 (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=74>). One may select from a variety of FD&C, D&C, and external D&C reds, yellows, oranges, greens, blues, and violets. Each is identified by category, color, and number, as for example, "D&C Yellow No. 8" and "FD&C Red No. 4." By selective combinations of the colorants, one can create distinctive colors (Table 4.4).

As a part of the National Toxicology Program of the U.S. Department of Health and Human Services, various substances, including color additives, are studied for toxicity and carcinogenesis. For color additives, the study protocols usually call for a 2-year study in which groups of male and female mice and rats are fed diets containing various quantities of the colorant. The killed and surviving animals are examined for evidence of long-term toxicity and carcinogenesis. Five categories of evidence of carcinogenic activity are used in reporting observations: (a) "clear evidence" of carcinogenic activity; (b) "some evidence"; (c) "equivocal evidence," indicating uncertainty; (d) "no evidence," indicating no observable effect; and (e) "inadequate study," for studies that cannot be evaluated because of major flaws.

The certification status of the colorants is continually reviewed, and changes are made in the list of certified colors in accordance with toxicology findings. These changes may be (a) the withdrawal of certification, (b) the transfer of a colorant from one certification category to another, or (c) the addition of new colors to the list. Before gaining certification, a color additive must be demonstrated to be safe. By FDA definition, "safe" means that there is convincing evidence that establishes with reasonable certainty that no harm will result from the intended use of the color additive (16).

It should be borne in mind, however, that on an individual basis, some persons may demonstrate an allergic-type response

Table 4.4 EXAMPLES OF COLOR FORMULATIONS

SHADE OR COLOR	FD&C DYE	% OF BLEND
Orange	Yellow No. 6	95
	or	
	Yellow No. 5	5
Cherry	Red No. 40	100
	Red No. 40	100
	or	
Strawberry	Red No. 40	99
	Blue No. 1	1
	Red No. 40	100
Lemon	or	
	Red No. 40	95
	Red No. 3	5
Lime	Yellow No. 5	100
Grape	Yellow No. 5	95
	Blue No. 1	5
	Red No. 40	80
Raspberry	Blue No. 1	20
	Red No. 3	75
	Yellow No. 6	20
Butterscotch	Blue No. 1	5
	Yellow No. 5	74
	Red No. 40	24
Chocolate	Blue No. 1	2
	Red No. 40	52
	Yellow No. 5	40
Caramel	Blue No. 1	8
	Yellow No. 5	64
	Red No. 3	21
Cinnamon	Yellow No. 6	9
	Blue No. 1	6
	Yellow No. 5	60
	Red No. 40	35
	Blue No. 1	5

to certain color additives and should avoid such agents accordingly.

Each certified color additive is subject to a host of chemical standards which must be met, including: chemical identity, purity, and specifically stated levels of allowable impurities (17).

In addition, they must be shown to not interfere with the therapeutic efficacy of a pharmaceutical product nor should they interfere with the performance of quality control assay procedures.

A colorant becomes an integral part of a pharmaceutical formulation, and its exact quantitative amount must be reproducible each time the formulation is prepared or else the preparation would have a different appearance from batch to batch. This requires a high degree of skill, for the amount of colorant generally added to liquid preparations ranges from 0.0005% to 0.001% depending upon the colorant and the depth of color desired. Because of their color potency, dyes generally are added to pharmaceutical preparations in the form of diluted solutions rather than as concentrated dry powders. This permits greater accuracy in measurement and more consistent color production (18).

In addition to liquid dyes in the coloring of pharmaceuticals, lake pigments may also be used. An FD&C lake is a pigment consisting of a substratum of alumina hydrate on which the dye is adsorbed or precipitated. Having aluminum hydroxide as the substrate, the lakes are insoluble in nearly all solvents.

Lakes in pharmaceuticals are commonly used in the form of fine dispersions or suspensions. The pigment particles may range in size from $<1\ \mu\text{m}$ up to $30\ \mu\text{m}$. The finer the particle, the less chance for color speckling in the finished product. Blends of various lake pigments may be used to achieve a variety of colors, and various vehicles, such as glycerin, propylene glycol, and sucrose-based syrup, may be employed to disperse the colorants.

Colored empty gelatin capsule shells may be used to hold a powdered drug mixture. Many commercial capsules are prepared with a capsule body of one color and a cap of a different color, resulting in a two-colored capsule. This makes certain commercial products more readily identifiable than solid-colored capsules. For powdered drugs dispensed as such or compressed into tablets, a generally larger proportion of dye is required (about 0.1%) to achieve the desired hue than with liquid preparations.

Both dyes and lakes are used to color sugar-coated tablets, film-coated tablets, direct compression tablets, pharmaceutical suspensions, and other dosage forms (19). Traditionally, sugar-coated tablets have been colored with syrup solutions containing varying amounts of the water-soluble dyes, starting with very dilute solutions, working up to concentrated color syrup solutions. As many as 30 to 60 coats are common. With the lakes, fewer color coats are used. Appealing tablets have been made with as few as 8 to 12 coats using lakes dispersed in syrup. Water-soluble dyes in aqueous vehicles or lakes dispersed in organic solvents may be effectively sprayed on tablets to produce attractive film coatings. There is continued interest today in chewable tablets, because of the availability of many direct compression materials such as dextrose, sucrose, mannitol, sorbitol, and spray-dried lactose. The direct compression colored chewable tablets may be prepared with 1 lb of lake per 1,000 lb of tablet mix. For aqueous suspensions, FD&C water-soluble colors or lakes may be satisfactory. In other suspensions, FD&C lakes are necessary. The lakes, added to either the aqueous or the nonaqueous phase, generally at a level of 1 lb of color per 1,000 lb of suspension, require homogenization or mechanical blending to achieve uniform coloring.

For the most part, ointments, suppositories, and ophthalmic and parenteral products assume the color of their ingredients and do not contain color additives. Should a dye lose the certification status it held when a product was first formulated, manufactured, and marketed, the manufacturer must reformulate within a reasonable length of time, using only color additives certified at the new date of manufacture.

In addition to esthetics and the certification status of a dye, a formulation pharmacist must select the dyes to be used in a particular formula on the basis of their physical and chemical properties. Of prime importance is the solubility of a prospective dye in the vehicle to be used for a liquid formulation or in a solvent to be employed during a pharmaceutical process, as when the dye is sprayed on a batch of tablets. In general, most dyes are broadly grouped into those that are water

soluble and those that are oil soluble; few if any dyes are both. Usually, a water-soluble dye is also adequately soluble in commonly used pharmaceutical liquids like glycerin, alcohol, and glycol ethers. Oil-soluble dyes may also be soluble to some extent in these solvents and in liquid petrolatum (mineral oil), fatty acids, fixed oils, and waxes. No great deal of solubility is required, since the concentration of dye in a given preparation is minimal.

Another important consideration when selecting a dye for use in a liquid pharmaceutical is the pH and pH stability of the preparation to be colored. Dyes can change color with a change in pH, and the dye must be selected so that no anticipated pH change will alter the color during the usual shelf life. The dye also must be chemically stable in the presence of the other formulative ingredients and must not interfere with the stability of the other agents. To maintain their original colors, FD&C dyes must be protected from oxidizing agents, reducing agents (especially metals, including iron, aluminum, zinc, and tin), strong acids and alkalis, and excessive heating. Dyes must also be reasonably photostable; that is, they must not change color when exposed to light of anticipated intensities and wavelengths under the usual conditions of shelf storage. As required, amber or opaque glass or plastic containers may be used to protect photolabile ingredients, including active therapeutic ingredients and colorants.

Preservatives

In addition to the stabilization of pharmaceutical preparations against chemical and physical degradation due to changed environmental conditions within a formulation, certain liquid and semisolid preparations must be preserved against microbial contamination.

Sterilization and Preservation

Although some types of pharmaceutical products, for example, ophthalmic and injectable preparations, are sterilized by physical methods (autoclaving for 20 minutes at 15 lb pressure and 121°C, dry heat at 180°C for

1 hour, or bacterial filtration) during manufacture, many of them also require an antimicrobial preservative to maintain their aseptic condition throughout storage and use. Other types of preparations that are not sterilized during their preparation but are particularly susceptible to microbial growth because of the nature of their ingredients are protected by the addition of an antimicrobial preservative. Preparations that provide excellent growth media for microbes are most aqueous preparations, especially syrups, emulsions, suspensions, and some semisolid preparations, particularly creams. Certain hydroalcoholic and most alcoholic preparations may not require the addition of a chemical preservative when the alcoholic content is sufficient to prevent microbial growth. Generally, 15% v/v alcohol will prevent microbial growth in acid media and 18% v/v in alkaline media. Most alcohol-containing pharmaceuticals, such as elixirs, spirits, and tinctures, are self-sterilizing and do not require additional preservation. The same applies to other individual pharmaceuticals that by virtue of their vehicle or other formulative agents may not permit the growth of microorganisms.

Preservative Selection

When experience or shelf storage experiments indicate that a preservative is required in a pharmaceutical preparation, its selection is based on many considerations, including some of the following:

- The preservative prevents the growth of the type of microorganisms considered the most likely contaminants of the preparation.
- The preservative is soluble enough in water to achieve adequate concentrations in the aqueous phase of a system with two or more phases.
- The proportion of preservative remaining undissociated at the pH of the preparation makes it capable of penetrating the microorganism and destroying its integrity.
- The required concentration of the preservative does not affect the safety or comfort of the patient when the pharmaceutical preparation is administered by the usual

or intended route; that is, it is nonirritating, nonsensitizing, and nontoxic.

- The preservative has adequate stability and will not be reduced in concentration by chemical decomposition or volatilization during the desired shelf life of the preparation.
- The preservative is completely compatible with all other formulative ingredients and does not interfere with them nor do they interfere with the effectiveness of the preservative agent.
- The preservative does not adversely affect the preparation's container or closure.

General Preservative Considerations

Microorganisms include molds, yeasts, and bacteria, with bacteria generally favoring a slightly alkaline medium and the others an acid medium. Although few microorganisms can grow below pH 3 or above pH 9, most aqueous pharmaceutical preparations are within the favorable pH range and therefore must be protected against microbial growth. To be effective, a preservative agent must be dissolved in sufficient concentration in the aqueous phase of a preparation. Furthermore, only the undissociated fraction or molecular form of a preservative possesses preservative capability, because the ionized portion is incapable of penetrating the microorganism. Thus, the preservative selected must be largely undissociated at the pH of the formulation being prepared. Acidic preservatives like benzoic, boric, and sorbic acids are more undissociated and thus more effective as the medium is made more acid. Conversely, alkaline preservatives are less effective in acid or neutral media and more effective in alkaline media. Thus, it is meaningless to suggest preservative effectiveness at specific concentrations unless the pH of the system is mentioned and the undissociated concentration of the agent is calculated or otherwise determined. Also, if formulative materials interfere with the solubility or availability of the preservative agent, its chemical concentration may be misleading, because it may not be a true measure of the effective concentration.

It is essential for the research pharmacist to examine all formulative ingredients as one affects the other to ensure that each agent is free to do its job. In addition, the preservative must not interact with a container or closure.

The FDA recommends that in the pharmaceutical development process, the lowest effective concentration of an antimicrobial preservative should be used and that it should be demonstrated to be effective by an antimicrobial preservative effectiveness test. The concentration used should be validated in terms of efficacy and safety, with the effectiveness confirmed to last throughout the intended shelf life of the product (19).

Mode of Action

Preservatives interfere with microbial growth, multiplication, and metabolism through one or more of the following mechanisms:

- Modification of cell membrane permeability and leakage of cell constituents (partial lysis)
- Lysis and cytoplasmic leakage
- Irreversible coagulation of cytoplasmic constituents (e.g., protein precipitation)
- Inhibition of cellular metabolism, such as by interfering with enzyme systems or inhibition of cell wall synthesis
- Oxidation of cellular constituents
- Hydrolysis

Examples of the preservatives and their concentrations commonly employed in pharmaceutical preparations are benzoic acid (0.1% to 0.2%), sodium benzoate (0.1% to 0.2%), alcohol (15% to 20%), phenylmercuric nitrate and acetate (0.002% to 0.01%), phenol (0.1% to 0.5%), cresol (0.1% to 0.5%), chlorobutanol (0.5%), benzalkonium chloride (0.002% to 0.01%), and combinations of methylparaben and propylparaben (0.1% to 0.2%), the latter being especially good against fungus. The required proportion varies with the pH, dissociation, and other factors already indicated as well with the presence of other formulative ingredients with inherent preservative capabilities.

For each type of preparation to be preserved, the research pharmacist must

consider the influence of the preservative on the comfort of the patient. For instance, a preservative in an ophthalmic preparation must have an extremely low degree of irritant qualities, which is characteristic of chlorobutanol, benzalkonium chloride, and

phenylmercuric nitrate, frequently used in ophthalmic preparations. In all instances, the preserved preparation must be biologically tested to determine its safety and efficacy and shelf-tested to determine its stability for the intended shelf life of the product.

CLINICAL



CASE STUDY

SUBJECTIVE INFORMATION

HPI: Jen, an 8-year-old female is 4'1" tall, weighs 27 kg and has no known allergies.

She was brought to the clinic by her mother to seek advice on treating a "dry hacking" cough. Her mother states that Jen has had the cough for the past 4 weeks; it is a dry, hacking cough that does not produce any mucous. She experiences these coughs in 2- to 3-minute bouts once or twice daily, after coming in from recess or playing outside. At school, the nurse's office gives her water and a lozenge. After school and at bedtime, she also occasionally experiences the cough. Jen does not complain of stuffiness or increased nasal discharge. However, she has recently complained of a headache that was successfully treated with acetaminophen.

PMH: Over the past 2 months, Jen has had two episodes of sinusitis requiring antibiotic treatment. Her vaccinations are up to date and the rest of her history is negative.

MEDICATION RECORD

1/21 Augmentin 400/5 100 mL 1 tsp bid × 10 days.

4/14 Cefdinir 125/5 200 mL 7 mL bid × 10 days.

FH: The father (age 44) has diabetes mellitus type 2 treated with oral agents and high blood pressure. The mother (age 39) denies any health problems. Two other siblings are reported healthy.

OBJECTIVE INFORMATION

A physical exam reveals a well-nourished, well-developed female child who appears

normal for her age. BP, 92/64; HR, 74 bpm; RR, 23 rpm; and temperature of 38°C.

ASSESSMENT

Patient is an 8-year-old female with a dry, hacking cough. She is not on any medications at this time. Cough seems to be aggravated after periods of exertion or exercise. The mother says she is concerned that some medicines might make Jen tired or drowsy while she is at school so she would like one that is least likely to produce drowsiness/sedation.

Jen's mother also wants a product she can give to Jen before school (7:30 AM) that will last until the evening when she returns home. Also, she says that Jen does not like the taste of many medications and is concerned that Jen may not like what is recommended and refuse to take it. Also, she says that Jen prefers strawberry flavors.

PLAN

Three commonly used systemic antitussive medications include codeine, dextromethorphan, and diphenhydramine. Only dextromethorphan will not cause significant drowsiness as will codeine and diphenhydramine. One product that last up to 12 hours is Delsym. Dextromethorphan products do not necessarily taste very good. An option for improving the flavor of Delsym would be to add a commercial flavor. For example, FLAVORx flavorings could be used as follows: For Delsym, 120 mL, strawberry cream 24 drops or 0.7 mL, with vanilla 24 drops or 0.7 mL

APPLYING THE PRINCIPLES AND CONCEPTS

Group Activities

1. Develop a listing of examples where patients misunderstand the intent of the administration of a pharmaceutical dosage form.
2. Develop a listing of examples where patients misuse/abuse a pharmaceutical dosage form.
3. Explain the appropriate use of specific dosage forms for different patient types, for example, geriatric, pediatric, visually impaired, hearing impaired. Identify and list the most common hurdles or obstacles for these patient populations with respect to medication compliance and discuss ways to overcome these barriers, that is, FLAVORx for liquids for children and PillGlide for children transitioning to tablets.
4. Identify four ophthalmic products with differing preservative agents and provide a rationale for the selection of the specific preservative in the product.
5. Identify elixir dosage form products that contain minimal or no alcohol content. Explain the reasons for this misnomer.
6. Prepare a chart listing which flavors pair well with certain medications based upon their chemical structure and their palatability issues (bitter, salty, etc.). Different groups can select medications with different chemical structures.

Individual Activities

1. Given a specific dosage form, list the signs of degradation a pharmacist might observe indicating product instability.
2. Given a concentration of drug in a liquid dosage form, determine its type of degradation rate and calculate its half-life and when its concentration will be 90% of the labeled amount.
3. Compare and contrast a zero-order rate of degradation and a first-order rate of degradation.
4. Make a listing of drugs that follow a zero-order rate of degradation in a liquid dosage form.
5. Make a listing of drugs that follow first-order rates of degradation in a liquid dosage form.

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13 Solutions

OBJECTIVES

After reading this chapter, the student will be able to:

1. Define the various types of oral and topical liquid dosage forms
2. List the advantages and disadvantages of using liquid dosage forms in extemporaneous compounded prescriptions and in patient therapy
3. Compare and contrast liquid dosage forms to solid oral dosage forms
4. Define solubility and describe how different factors increase or decrease solute solubility in a given solvent
5. Evaluate and select a proper solvent and delivery system for a given solute, purpose, and/or patient population

In physicochemical terms, solutions may be prepared from any combination of a solid, liquid, and gas, the three states of matter. For example, a solid solute may be dissolved in another solid, a liquid, or a gas, and the same being true for a liquid solute and for a gas; nine types of homogeneous mixtures are possible. In pharmacy, however, interest in solutions is for the most part limited to preparations of a solid, a liquid, and less frequently a gas solute in a liquid solvent.

In pharmaceutical terms, solutions are "liquid preparations that contain one or more chemical substances dissolved in a suitable solvent or mixture of mutually miscible solvents" (1). Because of a particular pharmaceutical solution's use, it may be classified as oral, otic, ophthalmic, or topical. Still other solutions, because of their composition or use, may be classified as other dosage forms. For example, aqueous solutions containing a sugar are classified as syrups (even though some syrups may contain some alcohol), sweetened hydroalcoholic (combinations of water and ethanol) solutions are termed elixirs, and solutions of aromatic materials are termed spirits if the solvent is alcoholic or aromatic waters if the solvent is aqueous. Solutions prepared by

extracting active constituents from crude drugs are termed tinctures or fluidextracts, depending on their method of preparation and concentration. Tinctures may also be solutions of chemical substances dissolved in alcohol or in a hydroalcoholic solvent. Certain solutions prepared to be sterile and pyrogen-free and intended for parenteral administration are classified as injections. Although other examples could be cited, it is apparent that a solution, as a distinct type of pharmaceutical preparation, is much further defined than the physicochemical definition of the term solution.

Oral solutions, syrups, elixirs, spirits, and tinctures are prepared and used for the specific effects of the medicinal agents they carry. In these preparations, the medicinal agents are intended to provide systemic effects. The fact that they are administered in solution form usually means that they are soluble in aqueous systems and their absorption from the gastrointestinal tract into the systemic circulation may be expected to occur more rapidly than from suspension or solid dosage forms of the same medicinal agent.

Solutes other than the medicinal agent are usually present in orally administered solutions. These additional agents are frequently

included to provide color, flavor, sweetness, or stability. In formulating or compounding a pharmaceutical solution, the pharmacist must use information on the solubility and stability of each solute with regard to the solvent or solvent system. Combinations of medicinal or pharmaceutical agents that will result in chemical and/or physical interactions affecting the therapeutic quality or pharmaceutical stability of the product must be avoided.

For single-solute solutions and especially for multiple-solute solutions, the pharmacist must be aware of the solubility characteristics of the solutes and the features of the common pharmaceutical solvents. Each chemical agent has its own solubility in a given solvent. For many medicinal agents, their solubilities in the usual solvents are stated in the *United States Pharmacopeia–National Formulary* (USP–NF) as well as in other reference books.

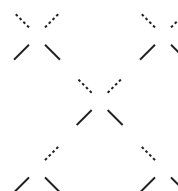
SOLUBILITY

Attractive forces between atoms lead to the formation of molecules and ions. The intermolecular forces, which are developed between like molecules, are responsible for the physical state (solid, liquid, or gas) of the substance under given conditions, such as temperature and pressure. Under ordinary conditions, most organic compounds, and thus most drug substances, form molecular solids.

When molecules interact, attractive and repulsive forces are in effect. The attractive forces cause the molecules to cohere, whereas the repulsive forces prevent molecular interpenetration and destruction. When the attractive and repulsive forces are equal, the potential energy between two molecules is minimal and the system is most stable.

Dipolar molecules frequently tend to align themselves with other dipolar molecules so that the negative pole of one molecule points toward the positive pole of the other. Large groups of molecules may be associated through these weak attractions, known as dipole–dipole or van der Waals forces. Other attractions also occur between polar and nonpolar molecules and ions. These include ion–dipole forces and hydrogen bonding. The latter is of particular interest. Because of small

size and large electrostatic field, the hydrogen atom can move in close to an electronegative atom, forming an electrostatic type of association, a hydrogen bond or a hydrogen bridge. Hydrogen bonding involves strongly electronegative atoms such as oxygen, nitrogen, and fluorine. Such a bond exists in water, represented by the dotted lines.



Hydrogen bonds also exist between some alcohol molecules, esters, carboxylic acids, aldehydes, and polypeptides.

When a solute dissolves, the substance's intermolecular forces of attraction must be overcome by forces of attraction between the solute and the solvent molecules. This entails breaking the solute–solute forces and the solvent–solvent forces to achieve the solute–solvent attraction.

The solubility of an agent in a particular solvent indicates the maximum concentration to which a solution may be prepared with that agent and that solvent. When a solvent at a given temperature has dissolved all of the solute possible, it is said to be saturated. To emphasize the possible variation in solubility between two chemical agents and, therefore, in the amounts of each required to prepare a saturated solution, two official aqueous saturated solutions are cited as examples, Calcium Hydroxide Topical Solution, USP, and Potassium Iodide Oral Solution, USP. The first solution, prepared by agitating an excess amount of calcium hydroxide with purified water, contains only about 140 mg of dissolved solute per 100 mL of the solution at 25°C, whereas potassium iodide solution contains about 100 g of solute per 100 mL of the solution, more than 700 times as much solute as in the calcium hydroxide topical solution. Thus, the maximum possible concentration to which a pharmacist may prepare a solution varies greatly and depends in part on the chemical constitution of the solute.

Through selection of a different solubilizing agent or a different chemical salt form of the medicinal agent, alteration of the pH of a solution, or substitution in part or in whole of the solvent, a pharmacist can, in certain instances, dissolve greater quantities of a solute than would otherwise be possible. For example, iodine granules are soluble in water only to the extent of 1 g in about 3,000 mL. Using only these two agents, the maximum concentration possible would be approximately 0.03% of iodine. However, through the use of an aqueous solution of potassium iodide or sodium iodide as the solvent, much larger amounts of iodine may be dissolved as the result of the formation of a water-soluble complex with the iodide salt. This reaction is taken advantage of, for example, in Iodine Topical Solution, USP, prepared to contain about 2% iodine and 2.4% sodium iodide.

Temperature is an important factor in determining the solubility of a drug and in preparing its solution. Most chemicals absorb heat when they are dissolved and are said to have a positive heat of solution, resulting in increased solubility with an increase in temperature. A few chemicals have a negative heat of solution and exhibit a decrease in solubility with a rise in temperature. Other factors in addition to temperature affect solubility. These include the various chemical and other physical properties of the solute and the solvent, pressure, the pH of the solution, the state of subdivision of the solute, and the physical agitation applied to the solution as it dissolves. The solubility of a pure chemical substance at a given temperature and pressure is constant; however, its rate of solution, that is, the speed at which it dissolves, depends on the particle size of the substance and the extent of agitation. The finer the powder, the greater the surface area, which comes in contact with the solvent, and the more rapid the dissolving process. Also, the greater the agitation, the more unsaturated solvent passes over the drug and the faster the formation of the solution.

The solubility of a substance in a given solvent may be determined by preparing a saturated solution of it at a specific temperature and by determining by chemical analysis the amount of chemical dissolved in a given weight of solution. The amount of solvent required to dissolve the amount of solute can be determined by a

simple calculation. The solubility may then be expressed as grams of solute dissolving in milliliters of solvent; for example, "1 g of sodium chloride dissolves in 2.8 mL of water." When the exact solubility has not been determined, general expressions of relative solubility may be used. These terms are defined in the USP and presented in Table 13.1 (1).

Many of the important organic medicinal agents are either weak acids or weak bases, and their solubility depends on a large measure on the pH of the solvent. These drugs react either with strong acids or strong bases to form water-soluble salts. For instance, the weak bases, including many of the alkaloids (atropine, codeine, and morphine), antihistamines (diphenhydramine and promethazine), local anesthetics (cocaine, procaine, and tetracaine), and other important drugs, are not very water soluble, but they are soluble in dilute solutions of acids. Pharmaceutical manufacturers have prepared many acid salts of these organic bases to enable the preparation of aqueous solutions. However, if the pH of the aqueous solution of these salts is changed by the addition of alkali, the free base may separate from solution unless it has adequate solubility in water. Organic medicinals that are weak acids include the barbiturate drugs (e.g., phenobarbital) and the sulfonamides (e.g., sulfadiazine and sulfacetamide). These and other weak acids form water-soluble salts in basic solution and may separate from solution by a lowering of the pH. Table 13.2 presents the comparative solubilities of some typical examples of weak acids and weak bases and their salts.

Table 13.1 **RELATIVE TERMS OF SOLUBILITY (2)**

DESCRIPTIVE TERM	PARTS OF SOLVENT REQUIRED FOR 1 PART OF SOLUTE
Very soluble	<1
Freely soluble	1–10
Soluble	10–30
Sparingly soluble	30–100
Slightly soluble	100–1,000
Very slightly soluble	1,000–10,000
Practically insoluble or insoluble	>10,000

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Table 13.2 WATER AND ALCOHOL SOLUBILITIES OF SOME WEAK ACIDS, WEAK BASES, AND THEIR SALTS

DRUG	WATER	ALCOHOL
Atropine	455.0	2
Atropine sulfate	0.5	5
Codeine	120.0	2
Codeine sulfate	30.0	1,280
Codeine phosphate	2.5	325
Morphine	5,000.0	210
Morphine sulfate	16.0	565
Phenobarbital	1,000.0	8
Phenobarbital sodium	1.0	10
Procaine	200.0	Soluble
Procaine hydrochloride	1.0	15
Sulfadiazine	13,000.0	Sparingly soluble
Sodium sulfadiazine	2.0	Slightly soluble

Although there are no exact rules for unerringly predicting the solubility of a chemical agent in a particular liquid, experienced pharmaceutical chemists can estimate the general solubility of a chemical compound based on its molecular structure and functional groups. The information gathered on a great number of individual chemical compounds has led to the characterization of the solubilities of

groups of compounds, and though there may be an occasional inaccuracy with respect to an individual member of a group of compounds, the generalizations nonetheless are useful. As demonstrated by the data in Table 13.2 and other similar data, salts of organic compounds are more soluble in water than are the corresponding organic bases. Conversely, the organic bases are more soluble in organic solvents, including alcohol, than are the corresponding salt forms. Perhaps the most widely written guideline for the prediction of solubility is “like dissolves like,” meaning a solvent having a chemical structure most similar to that of the intended solute will be most likely to dissolve it. Thus, organic compounds are more soluble in organic solvents than in water. Organic compounds may, however, be somewhat water soluble if they contain polar groups capable of forming hydrogen bonds with water. In fact, the greater the number of polar groups present, the greater will likely be the organic compound’s solubility in water. Polar groups include OH, CHO, COH, CHOH, CH₂OH, COOH, NO₂, CO, NH₂, and SO₃H. The introduction of halogen atoms into a molecule tends to decrease water solubility because of an increase in the molecular weight of the compound without a proportionate increase in polarity. An increase in the molecular weight of an organic compound without a change in polarity reduces solubility in water. Table 13.3 demonstrates some of these generalities with specific chemical examples.

Table 13.3 SOLUBILITIES OF SELECTED ORGANIC COMPOUNDS IN WATER AS A DEMONSTRATION OF CHEMICAL STRUCTURE-SOLUBILITY RELATIONSHIP

COMPOUND	FORMULA	MILLILITERS OF WATER REQUIRED TO DISSOLVE 1 G OF COMPOUND
Benzene	C ₆ H ₆	1,430.0
Benzoic acid	C ₆ H ₅ COOH	275.0
Benzyl alcohol	C ₆ H ₅ CH ₂ OH	25.0
Phenol	C ₆ H ₅ OH	15.0
Pyrocatechol	C ₆ H ₄ (OH) ₂	2.3
Pyrogallol	C ₆ H ₃ (OH) ₃	1.7
Carbon tetrachloride	CCl ₄	2,000.0
Chloroform	CHCl ₃	200.0
Methylene chloride	CH ₂ Cl ₂	50.0

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As with organic compounds, the pharmacist is aware of some general patterns of solubility that apply to inorganic compounds. For instance, most salts of monovalent cations, for example, sodium, potassium, and ammonium, are water soluble, whereas divalent cations, for example, calcium, magnesium, and barium, usually form water-soluble compounds with nitrate, acetate, and chloride anions but not with carbonate, phosphate, or hydroxide anions. To be sure, certain combinations of anion and cation seem to be similar in makeup but do not have similar solubility characteristics. For instance, magnesium sulfate (Epsom salt) is soluble, but calcium sulfate is only slightly soluble; barium sulfate is very insoluble (1 g dissolves in about 400,000 mL of water) and is used as an opaque medium for x-ray observation of the intestinal tract, but barium sulfide and barium sulfite are more soluble, and their oral use can result in poisoning; and mercurous chloride (HgCl) is insoluble and was formerly used as a cathartic, but mercuric chloride (HgCl_2) is soluble in water and is a deadly poison if taken internally. In many instances, solubilities of drugs and their differentiation from other drugs are critical to the pharmacist for avoidance of compounding failures or therapeutic disasters.

The ability of a solvent to dissolve organic as well as inorganic solutes depends on its effectiveness in overcoming the electronic forces that hold the atoms of the solute together and the corresponding lack of resistance on the part of the atoms themselves to resist the solvent action. During dissolution, the molecules of the solvent and the solute become uniformly mixed, and cohesive forces of the atoms are replaced by new forces as a result of the attraction of the solute and solvent molecules for one another.

The student may find the following general rules of solubility useful.

Inorganic Molecules

1. If both the cation and anion of an ionic compound are monovalent, the solute-solute attractive forces are usually easily overcome, and, therefore, these compounds are generally water soluble (e.g., NaCl , LiBr , KI , NH_4NO_3 , and NaNO_2).
2. If only one of the two ions in an ionic compound is monovalent, the solute-solute interactions are also usually easily overcome and the compounds are water soluble (e.g., BaCl_2 , MgI_2 , Na_2SO_4 , and Na_3PO_4).
3. If both the cation and anion are multivalent, the solute-solute interaction may be too great to be overcome by the solute-solvent interaction, and the compound may have poor water solubility (e.g., CaSO_4 , BaSO_4 , and BiPO_4 ; exceptions: ZnSO_4 , FeSO_4).
4. Common salts of alkali metals (e.g., Na , K , Li , Cs , and Rb) are usually water soluble (exception: Li_2CO_3).
5. Ammonium and quaternary ammonium salts are water soluble.
6. Nitrates, nitrites, acetates, chlorates, and lactates are generally water soluble (exceptions: silver and mercurous acetate).
7. Sulfates, sulfites, and thiosulfates are generally water soluble (exceptions: calcium and barium salts).
8. Chlorides, bromides, and iodides are water soluble (exceptions: salts of silver and mercurous ions).
9. Acid salts corresponding to an insoluble salt will be more water soluble than the original salt.
10. Hydroxides and oxides of compounds other than alkali metal cations and the ammonium ion are generally water insoluble.
11. Sulfides are water insoluble except for their alkali metal salts.
12. Phosphates, carbonates, silicates, borates, and hypochlorites are water insoluble except for their alkali metal salts and ammonium salts.

Organic Molecules

1. Molecules having one polar functional group are usually soluble to total chain lengths of five carbons.
2. Molecules having branched chains are more soluble than the corresponding straight-chain compound.

3. Water solubility decreases with an increase in molecular weight.
4. Increased structural similarity between solute and solvent is accompanied by increased solubility.

It is the pharmacist's knowledge of the chemical characteristics of drugs that permits the selection of the proper solvent for a particular solute. However, in addition to the factors of solubility, the selection is based on such additional characteristics as clarity, low toxicity, viscosity, compatibility with other formulative ingredients, chemical inertness, palatability, odor, color, and economy. In most instances, especially for solutions to be taken orally, used intranasally, used ophthalmically, or injected, water is the preferred solvent because it comes closer to meeting these criteria than other solvents. When water is used as the primary solvent, commonly an auxiliary solvent is also employed to augment the solvent action of water or to contribute to a product's chemical or physical stability. Alcohol, glycerin, and propylene glycol, perhaps the most widely used auxiliary solvents, have been quite effective in contributing to the desired characteristics of pharmaceutical solutions and in maintaining their stability.

Other solvents, such as acetone, ethyl oxide, and isopropyl alcohol, are too toxic to be permitted in pharmaceutical preparations to be taken internally, but they are useful as reagent solvents in organic chemistry and in the preparatory stages of drug development, as in the extraction or removal of active constituents from medicinal plants. For purposes such as this, certain solvents are officially recognized in the compendia. A number of fixed oils, such as corn oil, cottonseed oil, peanut oil, and sesame oil, are useful solvents, particularly in the preparation of oleaginous injections, and are recognized in the official compendia for this purpose.

SOME SOLVENTS FOR LIQUID PREPARATIONS

The following agents find use as solvents in the preparation of solutions.

Alcohol, USP: Ethyl Alcohol, Ethanol, C_2H_5OH

Next to water, alcohol is the most useful solvent in pharmacy. It is used as a primary solvent for many organic compounds. Together with water, it forms a hydroalcoholic mixture that dissolves both alcohol-soluble and water-soluble substances, a feature especially useful in the extraction of active constituents from crude drugs. By varying the proportion of the two agents, the active constituents may be selectively dissolved and extracted or allowed to remain behind, according to their particular solubility characteristics in the menstruum. Alcohol, USP, is 94.9% to 96.0% C_2H_5OH by volume (i.e., v/v) when determined at 15.56°C, the US government's standard temperature for alcohol determinations. Dehydrated Alcohol, USP, also called absolute alcohol, contains not less than 99.5% C_2H_5OH by volume and is used when an essentially water-free alcohol is desired.

Alcohol has been well recognized as a solvent and excipient in the formulation of oral pharmaceutical products. Certain drugs are insoluble in water and must be dissolved in an alternative vehicle. Alcohol is often preferred because of its miscibility with water and its ability to dissolve many water-insoluble ingredients, including drug substances, flavorants, and antimicrobial preservatives. Alcohol is frequently used with other solvents, such as glycols and glycerin, to reduce the amount of alcohol required. It is also used in liquid products as an antimicrobial preservative alone or with parabens, benzoates, sorbates, and other agents.

However, aside from its pharmaceutical advantages as a solvent and a preservative, concern has been expressed over the undesired pharmacologic and potential toxic effects of alcohol when ingested in pharmaceutical products, particularly by children. Thus, the U.S. Food and Drug Administration (FDA) has proposed that insofar as possible manufacturers of over-the-counter (OTC) oral drug products restrict the use of alcohol and include appropriate warnings in the labeling. For OTC oral products intended for children under 6 years of age,

the recommended alcohol content limit is 0.5%; for products intended for children 6 to 12 years of age, the recommended limit is 5%; and for products recommended for children over 12 years of age and for adults, the recommended limit is 10%.

Diluted Alcohol, NF

Diluted Alcohol, NF, is prepared by mixing equal volumes of Alcohol, USP, and Purified Water, USP. The final volume of such mixtures is not the sum of the individual volumes of the two components because the liquids contract upon mixing; the final volume is generally about 3% less than what would otherwise be expected. Thus, when 50 mL of each component is combined, the resulting product measures approximately 97 mL. It is for this reason that the strength of Diluted Alcohol, NF, is not exactly half that of the more concentrated alcohol but slightly greater, approximately 49%. Diluted alcohol is a useful hydroalcoholic solvent in various pharmaceutical processes and preparations.

Rubbing Alcohol

Rubbing alcohol contains about 70% ethyl alcohol by volume, the remainder consisting of water, denaturants with or without color additives and perfume oils, and stabilizers. Each 100 mL must contain not less than 355 mg of sucrose octaacetate or 1.4 mg of denatonium benzoate, bitter substances that discourage accidental or abusive oral ingestion. According to the Internal Revenue Service, U.S. Treasury Department, the denaturant employed in rubbing alcohol is formula 23-H, which is composed of 8 parts by volume of acetone, 1.5 parts by volume of methyl isobutyl ketone, and 100 parts by volume of ethyl alcohol. The use of this denaturant mixture makes the separation of ethyl alcohol from the denaturants virtually impossible with ordinary distillation apparatus. This discourages the illegal removal for use as a beverage of the alcoholic content of rubbing alcohol.

The product is volatile and flammable and should be stored in a tight container remote from fire. It is employed as a rubefacient externally and as a soothing rub for bedridden

patients, a germicide for instruments, and a skin cleanser prior to injection. It is also used as a vehicle for topical preparations. Synonym: alcohol rubbing compound.

Glycerin, USP (Glycerol), $\text{CH}_2\text{OH}\cdot\text{CHOH}\cdot\text{CH}_2\text{OH}$

Glycerin is a clear syrupy liquid with a sweet taste. It is miscible with both water and alcohol. As a solvent, it is comparable with alcohol, but because of its viscosity, solutes are slowly soluble in it unless it is rendered less viscous by heating. Glycerin has preservative qualities and is often used as a stabilizer and as an auxiliary solvent in conjunction with water or alcohol. It is used in many internal preparations.

Isopropyl Rubbing Alcohol

Isopropyl rubbing alcohol is about 70% by volume isopropyl alcohol, the remainder consisting of water with or without color additives, stabilizers, and perfume oils. It is used externally as a rubefacient and soothing rub and as a vehicle for topical products. This preparation and a commercially available 91% isopropyl alcohol solution are commonly employed by diabetic patients in preparing needles and syringes for hypodermic injections of insulin and for disinfecting the skin.

Propylene Glycol, USP, $\text{CH}_3\text{CH}(\text{OH})\text{CH}_2\text{OH}$

Propylene glycol, a viscous liquid, is miscible with water and alcohol. It is a useful solvent with a wide range of applications and is frequently substituted for glycerin in modern pharmaceutical formulations.

Purified Water, USP, H_2O

Naturally occurring water exerts its solvent effect on most substances it contacts and, thus, is impure, containing varying amounts of dissolved inorganic salts, usually sodium, potassium, calcium, magnesium, and iron; chlorides; sulfates; and bicarbonates, along with dissolved and undissolved organic matter and microorganisms. Water found in

most cities and towns where water is purified for drinking usually contains less than 0.1% of total solids, determined by evaporating a 100-mL sample to dryness and weighing the residue (which weighs <100 mg). Drinking water must meet the U.S. Public Health Service regulations with respect to bacteriologic purity. Acceptable drinking water should be clear, colorless, odorless, and neutral or only slightly acidic or alkaline, the deviation from neutral being due to the nature of the dissolved solids and gases (carbon dioxide contributing to the acidity and ammonia to the alkalinity of water).

Ordinary drinking water from the tap is not acceptable for the manufacture of most aqueous pharmaceutical preparations or for the extemporaneous compounding of prescriptions because of the possible chemical incompatibilities between dissolved solids and the medicinal agents being added. Signs of such incompatibilities are precipitation, discoloration, and occasionally effervescence. Its use is permitted in washing, in extraction of crude vegetable drugs, in preparation of certain products for external use, and when the difference between tap water and purified water is of no consequence. Naturally, when large volumes of water are required to clean pharmaceutical machinery and equipment, tap water may be economically employed so long as a residue of solids is prevented by using purified water as the final rinse or by wiping the water dry with a meticulously clean cloth.

Purified Water, USP, is obtained by distillation, ion exchange treatment, reverse osmosis, or other suitable process. It is prepared from water complying with the federal Environmental Protection Agency with respect to drinking water. Purified Water, USP, has fewer solid impurities than ordinary drinking water. When evaporated to dryness, it must not yield more than 0.001% of residue (1 mg of solids per 100 mL of water). Thus, purified water has only 1% as much dissolved solids as tap water. Purified Water, USP, is intended for use in the preparation of aqueous dosage forms except those intended for parenteral administration (injections). Water for Injection, USP; Bacteriostatic

Water for Injection, USP; or Sterile Water for Injection, USP, is used for injections. These are discussed in Chapter 15.

The main methods used in the preparation of purified water are distillation, ion exchange, and reverse osmosis; these methods are described briefly next.

Distillation Method

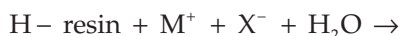
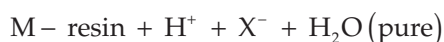
Many stills in various sizes and styles with capacities ranging from about 0.5 to 100 gallons of distillate per hour are available to prepare purified water. Generally, the first portion of aqueous distillate (about the first 10% to 20%) must be discarded because it contains many foreign volatile substances usually found in urban drinking water, the usual starting material. Also, the last portion of water (about 10% of the original volume of water) remaining in the distillation apparatus must be discarded and not subjected to further distillation because distillation to dryness would undoubtedly result in decomposition of the remaining solid impurities to volatile substances that would distill and contaminate the previously collected portion of distillate.

Ion Exchange Method

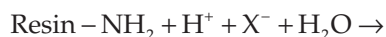
On a large or small scale, ion exchange for the preparation of purified water offers a number of advantages over distillation. For one thing, the requirement of heat is eliminated and with it, the costly and troublesome maintenance frequently encountered in the operation of the more complex distillation apparatus. Because of the simpler equipment and the nature of the method, ion exchange permits ease of operation, minimal maintenance, and a more mobile facility. Many pharmacies and small laboratories that purchase large volumes of distilled water from commercial suppliers for use in their work would no doubt benefit financially and in convenience through the installation of an ion exchange demineralizer in the work area.

The ion exchange equipment in use today generally passes water through a column of cation and anion exchangers consisting of water-insoluble synthetic polymerized phenolic, carboxylic, amino, or sulfonated resins of high molecular weight. These resins

are mainly of two types: (a) the cations, or acid exchangers, which permit the exchange of the cations in solution (in the tap water) with hydrogen ion from the resin, and (b) the anions, or base exchange resins, which permit the removal of anions. These two processes are successively or simultaneously employed to remove cations and anions from water. The processes are indicated as follows, with M^+ indicating the metal or cation (as Na^+) and the X^- indicating the anion (as Cl^-). Cation exchange:



Anion exchange:



Water purified in this manner, referred to as demineralized or deionized water, may be used in any pharmaceutical preparation or prescription calling for distilled water.

Reverse Osmosis

Reverse osmosis is one of the processes referred to in the industry as cross-flow (or tangential flow) membrane filtration (2). In this process, a pressurized stream of water is passed parallel to the inner side of a filter membrane core. A portion of the feed water, or influent, permeates the membrane as filtrate, while the balance of the water sweeps tangentially along the membrane to exit the system without being filtered. The filtered portion is called the permeate because it has permeated the membrane. The water that has passed through the system is called the concentrate because it contains the concentrated contaminants rejected by the membrane. Whereas in osmosis the flow through a semipermeable membrane is from a less concentrated solution to a more concentrated solution, the flow in this cross-flow system is from a more concentrated to a less concentrated solution, thus the term reverse osmosis. Depending on their pore size, cross-flow filter membranes can remove particles

defined in the range of microfiltration (0.1 to 2 μm , e.g., bacteria), ultrafiltration (0.01 to 0.1 μm , e.g., virus), nanofiltration (0.001 to 0.01 μm , e.g., organic compounds in the molecular weight range of 300 to 1,000), and reverse osmosis (particles $<0.001 \mu m$). Reverse osmosis removes virtually all viruses, bacteria, pyrogens, and organic molecules and 90% to 99% of ions (2).

PREPARATION OF SOLUTIONS

Most pharmaceutical solutions are unsaturated with solute. Thus, the amounts of solute to be dissolved are usually well below the capacity of the volume of solvent employed. The strengths of pharmaceutical preparations are usually expressed in terms of percent strength, although for very dilute preparations, expressions of ratio strength may be used. These expressions and examples are shown in Table 13.4.

The symbol % used without qualification (as with w/v, v/v, or w/w) means percent weight in volume for solutions or suspensions of solids in liquids, percent weight in volume for solutions of gases in liquids, percent volume in volume for solutions of liquids in liquids, and weight in weight for mixtures of solids and semisolids.

Some chemical agents in a given solvent require an extended time to dissolve. To hasten dissolution, a pharmacist may employ one of several techniques, such as applying heat, reducing the particle size of the solute, using a solubilizing agent, and/or subjecting the ingredients to vigorous agitation. Most chemical agents are more soluble at elevated temperatures than at room temperature or below because an endothermic reaction between the solute and the solvent uses the energy of the heat to enhance dissolution. However, elevated temperatures cannot be maintained for pharmaceuticals, and the net effect of heat is simply an increase in the rate of solution rather than an increase in solubility. An increased rate is satisfactory to the pharmacist because most solutions are unsaturated anyway and do not require a concentration of solute above the normal capacity of the solvent at room temperature. Pharmacists are reluctant to use heat to

Table 13.4 COMMON METHODS OF EXPRESSING THE STRENGTHS OF PHARMACEUTICAL PREPARATIONS

EXPRESSION	ABBREVIATED EXPRESSION	MEANING AND EXAMPLE
Percent weight in volume	% w/v	Grams of constituent in 100 mL of preparation (e.g., 1% w/v = 1 g constituent in 100 mL preparation)
Percent volume in volume	% v/v	Milliliters of constituent in 100 mL of preparation (e.g., 1% v/v = 1 mL constituent in 100 mL preparation)
Percent weight in weight	% w/w	Grams of constituent in 100 g of preparation (e.g., 1% w/w = 1 g constituent in 100 g preparation)
Ratio of strength to weight in volume	—:— w/v	Grams of constituent in stated milliliters of preparation (e.g., 1:1,000 w/v = 1 g constituent in 1,000 mL preparation)
Ratio of strength to volume in volume	—:— v/v	Milliliters of constituent in milliliters of preparation (e.g., 1:1,000 v/v = 1 mL constituent in 1,000 mL preparation)
Ratio of strength to weight in weight	—:— w/w	Grams of constituent in stated number of grams of preparation (e.g., 1:1,000 w/w = 1 g constituent in 1,000 g preparation)

facilitate solution, and when they do, they are careful not to exceed the minimally required temperature, for many medicinal agents are destroyed at elevated temperatures and the advantage of rapid solution may be completely offset by drug deterioration. If volatile solutes are to be dissolved or if the solvent is volatile (as is alcohol), the heat would encourage the loss of these agents to the atmosphere and must therefore be avoided. Pharmacists are aware that certain chemical agents, particularly calcium salts, undergo exothermic reactions as they dissolve and give off heat. For such materials, the use of heat would actually discourage the formation of a solution. The best pharmaceutical example of this type of chemical is calcium hydroxide, which is used in the preparation of Calcium Hydroxide Topical Solution, USP. Calcium hydroxide is soluble in water to the extent of 140 mg/100 mL of solution at 25°C (about 77°F) and 170 mg/100 mL of solution at 15°C (about 59°F). Obviously, the temperature at which the solution is prepared or stored can affect the concentration of the resultant solution.

In addition to or instead of raising the temperature of the solvent to increase the rate of solution, a pharmacist may choose to decrease the particle size of the solute. This may be accomplished by comminution (grinding a solid to a fine state of subdivision) with a mortar and pestle on a small scale or industrial

micronizer on a larger scale. The reduced particle size increases the surface area of the solute. If the powder is placed in a suitable vessel (e.g., a beaker, graduated cylinder, bottle) with a portion of the solvent and is stirred or shaken, as suited to the container, the rate of solution may be increased by the continued circulation of fresh solvent to the drug's surface and the constant removal of newly formed solution from the drug's surface.

Most solutions are prepared by simple mixing of the solutes with the solvent. On an industrial scale, solutions are prepared in large mixing vessels with ports for mechanical stirrers (Fig. 13.1). When heat is desired, thermostatically controlled mixing tanks may be used.

**FIGURE 13.1** Large-scale pharmaceutical mixing vessels. (Courtesy of Schering Laboratories.)

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ORAL SOLUTIONS AND PREPARATIONS FOR ORAL SOLUTION

Most solutions intended for oral administration contain flavorants and colorants to make the medication more attractive and palatable. When needed, they may also contain stabilizers to maintain the chemical and physical stability of the medicinal agents and preservatives to prevent the growth of microorganisms in the solution. The formulation pharmacist must be wary of chemical interactions between the various components of a solution that may alter the preparation's stability and/or potency. For instance, esters of *p*-hydroxybenzoic acid (methyl-, ethyl-, propyl-, and butylparabens), frequently used preservatives in oral preparations, have a tendency to partition into certain flavoring oils (3). This partitioning effect could reduce the effective concentration of the preservatives in the aqueous medium of a pharmaceutical product below the level needed for preservative action.

Liquid pharmaceuticals for oral administration are usually formulated such that the patient receives the usual dose of the medication in a conveniently administered volume, as 5 (one teaspoonful), 10, or 15 mL (one tablespoonful). A few solutions have unusually large doses, for example, Magnesium Citrate Oral Solution, USP, with a usual adult dose of 200 mL. On the other hand, many solutions for children are given by drop with a calibrated dropper usually furnished by the manufacturer in the product package.

Dry Mixtures for Solution

A number of medicinal agents, particularly certain antibiotics, for example, penicillin V, have insufficient stability in aqueous solution to meet extended shelf-life periods. Thus, commercial manufacturers of these products provide them to the pharmacist in dry powder or granule form for reconstitution with a prescribed amount of purified water immediately before dispensing to the patient. The dry powder mixture contains

all of the formulative components, including drug, flavorant, colorant, buffers, and others, except for the solvent. Once reconstituted by the pharmacist, the solution remains stable when stored in the refrigerator for the labeled period, usually 7 to 14 days, depending on the preparation. This is a sufficient period for the patient to complete the regimen usually prescribed. However, in case the medication remains after the patient completes the course of therapy, the patient should be instructed to discard the remaining portion, which would be unfit for use at a later time.

Examples of dry powder mixtures intended for reconstitution to oral solutions are the following:

- Cloxacillin Sodium for Oral Solution, USP (Teva), an anti-infective antibiotic
- Penicillin V Potassium for Oral Solution, USP (Veetids, Geneva), an anti-infective antibiotic
- Potassium Chloride for Oral Solution, USP (K-LOR, Abbott), a potassium supplement

Oral Solutions

The pharmacist may be called on to dispense a commercially prepared oral solution; dilute the concentration of a solution, as in the preparation of a pediatric form of an adult product; prepare a solution by reconstituting a dry powder mixture; or extemporaneously compound an oral solution from bulk ingredients.

In each instance, the pharmacist should be sufficiently knowledgeable about the dispensed product to expertly advise the patient of the proper use, dosage, method of administration, and storage of the product. Knowledge of the solubility and stability characteristics of the medicinal agents and the solvents employed in the commercial products is useful to the pharmacist for informing the patient of the advisability of mixing the solution with juice, milk, or other beverage upon administration. Information regarding the solvents used in each commercial product appears on the product label and in the accompanying package insert. Table 13.5 presents examples of some oral solutions. Some solutions of special

Table 13.5 EXAMPLES OF ORAL SOLUTIONS BY CATEGORY

ORAL SOLUTION	REPRESENTATIVE COMMERCIAL PRODUCTS	CONCENTRATION OF COMMERCIAL PRODUCT	COMMENTS
Antidepressants			
Escitalopram oxalate	Lexapro (Forest)	1 mg/mL	For major depressive disorder
Fluoxetine HCl	Prozac Liquid (Dista)	20 mg fluoxetine/5 mL	For depression, obsessive-compulsive disorder
Nortriptyline HCl	Pamelor Oral Solution (Mallinckrodt)	10 mg nortriptyline/5 mL	Tricyclic antidepressant
Antinauseant			
Ondansetron HCl	Zofran Oral Solution (GlaxoSmithKline)	4 mg/5 mL	For prevention of nausea and vomiting due to cancer-related therapies
Antiperistaltic			
Diphenoxylate HCl, atropine Sulfate	Lomotil Liquid (Pfizer)	2.5 mg diphenoxylate HCl, 0.025 mg atropine sulfate/5 mL	For diarrhea. Diphenoxylate is related structurally and pharmacologically to the opioid meperidine. Atropine sulfate in subtherapeutic amounts discourages (by virtue of side effects) deliberate overdosage.
Loperamide HCl	Imodium A-D Liquid (Ortho-McNeil)	1 mg loperamide HCl/5 mL	For diarrhea in adults and children aged 6 years and older. Structurally related to haloperidol
Antipsychotics			
Haloperidol	Haloperidol Oral Solution	2 mg haloperidol/mL	Primarily for severe neuropsychiatric conditions when oral medication is preferred and tablets and capsules are impractical. Concentrated solutions used by adding desired amount of concentrate by calibrated dropper to soup or a beverage
Perphenazine	Perphenazine Oral Solution	16 mg perphenazine/5 mL	
Thiothixene HCl	Navane concentrate (Roerig)	Equivalent of 5 mg thiothixene/mL	
Antiretroviral			
Emtricitabine	Emtriva (Gilead)	10 mg/mL	Indicated, in combination with other antiretrovirals, for the treatment of HIV-1 infections
Bronchodilator			
Theophylline	Theophylline Oral Solution (Roxane)	80 mg theophylline/15 mL	Alcohol-free solution for the treatment of bronchial asthma and reversible bronchospasm associated with chronic bronchitis and emphysema
Cathartics			
Magnesium Citrate, USP		Magnesium citrate equivalent to 1.55–1.9 g/100 mL magnesium oxide	Discussed in text

(Continued)

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Table 13.5 EXAMPLES OF ORAL SOLUTIONS BY CATEGORY (Continued)

ORAL SOLUTION	REPRESENTATIVE COMMERCIAL PRODUCTS	CONCENTRATION OF COMMERCIAL PRODUCT	COMMENTS
Sodium phosphate	Phospho-Soda (Fleet)	2.4 g monobasic sodium phosphate, 0.9 g dibasic sodium phosphate/5 mL	Works as a laxative within 1 hour taken before meals or overnight taken at bedtime. Usual dose is 10–20 mL, best diluted in half glass of water and followed with full glass of water
Corticosteroid			
Prednisolone sodium phosphate	Pediapred Oral Solution (USB)	5 mg prednisolone (as sodium phosphate)/5 mL	Synthetic adrenocortical steroid with mainly glucocorticoid properties indicated for endocrine, rheumatic, collagen, allergic, and other disorders
Dementia			
Memantine HCl	Namenda Oral Solution (Forest)	2 mg/mL	Treatment of moderate to severe dementia of the Alzheimer type
Dental Caries Protectant			
Sodium fluoride	Pediaflor Drops (Ross)	0.5 mg/mL	Prophylaxis of dental caries; for use when community water supply is inadequately fluoridated
Electrolyte Replenisher			
Potassium chloride	Kaochlor 10% Liquid (Pharmacia)	20 mEq KCl/15 mL in flavored aqueous vehicle	For hypopotassemia (low blood level of potassium). Condition may be prompted by severe or chronic diarrhea, low dietary intake of potassium, increased renal excretion of potassium, or other causes. Solution is diluted with water or fruit juice.
Fecal Softener			
Docusate sodium	Colace Syrup (Purdue)	10 mg docusate sodium/mL	Usually 50–200 mg measured by calibrated dropper, mixed with milk, fruit juice, or other liquid to mask the taste. Softens fecal mass by lowering the surface tension, permitting normal bowel habits, particularly in geriatric, pediatric, cardiac, obstetric, and surgical patients. Taken for several days or until the bowel movements are normal
Hematinic			
Ferrous sulfate	Fer-In-Sol Drops (Mead Johnson Nutritional)	15 mg/0.6 mL	For prevention and treatment of iron deficiency anemias. Usual prophylactic dose 0.3 or 0.6 mL, measured by calibrated dropper, mixed with water or juice. Dosage form intended primarily for infants and children
Histamine H2 Antagonist			
Cimetidine HCl	Tagamet HCl Liquid (GlaxoSmithKline Consumer)	300 mg/5 mL	For peptic ulcer disease, pathologic hypersecretory conditions, for example, Zollinger-Ellison syndrome
Immunosuppressant			
Cyclosporine	Sandimmune Oral Solution (Novartis) Neoral Oral Solution (Novartis)	100 mg/mL	For prophylaxis of organ rejection

Table 13.5 EXAMPLES OF ORAL SOLUTIONS BY CATEGORY (Continued)

ORAL SOLUTION	REPRESENTATIVE COMMERCIAL PRODUCTS	CONCENTRATION OF COMMERCIAL PRODUCT	COMMENTS
Opioid Agonist Analgesic			
Methadone HCl	Methadone HCl (Roxane)	1 or 2 mg/mL	For relief of severe pain; detoxification, maintenance treatment of opioid addiction
Vitamin D			
Ergocalciferol	Calciferol Drops (Schwartz)	8,000 U/mL	Water-insoluble ergocalciferol (vitamin D ₂) in propylene glycol. Usual prophylactic dose is about 400 U; therapeutic dose may be as high as 200,000–500,000 U daily in treating rickets.

pharmaceutical interest are described later in this chapter.

Oral Rehydration Solutions

Rapid fluid loss associated with diarrhea can lead to dehydration and ultimately death in some patients, particularly infants. More than 5 million children younger than 4 years of age die of diarrhea each year worldwide (4). Diarrhea is characterized by an increased frequency of loose, watery stools, and because of the rapid fluid loss, dehydration can be an outcome. During diarrhea, the small intestine secretes far more than the normal amount of fluid and electrolytes, and this simply exceeds the ability of the large intestine to reabsorb it. This fluid loss, which occurs mostly from the body's extracellular fluid compartment, can lead to a progressive loss of blood volume culminating in hypovolemic shock.

Diarrhea is a normal physiologic body response to rid itself of a noxious or toxic substance, such as rotavirus or *Escherichia coli*. Thus, the treatment approach is to allow the diarrhea to proceed and not to terminate it too quickly but promptly replace the lost fluid and electrolytes to prevent dehydration. The loss of fluid during diarrhea is accompanied by depletion of sodium, potassium, and bicarbonate ions; if severe, the loss can result in acidosis, hyperpnea, and vomiting as well as hypovolemic shock. If continuous, bouts of vomiting and diarrhea can cause malnutrition as well. Consequently, the goal is to replace lost fecal water with an

oral rehydration solution and use nutritional foods, such as soybean formula and bran.

Oral rehydration solutions are usually effective in treatment of patients with mild volume depletion, 5% to 10% of body weight. These are available OTC and are relatively inexpensive, and their use has diminished the incidence of complications associated with parenterally administered electrolyte solutions. Therapy with these solutions is based on the observation that glucose is actively absorbed from the small intestine, even during bouts of diarrhea. This active transport of glucose is advantageous because it is coupled with sodium absorption. Almost in domino fashion, sodium absorption promotes anion absorption, which in turn promotes water absorption to short-circuit dehydration. To produce maximal absorption of sodium and water, studies have demonstrated that the optimal concentrations of glucose and sodium in an isotonic solution are 110 mM (2%) glucose and 60 mEq/L of sodium ion, respectively. Bicarbonate and/or citrate ions are also included in these solutions to help correct the metabolic acidosis caused by diarrhea and dehydration.

A liter of typical oral rehydration solution contains 45 mEq Na⁺, 20 mEq K⁺, 35 mEq Cl⁻, 30 mEq citrate, and 25 g dextrose. These formulations are available in liquid or powder packet form for reconstitution. It is important that the user add the specific amount of water needed to prepare the powder forms. Furthermore, these products should not be mixed with or given with other electrolyte-containing liquids, such as milk or fruit juices.

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Otherwise, there is no method to calculate how much electrolyte the patient actually received. Commercial ready-to-use oral electrolyte solutions to prevent dehydration or achieve rehydration include Pedialyte Solution (Ross) and Rehydralyte Solution (Ross). These products also contain dextrose or glucose. Infalyte Oral Solution (Bristol-Myers Squibb) contains electrolytes in a syrup of rice solids. The rice-based formula produces a lower osmotic effect than the dextrose- or glucose-based formulas and is thought to be more effective in reducing stool output and shortening the duration of diarrhea. The success of the commercial solutions is based on the physiologic design of the formulation.

Oral Colonic Lavage Solution

Traditionally, preparation of the bowel for procedures such as a colonoscopy consisted of administration of a clear liquid diet for 24 to 48 hours preceding the procedure, administration of an oral laxative such as magnesium citrate or bisacodyl the night before, and a cleansing enema administered 2 to 4 hours prior to the procedure. Typically, to circumvent hospitalization of the patient the night before the procedure, patients were allowed to perform this regimen at home. However, while the results have been satisfactory, that is, the bowel is cleared for the procedure, poor compliance with and acceptance of this regimen can cause problems during the procedure. Furthermore, additive effects of malnutrition and poor oral intake prior to the procedure can cause more patient problems.

Consequently, an alternative method to prepare the gastrointestinal tract has been devised. This procedure requires less time and dietary restriction and obviates the cleansing enemas. This method entails oral administration of a balanced solution of electrolytes with polyethylene glycol (PEG-3350-Electrolyte Solution), that is, Colyte (Alaven Pharmaceuticals). Before dispensing it to the patient, the pharmacist reconstitutes this powder with water, creating an iso-osmotic solution having a mildly salty taste. The PEG acts as an osmotic agent in the gastrointestinal tract, and the balanced electrolyte concentration results in virtually

no net absorption or secretion of ions. Thus, a large volume of this solution can be administered without a significant change in water or electrolyte balance.

The formulation of this oral colonic lavage solution is as follows:

PEG-3350	240.00 g
Sodium sulfate	22.72 g
Sodium bicarbonate	6.72 g
Sodium chloride	5.84 g
Potassium chloride	2.98 g

In 4,000 mL disposable container

The recommended adult dose of this product is 4 L of solution before the gastrointestinal procedure. The patient is instructed to drink 240 mL of solution every 10 minutes until about 4 L is consumed. The patient is advised to drink each portion quickly rather than sipping it continuously. Usually, the first bowel movement will occur within 1 hour. Several regimens are used, and one method is to schedule patients for a midmorning procedure, allowing the patient 3 hours for drinking and a 1-hour waiting period to complete bowel evacuation.

To date, this approach to bowel evacuation has been associated with a low incidence of side effects (primarily nausea, transient abdominal fullness, bloating, and occasionally cramps and vomiting). Ideally, the patient should not have taken any food 3 to 4 hours before beginning to take the solution. In no case should solid foods be taken by the patient for at least 2 hours before the solution is administered. No foods except clear liquids are permitted after this product is administered and prior to the examination. The product must be stored in the refrigerator after reconstitution, and this aids somewhat in decreasing the salty taste of the product.

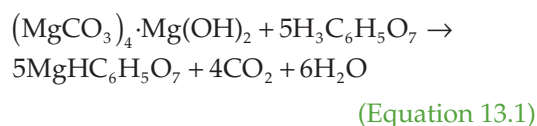
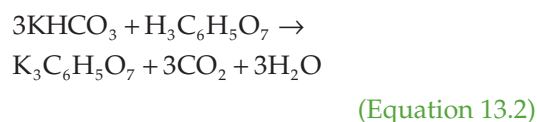
PEG-ES solutions are employed for unlabeled use in the management of acute iron overdose in children.

Magnesium Citrate Oral Solution

Magnesium citrate oral solution is a colorless to slightly yellow clear effervescent liquid having a sweet, acidulous taste and a lemon

flavor. It is commonly referred to as citrate or as citrate of magnesia. It is required to contain an amount of magnesium citrate equivalent to 1.55 to 1.9 g of magnesium oxide in each 100 mL.

The solution is prepared by reacting official magnesium carbonate with an excess of citric acid (Equation 13.1), flavoring and sweetening the solution with lemon oil and syrup, filtering with talc, and then carbonating it by the addition of either potassium or sodium bicarbonate (Equation 13.2). The solution may be further carbonated by the use of carbon dioxide under pressure:



The solution provides an excellent medium for the growth of molds, and any mold spores present during the manufacture of the solution must be killed if the preparation is to remain stable. For this reason, during the preparation of the solution, the liquid is heated to boiling (prior to carbonation); boiled water is employed to bring the solution to its proper volume; and boiling water is used to rinse the final container. The final solution may be sterilized.

The solution is employed as a saline cathartic, with the citric acid, lemon oil, syrup, carbonation, and the low temperature of the refrigerated solution all contributing to the patient's acceptance of the large volume of medication. For many patients, it is a pleasant way of taking an otherwise bitter saline cathartic.

Sodium Citrate and Citric Acid Oral Solution

This official solution contains sodium citrate 100 mg and citric acid 67 mg in each milliliter of aqueous solution. The solution is administered orally in doses of 10 to 30 mL as frequently as four times daily as a systemic

alkalinizer. Systemic alkalinization is useful for patients for whom long-term maintenance of an alkaline urine is desirable, such as those with uric acid and cystine calculi of the urinary tract. The solution is also a useful adjuvant when administered with uricosuric agents in gout therapy because urates tend to crystallize out of an acid urine.

SYRUPS

Syrups are concentrated aqueous preparations of a sugar or sugar substitute with or without flavoring agents and medicinal substances. Syrups containing flavoring agents but not medicinal substances are called nonmedicated or flavored vehicles (syrups). Some official, previously official, and commercially available nonmedicated syrups are presented in Table 13.6. These syrups are intended to serve as pleasant-tasting vehicles for medicinal substances to be added in the extemporaneous compounding of prescriptions or in the preparation of a standard formula for a medicated syrup, which is a syrup containing a therapeutic agent. Due to the inability of some children and elderly people to swallow solid dosage forms, it is fairly common today for a pharmacist to be asked to prepare an oral liquid dosage form of a medication available in the pharmacy only as tablets or capsules. In these instances, drug solubility, stability, and bioavailability must be considered case by case (5,6). The liquid dosage form selected for compounding may be a solution or a suspension, depending on the chemical and physical characteristics of the particular drug and its solid dosage form. Vehicles are commercially available for this purpose (6).

Medicated syrups are commercially prepared from the starting materials, that is, by combining each of the individual components of the syrup, such as sucrose, purified water, flavoring agents, coloring agents, the therapeutic agent, and other necessary and desirable ingredients. Naturally, medicated syrups are employed in therapeutics for the value of the medicinal agent present in the syrup.

Syrups provide a pleasant means of administering a liquid form of a disagreeable-tasting drug. They are particularly effective in the

Table 13.6 EXAMPLES OF NONMEDICATED SYRUPS (VEHICLES)

SYRUP	COMMENTS
Cherry syrup	Sucrose-based syrup with cherry juice about 47% by volume. Tart fruit flavor is attractive to most patients, and acidic pH makes it useful as a vehicle for drugs requiring an acid medium.
Cocoa syrup	Suspension of cocoa powder in aqueous vehicle sweetened and thickened with sucrose, liquid glucose, glycerin; flavored with vanilla, sodium chloride. Particularly effective in administering bitter-tasting drugs to children
Orange syrup	Sucrose-based syrup uses sweet orange peel tincture, citric acid as the source of flavor and tartness. Resembles orange juice in taste; good vehicle for drugs stable in acidic medium
Ora-Sweet, Ora-Sweet SF	Commercial vehicles for extemporaneous compounding of (Paddock Laboratories) syrups. Both have a pH of 4–4.5 and are alcohol-free. Ora-Sweet SF is sugar-free.
Ora-Blend	A preblended combination of Ora-Sweet and Ora-Plus (1:1) and Ora-Sweet SF and Ora-Plus (1:1)
PCCA Acacia Syrup	A sweet, demulcent suspending vehicle with a mild vanilla flavor
PCCA-Plus Oral Suspending Vehicle	A preserved, buffered vehicle with demulcent qualities
PCCA Sweet SF	A sugar-free syrup containing sorbitol and can be used in diabetic patients as well as others
PCCA Syrup	A syrup vehicle with less sucrose than Syrup NF
Raspberry syrup	Sucrose-based syrup with raspberry juice about 48% by volume. Pleasant-flavored vehicle to disguise salty or sour taste of saline medicaments
SyrSpend™ SF Suspension Vehicle	A low osmolality suspending vehicle using modified starch technology. It is buffered at pH 4.2; it is sugar-free and paraben-free; it is available in unflavored, cherry, and grape formulations.
SyrSpend™	
SF Alka	An alkaline suspension vehicle with a pH of about 7.0, when reconstituted as directed. It is low osmolality (<50 mOsmol), pleasant-tasting, sugar-free, alkaline medium available in unflavored and cherry formulas
Syrup	85% sucrose in purified water. Simple syrup may be used as the basis for flavored or medicated syrups.

administration of drugs to youngsters, since their pleasant taste usually dissipates any reluctance on the part of the child to take the medicine. The fact that syrups contain little or no alcohol adds to their favor among parents.

Any water-soluble drug that is stable in aqueous solution may be added to a flavored syrup. However, care must be exercised to ensure compatibility between the drug substance and the other formulative components of the syrup. Also, certain flavored syrups have an acidic medium, whereas others may be neutral or slightly basic, and the proper selection must be made to ensure the stability of any added medicinal agent. Perhaps

the most frequently found types of medications administered as medicated syrups are antitussive agents and antihistamines. This is not to imply that other types of drugs are not formulated into syrups; a variety of medicinal substances can be found in syrup form and among the many commercial products. Examples of medicated syrups are presented in Table 13.7.

Components of Syrups

Most syrups contain the following components in addition to the purified water and any medicinal agents present: (a) the sugar,

Table 13.7 EXAMPLES OF MEDICATED SYRUPS BY CATEGORY

SYRUP	REPRESENTATIVE COMMERCIAL PRODUCTS	CONCENTRATION OF COMMERCIAL PRODUCT ^a	COMMENTS
Analgesic			
Meperidine HCl	Demerol Syrup (Sanofi-Synthelabo)	50 mg/5 mL	Opioid analgesic for the relief of moderate to severe pain, adjunct to general anesthesia
Anticholinergics			
Dicyclomine HCl	Bentyl (Axcan Scandipharma)	10 mg/5 mL	Adjunctive therapy in the treatment of peptic ulcer
Oxybutynin chloride	Various	5 mg/5 mL	Relief of symptoms with voiding in patients with uninhibited neurogenic and reflex neurogenic bladder
Antiemetics			
Chlorpromazine HCl	Thorazine Syrup (GlaxoSmithKline)	10 mg HCl/5 mL	Control of nausea and vomiting
Dimenhydrinate	Children's Dramamine Liquid (Pharmacia)	12.5 mg/5 mL	Control of nausea, vomiting, motion sickness
Prochlorperazine edisyate	Various	5 mg/5 mL	Control of nausea and vomiting
Promethazine HCl	Various	6.25, 25 mg/5 mL	Control of nausea, vomiting, motion sickness, allergic reactions
Anticonvulsant			
Sodium valproate	Depakene Syrup (Abbott)	250 mg as sodium salt/5 mL	Sole or adjunctive therapy in simple (petit mal), complex absence seizure disorders
Antihistamines			
Chlorpheniramine maleate	Chlor-Trimeton Allergy Syrup (Schering-Plough)	2 mg/5 mL	For prevention, treatment of allergic reactions
Desloratadine	Clarinet Syrup (Schering)	0.5 mg/1 mL	For relief of nasal and nonnasal symptoms of allergic rhinitis and urticaria
Hydroxyzine HCl	Atarax Syrup (Roerig)	10 mg/5 mL	
Antipsychotic			
Citalopram hydrobromide	Celexa (Forest)	10 mg/5 mL	For depression
Lithium citrate	Various	8 mEq/5 mL	Management of psychotic disorders
Risperidone	Risperdal (Janssen)	1 mg/mL	For treatment of schizophrenia
Antitussives			
Dextromethorphan	Benylin Adult Cough Formula (Warner-Lambert)	15 mg/5 mL	For relief of cough
Diphenhydramine	Benadryl Allergy Liquid Medication (McNeil)	12.5 mg/5 mL	For control of coughs due to colds or allergy
Antiviral			
Amantadine HCl	Symmetrel Syrup (Endo)	50 mg/5 mL	Prevention of respiratory infections caused by A2 (Asian) viral strains. Treatment of idiopathic Parkinson disease

(Continued)

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Table 13.7 EXAMPLES OF MEDICATED SYRUPS BY CATEGORY (Continued)

SYRUP	REPRESENTATIVE COMMERCIAL PRODUCTS	CONCENTRATION OF COMMERCIAL PRODUCT ^a	COMMENTS
Lamivudine	Epivir Oral Solution (GlaxoSmithKline)	10 mg/mL	Treatment of HIV
Ritonavir	Norvir (Abbott)	80 mg/mL	Treatment of HIV
Bronchodilators			
Albuterol sulfate	Proventil Syrup (Schering) Ventolin Syrup (Schering)	2 mg/5 mL	Relief of bronchospasm of obstructive airway disease; prevention of exercise- induced bronchospasm
Metaproterenol sulfate	Alupent Syrup (Boehringer Ingelheim)	10 mg/5 mL	
Cathartic			
Lactulose	Chronulac Syrup (Hoechst)	10 g/15 mL	15–30 mL qd as laxative
Cholinergic			
Pyridostigmine bromide	Mestinon Syrup (ICN Pharmaceuticals)	60 mg/5 mL	Treatment of myasthenia gravis
Decongestant			
Pseudoephedrine hydrochloride	Sudafed Children's Nondrowsy (Pfizer Consumer)	15 mg/5 mL	Temporary relief of nasal congestion of common cold, hay fever, upper respiratory allergies, sinusitis
Emetic			
Ipecac	Various	21 mg ether-soluble alkaloids of ipecac/15 mL	To induce vomiting in poisoning. Dose of 15 mL may be repeated in 20 min if vomiting does not occur. If after the second dose vomiting does not occur, the stomach should be emptied by gastric lavage.
Expectorant			
Guaifenesin	Guaifenesin Syrup (Roxane)	100 mg/5 mL	For symptomatic relief of respiratory conditions associated with cough and bronchial congestion
Fecal softener			
Docusate sodium	Colace Syrup (Purdue)	20 mg/5 mL	Stool softener by surface action
Gastrointestinal stimulant			
Metoclopramide	Various	5 mg/5 mL	Relief of symptoms of diabetic gastroparesis (gastric stasis) and gastroesophageal reflux
H ₂ receptor antagonist ranitidine HCl	Zantac Syrup (GlaxoSmithKline)	15 mg/mL	Treatment of duodenal ulcers and GERD
Hemostatic			
Aminocaproic acid	Amicar Syrup (Xanodyne)	1.25 g/5 mL	Treatment of excessive bleeding from systemic hyperfibrinolysis, urinary fibrinolysis
Hypnotic Sedative			
Chloral hydrate	Chloral Hydrate Syrup (Pharmaceutical Associates)	250 mg/5 mL	Sedative at 250 mg; hypnotic to induce sleep at 500 mg. Alcoholic beverages should be avoided. Usually diluted with water or some other beverage

^aA usual single dose unless otherwise stated.

usually sucrose, or sugar substitute used to provide sweetness and viscosity; (b) antimicrobial preservatives; (c) flavorants; and (d) colorants. Also, many types of syrups, especially those prepared commercially, contain special solvents (including alcohol), solubilizing agents, thickeners, or stabilizers.

Sucrose- and Nonsucrose-Based Syrups

Sucrose is the sugar most frequently employed in syrups, although in special circumstances, it may be replaced in whole or in part by other sugars or substances such as sorbitol, glycerin, and propylene glycol. In some instances, all glycogenetic substances (materials converted to glucose in the body), including the agents mentioned earlier, are replaced by nonglycogenetic substances, such as methylcellulose or hydroxyethylcellulose. These two materials are not hydrolyzed and absorbed into the blood stream, and their use results in an excellent syrup-like vehicle for medications intended for use by diabetic patients and others whose diet must be controlled and restricted to nonglycogenetic substances. The viscosity resulting from the use of these cellulose derivatives is much like that of a sucrose syrup. The addition of one or more artificial sweeteners usually produces an excellent facsimile of a true syrup.

The characteristic body that the sucrose and alternative agents seek to impart to the syrup is essentially the result of attaining the proper viscosity. This quality, together with the sweetness and flavorants, results in a type of pharmaceutical preparation that masks the taste of added medicinal agents. When the syrup is swallowed, only a portion of the dissolved drug actually makes contact with the taste buds, the remainder of the drug being carried past them and down the throat in the viscous syrup. This type of physical concealment of the taste is not possible for a solution of a drug in an unthickened, mobile aqueous preparation. In the case of antitussive syrups, the thick, sweet syrup has a soothing effect on the irritated tissues of the throat as it passes over them.

Most syrups contain a high proportion of sucrose, usually 60% to 80%, not only because of the desirable sweetness and

viscosity of such solutions but also because of their inherent stability in contrast to the unstable character of dilute sucrose solutions. The aqueous sugar medium of dilute sucrose solutions is an efficient nutrient medium for the growth of microorganisms, particularly yeasts and molds. On the other hand, concentrated sugar solutions are quite resistant to microbial growth because of the unavailability of the water required for the growth of microorganisms. This aspect of syrups is best demonstrated by the simplest of all syrups, Syrup, NF, also called simple syrup. It is prepared by dissolving 85 g of sucrose in enough purified water to make 100 mL of syrup. The resulting preparation generally requires no additional preservation if it is to be used soon; in the official syrup, preservatives are added if the syrup is to be stored. When properly prepared and maintained, the syrup is inherently stable and resistant to the growth of microorganisms. An examination of this syrup reveals its concentrated nature and the relative absence of water for microbial growth. Syrup has a specific gravity of about 1.313, which means that each 100 mL of syrup weighs 131.3 g. Because 85 g of sucrose is present, the difference between 85 and 131.3 g, or 46.3 g, represents the weight of the purified water. Thus, 46.3 g, or mL, of purified water is used to dissolve 85 g of sucrose. The solubility of sucrose in water is 1 g in 0.5 mL of water; therefore, to dissolve 85 g of sucrose, about 42.5 mL of water would be required. Thus, only a very slight excess of water (about 3.8 mL per 100 mL of syrup) is employed in the preparation of syrup. Although not enough to be particularly amenable to the growth of microorganisms, the slight excess of water permits the syrup to remain physically stable in varying temperatures. If the syrup were completely saturated with sucrose, in cool storage, some sucrose might crystallize from solution and, by acting as nuclei, initiate a type of chain reaction that would result in separation of an amount of sucrose disproportionate to its solubility at the storage temperature. The syrup would then be very much unsaturated and probably suitable for microbial growth. As formulated, the official

syrup is stable and resistant to crystallization and microbial growth. However, many of the other official syrups and a host of commercial syrups are not intended to be as nearly saturated as Syrup, NF, and therefore must employ added preservative agents to prevent microbial growth and to ensure their stability during their period of use and storage.

As noted earlier, sucrose-based syrup may be substituted in whole or in part by other agents in the preparation of medicated syrups. A solution of a polyol, such as sorbitol, or a mixture of polyols, such as sorbitol and glycerin, is commonly used. Sorbitol Solution, USP, which contains 64% by weight of the polyhydric alcohol sorbitol, is employed as shown in the following example formulations for medicated syrups (7):

Antihistamine Syrup

Chlorpheniramine maleate	0.4 g
Glycerin	25.0 mL
Syrup	83.0 mL
Sorbitol solution	282.0 mL
Sodium benzoate	1.0 g
Alcohol	60.0 mL
Color and flavor	qs
Purified water, to make	1,000.0 mL

Ferrous Sulfate Syrup

Ferrous sulfate	135.0 g
Citric acid	12.0 g
Sorbitol solution	350.0 mL
Glycerin	50.0 mL
Sodium benzoate	1.0 g
Flavor	qs
Purified water, to make	1,000.0 mL

Acetaminophen Syrup

Acetaminophen	24.0 g
Benzoic acid	1.0 g
Disodium calcium EDTA	1.0 g
Propylene glycol	150.0 mL
Alcohol	150.0 mL
Saccharin sodium	1.8 g
Purified water	200.0 mL
Flavor	qs

Sorbitol solution, to make	1,000.0 mL
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Cough and Cold Syrup

Dextromethorphan hydrobromide	2.0 g
Guaifenesin	10.0 g
Chlorpheniramine maleate	0.2 g
Phenylephrine hydrochloride	1.0 g
Sodium benzoate	1.0 g
Saccharin sodium	1.9 g
Citric acid	1.0 g
Sodium chloride	5.2 g
Alcohol	50.0 mL
Sorbitol solution	324.0 mL
Syrup	132.0 mL
Liquid glucose	44.0 mL
Glycerin	50.0 mL
Color	qs
Flavor	qs
Purified water, to make	1,000.0 mL

All materials used in the extemporaneous compounding and manufacturing of pharmaceuticals should be of USP–NF quality and obtained from FDA-approved sources.

Antimicrobial Preservative

The amount of a preservative required to protect a syrup against microbial growth varies with the proportion of water available for growth, the nature and inherent preservative activity of some formulative materials (e.g., many flavoring oils that are inherently sterile and possess antimicrobial activity), and the capability of the preservative itself. Among the preservatives commonly used in syrups with the usually effective concentrations are benzoic acid 0.1% to 0.2%, sodium benzoate 0.1% to 0.2%, and various combinations of methylparabens, propylparabens, and butylparabens totaling about 0.1%. Frequently, alcohol is used in syrups to assist in dissolving the alcohol-soluble ingredients, but normally, it is not present in the final product in amounts that would be considered to be adequate for preservation (15% to 20%). See Physical Pharmacy Capsule 13.1, Preservation of Syrups.



PHYSICAL PHARMACY CAPSULE 13.1

Preservation of Syrups

Syrups can be preserved by (a) storage at low temperature; (b) adding preservatives such as glycerin, benzoic acid, sodium benzoate, methylparaben, or alcohol in the formulation; or (c) the maintenance of a high concentration of sucrose as a part of the formulation. High sucrose concentrations will usually protect an oral liquid dosage form from growth of most microorganisms. A problem arises, however, when pharmacists must add other ingredients to syrups that can result in a decrease in the sucrose concentration. This may cause a loss of the preservative effectiveness of the sucrose. This can be overcome, however, by calculating the quantity of a preservative (such as alcohol) to add to the formula to maintain the preservative effectiveness of the final product.

EXAMPLE

Rx active drug	5 mL volume occupied
Other drug solids	3 mL volume occupied
Glycerin	15 mL
Sucrose	25 g
Ethanol	95% qs
Purified water q.s.	100 mL

How much alcohol would be required to preserve this prescription? We will use the free-water method to calculate the quantity of alcohol required.

Simple syrup contains 85 g sucrose per 100 mL of solution, which weighs 131.3 g (specific gravity, 1.313). It takes 46.3 mL of water to prepare the solution ($131.3 - 85 = 46.3$), and the sucrose occupies a volume of ($100 - 46.3 = 53.7$) 53.7 mL.

1. Because this solution is preserved, 85 g of sucrose preserves 46.3 mL of water, and 1 g of sucrose preserves 0.54 mL of water. With 25 g of sucrose present, the amount of water preserved is

$$25 \times 0.54 = 13.5 \text{ mL}$$

2. Because 85 g of sucrose occupies a volume of 53.7 mL, 1 g of sucrose will occupy a volume of 0.63 mL. The volume occupied by the sucrose in this prescription is

$$25 \times 0.63 = 15.75 \text{ mL}$$

3. The active drug and other solids occupy 8 mL ($5 + 3$) volume.
4. Each mL of glycerin can preserve an equivalent quantity of volume ($2 \times 15 = 30$), so 30 mL would be preserved.
5. The volume taken care of so far is $13.5 + 15.75 + 8 + 30 = 67.25$ mL. The quantity of free water remaining is

$$100 - 67.25 = 32.75 \text{ mL}$$

6. Because it requires about 18% alcohol to preserve the water,

$$0.18 \times 32.75 = 5.9 \text{ mL of alcohol (100\%)}$$

would be required.

7. If 95% ethanol is used, $5.9/0.95 = 6.21$ mL would be required.

To prepare the prescription, about 6.21 mL of 95% ethanol can be added with sufficient purified water to make 100 mL of the final solution.

Flavorant

Most syrups are flavored with synthetic flavorants or with naturally occurring materials, such as volatile oils (e.g., orange oil), vanillin, and others, to render the syrup pleasant tasting. Because syrups are aqueous preparations, these flavorants must be water soluble. However, sometimes a small amount of alcohol is added to a syrup to ensure the continued solution of a poorly water-soluble flavorant. Commercial flavoring systems (FLAVORx) may also be considered and used.

Colorant

To enhance the appeal of the syrup, a coloring agent that correlates with the flavorant employed (i.e., green with mint, brown with chocolate) is used. Generally, the colorant is water soluble, nonreactive with the other syrup components, and color stable at the pH range and under the intensity of light that the syrup is likely to encounter during its shelf life.

Preparation of Syrups

Syrups are most frequently prepared by one of four general methods, depending on the physical and chemical characteristics of the ingredients. Broadly stated, these methods are (a) solution of the ingredients with the aid of heat, (b) solution of the ingredients by agitation without the use of heat or the simple admixture of liquid components, (c) addition of sucrose to a prepared medicated liquid or to a flavored liquid, and (d) percolation of either the source of the medicating substance or the sucrose. Sometimes a syrup is prepared by more than one of these methods, and the selection may simply be a matter of preference on the part of the pharmacist. Many of the official syrups have no officially designated method of preparation.

Solution with the Aid of Heat

Syrups are prepared by this method when it is desired to prepare the syrup as quickly as possible and when the syrup's components are not damaged or volatilized by heat. In this method, the sugar is generally added

to the purified water, and heat is applied until the sugar is dissolved. Then, other heat-stable components are added to the hot syrup, the mixture is allowed to cool, and its volume is adjusted to the proper level by the addition of purified water. If heat-labile agents or volatile substances, such as volatile flavoring oils and alcohol, are to be added, they are generally added to the syrup after the sugar is dissolved by heat, and the solution is rapidly cooled to room temperature.

The use of heat facilitates rapid solution of the sugar and certain other components of syrups; however, caution must be exercised against becoming impatient and using excessive heat. Sucrose, a disaccharide, may be hydrolyzed into monosaccharides, dextrose (glucose), and fructose (levulose). This hydrolytic reaction is inversion, and the combination of the two monosaccharide products is invert sugar. When heat is applied in the preparation of a sucrose syrup, some inversion of the sucrose is almost certain. The speed of inversion is greatly increased by the presence of acids, the hydrogen ion acting as a catalyst to the reaction. Should inversion occur, the sweetness of the syrup is altered because invert sugar is sweeter than sucrose, and the normally colorless syrup darkens because of the effect of heat on the levulose portion of the invert sugar. When the syrup is greatly overheated, it becomes amber colored as the sucrose caramelizes. Syrups so decomposed are more susceptible to fermentation and to microbial growth than the stable, undecomposed syrups. Because of the prospect of decomposition by heat, syrups cannot be sterilized by autoclaving. The use of boiled purified water in the preparation of a syrup can enhance its permanency, and the addition of preservative agents, when permitted, can protect it during its shelf life. Storage in a tight container is a requirement for all syrups.

Solution by Agitation Without the Aid of Heat

To avoid heat-induced inversion of sucrose, a syrup may be prepared without heat by agitation. On a small scale, sucrose and other

formulative agents may be dissolved in purified water by placing the ingredients in a vessel larger than the volume of syrup to be prepared, permitting thorough agitation of the mixture. This process is more time consuming than the use of heat, but the product has maximum stability. Huge glass-lined or stainless steel tanks with mechanical stirrers or agitators are employed in large-scale preparation of syrups.

Sometimes, simple syrup or some other nonmedicated syrup, rather than sucrose, is employed as the sweetening agent and vehicle. In that case, other liquids that are soluble in the syrup or miscible with it may be added and thoroughly mixed to form a uniform product. When solid agents are to be added to a syrup, it is best to dissolve them in minimal amount of purified water and incorporate the resulting solution into the syrup. When solid substances are added directly to a syrup, they dissolve slowly because the viscous nature of the syrup does not permit the solid substance to distribute readily throughout the syrup to the available solvent and also because a limited amount of available water is present in concentrated syrups.

Addition of Sucrose to a Medicated Liquid or to a Flavored Liquid

Occasionally, a medicated liquid, such as a tincture or fluidextract, is employed as the source of medication in the preparation of a syrup. Many such tinctures and fluidextracts contain alcohol-soluble constituents and are prepared with alcoholic or hydroalcoholic vehicles. If the alcohol-soluble components are desired medicinal agents, some means of rendering them water soluble is employed. However, if the alcohol-soluble components are undesirable or unnecessary components of the corresponding syrup, they are generally removed by mixing the tincture or fluidextract with water, allowing the mixture to stand until separation of the water-insoluble agents is complete, and filtering them from the mixture. The filtrate is the medicated liquid to which the sucrose is added in preparation of the syrup. If the tincture or fluidextract is miscible with aqueous preparations, it may

be added directly to simple syrup or to a flavored syrup.

Percolation

In the percolation method, either sucrose may be percolated to prepare the syrup or the source of the medicinal component may be percolated to form an extractive to which sucrose or syrup may be added. This latter method really is two separate procedures: first the preparation of the extractive of the drug and then the preparation of the syrup.

An example of a syrup prepared by percolation is ipecac syrup, which is prepared by adding glycerin and syrup to an extractive of powdered ipecac obtained by percolation. The drug ipecac, which consists of the dried rhizome and roots of *Cephaelis ipecacuanha*, contains the medicinally active alkaloids emetine, cephaline, and psychotrine. These alkaloids are extracted from the powdered ipecac by percolation with a hydroalcoholic solvent.

The syrup is categorized as an emetic with a usual dose of 15 mL. This amount of syrup is commonly used in the management of poisoning in children when evacuation of the stomach contents is desirable. About 80% of children given this dose will vomit within half an hour. For a household emetic in the event of poisoning, 1-oz bottles of the syrup are sold without a prescription. Ipecac syrup also has some application as a nauseant expectorant in doses smaller than the emetic dose.

Evidence indicates that many bulimics—most commonly young women in their late teens to early 30s—use the syrup of ipecac to bring on attacks of vomiting in an attempt to lose weight (8). Pharmacists must be aware of this misuse of the syrup of ipecac and warn these individuals because one of the active ingredients in the syrup is emetine. With continual use of the syrup, emetine builds up toxic levels within the body tissues and can do irreversible damage to the heart muscles in 3 to 4 months, resulting in symptoms mimicking a heart attack. Shortness of breath is the most common symptom in patients who misuse the syrup of ipecac, but some persons describe

low blood pressure–related symptoms and irregularities of heartbeat.

ELIXIRS

Elixirs are clear, sweetened hydroalcoholic solutions intended for oral use and are usually flavored to enhance their palatability. Nonmedicated elixirs are employed as vehicles, and medicated elixirs are used for the therapeutic effect of the medicinal substances they contain. Compared with syrups, elixirs are usually less sweet and less viscous because they contain a lower proportion of sugar and consequently are less effective than syrups in masking the taste of medicinal substances. However, because of their hydroalcoholic character, elixirs are better able than aqueous syrups to maintain both water-soluble and alcohol-soluble components in solution. Also, because of their stable characteristics and the ease with which they are prepared (by simple solution), from a manufacturing standpoint, elixirs are preferred to syrups.

The proportion of alcohol in elixirs varies widely because the individual components of the elixirs have different water and alcohol solubility characteristics. Each elixir requires a specific blend of alcohol and water to maintain all of the components in solution. Naturally, for elixirs containing agents with poor water solubility, the proportion of alcohol required is greater than for elixirs prepared from components having good water solubility. In addition to alcohol and water, other solvents, such as glycerin and propylene glycol, are frequently employed in elixirs as adjunctive solvents.

Although many elixirs are sweetened with sucrose or with a sucrose syrup, some use sorbitol, glycerin, and/or artificial sweeteners. Elixirs having a high alcoholic content usually use an artificial sweetener, such as saccharin, which is required only in small amounts, rather than sucrose, which is only slightly soluble in alcohol and requires greater quantities for equivalent sweetness.

All elixirs contain flavorings to increase their palatability, and most elixirs have coloring agents to enhance their appearance.

Elixirs containing more than 10% to 12% of alcohol are usually self-preserving and do not require the addition of an antimicrobial agent.

Although the USP monographs for medicated elixirs provide standards, they do not generally provide official formulas. Formulations are left up to the individual manufacturers. Example formulations for some medicated elixirs are as follows (7):

Phenobarbital Elixir

Phenobarbital	4.0 g
Orange oil	0.25 mL
Propylene glycol	100.0 mL
Alcohol	200.0 mL
Sorbitol solution	600.0 mL
Color	q.s.
Purified water, to make	1,000.0 mL

Theophylline Elixir

Theophylline	5.3 g
Citric acid	10.0 g
Liquid glucose	44.0 g
Syrup	132.0 mL
Glycerin	50.0 mL
Sorbitol solution	324.0 mL
Alcohol	200.0 mL
Saccharin sodium	5.0 g
Lemon oil	0.5 g
FD&C Yellow No. 5	0.1 g
Purified water, to make	1,000.0 mL

Medicated elixirs are formulated so that a patient receives the usual adult dose of the drug in a convenient measure of elixir. For most elixirs, one or two teaspoonfuls (5 or 10 mL) provides the usual adult dose of the drug. One advantage of elixirs over their counterpart drugs in solid dosage forms is the flexibility and ease of dosage administration to patients who have difficulty swallowing solid forms.

A disadvantage of elixirs for children and for adults who choose to avoid alcohol is their alcoholic content. The reader may wish to refer to the discussion of alcohol as a solvent earlier in this chapter for FDA-recommended limits on alcohol content for OTC oral products.

Because of their usual content of volatile oils and alcohol, elixirs should be stored in tight, light-resistant containers and protected from excessive heat.

Preparation of Elixirs

Elixirs are usually prepared by simple solution with agitation and/or by admixture of two or more liquid ingredients. Alcohol-soluble and water-soluble components are generally dissolved separately in alcohol and in purified water, respectively. Then the aqueous solution is added to the alcoholic solution, rather than the reverse, to maintain the highest possible alcoholic strength at all times so that minimal separation of the alcohol-soluble components occurs. When the two solutions are completely mixed, the mixture is made to the volume with the specified solvent or vehicle. Frequently, the final mixture will be cloudy, principally because of separation of some of the flavoring oils by the reduced alcoholic concentration. If this occurs, the elixir is usually permitted to stand for a prescribed number of hours to ensure saturation of the hydroalcoholic solvent and to permit the oil globules to coalesce so that they may be more easily removed by filtration. Talc, a frequent filter aid in the preparation of elixirs, absorbs the excessive amounts of oils and therefore assists in their removal from the solution. The presence of glycerin, syrup, sorbitol, and propylene glycol in elixirs generally contributes to the solvent effect of the hydroalcoholic vehicle, assists in the dissolution of the solute, and enhances the stability of the preparation. However, the presence of these materials adds to the viscosity of the elixir and slows the rate of filtration.

Nonmedicated Elixirs

Nonmedicated elixirs may be useful to the pharmacist in the extemporaneous filling of prescriptions involving (a) the addition of a therapeutic agent to a pleasant-tasting vehicle and (b) dilution of an existing medicated elixir. In selecting a liquid vehicle for a drug substance, the pharmacist should be concerned with the solubility and stability

of the drug substance in water and alcohol. If a hydroalcoholic vehicle is selected, the proportion of alcohol should be only slightly above the amount needed to effect and maintain the drug's solution. When a pharmacist is called on to dilute an existing medicated elixir, the nonmedicated elixir he or she selects as the diluent should have approximately the same alcoholic concentration as the elixir being diluted. Also, the flavor and color characteristics of the diluent should not be in conflict with those of the medicated elixir, and all components should be chemically and physically compatible.

In years past, when pharmacists were called on more frequently than today to compound prescriptions, the three most commonly used nonmedicated elixirs were aromatic elixir, compound benzaldehyde elixir, and isoalcoholic elixir.

Medicated Elixirs

As noted previously, medicated elixirs are employed for the therapeutic benefit of the medicinal agent. Most official and commercial elixirs contain a single therapeutic agent. The main advantage of having only a single therapeutic agent is that the dosage of that single drug may be increased or decreased by simply taking more or less of the elixir, whereas when two or more therapeutic agents are present in the same preparation, it is impossible to increase or decrease the dose of one without an automatic and corresponding adjustment in the dose of the other, which may not be desired. Thus, for patients required to take more than a single medication, many physicians prefer them to take separate preparations of each drug so that if an adjustment in the dosage of one is desired, it may be accomplished without the concomitant adjustment of the other. Table 13.8 presents some examples of medicated elixirs. Some of these are briefly discussed next.

Antihistamine Elixirs

As indicated in Table 13.8, antihistamines are useful primarily in the symptomatic relief of certain allergic disorders. They suppress symptoms caused by histamine, one of the

Table 13.8 EXAMPLES OF MEDICATED ELIXIRS BY CATEGORY

ELIXIR	REPRESENTATIVE COMMERCIAL PRODUCTS	USUAL ADULT DOSE/VOLUME OF COMMERCIAL ELIXIR	COMMENTS
Adrenocortical Steroid			
Dexamethasone	Dexamethasone Elixir	500 mg/5 mL	Synthetic analog of hydrocortisone, about 30 times more potent. Commercial elixir is packaged with a calibrated dropper for accurate measurement of small doses; intended primarily for children; also has utility for adults with trouble swallowing tablets. Used for many indications: rheumatoid arthritis, skin diseases, allergies, inflammatory conditions. Commercial product contains 5% alcohol.
Analgesic, Antipyretic			
Acetaminophen	Children's Tylenol Elixir (McNeil)	160 mg/5 mL	Reduction of pain and lowering of fever particularly in patients sensitive to or unable to take aspirin. Elixir is especially useful for pediatric patients and is alcohol-free.
Anticholinergic, Antispasmodic			
Hyoscyamine sulfate	Alaven	0.125 mg/5 mL	Used to control gastric secretion, visceral spasm, hypermotility, abdominal cramps. Commercial product contains 20% alcohol.
Antihistamine			
Diphenhydramine HCl	Diphenhydramine HCl Elixir	12.5 mg/5 mL	Antihistamines are used for a variety of allergic reactions, for example, perennial and seasonal allergic rhinitis, vasomotor rhinitis, allergic skin manifestations of urticaria, reactions to insect bites. Commercial product contains 5.6% alcohol.
Antipsychotic			
Fluphenazine HCl	Fluphenazine HCl Elixir (Pharmaceutical Associates)	2.5 mg/5 mL	Management of psychotic disorders
Cardiotonic			
Digoxin	Various	50 mg/mL	Among other effects, increases the force of myocardial contraction. Used in congestive heart failure, atrial fibrillation, other cardiac conditions. Commercial product contains 10% alcohol.
Sedatives, Hypnotics			
Butabarbital sodium	Butisol Sodium Elixir (Medpointe)	30 mg/5 mL	In low dosage, sedatives; in higher dosage, hypnotics. Butabarbital sodium elixir contains 7% alcohol; phenobarbital elixir contains 14% alcohol.
Phenobarbital	Various	20 mg/5 mL	

chemical agents released during the antigen–antibody reaction of the allergic response. Although only minor differences exist in the properties of most antihistamines, one or another may be preferred by a prescriber because of experience in managing a specific type of allergic reaction. A prescriber's preference may also be based on the incidence of adverse effects that may be expected to occur. The incidence and severity of these effects do vary somewhat with the drug and the dose. The most common untoward effect is sedation, and patients taking antihistamines should be warned against engaging in activities requiring mental alertness, such as driving an automobile or tractor or operating machinery. Other common adverse effects include dryness of the nose, throat, and mouth; dizziness; and disturbed concentration. Among the most sedating antihistamines are diphenhydramine and doxylamine. In fact, diphenhydramine is used as a sleep aid in numerous OTC products for its ability to cause drowsiness.

Most antihistaminic agents are basic amines. By forming salts through interaction with acid, the compounds are rendered water soluble. These salt forms are used in elixirs, so the elixirs of the antihistamines are not required to contain a large proportion of alcohol. Because the acid salts of the antihistamines are used, the pH of these elixirs is on the acid side and must remain so if the drugs are to remain freely soluble in water. A pharmacist should keep this in mind when using one of these elixirs to compound a prescription with other components.

Barbiturate Sedative and Hypnotic Elixirs

The barbiturates are sedative and hypnotic agents that are used to produce various degrees of central nervous system depression. As the dose of these drugs is increased, the effects go from sedation to hypnosis to respiratory depression, the last being the cause of death in fatal barbiturate overdosage.

Barbiturates are administered in small doses in the daytime as sedatives to reduce restlessness and emotional tension. The appropriate dose for this purpose is the

amount that alleviates anxiety or tension but does not produce drowsiness or lethargy. Greater doses of the barbiturates may be given before bedtime as hypnotics to relieve insomnia.

Barbiturates have been classified according to the duration of their hypnotic effects, that is, long-acting, intermediate-acting, short-acting, or ultrashort-acting agents. The long-acting barbiturates, including phenobarbital, are considered most useful in maintaining daytime sedation and in treating some convulsive states and least useful as hypnotics. The intermediate-acting barbiturates include amobarbital; they are used primarily for short-term daytime sedation and are effective in treating insomnia. The barbiturates classified as short-acting include secobarbital; they are used similarly to the intermediate-acting barbiturates. The ultra-short-acting barbiturates, including thiopental, are given intravenously to induce anesthesia.

The most common untoward effects in patients taking barbiturates are drowsiness and lethargy. Large doses may produce residual sedation resembling the hangover following alcohol intoxication. Prolonged use of barbiturates may lead to psychic or physical dependence. This dependence, in susceptible individuals, leads to compulsive abuse of the drug with severe withdrawal symptoms following abstinence. In heavy chronic users, abrupt withdrawal may lead to convulsions, delirium, and occasionally to coma and death. Some pharmaceutical aspects of phenobarbital elixir are presented below.

Phenobarbital Elixir

Phenobarbital elixir is formulated to contain phenobarbital 0.4%, which provides about 20 mg of drug per teaspoonful (5 mL) of elixir. The elixir is commonly flavored with orange oil, colored red with an FDA-approved colorant, and sweetened with syrup. The official elixir contains about 14% alcohol, which is used to dissolve the phenobarbital. However, this amount is almost the very minimum required to keep the phenobarbital in solution. Therefore, glycerin is often added to enhance the solubility of phenobarbital.

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PGR2023-00051

Phenobarbital is a long-acting barbiturate with a duration of action of about 4 to 6 hours, a usual adult dose as a sedative of about 30 mg and a hypnotic dose of about 100 mg. The strength of the elixir permits convenient adjustment of dosage to achieve the proper degree of sedation in the treatment of infants, children, and certain adults. The elixir is commercially available from a variety of manufacturers under its nonproprietary name.

Digoxin Elixir

No official method of preparation is indicated for Digoxin Elixir, USP; however, it is required to contain 4.5 to 5.25 mg of digoxin per 100 mL of elixir, or about 0.25 mg/5 mL teaspoonful. The usual oral adult dose of digoxin as a cardiotonic agent is about 1.5 mg on initial therapy and about 0.5 mg for maintenance therapy.

Digoxin is a cardiotonic glycoside obtained from the leaves of *Digitalis lanata*. It is a white crystalline powder that is insoluble in water but soluble in dilute alcohol solutions. The official elixir contains about 10% alcohol. Digoxin is poisonous, and its dose must be carefully determined and administered to each individual patient. Adults generally take digoxin tablets rather than the elixir, which must be measured by the highly variable household teaspoon. The elixir is generally employed for children, and the commercial product available for this purpose is packaged with a calibrated dropper to facilitate accurate dosing.

Digoxin is one of many drugs available in more than a single dosage form. The prescriber frequently has the choice of a solid dosage form—a tablet or capsule—or a liquid. The advantages of each have been noted previously, but it is important to point out again that drugs administered in different dosage forms may exhibit different bioavailability characteristics, with varying patterns of drug release and rates and extents of absorption. Such differences have been noted for digoxin between tablets from different manufacturers and between tablets and oral liquid forms. Figure 13.2 shows the differences noted in one study of the serum digoxin levels following administration of 0.5 mg of digoxin by

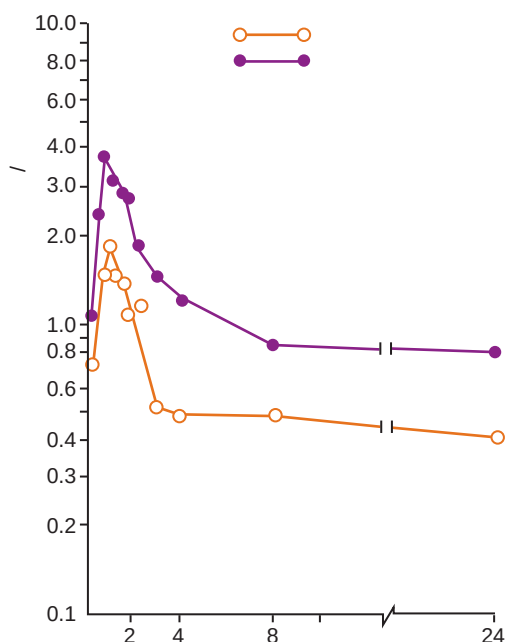


FIGURE 13.2 Serum digoxin concentrations following administration of digoxin 0.5 mg by oral tablet and elixir-like oral solution. (Adapted from Huffman DH, Azarnoff DL. Absorption of orally given digoxin preparations. JAMA 1972;222:957, with permission. Copyright © 2010 American Medical Association. All rights reserved.)

oral tablet and oral solution having an elixir-like vehicle. It can be readily observed that the serum digoxin levels following administration of the oral solution were considerably greater than from the oral tablet.

A patient taking a drug known to exhibit bioavailability problems and whose therapeutic dosage regimen has been successfully established with a particular drug product should not be changed to another product.

TINCTURES

Tinctures are alcoholic or hydroalcoholic solutions prepared from vegetable materials or from chemical substances. They vary in method of preparation, strength of the active ingredient, alcoholic content, and intended use in medicine or pharmacy. When they are prepared from chemical substances (e.g., iodine, thimerosal), tinctures are prepared by simple solution of the chemical agent in the solvent.

Depending on the preparation, tinctures contain alcohol in amounts ranging from approximately 15% to 80%. The alcohol content protects against microbial growth and keeps the alcohol-soluble extractives in solution. In addition to alcohol, other solvents, such as glycerin, may be employed. The solvent mix of each tincture is important in maintaining the integrity of the product. Tinctures cannot be mixed successfully with liquids too diverse in solvent character because the solute may precipitate. For example, compound benzoin tincture, prepared with alcohol as the sole menstruum, contains alcohol-soluble principles that are immediately precipitated from solution upon addition of water.

Because of the alcoholic content, tinctures must be tightly stoppered and not exposed to excessive temperatures. Also, because many of the constituents found in tinctures undergo a photochemical change upon exposure to light, many tinctures must be stored in light-resistant containers and protected from sunlight.

Medicated tinctures taken orally include Paregoric, USP, or camphorated tincture of opium. Usually, patients requiring oral medication nowadays prefer to take a tablet or capsule or a pleasant-tasting elixir or syrup. Tinctures have a rather high alcoholic content, and some physicians and patients alike prefer other forms of medication. Opium Tincture, USP, or laudanum, is much more potent than paregoric, and the two should not be confused. Opium Tincture contains 10% opium (which equates to 1% morphine) and camphorated tincture of opium contains 0.4% opium (which equates to 0.04% morphine). Any prescription for either one should be carefully evaluated and the dose checked and confirmed.

PROPER ADMINISTRATION AND USE OF LIQUID PERORAL DOSAGE FORMS

Most of the dosage forms discussed in this chapter are to be administered by mouth. Conveniently, these can be measured in a teaspoon or tablespoon, depending on the desired dosage. Preferably, however, these medicines should be measured out in calibrated devices

for administration. These devices ensure that the correct dose will be received, and household flatware can vary dramatically in the volume delivered. Even though these are liquids, it is recommended that the patient follow the administration of the liquid dosage form with a glassful of water.

The pharmacist must be careful in the selection of liquid products, given the patient's history and other concurrent medicines. For example, some syrups contain sucrose or another sugar, and the pharmacist must recall that such syrups would not be suitable for use in an oral prescription intended for a diabetic patient. Similarly, a product that is formulated as an elixir or syrup containing alcohol would not be suitable for a patient who receives concurrent medicines that possess an Antabuse-like activity; the patient may get violently ill from the concurrent ingestion of alcohol. Metronidazole and chlorpropamide have been implicated to cause this reaction when mixed with alcohol. Furthermore, if the patient is receiving another drug that causes drowsiness, the pharmacist must consult the prescribing physician to determine whether the prescribed elixir could be harmful to the patient.

TOPICAL SOLUTIONS AND TINCTURES

Generally, the topical solutions employ an aqueous vehicle, whereas the topical tinctures characteristically employ an alcoholic vehicle. As required, cosolvents or adjuncts to enhance stability or the solubility of the solute are employed.

Most topical solutions and tinctures are prepared by simple dissolving. However, certain solutions are prepared by chemical reaction; these, in particular, are discussed later in this section. Of the tinctures for topical use, one, compound benzoin tincture, is prepared by maceration of the natural components in the solvent; the others are prepared by simple solution.

Because of the nature of the active constituents or the solvents, many topical solutions and tinctures are self-preserved. Those that are not may contain suitable preservatives. Topical solutions and tinctures should be

packaged in containers that make them convenient to use. Those that are used in small volume, such as the anti-infectives, are usually packaged in glass or plastic bottles with an applicator tip as a part of the cap assembly or in plastic squeeze bottles that deliver the medication in drops. Many of the anti-infective solutions and tinctures contain a dye to delineate the area of application to the skin. In contrast to aqueous solutions, when the alcoholic tinctures are applied to abraded or broken skin, they sting.

Sprays

Sprays may be defined as aqueous or oleaginous solutions in the form of coarse droplets or as finely divided solids to be applied topically, most usually to the nasopharyngeal tract or to the skin. Many commercial sprays are used intranasally to relieve nasal congestion and inflammation and to combat infection and contain antihistamines, sympathomimetic agents, and antibiotic substances. Because of the noninvasive nature and quickness with which nasal sprays can deliver medication systemically, in the future, several drugs that typically have been administered by other routes may be taken nasally. Most notably, insulin and glucagon may be administered in this fashion. It has been demonstrated that the administration of glucagon via a nasal spray can relieve hypoglycemic symptoms within 7 minutes, a definite advantage over conventional emergency intravenous glucose or intramuscular glucagon.

Other sprays that are employed against sunburn and heat burn contain local anesthetics, antiseptics, skin protectants, and antipruritics. Throat sprays containing antiseptics, deodorants, and flavorants may be effectively employed to relieve conditions such as halitosis, sore throat, and laryngitis. Other sprays treat athlete's foot and other fungal infections. Numerous other medicinal and cosmetic uses of sprays are commonly available in pharmacies.

To break up a solution into small particles so that it may be effectively sprayed or to facilitate the spraying of a powder, several mechanical devices are commonly

employed. The plastic spray bottle, gently squeezed to issue a spray of its contents, is familiar to most. It is commonly used for nasal decongestant sprays as well as cosmetically, especially for body deodorant products. Recently, one-way pump sprays have been developed to deliver medication into the nose. These sprays are used for both prescription, such as Nasalide (Syntex), and nonprescription, such as Nostrilla (Boehringer Ingelheim), medicines. The advantage of these over conventional sprays is that the design prevents drawback contamination of nasal fluids into the bottle after administration, a definite advantage for someone trying to cope with viruses associated with the common cold. Pharmacists are familiar with medicinal atomizers, which emit medication in the form of fine droplets (Fig. 13.3). One type of atomizer has a rubber bulb at the end of the apparatus, which when squeezed causes a flow of air, some of which enters the glass reservoir and some of which exits from the opposite end of the system. The air forced into the reservoir causes the liquid to rise in a small dip tube, forcing the solution up and into the stream of air exiting the system. The air and the solution are forced through a jet opening, and the liquid is broken up into a spray, the droplets being carried by the airstream. In other similar apparatus, the stream of air caused by the depression of the bulb does not enter the reservoir of solution but passes swiftly over it, creating a pressure change and sucking the liquid into the dip tube and into the airstream, in which it exits the system. Examples of solutions and tinctures intended for application to the skin are presented in Tables 13.9 and 13.10. As shown



FIGURE 13.3 A common type of atomizer for spray administration of liquid medication. This model has an adjustable tip for directing the spray upward or downward to reach the otherwise inaccessible areas of the throat. (Courtesy of DeVilbiss Co.)

Table 13.9 EXAMPLES OF SOLUTIONS APPLIED TO THE SKIN

SOLUTION	CORRESPONDING COMMERCIAL SOLUTION	ACTIVE CONSTITUENT IN COMMERCIAL PRODUCT	VEHICLE	CATEGORY AND COMMENTS
Aluminum acetate	—	5%	Aqueous	Astringent
Aluminum subacetate	—	~2.45% aluminum oxide, 5.8% acetic acid	Aqueous	Astringent
Calcium hydroxide (limewater)	—	0.14%	Aqueous	Astringent
Chlorhexidine gluconate	Hibiclens Skin Cleanser (Molnlycke)	4%		Skin wound and general skin cleanser, surgical scrub, preoperative skin preparation. Effective for gram-positive and gram-negative bacteria such as <i>Pseudomonas aeruginosa</i>
Clindamycin phosphate	Cleocin T Topical Solution (Pfizer)	1%	Isopropyl alcohol, water	Treatment of acne vulgaris
Clotrimazole	Lotrimin Solution (Schering-Plough)	1%	PEG 400	Antifungal
Coal tar (liquor carbonis detergens; LCD)	—	20%	Alcohol	Antieczematic; antipsoriatic
Erythromycin	Erymax Topical Solution (Allergan)	2%	Polyethylene glycol/acetone/alcohol	Treatment of acne vulgaris
Fluocinolone acetonide	Synalar Topical Solution (E. Fougera)	0.01%	Propylene glycol	Adrenocortical steroid (topical anti-inflammatory)
Fluorouracil	Efudex Topical Solution (Valeant Pharmaceuticals)	2, 5%	Propylene glycol	Antineoplastic (actinic keratoses)
Hydrogen peroxide	—	3%	Aqueous	Topical anti-infective
Hydroquinone	Melanex Topical Solution (Neutrogena Dermatologics)	3%	Water, alcohol, propylene glycol	Temporary bleaching of hyperpigmented skin, for example, chloasma, melasma
Ketoconazole	Nizoral A-D (McNeil)	1%	Water	Treatment of dandruff
Minoxidil	Rogaine Topical Solution (Pfizer Consumer Health)	2, 5%	Alcohol, water, propylene glycol	Long-term topical treatment of male pattern baldness by stimulating hair regrowth
Povidone iodine	Betadine Solution (Purdue)	7.5, 10%	Aqueous	Topical anti-infective
Tolnaftate	Tinactin Solution (Schering-Plough)	1%	Polyethylene glycol	Topical antifungal
Undecylenic acid	Gordochom Solution (Gordon Laboratories)	25%	Oil base	Topical antifungal

Table 13.10 EXAMPLES OF TINCTURES APPLIED TO THE SKIN

TINCTURE	PERCENT ACTIVE CONSTITUENT IN COMMERCIAL TINCTURE	VEHICLE	CATEGORY AND COMMENTS
Green soap tincture	65%	Alcohol	Detergent. Also contains 2% lavender oil as perfume
Iodine tincture	2%	Alcohol, water	Topical anti-infective
Compound benzoin tincture	10% benzoin; 2% aloe; 8% storax; 4% Tolu balsam	Alcohol	Topical protectant. Prepared by maceration in alcohol
Podophyllin	Podocon-25	Benzoin tincture	Removal of soft genital warts

in these tables, most of these preparations are used as anti-infective agents. All medications intended for external use should be clearly labeled FOR EXTERNAL USE ONLY and kept out of the reach of children. In addition to their listing in Table 13.9, the following topical solutions are discussed because of their particular pharmaceutical interest.

Aluminum Acetate Topical Solution

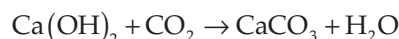
Aluminum acetate is colorless and has a faint acetous odor and a sweetish, astringent taste. It is widely applied topically as an astringent wash or wet dressing after dilution with 10 to 40 parts of water. It is frequently used in various types of dermatologic lotions, creams, and pastes. Commercial premeasured tablets and packets of powders are available for preparation of this solution. Synonym: Burow solution.

Aluminum Subacetate Topical Solution

The requirement for the amount of acetic acid differentiates aluminum acetate topical solution from aluminum subacetate topical solution. In the subacetate solution, the ratio of aluminum oxide to acetic acid is 1:2.35, whereas in the acetate solution, the ratio is 1:3.52. Aluminum subacetate topical solution, the stronger of the two, is used in preparation of aluminum acetate topical solution. Aluminum acetate topical solution, diluted first with 20 to 40 parts of water, is used externally as an astringent wash and wet dressing (modified Burow solution).

Calcium Hydroxide Topical Solution

Calcium hydroxide topical solution, commonly called limewater, must contain not less than 140 mg of $\text{Ca}(\text{OH})_2$ in each 100 mL of solution. Calcium hydroxide is less soluble in hot than in cold water, and cool purified water is the solvent. The solution is intended to be saturated with solute, and to ensure saturation, an excess of calcium hydroxide, 300 mg for each 100 mL of solution to be prepared, is agitated with the purified water, vigorously and repeatedly, for 1 hour. After this time, the excess calcium hydroxide is allowed to settle to the bottom of the container. This permits the solution to remain saturated should a portion of the dissolved solute at the solution's surface react with the carbon dioxide of the air to form insoluble calcium carbonate:



The calcium carbonate settles to the bottom of the container and, by appearance, is indistinguishable from the remaining excess of calcium hydroxide. The calcium hydroxide reserve dissolves as calcium is removed from the solution in the form of the carbonate, and, in this way, it continually maintains the saturation of the solution. After the solution stands for an appreciable length of time, the undissolved material at the bottom of the container is composed of varying proportions of calcium hydroxide and calcium carbonate. Because of the uncertainty of the residue's composition, one may not prepare additional quantities

of calcium hydroxide solution by adding more purified water.

The solution should be stored in well-filled, tightly stoppered containers to deter the absorption of carbon dioxide and should be kept in a cool place to maintain an adequate concentration of dissolved solute. Only the clear supernatant liquid is dispensed. This is best accomplished by the use of a siphon with care not to entrain the residue.

The solution is categorized as an astringent. For this purpose, it is generally employed in combination with other ingredients in dermatologic solutions and lotions to be applied topically. Synonyms: limewater, liquor calcis.

Coal Tar Topical Solution

Coal tar topical solution is an alcoholic solution containing 20% coal tar and 5% polysorbate 80. It is prepared by mixing the coal tar with two and a half times its weight of washed sand, adding the polysorbate 80 and most of the alcohol, and then macerating the mixture for 7 days in a closed vessel with frequent agitation followed by filtration and adjustment to the proper volume with alcohol. The final content is 81% to 86% ethyl alcohol.

Coal tar is a nearly black viscous liquid having a characteristic naphthalene-like odor and a sharp, burning taste. It is the tar obtained as a by-product during the destructive distillation of bituminous coal. It is slightly soluble in water and partially soluble in most organic solvents, including alcohol. In the preparation of the official solution, the coal tar is mixed with the sand to distribute it mechanically and create a large surface area of tar exposed to the solvent action of the alcohol. During the maceration, or soaking, the alcohol-soluble components of the tar dissolve, leaving the undissolved portion clinging to the sand. Filtration removes the sand and the insoluble tar components from the solution. The container in which the solution was prepared should be rinsed with alcohol, and the washings should be passed through the filter paper in the adjustment of the final volume of the solution.

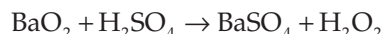
In the extemporaneous compounding of prescriptions and in the therapeutic application of this preparation to the skin, the solution is frequently mixed with aqueous preparations or simply diluted with water. Because coal tar is only slightly soluble in water, it would separate from the solution were it not for the polysorbate 80 in the preparation. This agent, commercially available as Tween 80 (ICI Americas) and as other brand name products, is an oily liquid that is a nonionic surfactant. It is quite effective in dispersing the water-insoluble components of coal tar upon admixture with an aqueous preparation.

Coal tar is a local antieczematic used in external treatment of a wide variety of chronic skin conditions after dilution with about nine volumes of water or in combination with other agents in various lotions, ointments, or solutions. Synonyms: liquor carbonis detergens; liquor picis carbonis; LCD.

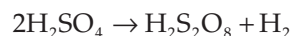
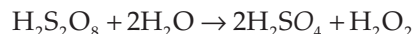
Hydrogen Peroxide Topical Solution

Hydrogen peroxide topical solution contains 2.5% to 3.5% (w/v) hydrogen peroxide, or H_2O_2 . Suitable preservatives, totaling not more than 0.05%, may be added.

One method of preparation uses the action of either phosphoric or sulfuric acid on barium peroxide:



Another method uses electrolytic oxidation of a cold solution of concentrated sulfuric acid to form persulfuric acid, which when hydrolyzed liberates hydrogen peroxide:



A solution prepared by this method usually contains about 30% hydrogen peroxide and is capable of liberating 100 times its volume of oxygen. A solution of this strength is commonly referred to as 100-volume peroxide. The dilute solution, which contains about 3% hydrogen peroxide and liberates 10 times its volume of oxygen, may be prepared from the concentrated solution.

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The solution is a clear, colorless liquid that may be odorless or have the odor of ozone. It usually deteriorates upon long standing, forming oxygen and water. Preservative agents, such as acetanilide, have been found to retard decomposition. Decomposition is enhanced by light and by heat, and for this reason, the solution should be preserved in tight, light-resistant containers, preferably at a temperature not exceeding 35°C (95°F). The solution is also decomposed by practically all organic matter and other reducing agents and reacts with oxidizing agents to liberate oxygen and water; metals, alkalis, and other agents can catalyze its decomposition.

Hydrogen peroxide solution is categorized as a local anti-infective for use topically on the skin and mucous membranes. Its germicidal activity is based on the release of nascent oxygen on contact with the tissues. However, because of the short duration of this release, the chief value of the preparation in the reduction of infection is probably its ability to cleanse wounds by mechanical action through the bubbling and frothing caused by the release of oxygen. It is also used to disinfect aseptic working environments. Synonym: peroxide.

Chlorhexidine Gluconate Solution

Since 1957, chlorhexidine gluconate has been employed extensively as a broad-spectrum antiseptic in clinical and veterinarian medicine. Its spectrum encompasses gram-positive and gram-negative bacteria, including *Pseudomonas aeruginosa*. In a concentration of 4% (Hibiclens, Molnlycke Health Care Inc.), it is used as a surgical scrub, hand wash, and skin wound and general skin cleanser. Procedures are established for all of these purposes to maximize the effectiveness of the chlorhexidine. Experience has demonstrated that irritation, dermatitis, and photosensitivity associated with topical use of chlorhexidine are rare.

In 1987, the FDA and the Council of Dental Therapeutics of the American Dental Association approved chlorhexidine gluconate 0.12% (Peridex, Procter & Gamble) as

the first prescription-only antiplaque, anti-gingivitis drug with antimicrobial activity. Microbiologic sampling of plaque has shown a reduction of aerobic and anaerobic bacteria ranging from 54% to 97% through 6 months of use when it is used as a mouth rinse. The oral rinse should be used twice daily for 30 seconds, morning and night, after tooth brushing. Usually a 15-mL dose of undiluted solution is used and expectorated after rinsing. The most common side effect of chlorhexidine is the formation of an extrinsic yellow-brown stain on the teeth and tongue after only a few days of use. The amount of stain depends on the concentration of chlorhexidine and individual susceptibility. Increased consumption of tannin-containing substances, such as tea, red wine, and port wine, will increase the level of discoloration. The developed stain can be periodically removed with dental prophylaxis.

Povidone Iodine Topical Solution

The agent povidone iodine is a chemical complex of iodine with polyvinylpyrrolidone, the latter agent being a polymer having an average molecular weight of about 40,000. The povidone iodine complex contains approximately 10% available iodine and slowly releases it when applied to the skin.

The preparation is employed topically as a surgical scrub and nonirritating antiseptic solution, with its effectiveness directly attributable to the presence and release of iodine from the complex. Commercial product: Betadine Solution (Purdue).

Thimerosal Topical Solution

Thimerosal is a water-soluble organic mercurial antibacterial agent used topically for its bacteriostatic and mild fungistatic properties. It is used mainly to disinfect skin prior to surgery and as a first aid application to wounds and abrasions. It has been applied to the eye, nose, throat, and urethra in dilutions of 1:5,000. It is also used as a preservative for various pharmaceutical preparations, including many vaccines and other biologic products.

Thimerosal topical solution contains 0.1% thimerosal. Also present are ethylenediamine solution and sodium borate to maintain the alkalinity (usually pH 9.8 to 10.3) required for the solution's stability. Monoethanolamine is used as an additional stabilizer. The solution is affected by light and must be maintained in light-resistant containers. Commercial product: Merthiolate Solution (Lilly).

Medicated Soaps and Shampoo Solutions

Medicated soaps and shampoos are liquid or solid preparations intended for topical application to the skin or scalp followed by subsequent rinsing with water. They are solution, emulsion, or surface-active products that readily form emulsions or foams upon the addition of water followed by rubbing. Incorporation of active pharmaceutical ingredients (APIs) in the soaps and shampoos combines the cleansing/degreasing abilities of the vehicle and facilitates the topical application of the API to affected areas of the body. The surface-active properties of the vehicle facilitate contact of the API with the skin or scalp. Medicated soap and shampoo formulations frequently contain antimicrobial agents to protect against bacteria, yeast, and mold contamination.

VAGINAL AND RECTAL SOLUTIONS

Vaginal Douches

Solutions may be prepared from powders as indicated earlier or from liquid solutions or liquid concentrates. In using liquid concentrates, the patient is instructed to add the prescribed amount of concentrate (usually a teaspoonful or capful) to a certain amount of warm water (frequently a quart). The resultant solution contains the appropriate amount of chemical agents in proper strength. The agents are similar to the ones described for douche powders. Examples are shown in Figure 13.4.

Powders are used to prepare solutions for vaginal douche, that is, for irrigation cleansing of the vagina. The powders themselves may be prepared and packaged in bulk or as unit packages. A unit package is designed to



FIGURE 13.4 Products for vaginal use, including solution concentrates, powder, and aerosol foam with insert device.

contain the appropriate amount of powder to prepare the specified volume of douche solution. The bulk powders are used by the teaspoonful or tablespoonful in preparation of the desired solution. The user simply adds the prescribed amount of powder to the appropriate volume of warm water and stirs until dissolved. Among the components of douche powders are the following:

1. Boric acid or sodium borate
2. Astringents, for example, potassium, alum, ammonium alum, and zinc sulfate
3. Antimicrobials, for example, oxyquinoline sulfate and povidone iodine
4. Quaternary ammonium compounds, for example, benzethonium chloride
5. Detergents, for example, sodium lauryl sulfate
6. Oxidizing agents, for example, sodium perborate
7. Salts, for example, sodium citrate and sodium chloride
8. Aromatics, for example, menthol, thymol, eucalyptol, methyl salicylate, and phenol

Douche powders are used for their hygienic effects. A few douche powders containing specific therapeutic anti-infective agents such as those mentioned in the discussion of vaginal suppositories are used against monilial and trichomonal infections.

Retention Enemas

A number of solutions are administered rectally for local effects (e.g., hydrocortisone) or for systemic absorption (e.g., aminophylline). In the case of aminophylline, rectal administration minimizes the undesirable gastrointestinal reactions associated with oral therapy. Clinically effective blood levels of the agents are usually obtained within 30 minutes following rectal instillation. Corticosteroids are administered as retention enemas or continuous drip as adjunctive treatment of some patients with ulcerative colitis.

Evacuation Enemas

Rectal enemas are used to cleanse the bowel. Commercially, many enemas are available in disposable plastic squeeze bottles containing a premeasured amount of enema solution. The agents are solutions of sodium phosphate and sodium biphosphate, glycerin and docusate potassium, and light mineral oil.

Instruction from a pharmacist is advantageous to ensure that the patient correctly uses these products. The patient should be advised to gently insert the tip of the product with steady pressure and be told that it is not absolutely necessary to squeeze all of the contents out of the disposable plastic bottle. The patient should be told that the product will most probably work within 5 to 10 minutes.

TOPICAL TINCTURES

Examples of tinctures for topical application to the skin are presented in Table 13.10. Those of particular pharmaceutical interest are discussed briefly as follows.

Iodine Tincture

Iodine tincture is prepared by dissolving 2% iodine crystals and 2.4% sodium iodide in an amount of alcohol equal to half the volume of tincture to be prepared and diluting the solution to volume with sufficient purified water. The sodium iodide reacts with the iodine to form sodium triiodide:



This reaction prevents formation of ethyl iodide from the interaction between iodine and alcohol, which would result in the loss of the antibacterial activity of the tincture. An added benefit of the triiodide form of iodine is its water solubility, which is important should the tincture, which contains between 44% and 50% alcohol, be diluted with water during use.

The tincture is a popular local anti-infective agent applied to the skin in general household first aid. The reddish-brown color, which produces a stain on the skin, is useful in delineating the application over the affected skin area. The tincture should be stored in a tight container to prevent loss of alcohol.

Compound Benzoin Tincture

Compound benzoin tincture is prepared by maceration in alcohol of 10% benzoin and lesser amounts of aloe, storax, and Tolu balsam totaling about 24% of starting material. The drug mixture is best macerated in a wide-mouthed container because it is difficult to introduce storax, a sticky semiliquid material, into a narrow-mouthed container. Generally, it is advisable to weigh the storax in the container in which it will be macerated to avoid possible loss through a transfer of the material from one container to another.

The tincture is categorized as a protectant. It is used to protect and toughen skin in the treatment of bedsores, ulcers, cracked nipples, and fissures of the lips and anus. It is also commonly used as an inhalant in bronchitis and other respiratory conditions, 1 teaspoonful commonly being added to a pint of boiling water. The volatile components of the tincture travel with the steam vapor and are inhaled by the patient. Because of the incompatibility of the alcoholic tincture and water, the mixture produces a milky product with some separation of resinous material. Alcohol or acetone may be used as necessary to remove the residue from the vaporizer after use.

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Compound tincture of benzoin serves as a delivery vehicle of podophyllum in the treatment of venereal warts. It is important that podophyllum not be systemically absorbed because it can cause peripheral neuropathy characterized by paresthesias, loss of sensation, and loss of deep tendon reflexes in the extremities, in addition to neuropathy of the central nervous system including lethargy, confusion, and coma. Second, the podophyllum is teratogenic and should be administered to a pregnant woman only when the risk-benefit ratio is extremely low. Thus, the nonocclusive compound tincture of benzoin is preferred to the occlusive flexible collodion.

Compound benzoin tincture is best stored in tight, light-resistant containers. Exposure to direct sunlight or to excessive heat should be avoided.

The tincture originated in the fifteenth or sixteenth century and, through the years, probably has acquired more synonyms than any other official preparation. A few of these are friar's balsam, Turlington drops, Persian balsam, Swedish balsam, Jerusalem balsam, Wade drops, and Turlington balsam of life.

Thimerosal Tincture

The same general remarks about thimerosal topical solution apply to thimerosal tincture except that sodium chloride and sodium borate are absent from the tincture and the vehicle of the tincture is water, acetone, and about 50% alcohol. A number of metals, notably copper, cause decomposition of the tincture, and for this reason, it must be manufactured and stored in glass or suitably resistant containers. Monoethanolamine and ethylenediamine are used as stabilizers in the official solution and tincture and are thought to be effective because of their chelating action on traces of metallic impurities that may be present at the time of preparation or may later gain access to the preparation.

The commercial preparation is colored orange red and has greenish fluorescence. The red stain it leaves on the skin defines the

area of application. It is a commonly used household antiseptic for application to abrasions and cuts and also in the preparation of patients for surgery.

TOPICAL ORAL (DENTAL) SOLUTIONS

A variety of medicinal substances are employed topically in the mouth for a number of purposes and in a wide range of dosage forms. Among the drugs and preparations included in this group are the following:

- Benzocaine: Topical anesthetic. Indicated for temporary relief of pain, soreness, and irritation in the mouth associated with teething, orthodontic appliances, new or poorly fitting dentures, and cancer sores
- Camphorated parachlorophenol: Dental anti-infective. A eutectic liquid composed of 65% camphor and 35% parachlorophenol, used in dentistry for sterilization of deep root canals
- Carbamide peroxide topical solution: Dental anti-infective. Acts as a chemomechanical cleansing and debriding agent through the release of bubbling oxygen. The commercial product (Gly-Oxide Liquid, GlaxoSmithKline) contains 10% carbamide in flavored anhydrous glycerin.
- Cetylpyridinium chloride solution and cetylpyridinium chloride lozenges: Local anti-infective. Commercial counterparts (Cepacol Mouthwash/Gargle and Cepacol Lozenges; Combe) contain 1:2,000 w/v and 1:1,500 w/v of cetylpyridinium chloride, respectively. Used primarily as a freshening mouth cleanser. Lozenges have benzyl alcohol as a local anesthetic in soothing throat irritations.
- Erythrosine sodium topical solution and erythrosine sodium soluble tablets: Diagnostic aid (dental disclosing agent). Solution applied to the teeth to reveal plaque left by inadequate brushing. Tablets chewed for the same purpose and are not to be swallowed
- Eugenol: Dental analgesic. Applied topically to dental cavities and dental

protectives. Eugenol is a pale yellow liquid having an aromatic odor of clove and a spicy taste.

- Lidocaine oral spray: Topical dental anesthetic. Applied through metered spray at 10 mg per spray; 20 mg per quadrant of gingiva and oral mucosa is usually employed (Xylocaine Oral Spray, AstraZeneca).
- Nystatin oral suspension: Antifungal. May be employed for oral fungal infections by retaining in the mouth as long as possible before swallowing
- Saliva substitutes: Electrolytes in a carboxymethylcellulose base. They are indicated for relief of dry mouth and throat in xerostomia.
- Sodium fluoride oral solution and sodium fluoride tablets: Dental caries prophylactic. Solution applied to the teeth; or when drinking water does not contain adequate fluoride, a dilute solution may be swallowed. Tablets containing sodium fluoride 1.1 or 2.2 mg are chewed or swallowed as required.
- Sodium fluoride and phosphoric acid gel and sodium fluoride and phosphoric acid topical solution: Dental caries prophylactic. Gel and solution applied to the teeth; each contains 1.23% of fluoride ion and 1% of phosphoric acid. Triamcinolone acetonide dental paste—topical anti-inflammatory agent. Applied to the oral mucous membranes as a 0.1% paste
- Zinc oxide–eugenol mixture: Temporary filling mix

In addition to these drugs and preparations, a host of other products for oral use are commercially available. Some of these products, such as teething lotions and toothache drops, are medicated, whereas others are used for hygienic purposes, such as dentifrices, denture products, and many of the mouthwashes. Among the variety of products is a like variety of physical forms—solutions, emulsions, ointments, pastes, aerosols, and so on, with the manufacture of each following the general procedures outlined in this text. One type of dosage form for oral use, the lozenge, has not been previously described.

MISCELLANEOUS SOLUTIONS

Aromatic Waters

Aromatic waters are clear, aqueous solutions saturated with volatile oils or other aromatic or volatile substances. Aromatic waters are no longer in widespread use. In years past, aromatic waters were prepared from a number of volatile substances, including orange flower oil, peppermint oil, rose oil, anise oil, spearmint oil, wintergreen oil, camphor, and chloroform. Naturally, the odors and tastes of aromatic waters are of the volatile substances from which they are prepared.

Most of the aromatic substances in the preparation of aromatic waters have very low solubility in water, and even though the water may be saturated, its concentration of aromatic material is still rather small. Aromatic waters may be used for perfuming and/or flavoring.

Diluted Acids

Diluted acids are aqueous solutions prepared by diluting the corresponding concentrated acids with purified water. The strength of a diluted acid is generally expressed on a percent weight-to-volume (% w/v) basis, that is, the weight in grams of solute per 100 mL of solution, whereas the strength of a concentrated acid is generally expressed in terms of percent weight to weight (% w/w), which indicates the number of grams of solute per 100 g of solution. To prepare a diluted acid from a concentrated one, it is necessary first to calculate the amount of solute required in the diluted product. Then the amount of concentrated acid required to supply the needed amount of solute can be determined.

To illustrate, concentrated hydrochloric acid contains not <35 g and not more than 38 g of solute (absolute HCl) per 100 g of acid and therefore is considered to be, on the average, 36.5% w/w in strength. Diluted hydrochloric acid contains 9.5 to 10.5 g of solute per 100 mL of solution and is therefore considered to be approximately 10% w/v in strength. If one wished to prepare 100 mL of the diluted acid from the concentrated acid, one would require 10 g of solute. The amount

of concentrated HCl required to supply this amount of solute may be calculated by the following proportion:

$$\frac{36.5 \text{ g (solute)}}{100 \text{ g (conc. acid)}} = \frac{10 \text{ g (solute)}}{x \text{ (g conc. acid)}}$$

Solving for x:

$$36.5x = 1,000 \text{ g}$$

$$x = 27.39 \text{ g (conc. acid)}$$

Thus, 27.39 g of concentrated acid is required to supply 10 g of solute needed for the preparation of 100 mL of the diluted acid. Although the required amount of concentrated acid may be accurately weighed, it is a cumbersome task, and as a rule, pharmacists prefer to measure liquids by volume. Therefore, in the preparation of diluted acids, the calculations are generally carried one step further to determine the volume of concentrated acid that corresponds to the calculated weight. Because this additional step requires the use of the concentrated acid's specific gravity, a brief review of specific gravity seems appropriate.

By definition, specific gravity is a ratio, expressed decimally, of the weight of a substance to the weight of an equal volume of a standard, both substances having the same temperature or the temperature of each being known. Water is used as the standard for liquids and solids and hydrogen or air for gases. In pharmacy, specific gravity calculations mainly involve liquids and solids, and water is an excellent choice for a standard because it is readily available and easily purified.

At 4°C, the density of water is 1 g per cubic centimeter. Because the USP states that 1 mL may be considered the equivalent of 1 cc, in pharmacy, water is assumed to weigh 1 g per milliliter. By the following equation used to calculate specific gravity, a substance having a density the same as water would have a specific gravity of 1.0:

$$\text{spgr} = \frac{\text{weight of a substance}}{\text{weight of an equal volume of water}}$$

In solving this equation, the same units of weight must be used in each part of the

ratio. These units cancel out, and the ratio is expressed decimally.

Specific gravity indicates the ratio of the weight of a substance to that of an equal volume of water. For example, 10 mL of a liquid weighs 20 g. An equal volume of water weighs 10 g, and the ratio in the equation is 20:10, yielding a specific gravity of 2.0. This indicates that the liquid is twice as heavy as water in equal volume. By the same token, a liquid having a specific gravity of 0.5 is half as heavy as water; a liquid with a specific gravity of 0.8 is eight-tenths as heavy as water and so on.

If both the volume of a liquid and its specific gravity are known, its weight may be calculated. For instance, if concentrated hydrochloric acid has a specific gravity of 1.17, it is that number times as heavy as water, and 100 mL of the acid would weigh 1.17 times as much as 100 mL of water. Because 100 mL of water weighs 100 g, 100 mL of the acid weighs 1.17 times that, or 117 g.

If one knows the weight of a liquid and its specific gravity, the volume of the liquid may be determined. For example, a liquid that is twice as heavy as water has a specific gravity of 2.0 and occupies half the volume that an equal weight of water occupies. If one has 100 g of this liquid and substitutes in the equation as indicated next, the volume of the liquid can be arrived at

$$2.0 = \frac{100 \text{ g}}{\text{weight of an equal volume of water}}$$

$$\begin{aligned} \text{weight of an equal volume of water} &= \frac{100 \text{ g}}{2.0} \\ &= 50 \text{ g} \end{aligned}$$

Because 50 g is the weight of an equal volume of water, it follows that the water must measure 50 mL. Since the volume of the water is an equal volume to the other liquid, that liquid must also measure 50 mL.

The volume represented by 27.39 g of the concentrated hydrochloric acid may be similarly determined by dividing the weight of the concentrated acid by its specific gravity and equating the weight of an equal volume of water to the volume of the acid:

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$$\frac{27.39 \text{ g}}{1.17} = 23.41 \text{ mg, weight of equal of water}$$

Thus, because 23.41 g of water measures 23.41 mL and it is equal in volume to the concentrated acid, the latter also measures 23.41 mL, and this is the amount required to prepare 100 mL of the 10% w/v diluted acid.

Once the aforementioned is thoroughly understood, the following simplified formula can be used to calculate the amount of a concentrated acid required in the preparation of a specific volume of the corresponding diluted acid:

$$\frac{\text{Percentage strength (w/v) of diluted acid} \times \text{Volume of diluted acid to be prepared}}{\text{Percentage strength of concentrated acid (w/w)} \times \text{Specific gravity of concentrated acid}} = \text{volume of concentrated acid to use}$$

Recalculating the preparation of 100 mL of diluted hydrochloric acid from the concentrated acid gives the following:

$$\frac{10 \times 100 \text{ mL}}{36.5 \times 1.17} = 23.41 \text{ mL of concentrated acid to use}$$

Most diluted acids have a strength of 10%w/v, with the exception of diluted acetic acid, which is 6%w/v. The strengths of these acids are commensurate with the concentrations generally used for medicinal or pharmaceutical purposes. The concentrations of the corresponding concentrated acids vary widely from one acid to another, depending on various properties of the solute such as solubility, stability, and ease of preparation. For instance, concentrated sulfuric acid is generally between 95% and 98%w/w, nitric acid between 69% and 71%w/w, and concentrated phosphoric acid between 85% and 88%w/w. As a result, the amounts of each concentrated acid required to prepare the corresponding diluted acid vary widely and must be calculated on an individual basis.

There is very little use of diluted acids in medicine today. However, because of its antibacterial effects, acetic acid finds application as a 1% solution in surgical dressings, as an

irrigating solution to the bladder in 0.25% concentration, and as a spermocidal in some proprietary contraceptive preparations.

Spirits

Spirits are alcoholic or hydroalcoholic solutions of volatile substances. Generally, the alcoholic concentration of spirits is rather high, usually over 60%. Because of the greater solubility of aromatic or volatile substances in alcohol than in water, spirits can contain a greater concentration of these materials than the corresponding aromatic waters. When mixed with water or with an aqueous preparation, the volatile substances present in spirits generally separate from the solution and form a milky preparation.

Spirits may be used pharmaceutically as flavoring agents and medicinally for the therapeutic value of the aromatic solute. As flavoring agents, they are used to impart the flavor of their solute to other pharmaceutical preparations. For medicinal purposes, spirits may be taken orally, applied externally, or used by inhalation, depending upon the particular preparation. When taken orally, they are generally mixed with a portion of water to reduce the pungency of the spirit. Depending on the materials, spirits may be prepared by simple solution, solution by maceration, or distillation. The spirits most recently official in the USP–NF are aromatic ammonia spirit, camphor spirit, compound orange spirit, and peppermint spirit.

NONAQUEOUS SOLUTIONS

Liniments

Liniments are alcoholic or oleaginous solutions or emulsions of various medicinal substances intended to be rubbed on the skin. Liniments with an alcoholic or hydroalcoholic vehicle are useful when rubefacient, counterirritant, or penetrating action is desired; oleaginous liniments are employed primarily when massage is desired. By their nature, oleaginous liniments are less irritating to the skin than alcoholic liniments. Liniments are not applied to skin areas that are broken or bruised because excessive irritation might result. The vehicle for a liniment

should therefore be selected for the type of action desired (rubefacient, counterirritant, or massage) and also on the solubility of the desired components in the various solvents. For oleaginous liniments, the solvent may be a fixed oil such as almond oil, peanut oil, sesame oil, or cottonseed oil or a volatile substance such as wintergreen oil or turpentine, or it may be a combination of fixed and volatile oils.

All liniments should bear a label indicating that they are suitable only for external use and must never be taken internally. Liniments that are emulsions or that contain insoluble matter must be shaken thoroughly before use to ensure even distribution of the dispersed phase, and these preparations should be labeled *SHAKE WELL*. Liniments should be stored in tight containers. Depending on their individual ingredients, liniments are prepared in the same manner as solutions, emulsions, or suspensions, as the case may warrant.

Collodions

Collodions are liquid preparations composed of pyroxylin dissolved in a solvent mixture usually composed of alcohol and ether with or without added medicinal substances. Pyroxylin (i.e., nitrocellulose, soluble gun cotton, collodion cotton), obtained by the action of a mixture of nitric and sulfuric acids on cotton, consists chiefly of cellulose tetranitrate. It has the appearance of raw cotton when dry but is harsh to the touch. It is frequently available commercially moistened with about 30% alcohol or other similar solvent.

One part of pyroxylin is slowly but completely soluble in 25 parts of a mixture of 3 volumes of ether and 1 volume of alcohol. It is also soluble in acetone and glacial acetic acid. Pyroxylin is precipitated from solution in these solvents upon the addition of water. Pyroxylin, like collodions, is exceedingly flammable and must be stored away from flame in well-closed containers, protected from light.

Collodions are intended for external use. When applied to the skin with a fine camel's

hair brush or glass applicator, the solvent rapidly evaporates, leaving a filmy residue of pyroxylin. This provides an occlusive protective coating to the skin, and when the collodion is medicated, it leaves a thin layer of that medication firmly placed against the skin. Naturally, collodions must be applied to dry tissues to adhere to the skin's surface. The products must be clearly labeled "for external use only" or with words of similar effect.

Collodion

Collodion is a clear or slightly opalescent viscous liquid prepared by dissolving pyroxylin (4%w/v) in a 3:1 mixture of ether and alcohol. The resulting solution is highly volatile and flammable and should be preserved in a tight container remote from fire at a temperature not exceeding 30°C.

The product is capable of forming a protective film on application to the skin and the volatilization of the solvent. The film is useful in holding the edges of an incised wound together. However, its presence on the skin is uncomfortable because of its inflexible nature. The following product, which is flexible, has a greater appeal when a pliable film is acceptable.

Flexible Collodion

Flexible collodion is prepared by adding 2% camphor and 3% castor oil to collodion. The castor oil renders the product flexible, permitting its comfortable use over skin areas that are normally moved, such as joints, fingers, and toes. The camphor makes the product waterproof. Physicians frequently apply the coating over bandages or stitched incisions to make them waterproof and to protect them from external stress.

Salicylic Acid Collodion

Salicylic acid collodion is a 10% solution of salicylic acid in flexible collodion. It is used for its keratolytic effects, especially in the removal of corns from the toes. Patients who use such products should be advised about their proper use. The product should be applied one drop at a time on the corn or wart, allowing time to dry before the next

drop is added. Because salicylic acid can irritate normal, healthy skin, every attempt must be made to ensure application directly on the corn or wart. A useful preventive measure is to line the adjacent healthy skin with some white petrolatum prior to application of the product. Proper tightening and storage of the product after use are absolutely necessary because of the volatility of the vehicle.

EXTRACTION METHODS FOR PREPARING SOLUTIONS

Certain pharmaceutical preparations are prepared by extraction, that is, by withdrawal of desired constituents from crude drugs through the use of selected solvents in which the desired constituents are soluble. Crude drugs are vegetable or animal drugs that have undergone no other processes than collection, cleaning, and drying. Because each crude drug contains a number of constituents that may be soluble in a given solvent, the products of extraction, termed *extractives*, do not contain just a single constituent but rather varying constituents, depending on the drug used and the conditions of the extraction. Tinctures, fluidextracts, and extracts are the pharmaceutical products most commonly prepared from extractives.

Plant materials are composed of heterogeneous mixtures of constituents, some of which are pharmacologically active and others pharmacologically inactive and considered inert. Among the varied plant constituents are sugars, starches, mucilages, proteins, albumins, pectins, cellulose, gums, inorganic salts, fixed and volatile oils, resins, tannins, coloring materials, and a number of very active constituents such as alkaloids and glycosides. The solvent systems used in extraction are selected on the basis of their capacity to dissolve the maximum amount of desired active constituents and the minimum amount of undesired constituents.

In many instances, the active constituents of a plant drug are of the same general chemical type, have similar solubility characteristics, and can be simultaneously extracted with a single solvent or a single solvent mixture. Extraction concentrates the active

constituents of a crude drug and removes from it the extraneous matter. In drug extraction, the solvent or solvent mixture is referred to as the *menstruum*, and the plant residue, which is exhausted of active constituents, is termed the *marc*.

The selection of the *menstruum* to use in the extraction of a crude drug is based primarily on its ability to dissolve the active constituents. Although water and alcohol and to a lesser extent glycerin are probably the most frequently employed solvents in drug extraction, acetic acid and organic solvents like ether may be used for special purposes.

Because of its ready availability, cheapness, and good solvent action for many plant constituents, water has some use in drug extraction, particularly in combination with other solvents. However, as a sole solvent, it has many disadvantages and is infrequently used alone. For one thing, most active plant constituents are complex organic chemical compounds that are less soluble in water than in alcohol. Although water has a great solvent action on such plant constituents as sugars, gums, starches, coloring principles, and tannins, most of these are not particularly desirable components of an extracted preparation. Water also tends to extract plant principles that separate upon standing in the extractive, leaving an undesired residue. Finally, unless preserved, aqueous preparations serve as excellent growth media for molds, yeasts, and bacteria. When water alone is employed as the *menstruum*, alcohol is frequently added to the extractive or to the final preparation as an antimicrobial preservative.

Hydroalcoholic mixtures are perhaps the most versatile and most widely employed *menstrua*. They combine the solvent effects of both water and alcohol, and the complete miscibility of these two agents permits flexible combining of the two agents to form solvent mixtures most suited to the extraction of the active principles from a particular drug. A hydroalcoholic *menstruum* generally provides inherent protection against microbial contamination and helps to prevent the separation of extracted material on standing. Alcohol is used alone as a *menstruum* only

when necessary because it is more expensive than hydroalcoholic mixtures.

Glycerin, a good solvent for many plant substances, is occasionally employed as a cosolvent with water or alcoholic menstrua because of its ability to extract and then prevent inert materials from precipitating upon standing. It is especially useful in this regard in preventing separation of tannin and tannin oxidation products in extractives. Because glycerin has preservative action, depending on its concentration in the final product, it may contribute to the stability of a pharmaceutical extractive.

Methods of Extraction

The principal methods of drug extraction are maceration and percolation. Generally, the method of extraction selected for a given drug depends on several factors, including the nature of the crude drug, its adaptability to each of the various extraction methods, and the interest in obtaining complete or nearly complete extraction of the drug.

Frequently, a combination of maceration and percolation is actually employed in the extraction of a crude drug. The drug is macerated first to soften the plant tissues and to dissolve much of the active constituents, and percolation separates the extractive from the marc.

Maceration

The term maceration comes from the Latin *macerare*, meaning to soak. It is a process in which the properly comminuted drug is permitted to soak in the menstruum until the cellular structure is softened and penetrated by the menstruum and the soluble constituents are dissolved.

In the maceration process, the drug to be extracted is generally placed in a wide-mouthed container with the prescribed menstruum, the vessel is stoppered tightly, and the contents are agitated repeatedly over a period usually ranging from 2 to 14 days. The agitation permits the repeated flow of fresh solvent over the entire surface area of the comminuted drug. An alternative to repeated shaking is to place the drug in a porous cloth

bag that is tied and suspended in the upper portion of the menstruum, much the same as a tea bag is suspended in water to make a cup of tea. As the soluble constituents dissolve in the menstruum, they tend to settle to the bottom because of an increase in the specific gravity of the liquid due to its added weight. Occasional dipping of the drug bag may facilitate the speed of the extraction. The extractive is separated from the marc by expressing the bag of drug and washing it with additional fresh menstruum, the washings being added to the extractive. If the maceration is performed with the drug loose, the marc may be removed by straining and/or filtration, with the marc being washed free of extractive by the additional passage of menstruum through the strainer or filter into the total extractive.

For drugs containing little or no cellular material, such as benzoin, aloe, and Tolu, which dissolve almost completely in the menstruum, maceration is the most efficient method of extraction.

Maceration is usually conducted at a temperature of 15°C to 20°C for 3 days or until the soluble matter is dissolved.

Percolation

The term *percolation*, from the Latin *per*, meaning through, and *colare*, meaning to strain, may be described generally as a process in which a comminuted drug is extracted of its soluble constituents by the slow passage of a suitable solvent through a column of the drug. The drug is packed in a special extraction apparatus termed a percolator, with the collected extractive called the percolate. Most drug extractions are performed by percolation, a process whereby coffee is routinely prepared.

In the process of percolation, the flow of the menstruum over the drug column is generally downward to the exit orifice, drawn by the force of gravity as well as the weight of the column of liquid. In certain specialized and more sophisticated percolation apparatus, additional pressure on the column is exerted with positive air pressure at the inlet and suction at the outlet or exit.

Percolators for drug extraction vary greatly as to their shape, capacities, composition,

and, most important, utility. Percolators employed in the large-scale industrial preparation of extractives are generally stainless steel or glass-lined metal vessels that vary greatly in size and in operation. Percolators used to extract leaves, for instance, may be 6 to 8 feet in diameter and 12 to 18 feet high. Other vegetable parts like seeds that are greater in density than leaves and would pack too tightly in percolators of such large dimensions are extracted in much smaller percolators. Some special industrial percolators are designed to percolate with hot menstrua; in others, pressure is used to force the menstruum through the drug columns.

Percolation on a small scale generally involves the use of glass percolators of various shapes for extraction of small amounts (perhaps up to 1,000 g) of crude drug. The shapes of percolators in common laboratory and small-scale use are (a) cylindrical, with little, if any, taper except for the lower orifice; (b) roundish, but with a definite taper downward; and (c) conical, or funnel shaped. Each type has a special utility in drug extraction.

The cylindrical percolator is particularly suited to the complete extraction of drugs with a minimal expenditure of menstruum. By the passage of the menstruum over the drug contained in a high, narrow column (rather than in a lower, wider column), each drug particle is more repeatedly exposed to the passing solvent. A funnel-shaped percolator is useful for drugs that swell a great deal during maceration, because the large upper surface permits expansion of the drug column with little risk of a too tightly packed column or breakage of a glass percolator.

Example Preparations Prepared by Extraction Processes

Fluidextracts

Fluidextracts are liquid preparations of vegetable drugs prepared by percolation. They contain alcohol as a solvent, preservative, or both and are made so that each milliliter contains the therapeutic constituents of 1 g of the standard drug that it represents. Because of their concentrated nature, many fluidextracts

are considered too potent to be safely self-administered, and their use per se is almost nonexistent in medical practice. Also, many fluidextracts are simply too bitter tasting or otherwise unpalatable to be accepted by the patient. Therefore, most fluidextracts today are either modified by the addition of flavoring or sweetening agents before use or used as the drug source of other liquid dosage forms, such as syrups.

Extracts

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

Extracts are potent preparations, usually between two and six times as potent on a weight basis as the crude drug. They contain primarily the active constituents of the crude drug, with a great portion of the inactive constituents and structural components of the crude drug having been removed. Their function is to provide in small amounts and in convenient, stable physical form the medicinal activity and character of the bulkier plants that they represent. As such, they have use in product formulation.

In the manufacture of most extracts, percolation is employed to remove the active constituents from the drug, with the percolates generally being reduced in volume by distillation under reduced pressure to reduce the degree of heat and to protect the drug substances against thermal decomposition. The extent of removal of the solvent determines the final physical character of the extract. Extracts are made in three forms: (a) semiliquid extracts or those of a syrupy consistency prepared without the intent of removing all or even most of the menstruum, (b) pilular or solid extracts of a plastic consistency prepared with nearly all of the menstruum removed, and (c) powdered extracts prepared to be dry by the removal of all of the menstruum insofar as is feasible or practical. Pilular and powdered extracts differ only by the slight amount of remaining

solvent in the former preparation, but each has its pharmaceutical advantage because of its physical form. For instance, the pilular extract is preferred in compounding a plastic dosage form such as an ointment

or paste or one in which a pliable material facilitates compounding, whereas the powdered form is preferred in the compounding of such dosage forms as powders, capsules, and tablets.

PHARMACEUTICS



CASE STUDY

SUBJECTIVE INFORMATION

You have been given the responsibility of formulating a new oral solution containing a nasal decongestant (phenylephrine) and cough suppressant (dextromethorphan) for treating the symptoms of a cold or influenza. The oral solution should have a reasonably pleasant taste and appearance, be stable and preserved, and contain a suitable dose combination so that one or two teaspoonfuls can be used per administration to a 6- to 12-year-old child.

OBJECTIVE INFORMATION

Phenylephrine hydrochloride ($C_9H_{13}NO_2 \cdot HCl$), molecular weight 203.67, is the salt form selected for this drug. Phenylephrine hydrochloride occurs as white or nearly white odorless crystals with a bitter taste. It melts at 140°C to 145°C (284°F to 293°F). It is freely soluble in water and in alcohol. It is stable in aqueous solution below pH 7. Above pH 7, degradation occurs apparently involving the side chain, with loss of the secondary amine function; the phenolic group remains intact. The presence of heavy metals, especially copper, can catalyze the decomposition. It has two dissociation constant (pK_a) values, one at 8.77 and one at 9.84.

Dextromethorphan ($C_{18}H_{25}NO$, MW 271.40) is a practically white to slightly yellow odorless crystalline powder that melts at 109.5°C to 112.5°C (229°F to 234.5°F). It is practically insoluble in water. Dextromethorphan hydrobromide ($C_{18}H_{25}NO \cdot HBr \cdot H_2O$, MW 370.32) occurs as practically white crystals or crystalline

powder with a faint odor and a melting range of 124°C to 126°C (255°F to 259°F). It is freely soluble in alcohol. It is stable in aqueous and hydroalcoholic solutions.

ASSESSMENT

The two drugs should be soluble and stable in a slightly acidic oral solution consisting of water and alcohol. The vehicle should be slightly thickened by a viscosity-increasing additive; it also should be sweetened and flavored. These drugs are bitter, so a flavor that will help mask the bitterness must be selected. The addition of a small amount of menthol may also be considered as a flavor enhancer. An appropriate preservative must be selected.

PLAN

An aqueous solution consisting of water, alcohol (low concentration, such as 5%), and glycerin (10%) adjusted to a pH in the range of 4 to 5 should be reasonable. Sucrose can be added as a sweetener (40%) and also for its viscosity-enhancing effect. It can be further thickened with methylcellulose (0.5%) or other cellulose polymer commonly used in oral liquids. A small amount of sorbitol (10%) will help give a smooth mouth feel and minimize cap lock of the container. Several flavor combinations can work, but raspberry and marshmallow work nicely to cover the bitter tastes of drugs. A blend of 0.05% methylparaben and 0.02% propylparaben can be added as a preservative. The addition of about 0.25% menthol will further enhance the flavoring and also impart an additional aromatic effect.

CLINICAL



CASE STUDY

HPI: Late one evening at the local pharmacy, the pharmacist notices a woman searching aimlessly in the nonprescription medication aisle. In hopes of being able to help this customer, the pharmacist approaches the woman and asks if he can help her find anything. The woman replies, “My husband and I are taking a family vacation to Florida tomorrow, and my son gets sick to his stomach when he flies. I was trying to find something that he could take for motion sickness.” After asking the woman a few questions, the pharmacist discovers that her 5-year-old son is quite finicky and will not take tablets, including chewables. The pharmacist recalls a similar situation from a while back for which he compounded an oral solution of dimenhydrinate (Dramamine), and he asked the woman if this would be a suitable option for her son. The woman expressed much gratitude and asked the pharmacist if he could have the solution ready for her by the morning. The pharmacist said that would be fine, and he obtained the following information about her son, J.M.

PMH: Motion sickness
Recurrent ear infections
SH: None
FH: Mother (–)
Father (+) for hypertension
ALL: NKDA
MEDS: None

PHARMACEUTICAL CARE PLAN

S: Mother states that her “finicky” son will not take oral tablets, including chewables.
O: Dimenhydrinate, a common nonprescription medication used for motion sickness, is no longer available in liquid form.

A: J.M. is a 5-year-old WM who has motion sickness on airplanes, and his family is leaving on vacation in the morning. Because the patient will not take tablets, the pharmacist plans to compound an oral solution of dimenhydrinate. The patient does not have any present medical conditions or a medication history that would contraindicate the use of dimenhydrinate.

- P:**
1. The pharmacist decides that to make the compound, he must first review information on the solubility and stability of dimenhydrinate. To do so, he consults Remington (9), where he reads that dimenhydrinate is “slightly soluble in water and freely soluble in alcohol and chloroform.”
 2. Although the pharmacist has prepared this solution before, he does not remember exactly how he did so. He does, however, remember that in the *US Pharmacist* journal, there is a monthly Contemporary Compounding section, which he thinks may be useful. He scans the journal archives in the pharmacy until he finds the article “Oral Solution Stops Motion Sickness” (10). He secures the appropriate issue and reads the article to review how to prepare the dimenhydrinate solution.
 3. Following the methods for preparation outlined in this article, the pharmacist prepares the compound from the following formula:
 4. **Rx:**
 5. Dimenhydrinate 12.5 mg/5 mL oral solution
 6. Dimenhydrinate 250 mg
 7. Glycerin qs
 8. Ora-Plus 50 mL
 9. Ora-Sweet or Ora-Sweet SF qs 100 mL

CLINICAL CASE STUDY CONT.

10. As the article suggests, the pharmacist packages the solution in a tight, light-resistant container. In addition, he labels the bottle take only as directed, keep out of the reach of children, may cause drowsiness, and contents should be discarded (6 months from the date of preparation).
 11. The pharmacist is working the next morning, so he plans to counsel the woman on her son's medication at that time. Based on the dimenhydrinate package directions, a 5-year-old child should take one-quarter to one-half of a tablet every 6 to 8 hours, not to exceed one and a half tablets in 24 hours or as directed by a doctor. Each manufactured tablet contains dimenhydrinate 50 mg, and the compounded oral solution contains dimenhydrinate 12.5 mg/5 mL. Thus, the pharmacist should instruct the woman to give J.M. 1 to 2 teaspoonfuls by mouth every 6 to 8 hours, not to exceed 5 teaspoonfuls every 24 hours.
- Because dimenhydrinate's onset of action is approximately 30 minutes, the pharmacist recommends that J. M. take the first dose about 30 minutes prior to the flight departure.
12. In addition to dosage information, the pharmacist counsels the mother on the possible side effects. The most common is drowsiness, which should prove useful in this situation. Other adverse effects include a dry mouth and constipation. However, these can be relieved or prevented by drinking plenty of fluid.
 13. Finally, the pharmacist reminds the mother that the solution may be stored at room temperature until the expiration date. After that time, any remaining contents should be discarded. The pharmacist also gives her the directions from the dimenhydrinate package along with the remaining tablets so that the patient and his family have the important product information that should accompany the medication (9,10).

APPLYING THE PRINCIPLES AND CONCEPTS

Group Activities

1. Compare and contrast the useful properties of various solvents used in liquid dosage forms.
2. Name medicinal preparations that utilize each of the following solvents: ethyl alcohol, diluted alcohol, rubbing alcohol, glycerin, isopropyl alcohol, propylene glycol, and purified water.
3. Consult the FDA Center for Drug Evaluation and Research's Data Standards Manual web site and distinguish which dosage forms are liquid formulations.
4. Discuss pertinent patient counseling points regarding each liquid dosage form.
5. Define the following and explain benefits for use and contraindications for use of syrups, elixirs, topical solutions, tinctures, and fluid extracts.
6. Amass a number of extemporaneous compounded prescriptions, which use liquids within their formulation.
7. List specific patient circumstances and therapeutic circumstances where alcoholic liquid dosage forms would be contraindicated.
8. Describe common indications for oral solutions and how these liquid formulations have improved patient medication adherence.

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Individual Activities

1. Name a prescription or nonprescription product that utilizes each of the following solvents: Alcohol USP, diluted alcohol, rubbing alcohol, glycerin, isopropyl rubbing alcohol, propylene glycol, and purified water.
2. Identify two advantages of purifying water with the ion exchange method versus the distillation method.
 - a. Describe two methods utilized to increase the rate of solute dissolution in a given solvent, and provide an example of each.
3. List the four main components of syrups and the role each play in the final formulation.
4. Construct a table of the four general methods utilized in preparing syrups, including advantages and disadvantages of each method.
5. Identify the role of nonmedicated elixirs and what components the pharmacist should be aware of in selecting an appropriate vehicle.
6. Compare and contrast aqueous solutions from nonaqueous solutions.
7. List the factors that determine the appropriate method of drug extraction.
8. Explain how the final dosage form can be determined by the process of extraction.

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14 Disperse Systems

OBJECTIVES

After reading this chapter, the student will be able to:

1. Differentiate between a suspension, an emulsion, a gel, and a magma
2. Compare and contrast the different disperse systems, and list advantages and disadvantages of each system
3. Compare and contrast the following emulsification theories: surface tension, oriented-wedge, and interfacial film
4. Define and differentiate the following terms from one another: lyophobic, lyophilic, hydrophobic, hydrophilic, amphiphilic, imbibition, swelling, syneresis, thixotropy, and xerogel
5. Evaluate and select a proper disperse system and delivery method for a given purpose, patient population, and/or patient circumstance

This chapter includes the main types of liquid preparations containing undissolved or immiscible drug distributed throughout a vehicle. In these preparations, the substance distributed is referred to as the *dispersed phase*, and the vehicle is termed the *dispersing phase* or *dispersion medium*. Together, they produce a *dispersed or disperse system*.

The particles of the dispersed phase are usually solid materials that are insoluble in the dispersion medium. In the case of emulsions, the dispersed phase is a liquid that is neither soluble nor miscible with the liquid of the dispersing phase. Emulsification results in the dispersion of liquid drug as fine droplets throughout the dispersing phase. In the case of an aerosol, the dispersed phase may be small air bubbles throughout a solution or an emulsion. Dispersions also consist of droplets of a liquid (solution or suspension) in air.

The particles of the dispersed phase vary widely in size, from large particles visible to the naked eye down to particles of colloidal dimension, falling between 1.0 nm

and 0.5 μm . A discussion on the difference between particles and molecules is provided in Physical Pharmacy Capsule 14.1. Dispersions containing coarse particles, usually 10 to 50 μm , are referred to as *coarse dispersions*; they include the *suspensions* and *emulsions*. Dispersions containing particles of smaller size are termed *fine dispersions* (0.5 to 10 μm) and, if the particles are in the colloidal range, *colloidal dispersions*. *Magnas* and *gels* are fine dispersions.

Largely because of their greater size, particles in a coarse dispersion have a greater tendency to separate from the dispersion medium than do the particles of a fine dispersion. Most solids in dispersion tend to settle to the bottom of the container because of their greater density than the dispersion medium, whereas most emulsified liquids for oral use are oils, which generally have less density than the aqueous medium in which they are dispersed, so they tend to rise toward the top of the preparation. Complete and uniform redistribution of the dispersed phase is essential to the accurate administration



PHYSICAL PHARMACY CAPSULE 14.1

Particles Versus Molecules

Particles of drug substances can actually range from an aggregation of two or more molecules to millions of molecules. The term “particle” should not be confused with “molecule.” The molecule is the smallest unit of any chemical compound that possesses all the native properties of that compound. Particles consist of numerous molecules, generally in a solid state (but can be liquid or gaseous). Dissolution is the solid to liquid transformation that converts solid drug particles to individual, dissolved liquid molecules. Even the smallest invisible drug particle contains billions of molecules. Most nonprotein or small molecule organic drugs have formula weights ranging from 150 to 500.

EXAMPLE

Let’s look at how many molecules may be present in a 1-ng particle of ibuprofen with a formula weight of 206:

$$\frac{(1 \text{ ng})(1 \text{ g})(6.02 \times 10^{23} \text{ molecules})}{(\text{particle})(1 \times 10^9)(206 \text{ g})(\text{Mole})} = 2.923 \times 10^{12} \text{ molecules}$$

This illustrates that a 1-ng invisible particle will contain 2,923,000,000,000 molecules.

of uniform doses. For a properly prepared dispersion, this should be accomplished by moderate agitation of the container.

The focus of this chapter is on dispersions of drugs administered orally or topically. The same basic pharmaceutical characteristics apply to dispersion systems administered by other routes. Included among these are ophthalmic and otic suspensions and sterile suspensions for injection, covered in Chapters 17 and 15, respectively.

SUSPENSIONS

Suspensions may be defined as preparations containing finely divided drug particles (the *suspensoid*) distributed somewhat uniformly throughout a vehicle in which the drug exhibits a minimum degree of solubility. Some suspensions are available in ready-to-use form, that is, already distributed through a liquid vehicle with or without stabilizers and other additives (Fig. 14.1). Other preparations are available as dry powders intended for suspension in liquid vehicles. Generally, this type of product is a powder mixture containing the drug and suitable

suspending and dispersing agents to be diluted and agitated with a specified quantity of vehicle, most often purified water. Figure 14.2 demonstrates preparation of this type of product. Drugs that are unstable if maintained for extended periods in the presence of an aqueous vehicle (e.g., many antibiotic drugs) are most frequently supplied as dry powder mixtures for reconstitution at the time of dispensing. This type of preparation is designated in the USP by a title of the form “for Oral Suspension.” Prepared suspensions not requiring reconstitution at the time of dispensing are simply designated as “Oral Suspension.”

Reasons for Suspensions

There are several reasons for preparing suspensions. For example, certain drugs are chemically unstable in solution but stable when suspended. In this instance, the suspension ensures chemical stability while permitting liquid therapy. For many patients, the liquid form is preferred to the solid form of the same drug because of the ease of swallowing liquids and the flexibility



FIGURE 14.1 Commercial oral suspension.

in administration of a range of doses. This is particularly advantageous for infants, children, and the elderly. The disadvantage of a disagreeable taste of certain drugs in solution form is overcome when the drug is administered as undissolved particles of an oral suspension. In fact, chemical forms of certain poor-tasting drugs have been specifically developed for their insolubility in a desired vehicle for the sole purpose of preparing a palatable liquid dosage form. For example, erythromycin estolate is a less water-soluble ester form of erythromycin and is used to prepare a palatable



FIGURE 14.2 Commercial antibiotic preparation for oral suspension following reconstitution with purified water. *Left*, dry powder mixture. *Right*, suspension after reconstitution with the specified amount of purified water.

liquid dosage form of erythromycin, the result being Erythromycin Estolate Oral Suspension, USP. Use of insoluble forms of drugs in suspensions greatly reduces the difficult taste-masking problems of developmental pharmacists, and selection of the flavorants to be used in a given suspension may be based on taste preference rather than on a particular flavorant's ability to mask an unpleasant taste. For the most part, oral suspensions are aqueous preparations with the vehicle flavored and sweetened to suit the anticipated taste preferences of the intended patient.

Features Desired in a Pharmaceutical Suspension

There are many considerations in the development and preparation of a pharmaceutically elegant suspension. In addition to therapeutic efficacy, chemical stability of the components of the formulation, permanency of the preparation, and aesthetic appeal of the preparation—desirable qualities in all pharmaceutical preparations—a few other features apply more specifically to the pharmaceutical suspension:

1. A properly prepared pharmaceutical suspension should settle slowly and should

be readily redispersed upon gentle shaking of the container.

- The particle size of the suspensoid should remain fairly constant throughout long periods of undisturbed standing.
- The suspension should pour readily and evenly from its container.

These main features of a suspension, which depend on the nature of the dispersed phase, the dispersion medium, and

pharmaceutical adjuncts, will be discussed briefly.

Sedimentation Rate of the Particles of a Suspension

The various factors involved in the rate of settling of the particles of a suspension are embodied in the equation of Stokes law, which is presented in the Physical Pharmacy Capsule 14.2.



PHYSICAL PHARMACY CAPSULE 14.2

Sedimentation Rate and Stokes Equation

Stokes equation:

$$\frac{dx}{dt} = \frac{d^2(\rho_p - \rho_e)g}{18\eta}$$

where

dx/dt is the rate of settling,
 d is the diameter of the particles,
 ρ_p is the density of the particle,
 ρ_e is the density of the medium,
 g is the gravitational constant, and
 η is the viscosity of the medium.

A number of factors can be adjusted to enhance the physical stability of a suspension, including the diameter of the particles and the density and viscosity of the medium. The effect of changing these is illustrated in the following example.

EXAMPLE

A powder has a density of 1.3 g/mL and an average particle diameter of 2.5 μm (assuming the particles to be spheres). According to the Stokes equation, this powder will settle in water (viscosity of 1 cP assumed) at this rate:

$$\frac{(2.5 \times 10^{-4})^2 (1.3 - 1.0) (980)}{18 \times 0.01} = 1.02 \times 10^{-4} \text{ cm/s}$$

If the particle size of the powder is reduced to 0.25 μm and water is still used as the dispersion medium, the powder will now settle at this rate:

$$\frac{(2.5 \times 10^{-5})^2 (1.3 - 1.0) (980)}{18 \times 0.01} = 1.02 \times 10^{-6} \text{ cm/s}$$

As is evident, a decrease in particle size by a factor of 10 results in a reduction in the rate of settling by a factor of 100. This enhanced effect is a result of the d factor in the Stokes equation being squared.

PHYSICAL PHARMACY CAPSULE 14.2 CONT.

If a different dispersion medium, such as glycerin, is used in place of water, a further decrease in settling will result. Glycerin has a density of 1.25 g/mL and a viscosity of 400 cP. The larger particle size powder (2.5 μm) will settle at this rate:

$$\frac{(2.5 \times 10^{-5})^2 (1.3 - 1.25)(980)}{18 \times 4} = 4.25 \times 10^{-10} \text{ cm/s}$$

The smaller particle size (0.25 μm) powder will now settle at this rate:

$$\frac{(2.5 \times 10^{-5})^2 (1.3 - 1.25)(980)}{18 \times 4} = 4.25 \times 10^{-10} \text{ cm/s}$$

A summary of these results is shown in the following table:

CONDITION	RATE OF SETTLING (CM/S)
2.5 μm powder in water	1.02×10^{-4}
0.25 μm powder in water	1.02×10^{-6}
2.5 μm powder in glycerin	4.25×10^{-8}
0.25 μm powder in glycerin	4.25×10^{-10}

As is evident from this table, a change in dispersion medium results in the greatest change in the rate of settling of particles. Particle size reduction also can contribute significantly to suspension stability. These factors are important in the formulation of physically stable suspensions.

The Stokes equation was derived for an ideal situation in which uniform, perfectly spherical particles in a very dilute suspension settle without producing turbulence, without colliding with other particles of the suspensoid, and without chemical or physical attraction or affinity for the dispersion medium. Obviously, the Stokes equation does not apply precisely to the usual pharmaceutical suspension in which the suspensoid is irregularly shaped and of various particle diameters, in which the fall of the particles *does* result in both turbulence and collision, and also in which the particles may have some affinity for the suspension medium. However, the basic concepts of the equation do give a valid indication of the factors that are important to suspension of the particles and a clue to the possible adjustments that can be made to a formulation to decrease the rate of sedimentation.

From the equation, it is apparent that the velocity of fall of a suspended particle

is greater for larger particles than it is for smaller particles, all other factors remaining constant. Reducing the particle size of the dispersed phase produces a slower *rate* of descent of the particles. Also, the greater the density of the particles, the greater the rate of descent, provided the density of the vehicle is not altered. Because aqueous vehicles are used in pharmaceutical oral suspensions, the density of the particles is generally greater than that of the vehicle, a desirable feature. If the particles were less dense than the vehicle, they would tend to float, and floating particles would be quite difficult to distribute uniformly in the vehicle. The rate of sedimentation may be appreciably reduced by increasing the viscosity of the dispersion medium, and within limits of practicality, this may be done. However, a product having too high a viscosity is not generally desirable because it pours with difficulty and it is equally difficult to redisperse the suspensoid. Therefore, if the viscosity of a suspension

is increased, it is done so only to a modest extent to avoid these difficulties.

The viscosity characteristics of a suspension may be altered not only by the vehicle used but also by the solid content. As the proportion of solid particles in a suspension increases, so does the viscosity. The viscosity of a pharmaceutical preparation may be determined through the use of a viscometer, such as a Brookfield viscometer, which measures viscosity by the force required to rotate a spindle in the fluid being tested (Fig. 14.3).

For the most part, the physical stability of a pharmaceutical suspension appears to be most appropriately adjusted by an alteration in the dispersed phase rather than through great changes in the dispersion medium. In most instances, the dispersion medium supports the adjusted dispersed phase. These adjustments are concerned mainly with particle size, uniformity of particle size, and separation of the particles so that they are not

likely to become greatly larger or to form a solid cake upon standing.

Physical Features of the Dispersed Phase of a Suspension

Probably the most important single consideration in a discussion of suspensions is the size of the particles. In most good pharmaceutical suspensions, the particle diameter is 1 to 50 μm .

Generally, particle size reduction is accomplished by dry milling prior to incorporation of the dispersed phase into the dispersion medium. One of the most rapid, convenient, and inexpensive methods of producing fine drug powders of about 10 to 50 μm size is *micropulverization*. Micropulverizers are high-speed attrition or impact mills that are efficient in reducing powders to the size acceptable for most oral and topical suspensions. For still finer particles, under 10 μm ,

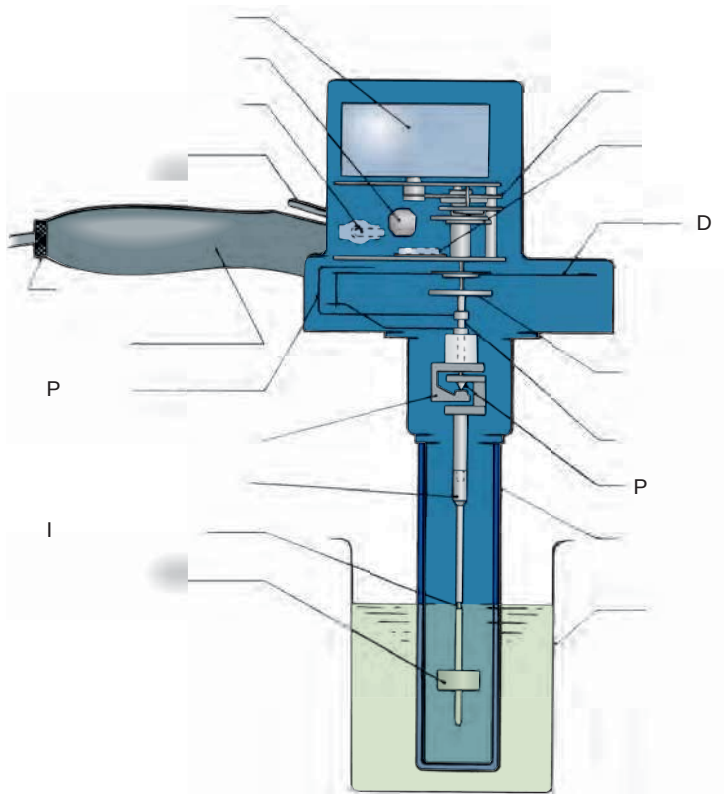


FIGURE 14.3 The Brookfield viscometer. (Courtesy of Brookfield Engineering Laboratories.)

fluid energy grinding, sometimes referred to as *jet milling* or *micronizing*, is quite effective. By this process, the shearing action of high-velocity compressed airstreams on the particles in a confined space produces the desired ultrafine or micronized particles. The particles to be micronized are swept into violent turbulence by the sonic and supersonic velocities of the airstreams. The particles are accelerated to high velocities and collide with one another, resulting in fragmentation. This method may be employed when the particles are intended for parenteral or ophthalmic suspensions. Particles of extremely small dimensions may also be produced by *spray drying*. A spray dryer is a cone-shaped apparatus into which a solution of a drug is sprayed and rapidly dried by a current of warm, dry air circulating in the cone. The resulting dry powder is collected. It is not possible for a pharmacist to achieve the same degree of particle size reduction with such comminuting equipment as the mortar and pestle. However, many micronized drugs are commercially available to the pharmacist in bulk, such as progesterone.

As shown by the Stokes equation, the reduction in the particle size of a suspensoid is beneficial to the stability of the suspension because the rate of sedimentation of the solid particles is reduced as the particles are decreased in size. The reduction in particle size produces slow, more uniform rates of settling. However, one should avoid reducing the particle size too much because fine particles have a tendency to form a compact cake upon settling to the bottom of the container. The result may be that the cake resists breakup with shaking and forms rigid aggregates of particles that are larger and less suspendable than the original suspensoid. The particle shape of the suspensoid can also affect caking and product stability. It has been shown that symmetrical barrel-shaped particles of calcium carbonate produced more stable suspensions than did asymmetrical needle-shaped particles of the same agent. The needle-shaped particles formed a tenacious sediment cake on standing that could not be redistributed, whereas the barrel-shaped particles did not cake upon standing (1).

To avoid formation of a cake, it is necessary to prevent agglomeration of the particles into larger crystals or into masses. One common method of preventing rigid cohesion of small particles of a suspension is intentional formation of a less rigid or loose aggregation of the particles held together by comparatively weak particle-to-particle bonds. Such an aggregation of particles is termed a *floc* or a *floccule*, with flocculated particles forming a type of lattice that resists complete settling (although flocs settle more rapidly than fine, individual particles) and thus are less prone to compaction than unflocculated particles. The flocs settle to form a higher sediment volume than unflocculated particles, the loose structure of which permits the aggregates to break up easily and distribute readily with a small amount of agitation.

There are several methods of preparing flocculated suspensions, the choice depending on the type of drug and the type of product desired. For instance, in the preparation of an oral suspension of a drug, clays such as diluted bentonite magma are commonly employed as the flocculating agent. The structure of the bentonite magma and of other clays used for this purpose also assists the suspension by helping to support the floc once formed. When clays are unsuitable as agents, as in a parenteral suspension, frequently a floc of the dispersed phase can be produced by an alteration in the pH of the preparation (generally to the region of minimum drug solubility). Electrolytes can also act as flocculating agents, apparently by reducing the electrical barrier between the particles of the suspensoid and forming a bridge so as to link them together. The carefully determined concentration of nonionic and ionic surface-active agents (surfactants) can also induce flocculation of particles in suspension and increase the sedimentation volume.

Dispersion Medium

Oftentimes, as with highly flocculated suspensions, the particles of a suspension settle too rapidly to be consistent with what might be termed a pharmaceutically elegant preparation. The rapid settling hinders accurate

measurement of dosage and, from an aesthetic point of view, produces too unsightly a supernatant layer. In many commercial suspensions, suspending agents are added to the dispersion medium to lend it structure. Carboxymethylcellulose (CMC), methylcellulose, microcrystalline cellulose, polyvinylpyrrolidone, xanthan gum, and bentonite are a few of the agents employed to thicken the dispersion medium and help suspend the suspensoid. When polymeric substances and hydrophilic colloids are used as suspending

agents, appropriate tests must be performed to show that the agent does not interfere with availability of the drug. These materials can bind certain medicinal agents, rendering them unavailable or only slowly available for therapeutic function. Also, the amount of the suspending agent must not be such to render the suspension too viscous to agitate (to distribute the *suspensoid*) or to pour. The study of flow characteristics is rheology. A summary of the concepts of rheology is found in Physical Pharmacy Capsule 14.3.



PHYSICAL PHARMACY CAPSULE 14.3

Rheology

Rheology, the study of flow, addresses the viscosity characteristics of powders, fluids, and semisolids. Materials are divided into two general categories, Newtonian and non-Newtonian, depending on their flow characteristics. Newtonian flow is characterized by constant viscosity, regardless of the shear rates applied. Non-Newtonian flow is characterized by a change in viscosity characteristics with increasing shear rates. Non-Newtonian flow includes plastic, pseudoplastic, and dilatant flow.

The Newton law of flow relates parallel layers of liquid: with the bottom layer fixed, when a force is placed on the top layer, the top plane moves at constant velocity, and each lower layer moves with a velocity directly proportional to its distance from the stationary bottom layer. The velocity gradient, or rate of shear (dv/dr), is the difference of velocity dv between two planes of liquid separated by the distance dr . The force (F'/A) applied to the top layer that is required to result in flow (rate of shear, G) is called the shearing stress (F). The relationship can be expressed:

$$\frac{F'}{A} = \eta \frac{dv}{dr}$$

where η is the viscosity coefficient or viscosity. This relationship is often written:

$$\eta = \frac{F}{G}$$

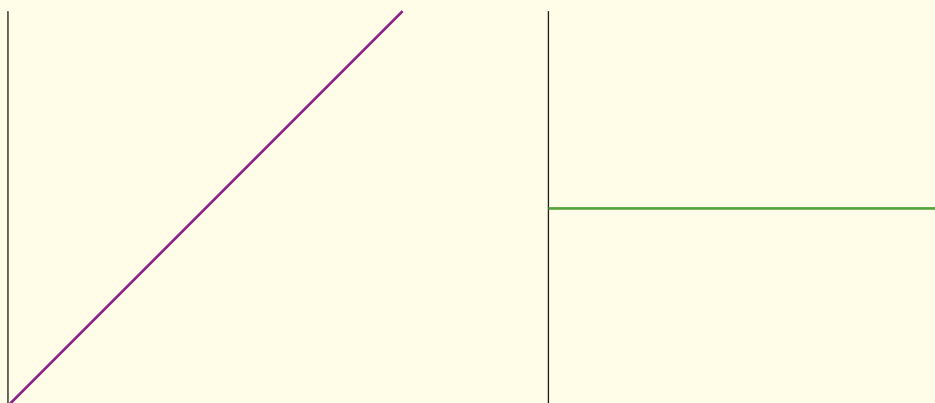
where

$$F = F'/A \text{ and} \\ G = dv/dr.$$

The higher the viscosity of a liquid, the greater the shearing stress required to produce a certain rate of shear. A plot of F versus G yields a rheogram. A Newtonian fluid will plot as a straight line with the slope of the line being η . The unit of viscosity is the *poise*, the shearing force required to produce a velocity of 1 cm/s between two parallel planes of liquid, each 1 cm² in area and separated by a distance of 1 cm. The most convenient unit to use is the centipoise, or cP (equivalent to 0.01 poise).

These basic concepts can be illustrated in the following two graphs.

PHYSICAL PHARMACY CAPSULE 14.3 CONT.

**EXAMPLE 1**

What is the shear rate when an oil is rubbed into the skin with a relative rate of motion between the fingers and the skin of about 10 cm/s and the film thickness is about 0.02 cm?

$$G = \frac{10 \text{ cm/s}}{0.02} = 500 \text{ s}^{-1}$$

The viscosity of Newtonian materials can be easily determined using a capillary viscometer, such as the Ostwald pipette, and the following relationship:

$$\eta' = ktd$$

where

- η' is viscosity;
- k is a coefficient, including such factors as the radius and length of the capillary, volume of the liquid flowing, pressure head, and so on;
- t is time; and
- d is density of the material.

The official compendia, the USP and NF, use kinematic viscosity, the absolute viscosity divided by the density of the liquid, as follows:

$$\text{Kinematic viscosity} = \eta' / \rho$$

The relative viscosity of a liquid can be obtained by using a capillary viscometer and comparing data with a second liquid of known viscosity, provided the densities of the two liquids are known, as follows:

$$\eta' / \eta'_o = (\rho t) / (\rho_o t_o)$$

EXAMPLE 2

At 25°C, water has a density of 1 g/mL and a viscosity of 0.895 cP. The time of flow of water in a capillary viscometer is 15 seconds. A 50% aqueous solution of glycerin has a flow time of 750 seconds. The density of the glycerin solution is 1.216 g/mL. What is the viscosity of the glycerin solution?

PHYSICAL PHARMACY CAPSULE 14.3 CONT.

$$\eta = \frac{(0.895)(750)(1.216)}{(1)(15)} = 54.4 \text{ cP}$$

EXAMPLE 3

The time of flow between marks on an Ostwald viscometer using water ($\rho = 1$) was 120 seconds at 20°C. The time for a liquid ($\rho = 1.05$) to flow through the same viscometer was 230 seconds. What is the absolute and relative viscosity of the liquid?

$$\eta = \frac{(0.01)(1.05)(230)}{(1.0)(120)}$$

$$\eta = 0.020 \text{ poise} = 2.0 \text{ cP}$$

Viscosity is related to temperature; thus,

$$\eta' = Ae^{E_v/RT}$$

where

A is a constant depending on the molecular weight and molar volume of the material,

E_v is the activation energy required to initiate flow between molecules,

R is the gas constant, and

T is the absolute temperature.

Viscosity is additive in ideal solutions, as follows:

$$\frac{1}{\eta} = \frac{1}{\eta_1} V_1 + \frac{1}{\eta_2} V_2$$

where

η is the viscosity of the solutions and

V_1 and V_2 are the volume fractions of the pure liquids.

EXAMPLE 4

What is the viscosity of the liquid resulting from mixing 300 mL of liquid A ($\eta = 1.0$ cP) and 200 mL of liquid B ($\eta = 3.4$ cP)?

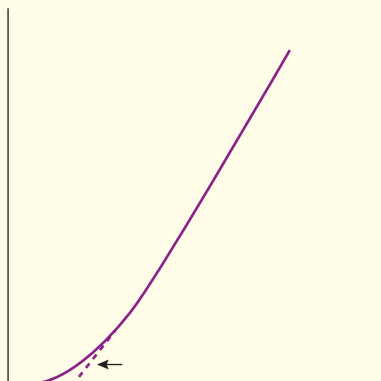
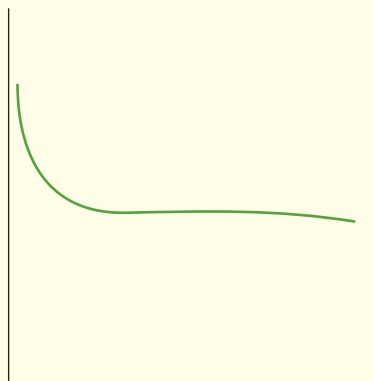
$$\frac{1}{\eta} = \frac{1(0.6)}{1.0} + \frac{1(0.4)}{3.4}$$

$$\eta = 1.4 \text{ cP}$$

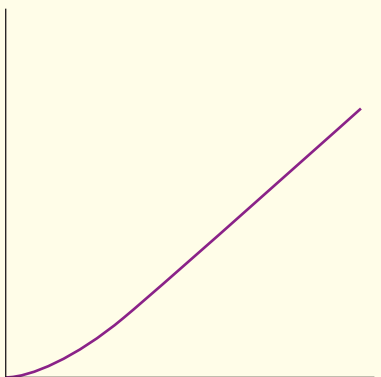
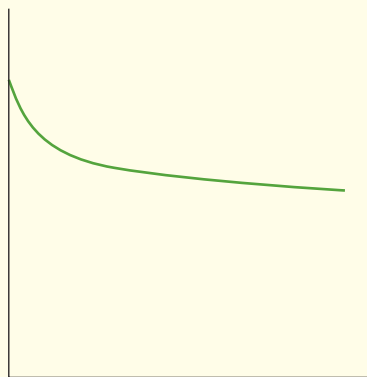
Non-Newtonian substances are those that fail to follow the Newton equation of flow. Example materials include colloidal solutions, emulsions, liquid suspensions, and ointments. There are three general types of non-Newtonian materials: plastic, pseudoplastic, and dilatant.

Substances that exhibit plastic flow are called *Bingham bodies*. Plastic flow does not begin until a shearing stress corresponding to a certain yield value is exceeded. The flow curve intersects the shearing stress axis and does not pass through the origin. The materials are elastic below the yield value.

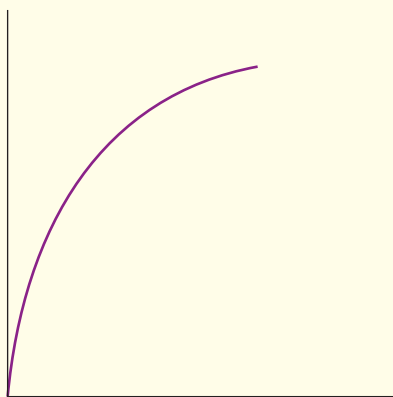
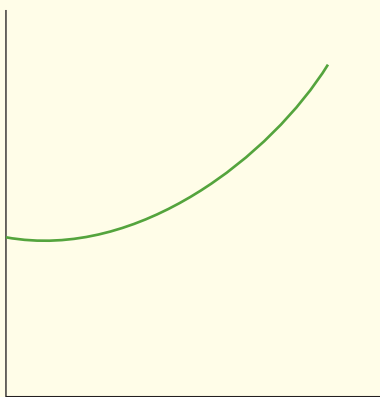
PHYSICAL PHARMACY CAPSULE 14.3 CONT.



Pseudoplastic substances begin flow when a shearing stress is applied; therefore, they exhibit no yield value. With increasing shearing stress, the rate of shear increases; consequently, these materials are also called shear-thinning systems. It is postulated that this occurs as the molecules, primarily polymers, align themselves along the long axis and slip or slide past each other.



Dilatant materials are those that increase in volume when sheared, and the viscosity increases with increasing shear rate. These are also called shear-thickening systems. Dilatant systems are usually characterized by having a high percentage of solids in the formulation.



PHYSICAL PHARMACY CAPSULE 14.3 CONT.

The viscosity of non-Newtonian materials is determined using a viscometer capable of producing differing shear rates, measuring the shear stress, and plotting the results. Other types of flow not detailed here include *thixotropic*, *antithixotropic*, and *rheopexic*. Thixotropic flow is used to advantage in some pharmaceutical formulations. It is a reversible gel-sol transformation. Upon setting, a network gel forms and provides a rigid matrix that will stabilize suspensions and gels. When stressed (by shaking), the matrix relaxes and forms a sol with the characteristics of a liquid dosage form for ease of use. All of these unique flow types can be characterized by studying their respective rheograms.

Support of the suspensoid by the dispersion medium may depend on several factors: the density of the suspensoid, whether it is flocculated, and the amount of material requiring support.

The solid content of a suspension intended for oral administration may vary considerably, depending on the dose of the drug to be administered, the volume of product to be administered, and the ability of the dispersion medium to support the concentration of drug while maintaining desirable features of viscosity and flow. Frequently, the usual adult oral suspension is designed to supply the dose of the particular drug in a convenient measure of 5 mL or 1 teaspoonful. Pediatric suspensions are formulated to deliver the appropriate dose of drug by administering a dose-calibrated number of drops or with the use of a teaspoon. Figure 14.4 shows commonly packaged oral suspensions administered as pediatric drops. Some are accompanied by a calibrated dropper, whereas other packages have the drop capability built into the container. On administration, the drops may be placed directly in the infant's mouth or mixed with a small portion of food. Because many of the suspensions of antibiotic drugs intended for pediatric use are prepared in a highly flavored, sweetened, colored base, they are frequently referred to by their manufacturers and also popularly as syrups, even though in fact they are suspensions.

Preparation of Suspensions

In the preparation of a suspension, the pharmacist must be acquainted with the characteristics of both the intended dispersed

phase and the dispersion medium. In some instances, the dispersed phase has an affinity for the vehicle to be employed and is readily wetted by it. Other drugs are not penetrated easily by the vehicle and have a tendency to clump together or to float on the vehicle. In the latter case, the powder must first be wetted to make it more penetrable by the dispersion medium. Alcohol, glycerin, propylene glycol, and other hygroscopic liquids are employed as wetting agents when an aqueous vehicle is to be used as the dispersion phase. They function by displacing the air in the crevices of the particles, dispersing the particles, and allowing penetration of dispersion medium into the powder. In large-scale preparation of suspensions, wetting agents



FIGURE 14.4 Oral pediatric suspensions showing package designs of a built-in dropper device and a calibrated dropper accompanying the medication container.

are mixed with the particles by an apparatus such as a colloid mill; on a small scale in the pharmacy, they are mixed with a mortar and pestle. Once the powder is wetted, the dispersion medium (to which have been added all of the formulation's soluble components, such as colorants, flavorants, and preservatives) is added in portions to the powder, and the mixture is thoroughly blended before subsequent additions of vehicle. A portion of the vehicle is used to wash the mixing equipment free of suspensoid, and this portion is used to bring the suspension to final volume and ensure that the suspension contains the desired concentration of solid matter. The final product is then passed through a colloid mill or other blender or mixing device to ensure uniformity.

Whenever appropriate, suitable preservatives should be included in the formulation of suspensions to preserve against bacterial and mold contamination.

An example formula for an oral suspension follows (2). The suspensoid is the antacid aluminum hydroxide, the preservatives are methylparaben and propylparaben, and syrup and sorbitol solution provide the viscosity and sweetness.

Aluminum hydroxide compressed gel	326.8 g
Sorbitol solution	282.0 mL
Syrup	93.0 mL
Glycerin	25.0 mL
Methylparaben	0.9 g
Propylparaben	0.3 g
Flavor	qs
Purified water, to make	1,000.0 mL

The parabens are dissolved in a heated mixture of the sorbitol solution, glycerin, syrup, and a portion of the water. The mixture is then cooled and the aluminum hydroxide added with stirring. The flavor is added and purified water to the volume. The suspension is then homogenized, using a hand homogenizer, homomixer, or colloid mill. A high-speed industrial-size mixer used to prepare dispersions of various types, including suspensions and emulsions, is shown in Figure 14.5. A large storage holding

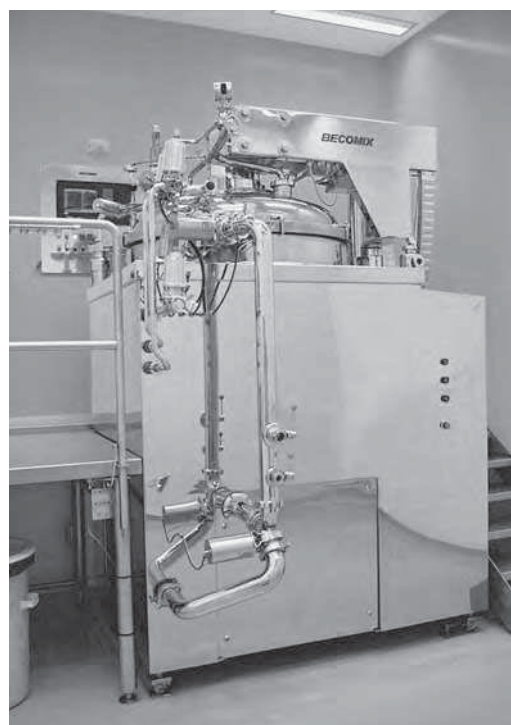


FIGURE 14.5 An industrial mixer for manufacture of disperse systems, including suspensions and emulsions. (Courtesy of Paddock Laboratories.)

tank with a liquid filling unit in the process of filling large-mouth suspension bottles is shown in Figure 14.6.

Sustained-Release Suspensions

The formulation of liquid oral suspensions having sustained-release capabilities has had only limited success because of the difficulty of maintaining the stability of sustained-release particles in liquid disperse systems (3). Product development research has centered on the same types of technologies used in preparing sustained-release tablets and capsules (e.g., coated beads, drug-impregnated wax matrix, microencapsulation, ion exchange resins). The use of a combination of ion exchange resin complex and particle coating *has* resulted in product success via the so-called Pennkinetic system. By this technique, ionic drugs are complexed with ion exchange resins, and the drug–resin complex particles coated with ethylcellulose (3). In liquid formulations (suspensions) of the coated particles, the drug remains adsorbed onto



FIGURE 14.6 Liquid filling. Bottles being conveyed after cleaning. As they pass through an indexing worm, the bottles are spaced accurately for filling and capping. (Courtesy of Paddock Laboratories.)

the resin but is slowly released by the ion exchange process in the gastrointestinal tract. An example of this product type is hydrocodone polistirex (Tussionex Pennkinetic Extended-Release Suspension, CellTech).

Extemporaneous Compounding of Suspensions

Unfortunately, not all medicines are available in a convenient, easy-to-take liquid dosage form. Consequently, patients who are not able to swallow solid medicines, such as infants and the elderly, may present a special need. Thus, the pharmacist may have to use a solid dosage form of the drug and extemporaneously compound a liquid product. A difficulty that confronts the pharmacist is a lack of ready information on stability of a drug in a liquid vehicle. It is known that drugs in liquid form have faster decomposition rates than in solid form and some are affected by the pH of the medium. Leucovorin calcium when compounded from crushed tablets or the injectable form is most stable in milk or antacid and is unstable in acidic solutions.

To overcome this information gap, the pharmacist can attempt to contact the manufacturer of the solid dosage form to attain stability information. A number of extemporaneous formulations have appeared in

the professional literature, such as for prednisone oral suspension (4) and ketoconazole suspension (5), and some manufacturers provide in the package insert a formula for preparation of an oral liquid form, such as Rifadin (rifampin, Aventis). A number of compilations of formulations based upon documented stability data and unpublished data compiled by manufacturers and practitioners are available for pharmacists to use, and hundreds of compounded liquid formulations are available through journals such as the *International Journal of Pharmaceutical Compounding*.

Typically, in formation of an extemporaneous suspension, the contents of a capsule are emptied into a mortar or tablets crushed in a mortar with a pestle. The selected vehicle is slowly added to and mixed with the powder to create a paste and then diluted to the desired volume. The selected vehicle can be a commercial product, such as the Ora family of preparations (Ora-Sweet, Ora-Sweet SF, Ora-Plus, Ora-Blend, Paddock Laboratories).

The extent of the formulation depends upon the patient. For example, a liquid suspension for a neonate should not include preservatives, colorings, flavorings, or alcohol because of the potential for each of these to cause either acute or long-term adverse effects. Because this liquid product will

probably be administered through a tube threaded through the mouth into the stomach and because taste is usually underdeveloped in the neonate, a flavoring agent is not required.

In the neonate, alcohol can alter liver function, cause gastric irritation, and effect neurologic depression. So unless it is absolutely necessary, it should be omitted from an extemporaneous formulation. Pharmacists must be cautious because some vehicles, such as Aromatic Elixir, NF, contain a significant amount of alcohol, 21% to 23%, and are not suitable for use in these patients. The same problem holds for liquid formulations for the elderly or any patient who may be receiving another medication that depresses the central nervous system or would cause the patient to get violently ill, for example, metronidazole (Flagyl) and disulfiram (Antabuse).

Preservatives have been implicated in adverse effects in preterm infants. Benzyl alcohol should be omitted from neonate formulations because this agent can cause a gasping syndrome characterized by a deterioration of multiple organ systems and eventually death. Propylene glycol has also been implicated in problems such as seizures and stupor in some preterm infants. Thus, formulations for neonates should be kept simple and not compounded to supply more than a few days of medicine.

To minimize stability problems of the extemporaneous product, it should be placed in an airtight, light-resistant container by the pharmacist and stored in the refrigerator by the patient. Because it is a suspension, the patient should be instructed to shake it well prior to use and watch for any color change or consistency change that might indicate a stability problem.

Packaging and Storage of Suspensions

All suspensions should be packaged in wide-mouth containers having adequate airspace above the liquid to permit thorough mixing by shaking and ease of pouring. Most suspensions should be stored in tight containers protected from freezing, excessive heat,

and light. It is important that suspensions be shaken before each use to ensure a uniform distribution of solid in the vehicle and thereby uniform and proper dosage.

Examples of Oral Suspensions

Examples of official and commercial oral suspensions are presented in Table 14.1. Antacid and antibacterial suspensions are briefly discussed next as examples of this dosage form. In addition, kaolin mixture with pectin is widely used in the treatment of diarrhea.

Antacid Oral Suspensions

Antacids are intended to counteract the effects of gastric hyperacidity and, as such, are employed by persons, such as peptic ulcer patients, who must reduce the level of acidity in the stomach. They are also widely employed and sold over the counter (OTC) to patients with acid indigestion and heartburn. Many patients belch or otherwise reflux acid from the stomach to the esophagus and take antacids to counter the acid in the esophagus and throat.

Most antacid preparations are composed of water-insoluble materials that act within the gastrointestinal tract to counteract the acid and/or soothe the irritated or inflamed linings of the gastrointestinal tract. A few water-soluble agents are employed, including sodium bicarbonate, but for the most part, water-insoluble salts of aluminum, calcium, and magnesium are employed; these include aluminum hydroxide, aluminum phosphate, dihydroxyaluminum aminoacetate, calcium carbonate, calcium phosphate, magaldrate, magnesium carbonate, magnesium oxide, and magnesium hydroxide. The ability of each of these to neutralize gastric acid varies with the chemical agent. For instance, sodium bicarbonate, calcium carbonate, and magnesium hydroxide neutralize acid effectively, whereas magnesium trisilicate and aluminum hydroxide do so less effectively and much more slowly. In selecting an antacid, it is also important to consider the possible adverse effects of each agent in relation to the individual patient. Each agent has its own peculiar potential for adverse effects.

Table 14.1 ORAL SUSPENSIONS BY CATEGORY

ORAL SUSPENSION	REPRESENTATIVE COMMERCIAL PRODUCTS	DRUG CONCENTRATION IN COMMERCIAL PRODUCT	COMMENTS
Antacids			
Alumina, magnesia, simethicone	Mylanta Liquid (Johnson & Johnson Merck)	Aluminum hydroxide, 200 mg; magnesium hydroxide, 200 mg; and simethicone, 20 mg/5 mL	Counteract gastric hyperacidity, relieve distress in the upper gastrointestinal tract
Magaldrate	Riopan Oral Suspension (Wyeth)	Hydroxymagnesium aluminate 540 mg aluminum (chemical entity of aluminum and magnesium hydroxides)	
Magnesia and alumina	Maalox Suspension (Novartis Consumer Health)	Aluminum hydroxide 225 mg; magnesium hydroxide 200 mg/5 mL	
Aluminum hydroxide, magnesium carbonate	Gaviscon Liquid Antacid (GlaxoSmithKline)	Aluminum hydroxide 95 mg; magnesium carbonate 358 mg/15 mL; sodium alginate	
Anthelmintics			
Pyrantel pamoate	Pin-X Oral Suspension (Effcon)	250 mg/5 mL	For worm infestations
Thiabendazole	Mintezol Oral Suspension (Merck)	500 mg/5 mL	
Antibacterials (Antibiotics)			
Ciprofloxacin	Cipro Oral Suspension (Schering-Plough)	50 and 100 mg/mL	Indicated in the treatment of specific susceptible microorganisms
Erythromycin estolate	Generic	125 and 250 mg/5 mL	Broad-spectrum macrolide antibiotic; bacteriostatic and bactericidal activity
Antibacterials (Nonantibiotic Anti-infectives)			
Methenamine mandelate	Mandelamine Suspension Forte (various)	500 mg/5 mL	Oleaginous vehicle; chemical combination of approximately equal parts of methenamine and mandelic acid; destroys most pathogens commonly infecting urinary tract. Acid urine is essential for activity; maximum efficacy at pH 5.5. Methenamine in acid urine is hydrolyzed to ammonia and the bactericidal agent, formaldehyde. Mandelic acid exerts its antibacterial action, contributes to acidification of urine. Usual dose 1 g up to 4 times a day. Suspension form especially useful for children, adults who do not swallow a tablet (also official and commercially available)

Table 14.1 ORAL SUSPENSIONS BY CATEGORY (Continued)

ORAL SUSPENSION	REPRESENTATIVE COMMERCIAL PRODUCTS	DRUG CONCENTRATION IN COMMERCIAL PRODUCT	COMMENTS
Sulfamethoxazole and trimethoprim	Bactrim Suspension (Roche), Septra Suspension (Monarch)	Trimethoprim 40 mg, sulfamethoxazole 200 mg/5 mL	For acute middle ear infection (otitis media) in children, urinary tract infections due to susceptible microorganisms
Sulfamethoxazole	Gantanol Suspension (various)	500 mg/5 mL	Bacteriostatic sulfa drug suspensions useful for urinary tract infections. Sulfonamides competitively inhibit bacterial synthesis of folic acid and paraaminobenzoic acid.
Sulfisoxazole acetyl oral suspension	Gantrisin Syrup and Gantrisin Pediatric Suspension (Roche)	500 mg/5 mL	
Antidiarrheal			
Bismuth subsalicylate	Pepto-Bismol Liquid (Procter & Gamble)	262 mg/15 mL	For indigestion without causing constipation, nausea, control of diarrhea. Unlabeled use for prevention and treatment of traveler's (enterotoxigenic <i>Escherichia coli</i>) diarrhea, but not the first line of therapy for either
Antiflatulent			
Simethicone	Mylicon Drops (AstraZeneca)	40 mg/0.6 mL	Symptomatic treatment of gastrointestinal distress due to gas. Reduces surface tension of gas bubbles, enabling them to coalesce and be released through belching or flatus
Antifungals			
Nystatin	Nilstat (Wyeth)	100,000 U/mL	Antibiotic with antifungal activity. Suspension is held in mouth as long as possible before swallowing in treatment of mouth infections caused by <i>Candida (Monilia) albicans</i> , other <i>Candida</i> spp.
Antiprotozoal			
Atovaquone	Mepron Suspension (GlaxoSmithKline)	750 mg/5 mL	Indicated for the prevention of <i>Pneumocystis carinii</i> pneumonia
Antipsychotics, Sedatives, Antiemetics			
Hydroxyzine pamoate	Vistaril Oral Suspension (Pfizer)	25 mg/5 mL	Management of anxiety, tension, psychomotor agitation
Diuretic			
Chlorothiazide	Diuril Oral (Salix)	250 mg/5 mL	Interferes with renal tubular electrolyte reabsorption; increases sodium, chloride excretion

(Continued)

Table 14.1 ORAL SUSPENSIONS BY CATEGORY (Continued)

ORAL SUSPENSION	REPRESENTATIVE COMMERCIAL PRODUCTS	DRUG CONCENTRATION IN COMMERCIAL PRODUCT	COMMENTS
HIV Infections			
Nevirapine	Viramune Oral Suspension antiretroviral agents in treating HIV-1 (Boehringer Ingelheim)	50 mg/5 mL	Used in combination with other infections
Nonsteroidal Anti-inflammatory			
Indomethacin	Indocin Oral Suspension (Merck & Co.)	25 mg/5 mL	Active treatment of moderate to severe rheumatoid arthritis (including acute flares of chronic illness), moderate to severe osteoarthritis, acute painful shoulder (bursitis or tendinitis), acute gouty arthritis
Psychotropic			
Paroxetine HCl	Paxil Oral Suspension (Apotex)	10 mg/5 mL	Indicated for the treatment of major depressive disorder

For instance, sodium bicarbonate can produce sodium overload and systemic alkalosis, a hazard to patients on sodium-restricted diets. Magnesium preparations may lead to diarrhea and are dangerous to patients with diminished renal function because of those patients' inability to excrete all of the magnesium ion that may be absorbed; the gastric acid converts insoluble magnesium hydroxide to magnesium chloride, which is water soluble and is partially absorbed. Calcium carbonate carries the potential to induce hypercalcemia and stimulation of gastric secretion and acid production, the latter effect known as acid rebound. Excessive use of aluminum hydroxide may lead to constipation and phosphate depletion with consequent muscle weakness, bone resorption, and hypercalciuria.

The use to which an antacid is to be put is a major consideration in its selection. For instance, in the occasional treatment of heartburn or other infrequent episodes of gastric distress, a single dose of sodium bicarbonate or a magnesium hydroxide preparation may be desired. However, for treatment of

acute peptic ulcer or duodenal ulcer in which the therapeutic regimen includes frequent administration of antacids, sodium bicarbonate provides too much sodium, and magnesium hydroxide induces diarrhea. Thus, in the treatment of ulcerative conditions, a combination of magnesium hydroxide and aluminum hydroxide is frequently used because the latter agent has some constipating effects that counter the diarrhea effects of the magnesium hydroxide.

When frequent dosage administration is required and when gastroesophageal reflux is being treated, liquid antacids generally are preferred to tablet forms. For one thing, the liquid suspensions assert more immediate action, because they do not require time to disintegrate. It is important that an antacid have a reasonably fast onset of action, because gastric emptying may not allow it much time in the stomach. Endoscopic studies have shown that very little antacid remains in the fasting stomach 1 hour after administration. Therefore, the U.S. Food and Drug Administration (FDA) requires that antacid tablets not intended to be chewed must

disintegrate within 10 minutes in simulated gastric conditions. Generally, frequent food snacks prolong the time an antacid remains in the stomach and can prolong its action.

Because many antacids, especially aluminum- and calcium-containing products, interfere with absorption of other drugs, especially the fluoroquinolone and tetracycline antibiotics and iron salts, pharmacists must caution their patients against taking such drugs concomitantly.

In addition to the suspension forms of antacids, a number of official and commercial liquid antacid preparations of the magma and gel type will be mentioned later in this chapter. Generally, these liquid forms are pleasantly flavored (usually with peppermint) to enhance their palatability and patient appeal. Because liquid antacid preparations characteristically contain a large amount of solid material, they must be shaken vigorously to redistribute the antacid prior to administration. Also, a large dose of antacid is frequently required. Thus, many patients prefer to swallow one or two tablespoonfuls of a liquid preparation than to swallow whole or chew the corresponding number of tablets (commonly three to six) for the equivalent dose of drug.

Antibacterial Oral Suspensions

The antibacterial oral suspensions include preparations of antibiotic substances (e.g., erythromycin derivatives and tetracycline and its derivatives), sulfonamides (e.g., sulfamethoxazole and sulfisoxazole acetyl), other anti-infective agents (e.g., methenamine mandelate and nitrofurantoin), or combinations of these (e.g., sulfamethoxazole–trimethoprim).

Many antibiotic materials are unstable when maintained in solution for an appreciable length of time, and therefore, from a stability standpoint, insoluble forms of the drug substances in aqueous suspension or as dry powder for reconstitution (discussed next) are attractive to manufacturers. The antibiotic oral suspensions, including those prepared by reconstitution, provide a convenient way to administer dosages to infants and children and to adult patients who prefer liquid preparations to solid ones. Many



FIGURE 14.7 Calibrated droppers used in the administration of pediatric medications.

of the oral suspensions that are intended primarily for infants are packaged with a calibrated dropper to assist in the delivery of the prescribed dose. Some commercial pediatric antibiotic oral suspensions are pictured in Figure 14.4 and calibrated droppers in Figure 14.7.

The dispersing phase of antibiotic suspensions is aqueous and usually colored, sweetened, and flavored to render the liquid more appealing and palatable. As noted previously, the palmitate form of chloramphenicol was selected for the suspension dosage form not only because of its water insolubility but also because it is flavorless, which eliminates the necessity to mask the otherwise bitter taste of the chloramphenicol base.

Rectal Suspensions

Barium Sulfate for Suspension, USP, may be employed orally or rectally for diagnostic visualization of the gastrointestinal tract. Mesalamine (5-aminosalicylic acid) suspension was introduced to the market in 1988 as Rowasa (Alaven) for treatment of Crohn disease, distal ulcerative colitis, proctosigmoiditis, and proctitis. It is no longer commercially available but is compounded by pharmacists.

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Colocort (Paddock Laboratories) is a hydrocortisone rectal suspension indicated as adjunctive therapy in the treatment of ulcerative colitis and is packaged in a convenient disposable single-dose enema designed for self-administration. It contains 100 mg of hydrocortisone in 60 mL of an aqueous solution also containing carbomer 934P, polysorbate 80, purified water, sodium hydroxide, and methylparaben.

Dry Powders for Oral Suspension

A number of official and commercial preparations consist of dry powder mixtures or granules that are intended to be suspended in distilled water or some other vehicle prior to oral administration. As indicated previously, these official preparations have “for Oral Suspension” in their official title to distinguish them from prepared suspensions.

Most drugs prepared as a dry mix for oral suspension are antibiotics. The dry products are prepared commercially to contain the antibiotic drug, colorants (FD&C dyes), flavorants, sweeteners (e.g., sucrose or sodium saccharin), stabilizing agents (e.g., citric acid, sodium citrate), suspending agents (e.g., guar gum, xanthan gum, methylcellulose), and preserving agents (e.g., methylparaben, sodium benzoate) that may be needed to enhance the stability of the dry powder or granule mixture or the liquid suspension. When called on to reconstitute and dispense one of these products, the pharmacist loosens the powder at the bottom of the container by lightly tapping it against a hard surface and then adds the label-designated amount of purified water, usually in portions, and shakes the slurry until all of the dry powder has been suspended (Fig. 14.2). It is important to add precisely the prescribed amount of purified water to the dry mixture if the proper drug concentration per dosage unit is to be achieved. Also, the use of purified water rather than tap water is needed to avoid the possibility of adding impurities that could adversely affect the stability of the resulting preparation. Generally, manufacturers provide the dry powder or granule mixture in a slightly oversized container

to permit adequate shaking of the contents after the entire amount of purified water has been added. Pharmacists must realize that an oversized bottle is provided with each of these products, and they must carefully measure out the required amount of purified water. They should not “eyeball” the amount of water to be added or fill up the bottle with purified water. There are devices available to aid in accurate reconstitution, including the Fillmaster and/or the Fillmaster Plus. Among the official antibiotic drugs for oral suspension are the following:

Amoxicillin for Oral Suspension,
USP (Amoxil for Oral Suspension,
GlaxoSmithKline)
Ampicillin for Oral Suspension, USP
(Principen for Oral Suspension, Geneva)
Cefaclor for Oral Suspension, USP (Ceclor
for Oral Suspension, Lilly)
Cefixime for Oral Suspension, USP
(Suprax Powder for Oral Suspension,
Lupin Pharma)
Cephalexin for Oral Suspension, USP
(Keflex for Oral Suspension, Victory
Pharma)
Dicloxacillin Sodium for Oral Suspension,
USP (Pathocil for Oral Suspension,
Wyeth-Ayerst)
Doxycycline for Oral Suspension, USP
(Vibramycin Monohydrate for Oral
Suspension, Pfizer)
Erythromycin Ethylsuccinate for Oral
Suspension, USP (E.E.S. Granules for Oral
Suspension, Arbor Pharmaceuticals)

Several official antibiotics for oral suspension are also combined with other drugs. For example, erythromycin ethylsuccinate plus acetyl sulfisoxazole granules for oral suspension is indicated for the treatment of acute middle ear infection caused by susceptible strains of *Haemophilus influenzae*. Probenecid is combined with ampicillin for reconstitution and ultimate use for the treatment of uncomplicated infections (urethral, endocervical, or rectal) caused by *Neisseria gonorrhoeae* in adults.

Among the official drugs other than antibiotics prepared as dry powder mixtures for reconstitution to oral suspension are

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cholestyramine (Questran, Par), used in the management of hyperlipidemia, and barium sulfate (Barosperse, Mallinckrodt), used orally or rectally as a radiopaque contrast medium to visualize the gastrointestinal tract as an aid to diagnosis. Barium sulfate was introduced into medicine about 1910 as a contrast medium for roentgen ray examination of the gastrointestinal tract. It is practically insoluble in water, and thus its administration even in the large doses required is safe because it is not absorbed from the gastrointestinal tract. The pharmacist must be careful not to confuse barium sulfate with other forms of barium, such as barium *sulfide* and barium *sulfite*, which are soluble salts and are poisonous. Barium sulfate is a fine, nongritty, odorless, and tasteless white powder. When prepared as a suspension and administered orally, it is used to diagnose conditions of the hypopharynx, esophagus, stomach, small intestine, and colon. The barium sulfate renders the gastrointestinal tract opaque to the x-ray so as to reveal any abnormality in the anatomic features of the tract. When administered rectally, barium sulfate allows visualization of the features of the rectum and colon.

Commercially, barium sulfate for diagnostic use is available as a bulk powder containing the required suspending agents for effective reconstitution to an oral suspension or enema. Enema units, which contain prepared suspension in a ready-to-use and disposable bag, are also available.

EMULSIONS

An emulsion is a dispersion in which the dispersed phase is composed of small globules of a liquid distributed throughout a vehicle in which it is immiscible (Fig. 14.8). In emulsion terminology, the dispersed phase is the *internal phase*, and the dispersion medium is the *external* or *continuous phase*. Emulsions with an oleaginous internal phase and an aqueous external phase are *oil-in-water* (o/w) emulsions. Conversely, emulsions having an aqueous internal phase and an oleaginous external phase are termed *water-in-oil* (w/o) emulsions. Because the external phase of an

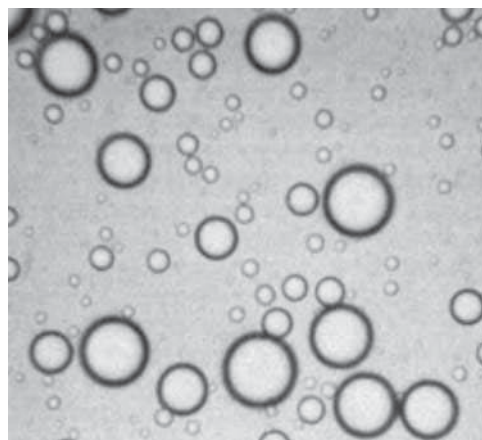


FIGURE 14.8 Mineral oil-in-water emulsion. The largest oil globule measures approximately 0.04 mm. (Courtesy of James C. Price, PhD, College of Pharmacy, University of Georgia.)

emulsion is continuous, an o/w emulsion may be diluted or extended with water or an aqueous preparation and a w/o emulsion, with an oleaginous or oil-miscible liquid. Generally, to prepare a stable emulsion, a third phase, an *emulsifying agent*, is necessary. Depending on their constituents, the viscosity of emulsions can vary greatly, and pharmaceutical emulsions may be prepared as liquids or semisolids. Based on the constituents and the intended application, liquid emulsions may be employed orally, topically, or parenterally and semisolid emulsions topically. Many pharmaceutical preparations that are actually emulsions are not classified as such because they fit some other pharmaceutical category more appropriately. For instance, emulsions include certain lotions, liniments, creams, ointments, and commercial vitamin drops that are discussed in this book under these various designations.

Purpose of Emulsions and of Emulsification

Emulsification enables the pharmacist to prepare relatively stable and homogeneous mixtures of two immiscible liquids. It permits administration of a liquid drug in the form of minute globules rather than in bulk. For orally administered emulsions, the o/w type permits palatable administration of

an otherwise distasteful oil by dispersing it in a sweetened, flavored aqueous vehicle. The reduced particle size of the oil globules may render the oil more digestible and more readily absorbed or, if that is not the intent, more effective in its task, as for example, the increased efficacy of mineral oil as a cathartic when emulsified.

Emulsions to be applied to the skin may be o/w or w/o, depending on such factors as the nature of the therapeutic agents, the desirability for an emollient or tissue-softening effect, and the condition of the skin. Medicinal agents that irritate the skin generally are less irritating in the internal phase of an emulsified topical preparation than in the external phase, from which direct contact with the skin is more prevalent. Naturally, the miscibility or solubility in oil and in water of a medicinal agent dictates to a great extent the vehicle, and its nature in turn suggests the phase of the emulsion that the resulting solution should become. On the unbroken skin, a w/o emulsion can usually be applied more evenly because the skin is covered with a thin film of sebum, and this surface is more readily wetted by oil than by water. A w/o emulsion is also more softening to the skin because it resists drying and removal by contact with water. On the other hand, if it is desirable to have a preparation that is easily removed from the skin with water, an o/w emulsion is preferred. Also, absorption through the skin (percutaneous absorption) may be enhanced by the diminished particle size of the internal phase. Other aspects of topical preparations are discussed in Chapters 10 and 11.

Theories of Emulsification

Many theories have been advanced in an attempt to explain how emulsifying agents promote emulsification and maintain the stability of the emulsion. Although certain of these theories apply rather specifically to certain types of emulsifying agents and to certain conditions (e.g., the pH of the phases of the system and the nature and relative proportions of the internal and external phases), they may be viewed in a general way to describe the manner in which emulsions may

be produced and stabilized. Among the most prevalent theories are the *surface tension theory*, the *oriented-wedge theory*, and the *plastic or interfacial film theory*.

All liquids have a tendency to assume a shape having the minimal surface area exposed. For a drop of a liquid, that shape is the sphere. A liquid drop has the shape of a sphere. It possesses internal forces that tend to promote association of the molecules to resist distortion of the sphere. If two or more drops of the same liquid come into contact with one another, the tendency is for them to join or to *coalesce*, making one larger drop having a smaller surface area than the total surface area of the individual drops. This tendency of liquids may be measured quantitatively, and when the surrounding of the liquid is air, it is referred to as the liquid's surface tension. When the liquid is in contact with a second liquid in which it is insoluble and immiscible, the force causing each liquid to resist breaking up into smaller particles is called interfacial tension. Substances that reduce this resistance encourage a liquid to break up into smaller drops or particles. These tension-lowering substances are *surface-active* (surfactant) or *wetting agents*. According to the *surface tension theory* of emulsification, the use of these substances as emulsifiers and stabilizers lowers the interfacial tension of the two immiscible liquids, reducing the repellent force between the liquids and diminishing each liquid's attraction for its own molecules. Thus, the surface-active agents facilitate the breaking up of large globules into smaller ones, which then have a lesser tendency to reunite or coalesce.

The *oriented-wedge* theory assumes monomolecular layers of emulsifying agent curved around a droplet of the internal phase of the emulsion. The theory is based on the presumption that certain emulsifying agents orient themselves about and within a liquid in a manner reflective of their solubility in that particular liquid. In a system containing two immiscible liquids, presumably the emulsifying agent is preferentially soluble in one of the phases and is embedded more deeply and tenaciously in that phase than the other. Because many molecules of substances upon

which this theory is based (e.g., soaps) have a hydrophilic or water-loving portion and a hydrophobic or water-hating portion (but usually lipophilic or oil loving), the molecules position or orient themselves into each phase. Depending on the shape and size of the molecules, their solubility characteristics, and thus their orientation, the wedge shape envisioned for the molecules causes either oil globules or water globules to be surrounded. Generally, an emulsifying agent having a greater hydrophilic than hydrophobic character will promote an o/w emulsion, and a w/o emulsion results from use of an emulsifying agent that is more hydrophobic than hydrophilic. Putting it another way, the phase in which the emulsifying agent is more soluble will become the continuous or external phase of the emulsion. Although this theory may not represent a totally accurate depiction of the molecular arrangement of the emulsifier molecules, the concept that water-soluble emulsifiers generally do form o/w emulsions is important and is frequently encountered in practice.

The *plastic* or *interfacial film theory* places the emulsifying agent at the interface between the oil and water, surrounding the droplets of the internal phase as a thin layer

of film adsorbed on the surface of the drops. The film prevents contact and coalescing of the dispersed phase; the tougher and more pliable the film, the greater the stability of the emulsion. Naturally, enough of the film-forming material must be available to coat the entire surface of each drop of the internal phase. Here again, the formation of an o/w or a w/o emulsion depends on the degree of solubility of the agent in the two phases, with water-soluble agents encouraging o/w emulsions and oil-soluble emulsifiers the reverse.

In actuality, it is unlikely that a single theory of emulsification can explain the means by which the many and varied emulsifiers promote emulsion formation and stability. It is more than likely that even within a given emulsion system, more than one of the aforementioned theories play a part. For instance, lowering of the interfacial tension is important in the initial formation of an emulsion, but the formation of a protective wedge of molecules or film of emulsifier is important for continued stability. No doubt certain emulsifiers are capable of both tasks. Physical Pharmacy Capsule 14.4 discusses Gibbs free energy and its application to the formulation of stable emulsions.



PHYSICAL PHARMACY CAPSULE 14.4

Gibbs Free Energy in an Emulsion

As previously discussed, pharmaceutical dispersions consist of two mutually insoluble phases or states of matter. In suspensions, settling and compaction of solid drug particles may occur as well as clumping or aggregation of particles (flocculation is aggregation that is reversible upon vigorous agitation or shaking). In emulsions, creaming (a reversible weak association of internal phase droplets) and cracking (an irreversible coalescence of internal phase droplets) may occur. The latter may result to minimize Gibbs free energy by minimizing the surface area of the internal phase.

Gibbs free energy states

$$\Delta G = \Delta A\gamma$$

where

Δ is the size of change in G and A ,
 ΔG naturally "seeks" to 0 or a minimum,

PHYSICAL PHARMACY CAPSULE 14.4 CONT.

A is the total surface area of dispersed particles, and γ is the interfacial tension, or interphase repulsion, that is,
 liquid repels liquid in emulsions,
 liquid repels solid in suspensions,
 liquid repels gas, and
 solid repels gas in inhalations.

A large " ΔG " forces "A" to a minimum unless " γ " is greatly reduced to compensate for a large "A."

Good emulsions and suspensions must have a very large "A" for dosing consistency; thus, they must also have a very small " γ ."

The natural instability of dispersions is due to

A large "A" and a large " γ ," which cause a large "G"

A large "G" and a large " γ ," which cause emulsified droplets and suspended particles, or the internal phase, to aggregate to reduce "A" to reduce "G"

Stable emulsions and suspensions must have a large "A" and a small "G" concurrently for consistent and uniform dosing. This is done by decreasing " γ ," which will decrease "G," which will decrease self-attraction of dispersed phase particles.

EXAMPLE

Area increase in o/w emulsion

Fifty milliliter of an oil in a graduated cylinder has a total A = 80 cm².

This 50 mL is processed to make 9.55×10^{13} droplets of 1×10^{-4} cm diameter each.

Each droplet has an A = 7.854×10^{-9} cm².

The total "A" of the 50 mL as 1- μ m diameter droplets is

$$(7.854 \times 10^{-9} \text{ cm}^2 / \text{droplet}) \times (9.55 \times 10^{13} \text{ droplets}) = 7.5 \times 10^5 \text{ cm}^2$$

$$\Delta A = \frac{7.5 \times 10^5 \text{ cm}^2}{80 \text{ cm}^2} = 9.38 \times 10^3$$

For this emulsion to be stable, the " γ " must be decreased by nearly 9,400 times to minimize "G."

Preparation of Emulsions

Emulsifying Agents

The initial step in preparation of an emulsion is selection of the emulsifier. To be useful in a pharmaceutical preparation, the emulsifying agent must be compatible with the other formulative ingredients and must not interfere with the stability or efficacy of the therapeutic agent. It should be stable and not deteriorate in the preparation. The emulsifier should be nontoxic with respect to its intended use and the amount to be consumed by the patient. Also, it should possess little odor, taste, or color. Of prime importance is the capability

of the emulsifying agent to promote emulsification and to maintain the stability of the emulsion for the intended shelf life of the product.

Various types of materials have been used in pharmacy as emulsifying agents, with hundreds, if not thousands, of individual agents tested for their emulsification capabilities. Although no attempt will be made here to discuss the merits of each of these agents in pharmaceutical emulsions, it would be well to point out the types of materials that are commonly used and their general application. Among the emulsifiers and stabilizers for pharmaceutical systems are the following:

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1. Carbohydrate materials, such as the naturally occurring agents acacia, tragacanth, agar, chondrus, and pectin. These materials form hydrophilic colloids, which, when added to water, generally produce o/w emulsions. Acacia is frequently used in the preparation of extemporaneous emulsions. Tragacanth and agar are commonly employed as thickening agents in acacia-emulsified products. Microcrystalline cellulose is employed in a number of commercial suspensions and emulsions as a viscosity regulator to retard particle settling and provide dispersion stability.
2. Protein substances, such as gelatin, egg yolk, and casein. These substances produce o/w emulsions. The disadvantage of gelatin as an emulsifier is that the emulsion frequently is too fluid and becomes more fluid upon standing.
3. High molecular weight alcohols, such as stearyl alcohol, cetyl alcohol, and glyceryl monostearate. These are employed primarily as thickening agents and stabilizers for o/w emulsions of certain lotions and ointments used externally. Cholesterol and cholesterol derivatives may also be employed in externally used emulsions to promote w/o emulsions.
4. Wetting agents, which may be anionic, cationic, or nonionic. These agents contain both hydrophilic and lipophilic groups, with the lipophilic protein of the molecule generally accounting for the surface activity of the molecule. In anionic agents, this lipophilic portion is negatively charged, but in the cationic agent, it is positively charged. Owing to their opposing ionic charges, anionic and cationic agents tend to neutralize each other and are thus considered incompatible. Nonionic emulsifiers show no inclination to ionize. Depending on their individual nature, certain members of these groups form o/w emulsions and others w/o emulsions. Anionic emulsifiers include various monovalent, polyvalent, and organic soaps, such as triethanolamine oleate, and sulfonates, such as sodium lauryl sulfate. Benzalkonium chloride, known primarily

for its bactericidal properties, may be employed as a cationic emulsifier. Agents of the nonionic type include the sorbitan esters and the polyoxyethylene derivatives, some of which appear in Table 14.2.

The ionic nature of a surfactant is a prime consideration. Nonionic surfactants are effective over pH range of 3 to 10, cationic surfactants are effective over

Table 14.2 HLB VALUES FOR SELECTED EMULSIFIERS

AGENT	HLB
Ethylene glycol distearate	1.5
Sorbitan tristearate (Span 65 ^a)	2.1
Propylene glycol monostearate	3.4
Triton X-15 ^b	3.6
Sorbitan monooleate (Span 80 ^a)	4.3
Sorbitan monostearate (Span 60 ^a)	4.7
Diethylene glycol monolaurate	6.1
Sorbitan monopalmitate (Span 40 ^a)	6.7
Sucrose dioleate	7.1
Acacia	8.0
Amercol L-101 ^c	8.0
Polyoxyethylene lauryl ether (Brij 30 ^a)	9.7
Gelatin	9.8
Triton X-45 ^b	10.4
Methylcellulose	10.5
Polyoxyethylene monostearate (Myrj 45 ^a)	11.1
Triethanolamine oleate	12.0
Tragacanth	13.2
Triton X-100 ^b	13.5
Polyoxyethylene sorbitan monostearate (Tween 60 ^a)	14.9
Polyoxyethylene sorbitan monooleate (Tween 80 ^a)	15.0
Polyoxyethylene sorbitan monolaurate (Tween 20 ^a)	16.7
Pluronic F 68 ^d	17.0
Sodium oleate	18.0
Potassium oleate	20.0
Sodium lauryl sulfate	40.0

^aICI Americas, Wilmington, Delaware.

^bRohm and Haas, Philadelphia, Pennsylvania.

^cAmerchol Corporation, Edison, New Jersey.

^dBASF-Wyandotte Chemical, Parsippany, New Jersey.

pH range of 3 to 7, and anionic surfactants require a pH greater than 8 (6).

5. Finely divided solids such as colloidal clays, including bentonite, magnesium hydroxide, and aluminum hydroxide. Generally, these form o/w emulsions when the insoluble material is added to the aqueous phase if there is a greater volume of the aqueous phase than of the oleaginous phase. However, if the powdered solid is added to the oil and the oleaginous phase volume predominates, a substance such as bentonite is capable of forming a w/o emulsion. The relative volume of internal and external phases of an emulsion is important, regardless of the type of emulsifier used. As the internal concentration of an emulsion increases, so does the viscosity of the emulsion to a certain point, after which the viscosity decreases sharply. At this point, the emulsion has undergone *inversion*, that is, it has changed from an o/w emulsion to a w/o or vice versa. In practice, emulsions may be prepared without inversion with as much as about 75% of the volume of the product being internal phase.

The HLB System

Generally, each emulsifying agent has a hydrophilic portion and a lipophilic portion, with one or the other being more or less predominant and influencing in the manner already described the type of emulsion. A method has been devised (7,8) whereby emulsifying or surface-active agents may be categorized on the basis of their chemical makeup as to their hydrophilic-lipophilic balance, or HLB. By this method, each agent is assigned an HLB value or number indicating the substance's polarity. Although the numbers have been assigned up to about 40, the usual range is between 1 and 20. Materials that are highly polar or hydrophilic have been assigned higher numbers than materials that are less polar and more lipophilic. Generally, surface-active agents having an assigned HLB value of 3 to 6 are greatly lipophilic and produce w/o emulsions, and agents with HLB values of about 8 to 18 produce o/w emulsions. Examples

Table 14.3 ACTIVITY AND HLB VALUE OF SURFACTANTS

ACTIVITY	ASSIGNED HLB
Antifoaming	1-3
Emulsifiers (w/o)	3-6
Wetting agents	7-9
Emulsifiers (o/w)	8-18
Solubilizers	15-20
Detergents	13-16

of assigned HLB values for some surfactants are shown in Table 14.2. The type of activity to be expected from surfactants of assigned HLB numbers is presented in Table 14.3.

In the HLB system, in addition to the emulsifying agents, values are assigned to oils and oil-like substances. One selects emulsifying agents having the same or nearly the same HLB value as the oleaginous phase of the intended emulsion. For example, mineral oil has an assigned HLB value of 4 if a w/o emulsion is desired and a value of 10.5 if an o/w emulsion is to be prepared. To prepare a stable emulsion, the emulsifying agent should have an HLB value similar to the one for mineral oil, depending on the type of emulsion desired. When needed, two or more emulsifiers may be combined to achieve the proper HLB value.

Physical Pharmacy Capsules 14.5 and 14.6 summarize the activities of surfactants and the calculations to determine the quantity of surfactant required for a stable emulsion.

Methods of Emulsion Preparation

Emulsions may be prepared by several methods, depending upon the nature of the components and the equipment. On a small scale, as in the laboratory or pharmacy, emulsions may be prepared using a dry Wedgwood or porcelain mortar and pestle; a mechanical blender or mixer, such as a Waring blender or a milkshake mixer; a hand homogenizer (Fig. 14.9); a bench-type homogenizer (Fig. 14.10); or sometimes a simple prescription bottle. On a large scale, large mixing tanks (Fig. 14.5) may be used to form the emulsion through the action of a high-speed impeller.



PHYSICAL PHARMACY CAPSULE 14.5

Blending of Surfactants

Wetting agents are surfactants with HLB values of 7 to 9. Wetting agents aid in attaining intimate contact between solid particles and liquids.

Emulsifying agents are surfactants with HLB values of 3 to 6 or 8 to 18. Emulsifying agents reduce interfacial tension between oil and water, minimizing surface energy through the formation of globules.

Detergents are surfactants with HLB values of 13 to 16. Detergents will reduce the surface tension and aid in wetting the surface and the dirt. The soil will be emulsified, and foaming generally occurs and a washing away of the dirt.

Solubilizing agents have HLB values of 15 to 20.

HLB values are additive, and often, surfactants are blended. For example, if 20 mL of an HLB of 9.0 is required, two surfactants (with HLB values of 8.0 and 12.0) can be blended in a 3:1 ratio. The following quantities of each will be required:

$$0.75 \times 8.0 = 6.0$$

$$0.25 \times 12.0 = 3.0$$

$$\text{Total HLB} = 9.0$$



PHYSICAL PHARMACY CAPSULE 14.6

Surface Area of Globules

The following is a sample calculation for determining the quantity of surfactant required to prepare a stable o/w emulsion.

A surface-active agent will spread itself as a single layer when applied to the surface of still water. The dimensions of a molecule can be determined by their surface orientation. For example, if a micropipette is used to deliver 3 μL of a surfactant to the clean, quiet surface of water, the area over which it spreads, determined experimentally using a film balance, is 12,000 cm^2 . The actual thickness of the film can be calculated by dividing the volume of surfactant applied by the surface area, as follows:

$$\frac{0.003 \text{ cm}^3}{12,000 \text{ cm}^2} = 2.5 \times 10^{-7} \text{ cm}$$

The surfactant has a density of 0.910 g/mL and a molecular weight of 325 g/mol. To calculate the cross-sectional area occupied by each molecule, divide the area of the monomolecular film by the number of molecules in the 3 mL of surfactant comprising the film, as follows:

1. Obtain the weight of the surfactant by multiplying the volume by the density (0.003 mL $\times$ 0.910 g/mL = 0.00273 g).
2. To calculate the number of moles present, divide the weight of the surfactant by its molecular weight (0.00273 g/325 g/mol = 8.4×10^{-6} mol).
3. The number of molecules present is the number of moles times Avogadro number ($8.4 \times 10^{-6} \times 6.02 \times 10^{23}$ = 5.0568×10^{18} molecules).

PHYSICAL PHARMACY CAPSULE 14.6 CONT.

4. The cross-sectional area can now be calculated by dividing the surface area by the number of molecules ($12,000 \text{ cm}^2 / 5.0568 \times 10^{18} \times 2.373 \times 10^{-15} \text{ cm}^2 \times 23.73 \times 10^{-16}$ or approximately 24 square angstroms).

The quantity of surfactant required to emulsify a selected quantity of oil for the preparation of an oil-in-water emulsion can be calculated as follows:

EXAMPLE

To emulsify 50 mL of oil to an average globular diameter of 1 μg , the volume of each globule is

$$V_i = \frac{4}{3}\pi r^3 = \frac{4}{3}\pi (0.5 \times 10^{-4})^3 = 0.524 \times 10^{-12} \text{ mL}$$

To calculate the number of globules per milliliter, divide 1 mL by the volume of each globule:

$$\frac{1 \text{ mL}}{0.524 \times 10^{-12} \text{ mL / globule}} = 1.91 \times 10^{12} \text{ globules / mL}$$

The surface area (S) of each individual globule will be

$$S = 4\pi r^2 = 4\pi (0.5 \times 10^{-4})^2 = 3.14 \times 10^{-8} \text{ cm}^2$$

and the surface area of all the globules in 1 mL of oil is

$$(1.91 \times 10^{12}) \times (3.14 \times 10^{-8}) = 6 \times 10^4 \text{ cm}^2$$

The number of surfactant molecules that will be adsorbed at the interface of the oil globules and the dispersion medium from 1 mL of oil is equal to the total surface area divided by the cross-sectional area of the surfactant:

$$\frac{6 \times 10^4 \text{ cm}^2}{2.373 \times 10^{-15} \text{ cm}^2 / \text{molecule}} = 2.528 \times 10^{19} \text{ molecules}$$

The number of moles of surfactant required to emulsify 1 mL of oil is equal to the number of molecules adsorbed at the interface divided by Avogadro number:

$$\frac{2.528 \times 10^{19} \text{ molecules}}{6.02 \times 10^{23} \text{ molecules / mole}} = 4.199 \times 10^{-5} \text{ moles}$$

and the quantity required for 50 mL will be

$$50 \text{ mL} \times 4.199 \times 10^{-5} \text{ moles / mL} = 2.095 \times 10^{-3} \text{ moles}$$

$$2.095 \times 10^{-3} \text{ moles} \times 325 \text{ g / mole} = 0.681 \text{ g, or } 681 \text{ mg}$$

Therefore, 681 mg of surfactant will be required to emulsify 50 mL of the oil.



FIGURE 14.9 Laboratory preparation of an emulsion using a hand homogenizer.

As desired, the product may be rendered finer by passage through a colloid mill, in which the particles are sheared between the small gap separating a high-speed rotor and the stator, or by passage through a large homogenizer, in which the liquid is forced under great pressure through a small valve opening. Industrial homogenizers have the capacity to handle as much as 100,000 L of product per hour.

In the small-scale extemporaneous preparation of emulsions, three methods may be used. They are the *continental* or *dry gum method*, the *English* or *wet gum method*, and the *bottle* or *Forbes bottle method*. In the first method, the emulsifying agent (usually acacia) is mixed with the oil before the addition of water, that is, dry gum. In the second method, the emulsifying agent is added to the water (in which it is soluble) to form a mucilage, and then the oil is slowly incorporated to form the emulsion, that is, wet gum. The bottle method is reserved for volatile oils or less viscous oils and is a variation of the dry gum method.

Continental or Dry Gum Method

The continental method is also referred to as the 4:2:1 method because for every 4 parts by volume of oil, 2 parts of water and 1 part of gum are added in preparing the initial or *primary emulsion*. For instance, if 40 mL of oil is to be emulsified, 20 mL of water and 10 g



FIGURE 14.10 Brinkmann Homogenizer Models PT 10/35 and PT 45/80 with accessories. The equipment is used for homogenization, dispersion, and emulsification of solids or liquids. Volumes range from 0.5 mL to 25 L. (Courtesy of Kinematica, Inc.)

of gum would be employed in the primary emulsion, with any additional water or other formulation ingredients added afterward. In this method, the acacia or other o/w emulsifier is triturated with the oil in a perfectly dry Wedgwood or porcelain mortar until thoroughly mixed. A mortar with a rough rather than smooth inner surface must be used to ensure proper grinding action and reduction of the globule size. A glass mortar is too smooth to produce the proper reduction of the internal phase. After the oil and

gum have been mixed, the two parts of water are added all at once, and the mixture is triturated immediately, rapidly, and continuously until the primary emulsion is creamy white and produces a crackling sound to the movement of the pestle. Generally, about 3 minutes of mixing is required to produce a primary emulsion. Other liquid formulative ingredients that are soluble in or miscible with the external phase may then be mixed into the primary emulsion. Solid substances such as preservatives, stabilizers, colorants, and any flavoring material are usually dissolved in a suitable volume of water (assuming water is the external phase) and added as a solution to the primary emulsion. Any substances that might interfere with the stability of the emulsion or the emulsifying agent are added as near last as is practical. For instance, alcohol has a precipitating action on gums such as acacia; thus, no alcohol or solution containing alcohol should be added directly to the primary emulsion, because the total alcoholic concentration of the mixture would be greater at that point than after other diluents were added. When all necessary agents have been added, the emulsion is transferred to a graduate and made to volume with water previously swirled about in the mortar to remove the last portion of emulsion.

Provided the dispersion of the acacia in the oil is adequate, the dry gum method can almost be guaranteed to produce an acceptable emulsion. Sometimes, however, the amount of acacia must be adjusted upward to ensure that an emulsion can be produced. For example, volatile oils, liquid petrolatum (mineral oil), and linseed oil usually require a 3:2:1 or 2:2:1 ratio for adequate preparation. Rather than using a mortar and pestle, the pharmacist can generally prepare an excellent emulsion using the dry gum method and an electric mixer or blender.

English or Wet Gum Method

By this method, the same proportions of oil, water, and gum are used as in the continental or dry gum method, but the order of mixing is different, and the proportion of ingredients may be varied during the preparation of the

primary emulsion as is deemed necessary by the operator. Generally, a mucilage of the gum is prepared by triturating in a mortar granular acacia with twice its weight of water. The oil is then added slowly in portions, and the mixture is triturated to emulsify the oil. Should the mixture become too thick, additional water may be blended into the mixture before another portion of oil is added. After all of the oil has been added, the mixture is thoroughly mixed for several minutes to ensure uniformity. Then, as with the continental or dry gum method, the other formulative materials are added, and the emulsion is transferred to a graduate and brought to volume with water.

Bottle or Forbes Bottle Method

The bottle method is useful for the extemporaneous preparation of emulsions from volatile oils or oleaginous substances of low viscosities. Powdered acacia is placed in a dry bottle, two parts of oil are added, and the mixture is thoroughly shaken in the capped container. A volume of water approximately equal to that of the oil is then added in portions and the mixture thoroughly shaken after each addition. When all of the water has been added, the primary emulsion thus formed may be diluted to the proper volume with water or an aqueous solution of other formulative agents.

This method is not suited for viscous oils because they cannot be thoroughly agitated in the bottle when mixed with the emulsifying agent. When the intended dispersed phase is a mixture of fixed oil and volatile oil, the dry gum method is generally employed.

Auxiliary Methods

An emulsion prepared by either the wet gum or the dry gum method can generally be increased in quality by passing it through a hand homogenizer. In this apparatus, the pumping action of the handle forces the emulsion through a very small orifice that reduces the globules of the internal phase to about 5 μm and sometimes less. The hand homogenizer is less efficient in reducing the particle size of very thick emulsions, and it should not be employed for emulsions

containing a high proportion of solid matter because of possible damage to the valve.

In Situ Soap Method

The two types of soaps developed by this method are calcium soaps and soft soaps. Calcium soaps are w/o emulsions that contain certain vegetable oils, such as oleic acid, in combination with limewater (synonym: Calcium Hydroxide Solution, USP). They are prepared simply by mixing equal volumes of the oil and limewater. The emulsifying agent in this instance is the calcium salt of the free fatty acid formed from the combination of the two entities. In the case of olive oil, the free fatty acid is oleic acid, and the resultant emulsifying agent is calcium oleate. A difficulty that sometimes arises when preparing this self-emulsifying product is that the amount of free fatty acids in the oil may be insufficient on a 1:1 basis with calcium hydroxide. Typically, to make up for this deficiency, a little excess of the olive oil, or even a small amount of oleic acid, is needed to ensure a nice, homogeneous emulsion. Otherwise, tiny droplets of water form on the surface of the preparation. Because the oil phase is the external phase, this formulation is ideal where occlusion and skin softening are desired, such as for itchy, dry skin or sunburned skin. A typical example of this emulsion is calamine liniment:

Calamine	
Zinc oxide aa	80.0 g
Olive oil	
Calcium hydroxide solution aa qs ad	1,000.0 mL

Microemulsions

Microemulsions are thermodynamically stable, optically transparent isotropic mixtures of a biphasic o/w system stabilized with surfactants. The diameter of droplets in a *microemulsion* may be in the range of 100 Å (10 mμ) to 1,000 Å, whereas in a *macroemulsion*, the droplets may be 5,000 Å in diameter (6). Both o/w and w/o microemulsions may be formed spontaneously by agitating the oil and water phases with carefully selected

surfactants. The type of emulsion produced depends on the properties of the oil and surfactants.

Hydrophilic surfactants may be used to produce transparent o/w emulsions of many oils, including flavor oils and vitamin oils such as A, D, and E. Surfactants in the HLB range of 15 to 18 have been used most extensively in the preparation of such emulsions. These emulsions are dispersions of oil, not true solutions; however, because of the appearance of the product, the surfactant is commonly said to solubilize the oil. Surfactants commonly used in the preparation of such oral liquid formulations are polysorbate 60 and polysorbate 80.

Among the advantages cited for the use of microemulsions in drug delivery are more rapid and efficient oral absorption of drugs than through solid dosage forms, enhanced transdermal drug delivery through increased diffusion into the skin, and the unique potential application of microemulsions in the development of artificial red blood cells and targeting of cytotoxic drugs to cancer cells (6).

Stability of Emulsions

Generally speaking, an emulsion is considered to be physically unstable if (a) the internal or dispersed phase upon standing tends to form aggregates of globules, (b) large globules or aggregates of globules rise to the top or fall to the bottom of the emulsion to form a concentrated layer of the internal phase, and (c) if all or part of the liquid of the internal phase separates and forms a distinct layer on the top or bottom of the emulsion as a result of the coalescing of the globules of the internal phase. In addition, an emulsion may be adversely affected by microbial contamination and growth and by other chemical and physical alterations.

Aggregation and Coalescence

Aggregates of globules of the internal phase have a greater tendency than do individual particles to rise to the top of the emulsion or fall to the bottom. Such a preparation of the globules is termed the *creaming* of

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the emulsion, and provided coalescence is absent, it is a reversible process. The term is taken from the dairy industry and is analogous to creaming or rising to the top of cream in milk that is allowed to stand. The creamed portion of an emulsion may be redistributed rather homogeneously upon shaking, but if the aggregates are difficult to disassemble or if insufficient shaking is employed before each dose, improper dosage of the internal phase substance may result. Furthermore, a creamed emulsion is not esthetically acceptable to the pharmacist or appealing to the consumer. More important, it increases the risk that the globules will coalesce.

According to the Stokes equation (Physical Pharmacy Capsule 14.1), the rate of separation of the dispersed phase of an emulsion may be related to such factors as the particle size of the dispersed phase, the difference in density between the phases, and the viscosity of the external phase. It is important to recall that the rate of separation is increased by increased particle size of the internal phase, larger density difference between the two phases, and decreased viscosity of the external phase. Therefore, to increase the stability of an emulsion, the globule or particle size should be reduced as fine as is practically possible, the density difference between the internal and external phases should be minimal, and the viscosity of the external phase should be reasonably high. Thickeners such as tragacanth and microcrystalline cellulose are frequently added to emulsions to increase the viscosity of the external phase. Upward creaming takes place in unstable emulsions of the o/w or the w/o type in which the internal phase has a lesser density than the external phase. Downward creaming takes place in unstable emulsions in which the opposite is true.

More destructive to an emulsion than creaming is coalescence of the globules of the internal phase and separation of that phase into a layer. Separation of the internal phase from the emulsion is called breaking, and the emulsion is described as being cracked or broken. This is irreversible, because the protective sheath about the globules of the internal phase no longer exists. Attempts

to reestablish the emulsion by agitation of the two separate layers are generally unsuccessful. Additional emulsifying agent and reprocessing through appropriate machinery are usually necessary to reproduce an emulsion.

Generally, care must be taken to protect emulsions against extremes of cold and heat. Freezing and thawing coarsen an emulsion and sometimes break it. Excessive heat has the same effect. Because emulsion products may be transported to and used in locations with climates of extremely high or low temperature, manufacturers must know their emulsions' stability before they may be shipped. For most emulsions, the industry performs tests at 5°C, 40°C, and 50°C (41°F, 104°F, and 122°F) to determine the product's stability. Stability at both 5°C and 40°C for 3 months is considered minimal. Shorter exposure periods at 50°C may be used as an alternative test.

Because other environmental conditions, such as the presence of light, air, and contaminating microorganisms, can adversely affect the stability of an emulsion, appropriate formulative and packaging steps are usually taken to minimize such hazards to stability. For light-sensitive emulsions, light-resistant containers are used. For emulsions susceptible to oxidative decomposition, antioxidants may be included in the formulation and adequate label warning provided to ensure that the container is tightly closed to air after each use. Many molds, yeasts, and bacteria can decompose the emulsifying agent, disrupting the system. Even if the emulsifier is not affected by the microbes, the product can be rendered unsightly by their presence and growth and will of course not be efficacious from a pharmaceutical or therapeutic standpoint. Because fungi (molds and yeasts) are more likely to contaminate emulsions than are bacteria, fungistatic preservatives, commonly combinations of methylparaben and propylparaben, are generally included in the aqueous phase of an o/w emulsion. Alcohol in the amount of 12% to 15% based on the external phase volume is frequently added to oral o/w emulsions for preservation.

Examples of Oral Emulsions

Mineral Oil Emulsion

Mineral oil emulsion, or liquid petrolatum emulsion, is an o/w emulsion prepared from the following formula:

Mineral oil	500 mL
Acacia (finely powdered)	125 g
Syrup	100 mL
Vanillin	40 mg
Alcohol	60 mL
Purified water, to make	1,000 mL

It is prepared by the dry gum method (4:2:1), mixing the oil with the acacia and adding 250 mL of purified water all at once to make the primary emulsion. To this is slowly added with trituration the remainder of the ingredients, with the vanillin dissolved in the alcohol. A substitute flavorant for the vanillin, a substitute preservative for the alcohol, a substitute emulsifying agent for the acacia, and an alternative method of emulsification may be used as desired.

The emulsion is employed as a lubricating cathartic with a usual dose of 30 mL. The usual dose of plain (unemulsified) mineral oil for the same purpose is 15 mL. The emulsion is much more palatable than the unemulsified oil. Both are best taken an hour before bedtime. There are a number of commercial preparations of emulsified oil, with many containing additional cathartic agents such as phenolphthalein, milk of magnesia, agar, and others.

Castor Oil Emulsion

Castor oil emulsion is used as a laxative for isolated occurrences of constipation and in preparation of the colon for radiographic and endoscopic examination. The castor oil in the emulsion works directly on the small intestine to promote bowel movement. This and other laxatives should not be used regularly or excessively, as they can lead to dependence for bowel movement. Overuse of castor oil may cause excessive loss of water and body electrolytes, which can have a debilitating effect. Laxatives should not be used when nausea, vomiting,

or abdominal pain is present, because these symptoms may indicate appendicitis, and use of a laxative in this instance could promote rupturing of the appendix.

The amount of castor oil in commercial emulsions varies from about 35% to 67%. The amount of oil influences the dose required. Generally, for an emulsion containing about two-thirds oil, the adult dose is 45 mL, about 3 tablespoonsful. For children 2 to 6 years of age, 15 mL is usually sufficient, and for children less than 2 years of age, 5 mL may be given. Castor oil is best taken on an empty stomach, followed with one full glass of water.

Simethicone Emulsion

Simethicone emulsion is a water-dispersible form of simethicone used as a defoaming agent for the relief of painful symptoms of excessive gas in the gastrointestinal tract. Simethicone emulsion works in the stomach and intestines by changing the surface tension of gas bubbles, enabling them to coalesce, freeing the gas for easier elimination. The emulsion in drop form is useful for relief of gas in infants due to colic, air swallowing, or lactose intolerance. The commercial product (Mylicon Drops, AstraZeneca) contains 40 mg of simethicone per 0.6 mL. Simethicone is also present in a number of antacid formulations (e.g., Mylanta, Johnson & Johnson Merck) as a therapeutic adjunct to relieve the discomfort of gas.

Examples of Topical Emulsions

Many of the hand and body lotions used to treat dry skin are o/w emulsions. A lotion is an emulsion liquid dosage form applied to the outer surface of the body. Historically, this term has also been applied to suspensions and solutions. A number of topical emulsions, or lotions, are used therapeutically to deliver a drug systemically. An example is Estrasorb (estradiol, Graceway), which contains estradiol for use in the treatment of hot flashes and night sweats accompanying menopause. It works by replacing the hormones lost during menopause. Corticosteroid-containing emulsions include Lotrimin AF (clotrimazole, Schering-Plough)

and Diprolene (augmented betamethasone dipropionate, Schering-Plough).

A shampoo is a solution, emulsion, or suspension dosage form used to clean the hair and scalp. It may contain an active pharmaceutical ingredient intended for topical application to the scalp.

GELS AND MAGMAS

Gels are defined as semisolid systems consisting of dispersions made up of either small inorganic particles or large organic molecules enclosing and interpenetrated by a liquid.

Gels are also defined as semirigid systems in which the movement of the dispersing medium is restricted by an interlacing three-dimensional network of particles or solvated macromolecules of the dispersed phase. A high degree of physical or chemical cross-linking may be involved. The increased viscosity caused by the interlacing and consequential internal friction is responsible for the semisolid state. A gel may consist of twisted matted strands often wound together by stronger types of van der Waals forces to form crystalline and amorphous regions throughout the system, such as tragacanth and CMC.

Some gel systems are as clear as water, and others are turbid because the ingredients may not be completely molecularly dispersed (soluble or insoluble), or they may form aggregates, which disperse light. The concentration of the gelling agents is mostly <10%, usually in 0.5% to 2.0% range, with some exceptions.

Gels in which the macromolecules are distributed so that no apparent boundaries exist between them and the liquids are called *single-phase gels*. When the gel mass consists of floccules of small, distinct particles, the gel is classified as a two-phase system and frequently called a *magma* or a *milk*. Gels and magmas are considered colloidal dispersions because they contain particles of colloidal dimension.

Colloidal Dispersions

Many of the various types of colloidal dispersions have been given appropriate names. For instance, *sol* is a general term to designate a

dispersion of a solid substance in a liquid, solid, or gaseous medium. However, more often than not, it is used to describe the solid-liquid dispersion system. To be more descriptive, a prefix such as *hydro-* for water (*hydrosol*) or *alco-* for alcohol (*alcosol*) may be employed to indicate the dispersion medium. The term *aerosol* has similarly been developed to indicate a dispersion of a solid or a liquid in a gaseous phase.

Although there is no precise point at which the size of a particle in a dispersion can be considered to be colloidal, there is a generally accepted size range. A substance is said to be colloidal when its particles fall between 1 nm and 0.5 μm . Colloidal particles are usually larger than atoms, ions, or molecules and, generally, consist of aggregates of many molecules, although in certain proteins and organic polymers, single large molecules may be of colloidal dimension and form colloidal dispersions. One difference between colloidal dispersions and true solutions is the larger particle size of the disperse phase of the colloidal dispersion. Another difference is the optical properties of the two systems. True solutions do not scatter light and, therefore, appear clear, but colloidal dispersions contain opaque particles that do scatter light and thus appear turbid. This turbidity is easily seen, even with dilute preparations, when the dispersion is observed at right angles to a beam of light passed through the dispersion (Tyndall effect). Although reference is made here to dilute colloidal dispersions, most pharmaceutical preparations contain high concentrations of colloidal particles, and in these instances, there is no difficulty in observing turbidity. In fact, certain preparations are opaque, depending on the concentration of the disperse phase. Also, the particle size of the dispersed phase in some pharmaceutical preparations is not uniform, and a preparation may contain particles within and outside of the colloidal range, giving the preparation more of an opaque appearance than if all particles were uniformly colloidal.

Particle size is not the only important criterion for establishing the colloidal state. The nature of the dispersing phase with respect

to the disperse phase is also of great importance. The attraction or lack of attraction between the disperse phase and the dispersion medium affects both ease of preparation and the character of the dispersion. Certain terminology has been developed to characterize the various degrees of attraction between the phases of a colloidal dispersion. If the disperse phase interacts appreciably with the dispersion medium, it is said to be *lyophilic*, meaning solvent loving. If the degree of attraction is small, the colloid is termed *lyophobic*, or solvent hating. These terms are more suitably used when reference is made to the specific dispersion medium, for a single substance may be lyophobic with respect to one dispersion medium and lyophilic with respect to another. For instance, starch is lyophilic in water but lyophobic in alcohol. Terms such as *hydrophilic* and *hydrophobic*, which are more descriptive of the nature of the colloidal property, have therefore been developed to refer to the attraction or lack of attraction of the substance specifically to water. Generally speaking, because of the attraction to the solvent of lyophilic substances in contrast to the lack of attraction of lyophobic substances, lyophilic colloidal systems are easier to prepare and have greater stability. A third type of colloidal sol, termed an *association* or *amphiphilic colloid*, is formed by grouping or association of molecules that exhibit both lyophilic and lyophobic properties.

Lyophilic colloids are large organic molecules capable of being solvated or associated with the molecules of the dispersing phase. These substances disperse readily upon addition to the dispersion medium to form colloidal dispersions. As more molecules of the substance are added to the sol, the viscosity characteristically increases, and when the concentration of molecules is sufficiently high, the liquid sol may become a semisolid or solid dispersion, termed a *gel*. Gels owe their rigidity to an intertwining network of the disperse phase that entraps and holds the dispersion medium. A change in temperature can cause certain gels to resume the sol or liquid state. Also, some gels become fluid on agitation, only to resume their solid or

semisolid state after remaining undisturbed for a period of time, a phenomenon known as *thixotropy*.

Lyophobic colloids are generally composed of inorganic particles. When these are added to the dispersing phase, there is little if any interaction between the two phases. Unlike lyophilic colloids, lyophobic materials do not spontaneously disperse but must be encouraged to do so by special individualized procedures. Their addition to the dispersion medium does not greatly affect the viscosity of the vehicle. Amphiphilic colloids form dispersions in both aqueous and nonaqueous media. Depending on their individual character and the nature of the dispersion medium, they may or may not become greatly solvated. However, they generally increase the viscosity of the dispersion medium with an increase in concentration.

For the most part, the colloidal sols and gels used in pharmacy are aqueous preparations. The various preparations composed of colloidal dispersions are prepared not according to any general method but according to the means best suited to the individual preparation. Some substances, such as acacia, are termed *natural colloids* because they are self-dispersing upon addition to the dispersing medium. Other materials that require special means for prompt dispersion are termed *artificial colloids*. They may require fine pulverization of coarse particles to colloidal size by a colloid mill or a micropulverizer, or colloidal size particles may be formed by chemical reaction under highly controlled conditions.

Terminology Related to Gels

A number of terms are commonly used in discussing some of the characteristics of gels, including imbibition, swelling, syneresis, thixotropy, and xerogel. *Imbibition* is the taking up of a certain amount of liquid without a measurable increase in volume. *Swelling* is the taking up of a liquid by a gel with an increase in volume. Only liquids that solvate a gel can cause swelling. The swelling of protein gels is influenced by pH and the presence of

electrolytes. *Syneresis* occurs when the interaction between particles of the dispersed phase becomes so great that on standing, the dispersing medium is squeezed out in droplets and the gel shrinks. Syneresis is a form of instability in aqueous and nonaqueous gels. Separation of a solvent phase is thought to occur because of the elastic contraction of the polymeric molecules; in the swelling process during gel formation, the macromolecules become stretched, and the elastic forces increase as swelling proceeds. At equilibrium, the restoring force of the macromolecules is balanced by the swelling forces, determined by the osmotic pressure. If the osmotic pressure decreases, as on cooling, water may be squeezed out of the gel. The syneresis of an acidic gel from *Plantago albicans* seed gum may be decreased by the addition of electrolyte, glucose, and sucrose and by increasing the gum concentration. pH has a marked effect on the separation of water. At low pH, marked syneresis occurs, possibly as a result of suppression of ionization of the carboxylic acid groups, loss of hydrating water, and the formation of intramolecular hydrogen bonds. This would reduce the attraction of the solvent for the macromolecule. *Thixotropy* is a reversible gel–sol formation with no change

in volume or temperature, a type of non-Newtonian flow. A *xerogel* is formed when the liquid is removed from a gel and only the framework remains. Examples include gelatin sheets, tragacanth ribbons, and aca-cia tears.

Classification and Types of Gels

Table 14.4 is a general classification of gels listing two classification schemes. The first scheme divides gels into inorganic and organic. Most *inorganic hydrogels* are two-phase systems, such as aluminum hydroxide gel and bentonite magma. Bentonite has also been used as an ointment base in about 10% to 25% concentrations. Most *organic gels* are single-phase systems and may include such gelling agents as carbomer and tragacanth and those that contain an organic liquid, such as *Plastibase*.

The second classification scheme divides gels into hydrogels and organogels with some additional subcategories. *Hydrogels* include ingredients that are dispersible as colloids or soluble in water; they include organic hydrogels, natural and synthetic gums, and inorganic hydrogels. Examples include hydrophilic colloids such as silica, bentonite, tragacanth, pectin, sodium

Table 14.4 GENERAL CLASSIFICATION AND DESCRIPTION OF GELS

CLASS	DESCRIPTION	EXAMPLES
Inorganic	Usually two-phase systems	Aluminum hydroxide gel Bentonite magma
Organic	Usually single-phase systems	Carbopol Tragacanth
Hydrogels	Organic hydrogels	Pectin paste, tragacanth jelly
	Natural and synthetic gums	Methylcellulose, sodium CMC, Pluronic
	Inorganic hydrogels	Bentonite gel (10%–25%), Veegum, silica
Organogels	Hydrocarbon type	Petrolatum, mineral oil/polyethylene gel (Plastibase)
	Animal, vegetable fats	Lard, cocoa butter
	Soap base greases	Aluminum stearate with heavy mineral oil gel
	Hydrophilic organogels	Carbowax bases (PEG ointment)
	Polar	
	Nonionic	

alginate, methylcellulose, sodium CMC, and alumina, which, in high concentration, form semisolid gels. Sodium alginate has been used to produce gels that can be employed as ointment bases. In concentrations $>2.5\%$ and in the presence of soluble calcium salts, a firm gel, stable between pH 5 and 10, is formed. Methylcellulose, hydroxy ethylcellulose, and sodium CMC are among the commercial cellulose products used in ointments. They are available in various viscosity types, usually high, medium, and low. *Organogels* include the hydrocarbons, animal and vegetable fats, soap base greases, and the hydrophilic organogels. Included in the hydrocarbon type is *Jelene*, or *Plastibase*, a combination of mineral oils and heavy hydrocarbon waxes with a molecular weight of about 1,300. Petrolatum is a semisolid gel consisting of a liquid component together with a protosubstance and a crystalline waxy fraction. The crystalline fraction provides rigidity to the structure, while the protosubstance, or gel former, stabilizes the system and thickens the gel. The hydrophilic organogels, or polar organogels, include the polyethylene glycols of high molecular weight, the *Carbowax*. They are soluble to about 75% in water and are completely washable. The gels look and feel like petrolatum. They are nonionic and stable. *Jellies* are a class of gels in which the structural coherent matrix contains a high proportion of liquid, usually water. They usually are formed by adding a thickening agent such as tragacanth or carboxymethyl cellulose to an aqueous solution of a drug substance. The resultant product is usually clear and uniformly semisolid. Jellies are subject to bacterial contamination and growth, so most are preserved with antimicrobials. Jellies should be stored with tight closure because water may evaporate, drying out the product.

Some substances, such as acacia, are termed natural colloids because they are self-dispersing in a dispersing medium. Other materials that require special treatment for prompt dispersion are called artificial colloids. The special treatment may involve fine pulverization to colloidal size with a colloid mill or a micropulverizer.

Preparation of Magmas and Gels

Some magmas and gels (inorganic) are prepared by freshly precipitating the disperse phase to achieve a fine degree of subdivision of the particles and a gelatinous character to those particles. The desired gelatinous precipitate results when solutions of inorganic agents react to form an insoluble chemical having a high attraction for water. As the microcrystalline particles of the precipitate develop, they strongly attract water to yield gelatinous particles, which combine to form the desired gelatinous precipitate. Other magmas and gels may be prepared by directly hydrating the inorganic chemical, which produces the disperse phase of the dispersion. In addition to the water vehicle, other agents as propylene glycol, propyl galate, and hydroxypropyl cellulose may be used to enhance gel formation.

Because of the high degree of attraction between the disperse phase and the aqueous medium in both magmas and gels, these preparations remain fairly uniform on standing, with little settling of the disperse phase. However, on long standing, a supernatant layer of the dispersion medium develops, but the uniformity of the preparation is easily reestablished by moderate shaking. To ensure uniform dosage, magmas and gels should be shaken before use, and a statement to that effect must be included on the label of such preparations. The medicinal magmas and gels are used orally for the value of the disperse phase.

Examples of Gelling Agents

Gelling agents include acacia, alginic acid, bentonite, carbomer, CMC sodium, ceto-stearyl alcohol, colloidal silicon dioxide, ethylcellulose, gelatin, guar gum, hydroxy ethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium aluminum silicate, maltodextrin, methylcellulose, polyvinyl alcohol (PVA), povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch, tragacanth, and xanthan gum. A few of the more common ones are discussed here.

Alginic acid is obtained from seaweed throughout the world, and the prepared product is a tasteless, practically odorless white to yellowish-white colored fibrous powder. It is used in concentrations of 1% to 5% as a thickening agent in gels. It swells in water to about 200 to 300 times its own weight without dissolving. Cross-linking with increased viscosity occurs upon the addition of a calcium salt, such as calcium citrate. Alginic acid can be dispersed in water vigorously stirred for approximately 30 minutes. Premixing with another powder or with a water-miscible liquid aids dispersion.

Bentonite is discussed later, in the section on preparation of bentonite magma.

Carbomer (Carbopol) resins, first described in the literature in 1955, are ingredients in a variety of dosage systems, including controlled-release tablets, oral suspensions, and topical gels. Carbomer resins are high molecular weight allyl pentaerythritol-cross-linked acrylic acid-based polymers modified with C_{10} to C_{30} alkyl acrylates. They are fluffy white dry powders with large bulk density. The 0.5% and 1.0% aqueous dispersions are pH 2.7 to 3.5 and 2.5 to 3.0, respectively. There are many carbomer resins, with viscosity ranges from 0 to 80,000 cP.

Carbomer 934 is highly effective in thick formulations such as viscous gels. Carbomer 934P is similar to 934 but is intended for oral and mucosal contact applications and is the most widely used in the pharmaceutical industry. In addition to thickening, suspending, and emulsifying in both oral and topical formulations, the 934 polymer is used in commercial products to provide sustained-release properties in the stomach and intestinal tract. Carbomer 940 forms sparkling clear water or hydroalcoholic gels. It is the most efficient of all the Carbopol resins and has very good nondrip properties.

The addition of alcohol to prepared carbomer gels may decrease their viscosity and clarity. An increase in the concentration of carbomer may be required to overcome the loss of viscosity. Also, gel viscosity depends on the presence of electrolytes and on the pH. Generally, a maximum of 3% electrolytes can be added before a rubbery mass forms.

Too much neutralization also will result in decreased viscosity that cannot be reversed by the addition of acid. Maximum viscosity and clarity occur at pH 7, but acceptable viscosity and clarity begin at pH 4.5 to 5.0 and extend to a pH of 11.

Carbomer preparations are primarily used in aqueous systems, although other liquids can be used. In water, a single particle of carbomer will wet very rapidly, but like many other powders, carbomer polymers tend to form clumps of particles when haphazardly dispersed in polar solvents. As the surfaces of these clumps solvate, a layer forms and prevents rapid wetting of the interior of the clumps. When this occurs, the slow diffusion of solvent through this solvated layer determines the mixing or hydration time. To achieve fastest dispersion of the carbomer, it is wise to take advantage of the very small particle size of the carbomer powder by adding it very slowly into the vortex of the liquid while very rapidly stirring it. Almost any device, like a simple sieve, that can sprinkle the powder on the rapidly stirred liquid is useful. The goal is to prevent clumping by slowly sprinkling the very fine powder over the rapidly agitated water.

A neutralizer is added to thicken the gel after the carbomer is dispersed. Sodium hydroxide or potassium hydroxide can be used in carbomer dispersions containing <20% alcohol. Triethanolamine will neutralize carbomer resins containing up to 50% ethanol. Other neutralizer agents include sodium carbonate, ammonia, and borax.

CMC in concentrations of 4% to 6% of medium viscosity can be used to produce gels; glycerin may be added to prevent drying. Precipitation can occur below pH 2; it is most stable at pH 2 to 10, and maximum stability is at pH 7 to 9. It is incompatible with ethanol.

CMC *sodium* is soluble in water at all temperatures. The sodium salt of CMC can be dispersed with high shear in cold water before the particles can hydrate and swell to sticky gel grains agglomerating into lumps. Once the powder is well dispersed, the solution is heated with moderate shear to about 60°C (140°F) for fastest dissolution. These

dispersions are sensitive to pH changes because of the carboxylate group. The viscosity of the product falls markedly below pH 5 or above pH 10.

Colloidal silicon dioxide can be used with other ingredients of similar refractive index to prepare transparent gels. Colloidal silicon dioxide adsorbs large quantities of water without liquefying. The viscosity is largely independent of temperature. Changes in pH may affect the viscosity: It is most effective at pH values up to about 7.5. Colloidal silicon dioxide (fumed silica) will form a gel when combined with 1-dodecanol and n-dodecane. These are prepared by adding the silica to the vehicle and sonicating for about 1 minute to obtain a uniform dispersion and sealing and storing at about 40°C (140°F) overnight to complete gelation. This gel is more hydrophobic than the others.

Gelatin is dispersed in hot water and cooled to form gels. As an alternative, moisten the gelatin with about three to five parts of an organic liquid that will not swell the polymer, such as ethyl alcohol or propylene glycol, followed by the addition of the hot water and cooling.

Magnesium aluminum silicate, or *Veegum*, in concentrations of about 10% forms a firm thixotropic gel. The material is inert and has few incompatibilities but is best used above pH 3.5. It may bind to some drugs and limit their bioavailability.

Methylcellulose is a long-chain substituted cellulose that can be used to form gels in concentrations up to about 5%. Because methylcellulose hydrates slowly in hot water, the powder is dispersed with high shear in about one-third of the required amount of water at 80°C to 90°C (176°F to 194°F). Once the powder is finely dispersed, the rest of the water is added cold or as ice with moderate stirring to cause prompt dissolution. Anhydrous alcohol or propylene glycol may be used to prewet the powders. Maximum clarity, fullest hydration, and highest viscosity will be obtained if the gel is cooled to 0°C to 10°C (32°F to 50°F) for about an hour. A preservative should be added. A 2% solution of methylcellulose 4,000 has a gel point about 50°C (122°F). High concentrations of electrolytes

will salt out the macromolecules and increase their viscosity, ultimately precipitating the polymer.

Plastibase, or *Jelene*, is a mixture of 5% low molecular weight polyethylene and 95% mineral oil. A polymer, it is soluble in mineral oil above 90°C, close to its melting point. When cooled below 90°C, the polymer precipitates and causes gelation. The mineral oil is immobilized in the network of entangled and adhering insoluble polyethylene chains, which probably even associate into small crystalline regions. This gel can be heated to about 60°C (140°F) without substantial loss of consistency.

Poloxamer, or *Pluronic*, gels are made from selected forms of polyoxyethylene-polyoxypropylene copolymers in concentrations ranging from 15% to 50%. Poloxamers generally are waxy white free-flowing granules that are practically odorless and tasteless. Aqueous solutions of poloxamers are stable in the presence of acids, alkalis, and metal ions. Commonly used poloxamers include the 124 (L-44 grade), 188 (F-68 grade), 237 (F-87 grade), 338 (F-108 grade), and 407 (F-127 grade) types, which are freely soluble in water. The "F" designation refers to the flake form. The "L" designation refers to the liquid form. The trade name Pluronic is used in the United States by BASF for pharmaceutical and industrial grade poloxamers. Pluronic F-127 has low toxicity and good solubilizing capacity and optical properties, and it is a good medium for topical drug delivery systems.

PVA is used at concentrations of about 2.5% in the preparation of various jellies that dry rapidly when applied to the skin. Borax is a good agent that will gel PVA solutions. For best results, disperse PVA in cold water, followed by hot water. It is less soluble in the cold water.

Povidone at the higher molecular weights can be used to prepare gels in concentrations up to about 10%. It has the advantage of being compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It has also been used to increase the solubility of a number of poorly soluble drugs.

Sodium alginate can be used to produce gels in concentrations up to 10%. Aqueous preparations are most stable at pH 4 to 10; below pH 3, alginic acid is precipitated. Sodium alginate gels for external use should be preserved, for example, with 0.1% chloroxylenol or the parabens. If the preparation is acidic, benzoic acid may be used. High concentrations will raise viscosity to the point of salting out the sodium alginate; this occurs at about 4% with sodium chloride.

Tragacanth gum has been used to prepare gels that are most stable at pH 4 to 8. These gels must be preserved with either 0.1% benzoic acid or sodium benzoate or a combination of 0.17% methylparaben and 0.03% propylparaben. These gels may be sterilized by autoclaving. Powdered tragacanth gum tends to form lumps when added to water. Thus, aqueous dispersions are prepared by adding the powder to vigorously stirred water. Also, the use of ethanol, glycerin, or propylene glycol to wet the tragacanth before mixing with water is very effective. If other powders are to be incorporated into the gel, they can be premixed with the tragacanth in the dry state.

Gel Formulation Considerations

In a gel preparation, the powdered polymers, when added to water, may form temporary gels that slow dissolution. As water diffuses into these loose clumps of powder, their exterior frequently turns into clumps of solvated particles encasing dry powder. The globs or clumps of gel dissolve very slowly because of their high viscosity and the low diffusion coefficient of the macromolecules.

As a hot colloidal dispersion of gelatin cools, the gelatin macromolecules lose kinetic energy. With reduced kinetic energy, or thermal agitation, the gelatin macromolecules are associated through dipole–dipole interaction into elongated or threadlike aggregates. The size of these association chains increases to the extent that the dispersing medium is held in the interstices among the interlacing network of gelatin macromolecules, and the viscosity increases to that of a semisolid. Gums, such as agar, Irish moss, algin, pectin, and

tragacanth, form gels by the same mechanism as gelatin.

Polymer solutions tend to be cast as gels because the solute consists of long, flexible chains of molecules of such thickness that they tend to become entangled, attract each other by secondary valency forces, and even crystallize. Cross-linking of dissolved polymer molecules also causes these solutions to gel. The reactions produce permanent gels, held together by primary valence forces. Secondary valence forces are responsible for reversible gel formation. For example, gelatin will form a gel when lowered to about 30°C, the gel melting point, but aqueous methylcellulose solutions will gel when heated above about 50°C because the polymer, being less soluble in hot water, precipitates. Lower temperatures, higher concentrations, and higher molecular weights promote gelation and produce stronger gels. The reversible gelation of gelatin will occur at about 25°C for 10% solutions, 30°C for 20% solutions, and about 32°C for 30% solutions (77°F, 86°F, and 90°F, respectively). Gelation is rarely observed for gelatin above 34°C (93°F), and regardless of concentration, gelatin solutions do not gel at 37°C (98.6°F). The gelation temperature or gel point of gelatin is highest at the isoelectric point. Water-soluble polymers have the property of thermal gelation, that is, they gel on heating, whereas natural gums gel on cooling. The thermal gelation is reversed on cooling.

Inorganic salts will compete with the water in a gel and cause gelation at lower concentrations. This is usually reversible; upon addition of water, the gels will reform. Because alcohol is not a solvent or precipitant, it may cause precipitation or gelation, lowering the dielectric constant of the medium and tending to dehydrate the hydrophilic solute. Alcohol lowers the concentrations at which electrolytes salt out hydrophilic colloids. Phase separation by adding alcohol may cause coacervation.

Aqueous polymer solutions, especially of cellulose derivatives, are stored for approximately 48 hours after dissolution to promote full hydration and maximum viscosity and clarity. Any salts are added at this point

rather than dissolving in water prior to adding polymer; otherwise, the solutions may not reach their full viscosity and clarity.

Examples of Magmas and Gels

One official magma, Bentonite Magma, NF, used as a suspending agent, finds application in the extemporaneous compounding of prescriptions. Sodium Fluoride and Phosphoric Acid Gel, USP, is applied topically to the teeth as a dental care prophylactic. Other official gels applied topically include Fluocinonide Gel, USP, an anti-inflammatory corticosteroid, and Tretinoin Gel, USP, an irritant that stimulates epidermal cell turnover, causes peeling, and is effective in the treatment of acne. Examples of such drugs and drug products are erythromycin and benzoyl peroxide topical gel (Benzamycin Topical Gel, Dermik Laboratories), clindamycin topical gel (Cleocin T Topical Gel, Pfizer), clindamycin and benzoyl peroxide topical gel (BenzaClin, Dermik), and benzoyl peroxide gel (Desquam-X 10 Gel, Westwood-Squibb) used in the control and treatment of acne vulgaris; hydroquinone gel (Solaquin Forte Gel, ICN), a bleach for hyperpigmented skin; salicylic acid gel (Compound W Gel, Medtech), a keratolytic; and desoximetasone gel (Topicort Gel, Taro) and augmented betamethasone dipropionate topical gel (Diprolene, Schering-Plough), anti-inflammatory and antipruritic agents.

Other official magmas and gels are employed as antacids: Aluminum Phosphate Gel, USP; Aluminum Hydroxide Gel, USP; and Dihydroxyaluminum Aminoacetate Magma, USP. Some of these preparations are discussed briefly next.

Bentonite Magma, NF

Bentonite magma is a preparation of 5% bentonite, a native colloidal hydrated aluminum silicate, in purified water. It may be prepared mechanically in a blender with the bentonite added directly to the purified water while the machine is running, or it may be prepared by sprinkling the bentonite, in portions, upon hot purified water, allowing each portion to become thoroughly wetted without stirring before another portion is added. By the

latter method, the mixture must be allowed to stand for 24 hours before it may be stirred. The standing period ensures complete hydration and swelling of the bentonite. Bentonite, which is insoluble in water, swells to approximately 12 times its volume upon addition to water. The NF monograph for bentonite contains a test for swelling power in which 2 g of a bentonite sample is added in portions to 100 mL water in a 100-mL glass-stoppered cylinder. At the end of a 2-hour period, the mass at the bottom of the cylinder is required to occupy an apparent volume of not less than 24 mL. Other required tests are for gel formation, fineness of powder, and pH, the latter being between 9.5 and 10.5. After bentonite magma has been allowed to stand undisturbed for some time, it sets to a gel. Upon agitation, the sol form returns. The process may be repeated indefinitely. As mentioned earlier, this phenomenon is termed *thixotropy*, and bentonite magma is a *thixotropic gel*. The thixotropy occurs only when the bentonite concentration is somewhat above 4%.

Bentonite magma is employed as a suspending agent. Its alkaline pH must be considered because it is undesirable for certain drugs. Furthermore, because the suspending capacity of the magma is drastically reduced if the pH is lowered to about pH 7, another suspending agent should be selected for drugs requiring a less alkaline medium rather than making bentonite magma more acidic.

Aluminum Hydroxide Gel, USP

Aluminum Hydroxide Gel, USP, is an aqueous suspension of a gelatinous precipitate composed of insoluble aluminum hydroxide and the hydrated aluminum oxide, equivalent to about 4% aluminum oxide. The disperse phase of the gel is generally prepared by a chemical reaction, using various reactants. Usually, the aluminum source of the reaction is aluminum chloride or aluminum alum, which yields the insoluble aluminum oxide and aluminum hydroxide precipitate. To the gel, the USP permits the addition of peppermint oil, glycerin, sorbitol, sucrose, saccharin, or other flavorants and sweeteners as well as suitable antimicrobial agents.

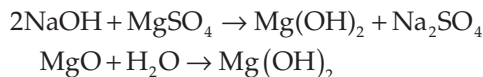
This antacid preparation is a white, viscous suspension. It is effective in neutralizing a portion of the gastric hydrochloric acid; coats the inflamed and perhaps ulcerated gastric surface by virtue of its gelatinous, viscous, and insoluble character; and is useful in the treatment of hyperacidity and peptic ulcers. The main disadvantage to its use is its constipating effects. The usual dose is 10 mL four or more times a day, that is, after meals and at bedtime. The analogous commercial product (Amphojel, Wyeth-Ayerst) at 10 mL has the capacity to neutralize about 13 mEq of acid. The preparation should be stored in a tight container, and freezing should be avoided.

Because it possesses a trivalent cation, aluminum hydroxide interferes with the bioavailability of tetracycline by chelating with the antibiotic in the gastrointestinal tract. Thus, when these two medicines are indicated for patient use, the doses should be staggered to ensure that the patient receives the benefit of both drugs. Aluminum hydroxide gel has also been implicated in decreasing the bioavailability of other drugs by adsorption onto the gel. This is usually illustrated by a decrease in the area under the concentration time curve (AUC) for the concomitantly administered drug. Suffice it to say that the clinical significance of the interaction may not be that great, but observation of the patient to ensure the proper therapeutic outcome is important. Thus, for example, if aluminum hydroxide gel is suspected of causing incomplete absorption of the second drug, an upward alteration in the dose of the second drug may be necessary provided the aluminum hydroxide gel administration remains the same.

Milk of Magnesia

Milk of magnesia is a preparation containing 7% to 8.5% magnesium hydroxide. It may be prepared by a reaction between sodium hydroxide and magnesium sulfate (1), diluted solutions being used to ensure a fine, flocculent, gelatinous precipitate of magnesium hydroxide. The precipitate so produced is washed with purified water to remove the sodium sulfate prior to its incorporation with additional purified water to prepare the

required volume of product. Commercially, the product is more economically produced by the direct hydration of magnesium oxide:



Irrespective of its method of preparation, milk of magnesia is an opaque white viscous preparation from which varying proportions of water separate on standing. For this reason, it should be shaken before use. The preparation has a pH of about 10, which may bring about a reaction between the magma and the glass container, imparting a bitter taste to the preparation. To minimize such an occurrence, 0.1% citric acid may be added. Also, flavoring oils at a concentration not exceeding 0.05% may be added to enhance the palatability of the preparation.

Milk of magnesia possesses reasonable acid-neutralizing ability, and a dose of 5 mL will neutralize about 10 mEq of stomach acid. However, to neutralize more acid, a higher dose, such as 15 mL, is usually necessary, and this may predispose the patient to the development of diarrhea, a common side effect of this drug. Thus, to circumvent the problem of diarrhea from magnesium hydroxide and the constipating effects of aluminum hydroxide, frequently these two drugs are combined in an antacid preparation. The combination results in a more palatable product with optimum buffering of stomach contents at a pH of 4 to 5 and less of a chance for either diarrhea or constipation to occur. When a laxative effect is desired, a bedtime dose of 30 to 60 mL of milk of magnesia will suffice very nicely by the next morning.

Milk of magnesia is best stored in a tight container, preferably at 0°C to 35°C. Freezing results in a coarsening of the disperse phase, and temperatures above 35°C decrease the gel structure.

Starch Glycerite

Starch	100 g
Benzoic acid	2 g
Purified water	200 g
Glycerin	700 g

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PGR2023-00051

The starch and benzoic acid are rubbed in the water to a smooth mixture. The glycerin is added and mixed. The mixture is heated to 140°C with constant gentle agitation until a translucent mass forms. The heat ruptures the starch grains and permits the water to reach and hydrate the linear and branched starch molecules, which trap the dispersion medium in the interstices to form a gel. Starch glycerite has been used as a topical vehicle and protectant.

Lubricating Jelly Formula

Methylcellulose, 4,000 cP	0.8%
Carbopol 934	0.24%
Propylene glycol	16.7%
Methylparaben	0.015%
Sodium hydroxide, qs ad	pH 7
Purified water, qs ad	100%

Disperse the methylcellulose in 40 mL of hot (80°C to 90°C) water. Chill overnight in a refrigerator to dissolve. Disperse the Carbopol 934 in 20 mL water. Adjust the pH of the dispersion to 7.0 by adding sufficient 1% sodium hydroxide solution (about 12 mL is required), and bring the volume to 40 mL with purified water. Dissolve the methylparaben in the propylene glycol. Mix the methylcellulose, Carbopol 934, and propylene glycol fractions, using caution to avoid incorporating air. Lubricating jellies are used to assist in medical procedures, to aid in insertion of various devices and drugs, including catheters and suppositories, and as vehicles for some drug products, especially in extemporaneous compounding.

Clear Aqueous Gel with Dimethicone

Water	59.8%
Carbomer 934	0.5%
Triethanolamine	1.2%
Glycerin	34.2%
Propylene glycol	2.0%
Dimethicone copolyol	2.3%

Prepare the carbomer gel, add the other ingredients, and mix well. Dimethicone copolyol is included to reduce the sticky feel associated with glycerin. These gels are commonly used as vehicles for drug products, especially for those that are extemporaneously compounded.

Poloxamer Gel Base

Pluronic F-127, NF	20–50 g
Purified water/buffer qs ad	100 mL

Poloxamer gel base is widely used as a vehicle for extemporaneous products. In a combination with isopropyl palmitate and lecithin, it is an absorption-enhancing topical vehicle.

PROPER ADMINISTRATION AND USE OF DISPERSE SYSTEMS

Many dosage forms discussed thus far in this chapter are for oral use. As with the oral solutions discussed in the previous chapter, they can be measured by spoonful or administered dropwise, depending on the appropriate dosage. It is very important that the patient understands the proper quantity of product to use. For example, differences in dosage can occur between product categories, such as OTC antidiarrheal suspensions (tablespoonfuls) versus OTC antacid suspensions (teaspoonfuls). Differences in dosage can also occur within a category, most notably in antacid suspensions. Some are recommended in teaspoon doses because of higher concentration, whereas others are suggested in tablespoon quantities. It is important, therefore, that the pharmacist ensures that the patient knows how much to use, and then use a calibrated device to make sure the right amount is taken.

Many reconstituted products, as mentioned earlier in the chapter, are suspensions. Several problems can emerge if the pharmacist is not careful to counsel the patient about them. Usually, the patient or guardian of the patient receives the product in an oversized bottle that allows for the proper shaking of the product prior to its use. To allay fears that the medicine may not all be in the bottle,

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the pharmacist must make the patient or the guardian aware of this and indicate that this feature enhances the ability to shake it up before administration. Furthermore, some patients do not make the connection that the medicine should be administered by mouth. Oral antibiotic suspensions intended to treat a middle ear infection have been mistakenly administered directly into the ear by some patients or guardians. Thus, the pharmacist should review with the patient the proper route of administration. Lastly, because these are reconstituted with purified water, stability problems with the drug usually dictate that it be stored in the refrigerator until it is consumed. The patient has to be informed of this. The consumer may overlook a tiny label directing refrigerator storage. Alternatively, not all suspensions need to be stored in the refrigerator, but because of prior experience with other liquid suspensions that necessitated refrigeration, a patient or guardian may assume that this is necessary.

Certain suspensions, such as aluminum hydroxide gel, cholestyramine, and kaolin, by virtue of their active ingredients interfere with absorption of other drugs. For example, cholestyramine has been shown to interfere with and decrease the bioavailability of warfarin, digoxin, and thyroid hormones. The pharmacist should be aware of this and make recommendations to help avoid this drug interaction whenever possible. The typical suggestion is to stagger the administration of the liquid cholestyramine away from other

drug administration by several hours, and giving warfarin at least 6 hours after the cholestyramine reportedly avoids the impaired warfarin bioavailability (9). However, warfarin undergoes enterohepatic recycling in the body, and if cholestyramine is present in the intestine because of earlier administration, it can bind it and decrease warfarin's reabsorption. In this instance, use of one of the two drugs should be discontinued by the physician. However, if concurrent use is necessary, the pharmacist should monitor the patient more frequently for the possibility of an altered anticoagulant response. This is important because if adjustments in warfarin dosage are made on the basis of cholestyramine interference and then the cholestyramine is discontinued, the warfarin dosage also must be decreased according to the patient's prothrombin time.

AEROSOLS

Pharmaceutical aerosols are pressurized dosage forms that, upon actuation, emit a fine dispersion of liquid and/or solid materials containing one or more active ingredients in a gaseous medium (Physical Pharmacy Capsule 14.7). Pharmaceutical aerosols are similar to other dosage forms because they require the same types of considerations with respect to formulation, product stability, and therapeutic efficacy. However, they differ from most other dosage forms in their dependence upon the function of the container, its



PHYSICAL PHARMACY CAPSULE 14.7

Partial Pressure and Aerosol Formulation

Aerosols generally contain an active drug in a liquid gas propellant, in a mixture of solvents with a propellant, or in a mixture with other additives and a propellant. The gas propellants can be formulated to provide desired vapor pressures for enhancing the delivery of the medication through the valve and actuator in accordance with the purpose of the medication. Aerosols are used as space sprays, surface sprays, aerated foams, and for oral inhalation.

Various propellants have properties that may be important including molecular weight, boiling point, vapor pressure, liquid density, and flash point. An example of a calculation to determine the vapor pressure of a certain mixture of hydrocarbon propellants follows.

PHYSICAL PHARMACY CAPSULE 14.7 CONT.

EXAMPLE

What is the vapor pressure of a 60:40 mixture of propane and isobutane? Information on the two propellants is as follows:

PROPERTY	PROPANE	ISOBUTANE
Molecular formula	C ₃ H ₈	C ₄ H ₁₀
Molecular weight	44.1	58.1
Boiling point (°F)	-43.7	10.9
Vapor pressure (psig at 70°F)	110	30.4
Liquid density (g/mL at 70°F)	0.50	0.56
Flash point (°F)	-156	-117

1. Assume an ideal solution:

$$n_{\text{propane}} = 60 / 44.1 = 1.36$$

$$n_{\text{isobutane}} = 40 / 58.1 = 0.69$$

2. From Raoult law, determine the number of moles of each propellant.
3. From Raoult law, the partial pressure exerted by the propane is

$$P_{\text{propane}} = [(n_{\text{propane}}) / (n_{\text{propane}} + n_{\text{isobutane}})] P_{\text{propane}}$$

$$P_{\text{propane}} = [(1.36) / (1.36 + 0.69)] 110 = 72.98 \text{ } \psi$$

4. The partial pressure exerted by the isobutane is

$$P_{\text{isobutane}} = [(0.69) / (1.36 + 0.69)] 30.4 = 10.23 \text{ } \psi$$

5. The vapor pressure exerted by both gases, P_T is

$$P_T = 72.98 + 10.23 = 83.21 \text{ } \psi \quad \text{at } 70^\circ\text{F}$$

The vapor pressure required for a specific application can be calculated in a similar manner, and different ratios of propellants may be used to obtain that pressure.

valve assembly, and an added component—the propellant—for the physical delivery of the medication in proper form.

The term *pressurized package* is commonly used when referring to the aerosol container or completed product. Pressure is applied to the aerosol system through the use of one or more liquefied or gaseous propellants. Upon activation of the valve assembly of the aerosol, the pressure exerted by the propellant forces the contents of the package out through the opening of the valve. The physical form in which the contents are emitted

depends on the formulation of the product and the type of valve. Aerosol products may be designed to expel their contents as a fine mist; a coarse, wet, or dry spray; a steady stream; or a stable or a fast-breaking foam. The physical form selected for a given aerosol is based on intended use. For instance, an aerosol for inhalation therapy, as in the treatment of asthma or emphysema, must present particles in the form of a fine liquid mist or as finely divided solid particles. Particles <6 μm will reach the respiratory bronchioles, and those <2 μm will reach the alveolar ducts

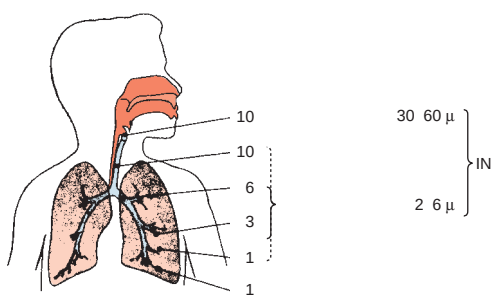


FIGURE 14.11 Relationship of INTAL (cromolyn sodium, Fisons) particle size to airway penetration. (Courtesy of Fisons Corporation.)

and alveoli (Fig. 14.11). By contrast, the particle size for a dermatologic spray intended for deposition on the skin is coarser and generally less critical to the therapeutic efficacy of the product. Some dermatologic aerosols present the medication in the form of a powder, a wet spray, a stream of liquid (usually a local anesthetic), or an ointment-like product. Other pharmaceutical aerosols include vaginal and rectal foams.

Aerosols used to provide an airborne mist are termed *space sprays*. Room disinfectants, room deodorizers, and space insecticides characterize this group of aerosols. The particle size of the released product is generally quite small, usually below $50\text{ }\mu\text{m}$, and must be carefully controlled so that the dispersed droplets or particles remain airborne for a long time. A 1-second burst from a typical aerosol space spray will produce 120 million particles, a substantial number of which will remain suspended in the air for an hour.

Aerosols intended to carry the active ingredient to a surface are termed *surface sprays* or *surface coatings*. The dermatologic aerosols can be placed in this group. Also included are a great many cosmetic and household aerosol products, including personal deodorant sprays, hair lacquers and sprays, perfumes and colognes, shaving lathers, toothpaste, surface pesticide sprays, paint sprays, spray starch, waxes, polishes, cleaners, and lubricants. A number of veterinary and pet products have been put into aerosol form, as have such food products as dessert toppings and food spreads. Some of these products are sprays; others, foams; and a few, pastes.

TYPES OF AEROSOLS

Inhalation aerosols, commonly known as metered-dose inhalers (MDIs), are intended to produce fine particles or droplets for inhalation through the mouth and deposition in the pulmonary tree. The design of the delivery system is intended to release measured quantities and of the appropriate quality of the active substance with each actuation.

Nasal aerosols, commonly known as nasal MDIs, produce fine particles or droplets for delivery through the nasal vestibule and deposition in the nasal cavity. Each actuation of the valve releases measured mass and appropriate quality of the active substance.

Lingual aerosols are intended to produce fine particles or droplets for deposition on the surface of the tongue. The design of the delivery system releases one dose with each actuation.

Topical aerosols produce fine particles or droplets for application to the skin. Topical aerosol drug products may be designed, as needed, to deliver a metered amount of formulation upon actuation of the designed valve or continuous release of formulation during depressed status of the valve.

Advantages of the Aerosol Dosage Form

Some features of pharmaceutical aerosols that may be considered advantages over other types of dosage forms are as follows:

1. A portion of medication may be easily withdrawn from the package without contamination or exposure to the remaining material.
2. By virtue of its hermetic character, the aerosol container protects medicinal agents adversely affected by atmospheric oxygen and moisture. Being opaque, the usual aerosol container also protects drugs adversely affected by light. This protection persists during the use and the shelf life of the product. If the product is packaged under aseptic conditions, sterility may also be maintained during the shelf life of the product.
3. Topical medication may be applied in a uniform thin layer to the skin without anything else touching the affected area. This method of application may reduce the irritation that

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sometimes accompanies mechanical (fingertip) application of topical preparations. The rapid volatilization of the propellant also provides a cooling, refreshing effect.

4. By proper formulation and valve control, the physical form and the particle size of the emitted product may be controlled, which may contribute to the efficacy of a drug, as with the fine controlled mist of an inhalant aerosol. Through the use of *metered valves*, dosage may be controlled.
5. Aerosol application is a clean process, requiring little or no washup by the user.

The Aerosol Principle

An aerosol formulation consists of two component parts: the *product concentrate* and the *propellant*. The product concentrate is the active ingredient of the aerosol combined with the required adjuncts, such as antioxidants, surface-active agents, and solvents, to prepare a stable and efficacious product. When the propellant is a liquefied gas or a mixture of liquefied gases, it frequently serves the dual role of propellant and solvent or vehicle for the product concentrate. In certain aerosol systems, compressed gases—carbon dioxide, nitrogen, and nitrous oxide—are employed as the propellant.

For many years, the liquefied gas propellants most used in aerosol products were the chlorofluorocarbons (CFCs). However, these propellants are being phased out and will be prohibited for nonessential use under federal regulations following recognition that they reduce the amount of ozone in the stratosphere, which results in an increase in the amount of ultraviolet radiation reaching the earth, an increase in the incidence of skin cancer, and other adverse environmental effects. Under the law, the FDA has the authority to exempt from the prohibition specific products under the agency's jurisdiction when there is sufficient evidence showing that (a) there are no technically feasible alternatives to the use of a CFC propellant in the product, (b) the product provides a substantial health or other public benefit unobtainable without the use of the CFC, and (c) the use does not involve a significant release of CFCs into the atmosphere, or, if it does, the release is warranted by the benefit conveyed. A number of metered-dose pharmaceutical products for oral inhalation have received such essential use exemptions. Among the CFCs used as propellants in pharmaceuticals were dichlorodifluoromethane, dichlorotetrafluoroethane, and trichloromonofluoromethane (Table 14.5).

Table 14.5 PHYSICAL PROPERTIES OF SOME FLUORINATED HYDROCARBON PROPELLANTS

CHEMICAL NAME	CHEMICAL FORMULA	NUMERIC DESIGNATION	VAPOR PRESSURE ^a 70°F	BOILING POINT (1 ATM) °F	LIQUID DENSITY (G/ML) 70°F
Trichloromonofluoromethane	CCl ₃ F	11	13.4	74.7	1.485
Dichlorodifluoromethane	CCl ₂ F ₂	12	13.4	74.1	1.485
Dichlorotetrafluoroethane	CClF ₂ CClF ₂	114	21.6	38.4	1.468
Chloropentafluoroethane	CClF ₂ CF ₃	115	17.5	-37.7	1.29
Monochlorodifluoromethane	CH ₃ CClF ₂	142 ^b	43.8	15.1	1.119
Difluoroethane	CH ₃ CHF ₂	152 ^b	76.4	-11.2	0.911
Octafluorocyclobutane	CF ₂ CF ₂ CF ₂ CF ₂	C318	40.1	21.1	1.513

^aPounds per square inch absolute, equal to psig + 14.7.

^bThe numeric designations for fluorinated hydrocarbon propellants were designed in the refrigeration industry to simplify communications. The numeric designations are arrived at by the following method: (a) The digit at the extreme right refers to the number of fluorine atoms in the molecule. (b) The second digit from the right is one *greater* than the number of hydrogen atoms in the molecule. (c) The third digit from the right is one *less* than the number of carbon atoms in the molecule; if this number is zero, it is omitted and a two-digit number is used. (d) A capital C before a number indicates the cyclic nature of a compound. (e) The small letters following a number indicate decreasing symmetry of isomeric compounds, with "a" indicating less symmetry than "a," and so forth. The number of chlorine atoms in a molecule may be determined by subtracting the total number of hydrogen and fluorine atoms from the total number of atoms which may be added to the carbon chain.

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Fluorinated hydrocarbons are gases at room temperature. They may be liquefied by cooling below their boiling point or by compression at room temperature. For example, dichlorodifluoromethane (Freon 12) will form a liquid when cooled to -30°C (-22°F) or when compressed to 70 psig (pounds per square inch gauge) at 21°C (70°F). Both of these methods for liquefying gases are employed in aerosol packaging, as discussed later in this section.

When a liquefied gas propellant or propellant mixture is sealed within an aerosol container with the product concentrate, equilibrium is quickly established between the portion of propellant that remains liquefied and that which vaporizes and occupies the upper portion of the aerosol container (Fig. 14.12). The vapor phase exerts pressure in all directions—against the walls of the container, the valve assembly, and the surface of the liquid phase, which is composed of the liquefied gas and the product concentrate. It is this pressure that, upon actuation of the aerosol valve, forces the liquid phase up the dip tube and out of the orifice of the valve into the atmosphere. As the propellant meets

the air, it expands and evaporates because of the drop in pressure, leaving the product concentrate as airborne liquid droplets or dry particles, depending upon the formulation. As the liquid phase is removed from the container, equilibrium between the propellant remaining liquefied and that in the vapor state is reestablished. Thus, even during expulsion of the product from the aerosol package, the pressure within remains virtually constant, and the product may be continuously released at an even rate and with the same propulsion. However, when the liquid reservoir is depleted, the pressure may not be maintained, and the gas may be expelled from the container with diminishing pressure until it is exhausted.

Aerosol Systems

The pressure of an aerosol is critical to its performance. It can be controlled by (a) the type and amount of propellant and (b) the nature and amount of product concentrate. Thus, each formulation is unique unto itself, and a specific amount of propellant to be employed in aerosol products cannot be firmly stated,

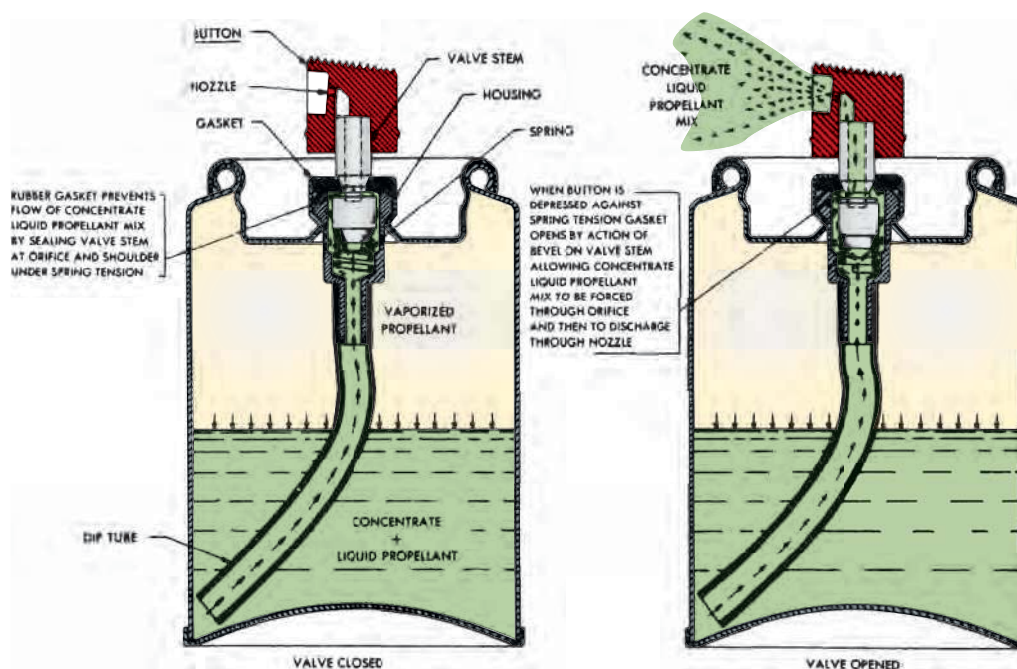


FIGURE 14.12 Cross-section sketches of contents and operation of a typical two-phase aerosol system. (Courtesy of Armstrong Laboratories, Division of Aerosol Techniques.)

although some general statements may be made. Space sprays generally contain a greater proportion of propellant than do aerosols intended for surface coating; hence, they are released with greater pressure, and the resultant particles are projected more violently from the valve. Space aerosols usually operate at 30 to 40 psig at 21°C and may contain as much as 85% propellant. Surface aerosols commonly contain 30% to 70% propellant with pressures between 25 and 55 psig at 21°C. Foam aerosols usually operate between 35 and 55 psig at 21°C and may contain only 6% to 10% propellant.

Foam aerosols may be considered to be emulsions because the liquefied propellant is partially emulsified with the product concentrate rather than being dissolved in it. Because the fluorinated hydrocarbons are nonpolar organic solvents having no affinity for water, the liquefied propellant does not dissolve in the aqueous formulation. The use of surfactants or emulsifiers in the formulation encourages the mixing of the two components to enhance the emulsion. Shaking of the package prior to use further mixes the propellant throughout the product concentrate. When the aerosol valve is activated, the mixture is expelled to the atmosphere, where the propellant globules vaporize rapidly, leaving the active ingredient in the form of a foam.

Blends of the various liquefied gas propellants are generally used in pharmaceutical aerosols to achieve the desired vapor pressure and to provide the proper solvent features for a given product. Some propellants are eliminated from use in certain products because of their reactivity with other formulative materials or with the proposed container or valve components. For instance, trichloromonofluoromethane tends to form free hydrochloric acid when formulated with systems containing water or ethyl alcohol, the latter a commonly used cosolvent in aerosol systems. The free hydrochloric acid not only affects the efficacy of the product but also corrodes some container components.

The physiologic effect of the propellant must also be considered in formulating an aerosol to ensure safety of the product in its intended use. Even though an individual

propellant or propellant blend and the active ingredient of a formulation are nontoxic when tested individually, the use of the combination in aerosol form may have undesirable features. For instance, when an active ingredient ordinarily used in a nasal or oral spray is placed in a fine aerosol mist, it may reach deeper into the respiratory tract than desired and result in irritation. With new dermatologic, vaginal, and rectal aerosol products, the influence of the aerosol form of the drug on the recipient tissue membranes must be evaluated for irritating effects and changes in the absorption of the drug from the site of application. The absorption pattern of a drug may change because of an increased rate of solubility of the fine particles usually produced in aerosol products.

Although the fluorinated hydrocarbons have a relatively low order of toxicity and are generally nonirritating, certain individuals who use an inhalation aerosol may be sensitive to the propellant agent and may exhibit cardiotoxic effects following rapid and repeated use (10).

Two-Phase Systems

As noted previously, the two-phase aerosol system consists of the liquid phase, containing the liquefied propellant and product concentrate, and the vapor phase.

Three-Phase Systems

The three-phase system consists of a layer of water-immiscible liquid propellant, a layer of highly aqueous product concentrate, and the vapor phase. Because the liquefied propellant usually has a greater density than the aqueous layer, it generally resides at the bottom of the container with the aqueous phase floating above it. As with the two-phase system, upon activation of the valve, the pressure of the vapor phase causes the liquid phase to rise in the dip tube and be expelled from the container. To avoid expulsion of the reservoir of liquefied propellant, the dip tube must extend only within the aqueous phase (product concentrate) and not down into the layer of liquefied propellant. The aqueous product is broken up into a spray by the mechanical action of the valve. If the container is shaken

immediately prior to use, some liquefied propellant may be mixed with the aqueous phase and be expelled through the valve to facilitate the dispersion of the exited product or the production of foam. The vapor phase within the container is replenished from the liquid propellant phase.

Compressed Gas Systems

Compressed rather than liquefied gases may be used to prepare aerosols. The pressure of the compressed gas in the head space of the aerosol container forces the product concentrate up the dip tube and out of the valve. The use of gases that are insoluble in the product concentrate, as is nitrogen, will result in emission of a product in essentially the same form as it was placed in the container. An advantage of nitrogen as a propellant is its inert behavior toward other formulative components and its protective influence on products subject to oxidation. Also, nitrogen is an odorless and tasteless gas and thus does not contribute adversely to the smell or taste of a product.

Other gases, such as carbon dioxide and nitrous oxide, which are slightly soluble in the liquid phase of aerosol products, may be employed when their expulsion with the product concentrate is desired to achieve spraying or foaming.

Unlike aerosols prepared with liquefied gas propellants, compressed gas-filled aerosols have no reservoir of propellant. Thus, higher gas pressures are required in these systems, and the pressure in these aerosols diminishes as the product is used.

Aerosol Container and Valve Assembly

The effectiveness of a pharmaceutical aerosol depends on achieving the proper combination of formulation, container, and valve assembly. The formulation must not chemically interact with the container or valve components so as to interfere with the stability of the formulation or with the integrity and operation of the container and valve assembly. The container and valve must be capable of withstanding the pressure

required by the product, it must resist corrosion, and the valve must contribute to the form of the product to be emitted.

Containers

Various materials have been used in the manufacture of aerosol containers, including (a) glass, uncoated or plastic coated; (b) metal, including tin-plated steel, aluminum, and stainless steel; and (c) plastics. The selection of the container for an aerosol product is based on its adaptability to production methods, compatibility with formulation components, ability to sustain the pressure intended for the product, the interest in design and aesthetic appeal on the part of the manufacturer, and cost.

Were it not for their brittleness and danger of breakage, glass containers would be preferred for most aerosols. Glass presents fewer problems with respect to chemical compatibility with the formula than do metal containers, and it is not subject to corrosion. Glass is also more adaptive to creativity in design. On the negative side, glass containers must be precisely engineered to provide the maximum in pressure safety and impact resistance. Plastic coatings are commonly applied to the outer surface of glass containers to render them more resistant to accidental breakage, and in the event of breaking, the plastic coating prevents the scattering of glass fragments. When the total pressure of an aerosol system is below 25 psig and no more than 50% propellant is used, glass containers are considered quite safe. When required, the inner surface of glass containers may be coated to render them more chemically resistant to formulation materials.

Tin-plated steel containers are the most widely used metal containers for aerosols. Because the starting material is in sheets, the completed aerosol cylinders are seamed and soldered to provide a sealed unit. When required, special protective coatings are employed within the container to prevent corrosion and interaction between the container and formulation. The containers must be carefully examined prior to filling to ensure that there are no flaws in the seam or

in the protective coating that would render the container weak or subject to corrosion.

Most aluminum containers are manufactured by extrusion or by other methods that make them seamless. They have the advantage over the seam type of container of greater safety against leakage, incompatibility, and corrosion. Stainless steel is employed to produce containers for certain small-volume aerosols in which a great deal of chemical resistance is required. The main limitation of stainless steel containers is their high cost.

Plastic containers have met with varying success in the packaging of aerosols because of their inherent problem of being permeated by the vapor within the container. Also, certain drug-plastic interactions affect the release of drug from the container and reduce the efficacy of the product.

Valve Assembly

The function of the valve assembly is to permit expulsion of the contents of the can in the desired form, at the desired rate, and in the case of metered valves, in the proper amount or dose. The materials used in the manufacture of valves must be inert to the formulations and must be approved by the FDA. Among the materials used in the manufacture of the various valve parts are plastic, rubber, aluminum, and stainless steel.

The usual aerosol valve assembly is composed of the following parts (Fig. 14.13):

1. *Actuator*: the button the user presses to activate the valve assembly for emission of the product. The actuator permits easy opening and closing of the valve. It is through the orifice in the actuator that the product is discharged. The design of the inner chamber and size of the emission orifice of the actuator contribute to the physical form (mist, coarse spray, solid stream, or foam) in which the product is discharged. The type and quantity of propellant used and the actuator design and dimensions control the particle size of the emitted product. Larger orifices (and less propellant) are used for products to be emitted as foams and solid streams than for those intended to be sprays or mists.

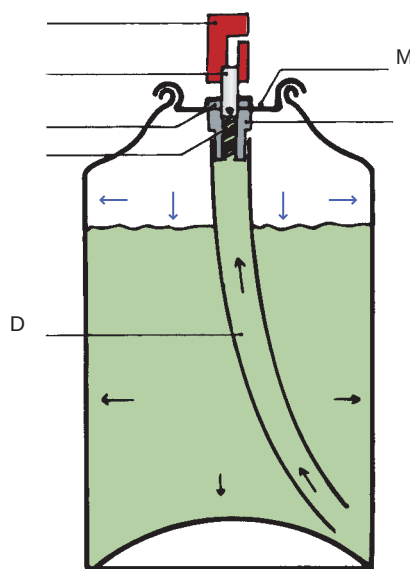


FIGURE 14.13 Valve assembly components.

2. *Stem*: supports the actuator and delivers the formulation in the proper form to the chamber of the actuator
3. *Gasket*: placed snugly with the stem and prevents leakage of the formulation when the valve is closed
4. *Spring*: holds the gasket in place and is the mechanism by which the actuator retracts when pressure is released, returning the valve to the closed position
5. *Mounting cup*: attached to the aerosol can or container and holds the valve in place. Because the underside of the mounting cup is exposed to the formulation, it must receive the same consideration as the inner part of the container with respect to meeting criteria of compatibility. If necessary, it may be coated with an inert material (e.g., an epoxy resin or vinyl) to prevent an undesired interaction.
6. *Housing*: Directly below the mounting cup, the housing links the dip tube and the stem and actuator. With the stem, its orifice helps to determine the delivery rate and the form in which the product is emitted.
7. *Dip tube*: extends from the housing down into the product; brings the formulation from the container to the valve. The viscosity of the product and its intended

delivery rate dictate to a large extent the inner dimensions of the dip tube and housing for a particular product.

The actuator, stem, housing, and dip tube are generally made of plastic, the mounting cup and spring of metal, and the gasket of rubber or plastic resistant to the formulation.

Metered-Dose Inhalers

Metering valves are employed when the formulation is a potent medication, as in inhalation therapy (Fig. 14.14). In these metered valve systems, the amount of material discharged is regulated by an auxiliary valve chamber by virtue of its capacity or dimensions. A single depression of the actuator causes evacuation of this chamber and delivery of its contents. The integrity of the chamber is controlled by a dual valve mechanism. When the actuator valve is closed,



FIGURE 14.14 Metered-dose inhaler. Each metered dose is delivered through the mouthpiece upon actuation of the aerosol unit's valve. (Courtesy of Boehringer Ingelheim.)

the chamber is sealed from the atmosphere. However, in this position, the chamber is permitted to fill with the contents of the container, to which it is open. Depression of the actuator causes a simultaneous reversal of positions; the chamber becomes open to the atmosphere, releasing its contents, at the same time becoming sealed from the contents of the container. Upon release of the actuator, the system is restored for the next dose. The USP contains a test to determine quantitatively the amount of medication from a metered valve.

As noted previously, the effectiveness of delivering medication to the lower reaches of the lungs for local or systemic effects depends in part on the particle size of the inhaled drug. Breathing patterns and the depth of respiration also play important roles in the deposition of inhaled aerosols to the lungs. Analysis of dose uniformity (11), particle size distribution patterns (12–14), and the respirable fractions of aerosol-delivered particles (15,16) are areas of research in developing aerosol products for optimal oral inhalation therapy.

A unique translingual aerosol formulation of nitroglycerin (Nitrolingual Spray, Rhône-Poulenc Rorer) permits a patient to spray droplets of nitroglycerin onto or under the tongue for acute relief of an attack or for prophylaxis of angina pectoris due to coronary artery disease. The product is not to be inhaled. At the onset of an attack, two metered spray emissions, each containing 0.4 mg of nitroglycerin, are administered. The product contains 200 doses of nitroglycerin in a propellant mixture of dichlorodifluoromethane and dichlorotetrafluoroethane.

Filling Operations

As explained earlier, fluorinated hydrocarbon gases may be liquefied by cooling below their boiling point or by compressing the gas at room temperature. These two features are used in the filling of aerosol containers with propellant.

Cold Filling

In the cold method, both the product concentrate and the propellant must be cooled to -34.5°C to -40°C (-30°F to 40°F). This

temperature is necessary to liquefy the propellant gas. The cooling system may be a mixture of dry ice and acetone or a more elaborate refrigeration system. After the chilled product concentrate has been quantitatively metered into an equally cold aerosol container, the liquefied gas is added. The heavy vapors of the cold liquid propellant generally displace the air in the container. However, in the process, some of the propellant vapors are also lost. When sufficient propellant has been added, the valve assembly is inserted and crimped into place. Because of the low temperatures required, aqueous systems cannot be filled by this process, because the water turns to ice. For nonaqueous systems, some moisture usually appears in the final product due to the condensation of atmospheric moisture within the cold containers.

Pressure Filling

By the pressure method, the product concentrate is quantitatively placed in the aerosol container (Fig. 14.15), the valve assembly is inserted and crimped into place, and the liquefied gas, under pressure, is metered into the valve stem from a pressure burette (Fig. 14.16). The desired amount of propellant is allowed to enter the container under its own vapor pressure. When the pressure in the container equals that in the burette, the propellant stops flowing. Additional propellant may be added by increasing the pressure in

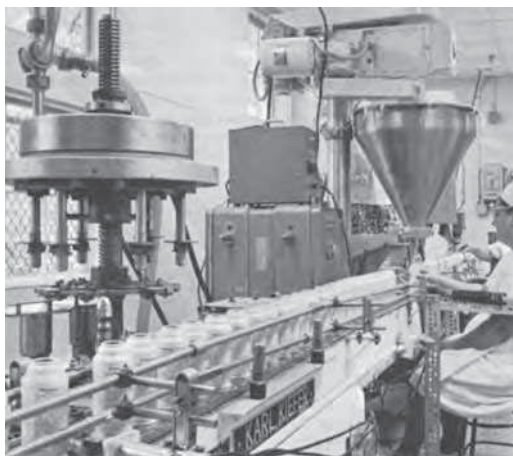


FIGURE 14.15 Filling the aerosol cans with the drug mixture. (Courtesy of Pennwalt Corp.)

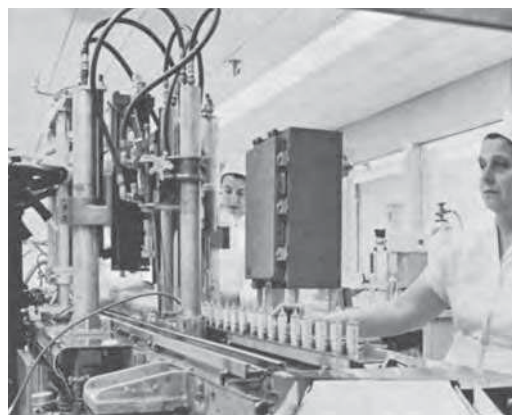


FIGURE 14.16 Pressure filling of aerosol containers. (Courtesy of Pennwalt Corp.)

the filling apparatus through the use of compressed air or nitrogen gas. The trapped air in the package may be ignored if it does not interfere with the quality or stability of the product, or it may be evacuated with a special apparatus. After the container is filled with sufficient propellant, the valve actuator is tested for proper function. This spray testing also rids the dip tube of pure propellant prior to consumer use.

Pressure filling is used for most pharmaceutical aerosols. It has two advantages over cold filling: There is less danger of moisture contamination of the product, and less propellant is lost in the process.

When compressed gases are employed as the propellant in aerosol systems, the gas is transferred from large steel cylinders into the aerosol containers. Prior to filling, the product concentrate is placed in the container, the valve assembly is crimped into place, and the air is evacuated from the container by a vacuum pump. The compressed gas is then passed into the container through a pressure-reducing valve attached to the gas cylinder; when the pressure within the aerosol container is equal to the predetermined and regulated delivery pressure, the gas flow stops, and the aerosol valve is restored to the closed position. For gases like carbon dioxide and nitrous oxide, which are slightly soluble in the product concentrate, the container is manually or mechanically shaken during the filling operation to achieve the desired

pressure in the head space of the aerosol container.

Testing the Filled Containers

After filling by either method, the aerosol container is tested under various environmental conditions for leaks or weakness in the valve assembly or container.

Filled aerosol containers are also tested for proper function of the valve. The *valve discharge rate* is determined by discharging a portion of the contents of a previously weighed aerosol during a period and calculating, by the difference in weight, the grams of contents discharged per unit of time. As is deemed desirable, aerosols may be tested for their spray patterns, for particle size distribution of the spray, and for accuracy and reproducibility of dosage when using metered valves.

Packaging, Labeling, and Storage

A unique aspect of pharmaceutical aerosols compared to other dosage forms is that the product is actually packaged as part of the manufacturing process. With most other dosage forms, the product is completely manufactured and then placed in the appropriate container.

Most aerosol products have a protective cap or cover that fits snugly over the valve and mounting cup. This protects the valve against contamination with dust and dirt. The cap, which is generally made of plastic or metal, also serves a decorative function.

Medicinal aerosols that are to be dispensed only upon prescription usually are labeled by the manufacturer with plastic peel-away labels or easily removed paper labels so that the pharmacist may easily replace the manufacturer's label with his label containing the directions for use specified by the prescribing practitioner. Most other types of aerosols have the manufacturer's label printed directly on the container or on firmly affixed paper.

In addition to the usual labeling requirements for pharmaceutical products, aerosols have special requirements for use and storage. For example, for safety, labels must warn users not to puncture pressurized containers,

not to use or store them near heat or an open flame, and not to incinerate them. Exposure to temperatures above 49°C (120°F) may burst an aerosol container. Most medications in aerosol containers are intended for use at ambient room temperatures. When the canisters are cold, less than the usual spray may result. This may be particularly important to users of metered-dose inhalation sprays. These products are generally recommended for storage between 15°C and 30°C (59°F and 86°F). Pharmaceutical aerosols are labeled with regard to shaking before use, holding at the proper angle and/or distance from the target; there are special detailed instructions for inhaler devices.

Aerosols should be maintained with the protective caps in place to prevent accidental activation of the valve assembly or contamination by dust and other foreign materials. Examples of pharmaceutical aerosols are shown in Figure 14.17 and presented in Table 14.6.

Proper Administration and Use of Pharmaceutical Aerosols

The pharmacist should make every attempt to educate the patient about aerosol dosage forms, particularly for oral or nasal



FIGURE 14.17 Pharmaceutical aerosols.

Table 14.6 EXAMPLES OF INHALATION AEROSOLS

AEROSOL	REPRESENTATIVE COMMERCIAL PRODUCTS	CATEGORY AND COMMENTS
Albuterol	Proventil Inhalation Aerosol (Key) Ventolin Inhalation Aerosol (GlaxoSmithKline)	Beta-adrenergic agonist for prevention and relief of bronchospasm in patients with reversible obstructive airway disease and for relief of exercise-induced bronchospasm
Beclomethasone dipropionate	Beclovent Inhalation Aerosol (Glaxo Wellcome) Vanceril Inhaler (Schering)	Adrenocortical steroid; aerosol for oral inhalation to control bronchial asthma in patients requiring chronic treatment with corticosteroids plus other therapy, for example, xanthines, sympathomimetics
	Beconase Nasal Inhaler (GlaxoSmithKline) Vancenase Pockethaler Nasal Inhaler (Schering)	Adrenocortical steroid; aerosol for intranasal relief of seasonal or perennial rhinitis in cases poorly responsive to conventional treatment
Cromolyn sodium	Intal Inhaler (King)	Antiasthmatic, antiallergic, mast cell stabilizer; metered dose for oral use to prevent exercise-induced bronchospasm, acute bronchospasm induced by environmental pollutants and known allergens
Ipratropium bromide	Atrovent Inhalation Aerosol (Boehringer Ingelheim)	Anticholinergic (parasympatholytic) bronchodilator for bronchospasm
Metaproterenol sulfate	Alupent Inhalation Aerosol (Boehringer Ingelheim)	Sympathomimetic for bronchospasm in patients with reversible obstructive airway disease
Salmeterol xinafoate	Serevent Inhalation Aerosol (GlaxoSmithKline)	Beta-adrenergic agonist for long-term maintenance treatment of asthma, prevention of bronchospasm in patients with reversible obstructive airway disease
Terbutaline sulfate	Brethine (AAlPharma)	Beta-adrenergic agonist for relief of bronchospasm
Triamcinolone acetonide	Azmacort (Kos)	For patients who require chronic treatment with corticosteroids to control symptoms of bronchial asthma

administration, because these are only effective when properly used. To complement verbal instructions, the pharmacist should provide the patient with the written instructions in the product package. It is difficult to predict what percentage of patients will read or understand the printed instruction. Thus, the pharmacist must verbally transmit instruction for proper use. Using the oral metered aerosols as a model, the pharmacist should demonstrate how the inhaler is assembled, stored, and cleaned. The patient should be told whether the inhaler

requires shaking before use and how to hold it between the index finger and thumb so that the aerosol canister is upside down. The patient should understand that coordination must be achieved between inhalation (after exhaling as completely as possible) and pressing down the inhaler to release one dose. The patient should be instructed to hold the breath for several seconds or as long as possible to gain the maximum benefit from the medication, then remove the inhaler from the mouth, and exhale slowly through pursed lips.

Some patients cannot use MDIs properly. Thus, after a new prescription is dispensed, it is advisable for the pharmacist to follow up with the patient to make sure the patient can use the inhaler. If the patient cannot use the inhaler, it is advisable for the pharmacist to recommend to the patient or the patient's physician the use of an extender device with the inhaler. Extender devices, or spacers, were originally developed for patients who could not learn to coordinate release of the medication with inhalation. These are now considered an important therapeutic aid because they can effectively assist the delivery of medication despite improper patient inhalation technique. By placing an extender device between the MDI's mouthpiece and the patient's mouth, the patient is permitted to separate activation of the aerosol from inhalation by up to 3 to 5 seconds (a valve in the spacer opens when the patient inhales). Another advantage of the extender is that aerosol velocity is reduced and droplet size is decreased because there is time for evaporation of the fluorohydrocarbon propellant. Thus, extender devices also cause less deposition of medication in the oropharynx. Extender devices can be used with most pressurized canisters, such as Brethancer Inhaler (Novartis) and InspirEase (Key).

To ensure continuity of therapy, it is wise for the pharmacist to share with the patient ways to assess how much medication is left in the canister. This is important to ensure continuity of therapy, especially for those who have respiratory illness and may need their medication on a moment's notice.

Examples of oral *inhalation aerosols* (solutions and powders) include Asmanex Twisthaler (mometasone furoate inhalation powder, Schering), Ventavis (iloprost inhalation solution, Cotherix), Pulmicort Flexhaler (budesonide inhalation powder, AstraZeneca), Atrovent HFA (ipratropium bromide HFA inhalation aerosol, Boehringer Ingelheim), and Brovana (arformoterol tartrate inhalation solution, Sepracor Inc.).

For topical administration of aerosol dosage forms, the patient should first clean the affected area gently and pat it dry. Holding

the canister with the nozzle pointing toward the body area and about 6 to 8 inch away, the patient should press down the button to deliver enough medication to cover the area. The patient should allow the spray to dry and not cover the area with a bandage or dressing unless instructed to do so by the physician. The patient should avoid accidentally spraying the product into the eyes or mouth. If it is necessary to apply the product to a facial area, the patient should spray the product into the palm of the hand and apply it by this means.

As presented in Table 14.6, a number of drug substances are administered through pressure-packaged inhalation aerosols like the type shown in Figure 14.14. For the inhaled drug substance or solution to reach the bronchial tree, the inhaled particles must be just a few microns in size.

Topical Aerosols

Convenient aerosol packages for use on the skin include the anti-infective agents povidone iodine, tolnaftate, and thimerosal; the adrenocortical steroids betamethasone dipropionate and valerate, dexamethasone, and triamcinolone acetonide; and the local anesthetic dibucaine hydrochloride.

The use of topical aerosols provides the patient a means of applying the drug in a convenient manner. The preparation may be applied to the desired surface area without the use of the fingertips, making the procedure less messy than with most other types of topical preparations. Among the disadvantages to the use of topical aerosols are the difficulty in applying the medication to a small area and the greater expense associated with the aerosol package.

Vaginal and Rectal Aerosols

Aerosol foams containing estrogenic substances and contraceptive agents are commercially available. The foams are used intravaginally in the same manner as for creams. The aerosol package contains an inserter that is filled with foam and the contents placed in the vagina through activation of the plunger. The foams are generally o/w

emulsions resembling light creams. They are water miscible and nongreasy.

Some commercial rectal foams use inserters. One such product, Proctofoam (Alaven Pharmaceuticals), contains pramoxine hydrochloride to relieve inflammatory anorectal disorders (Fig. 14.18).

FOAMS

A foam is an emulsion dosage form containing dispersed gas bubbles. When dispensed, it has a fluffy, semisolid consistency. Medicated foams are emulsions containing a dispersed phase of gas bubbles in a liquid continuous phase containing the active pharmaceutical ingredient. Medicated foams are packaged in pressurized containers or special dispensing devices and are intended for application to the skin or mucous membranes. The medicated foam is formed at the time of application. Surfactants are used to ensure the dispersion of the gas and the two phases. Medicated foams have a fluffy, semisolid consistency and can be formulated to break to a liquid quickly or to remain as foam to ensure prolonged contact. Medicated foams intended to treat severely injured skin or open wounds must be sterile.

PREPARATION OF FOAMS

A foam may contain one or more active pharmaceutical ingredients, surfactants, aqueous or nonaqueous liquids, and propellants. If the propellant is in the internal, or discontinuous, phase, a stable foam is discharged. If the propellant is in the external, or continuous, phase, a spray or a quick-breaking foam is discharged. Quick-breaking foams formulated with alcohol create a cooling sensation when applied to the skin and may have disinfectant properties.

Foams containing flammable components should be appropriately labeled. Labeling indicates that a foam drug product must be



FIGURE 14.18 Foam for anal and perianal use. To fill the applicator, the foam container is shaken vigorously and held upright, and the applicator tip placed on the container opening. With the plunger of the applicator drawn out all the way, pressure is exerted on the container cap, and foam fills the applicator tube. (Courtesy of Reed & Carnrick.)

shaken well to ensure uniformity prior to dispensing. The instructions for use must clearly note special precautions that are necessary to preserve sterility. In the absence of a metering valve, the delivered volume may be variable.

PHARMACEUTICS



CASE STUDY

SUBJECTIVE INFORMATION

Working for an innovative pharmaceutical company, you have received a request to develop an oral liquid formulation for a new organ rejection drug. The drug must be formulated so that a 5-mg dose can be reasonably easily administered either as the dosage form or immediately after mixing with water or juice. The formulation should be stable and easy to manipulate. The problem is that the drug is not water soluble but a solution dosage form is desired.

OBJECTIVE INFORMATION

The drug has a molecular weight of 1015.2 and occurs as a white to off-white powder that is insoluble in water but freely soluble in benzyl alcohol, chloroform, acetone, and acetonitrile.

The drug may be prepared as an aqueous suspension or as a solution in a water-miscible liquid that can be diluted prior to administration. A reasonable dispersant liquid for the insoluble drug may include a blend of lecithin products that would form liposomes upon dilution in an aqueous vehicle. Some commercial blends occur as honey-colored fluids with a typical odor and nutty taste. These can be diluted with water and have densities of approximately 1 to 1.2 and viscosities in the range of 5,000 mPa.

It may be wise to add a dispersant such as polysorbate 80 to aid in mixing when this is added to water or juice. Polysorbate 80 (Tween 80, polyoxyethylene 20 sorbitan monooleate, $C_{64}H_{124}O_{26}$) has a molecular weight of 1,310 and occurs as a yellow

oily liquid with a characteristic odor and a warm, somewhat bitter taste. It has a specific gravity of 1.06 to 1.09, and its HLB is 15.0; it forms o/w emulsions. It is stable in the presence of electrolytes, weak acids, and weak bases. It should be stored in a well-closed, light-resistant container in a cool place (5).

ASSESSMENT

After viewing the options, you decide to select a solvent system for the drug and prepare it as a solution. The patient can obtain the dose and dilute it immediately prior to administration. This meets the criteria of stability and ease of administration.

You select a commercial dispersant liquid for oral use containing 50% phosphatidylcholine in propylene glycol, sunflower seed oil glycerides, soy acid, alcohol, and ascorbyl palmitate. This product is used as a dispersant, emulsifier, penetrant, and solubilizer for pharmaceuticals, creams, lotions, emulsions, and liposome preparations for dermatology. It is suitable for oral use.

PLAN

You formulate the product as a 5-mg dose in 1 mL of the vehicle containing 0.5% polysorbate 80 in the described dispersant liquid. This will provide a stable, easy-to-use product.

For administration, the proper quantity of the oral liquid will be added to approximately 2 to 4 oz of water or juice. The preparation should be vigorously stirred and taken at once. Various juices can be used depending on the preference of the patient.

CLINICAL



CASE STUDY

HPI: M.H. is a 31-year-old WF who presents to the pharmacy with a prescription for metronidazole. Upon questioning, the patient reveals that she just returned from an appointment with her gynecologist. She has been having symptoms that she describes as “an unusual yellowish smelly discharge with itching and burning.” The patient continues, “At first I thought it was just another yeast infection, but the discharge seemed a little different. I did not want to use another OTC product that might not work, so I went to see my doctor.” Her gynecologist informed her that she had *trichomonal vaginitis*, a sexually transmitted disease (STD). When handing the prescription to the pharmacist, she complains that she “hates this medicine. I don’t like taking pills even if they aren’t big. And they leave an awful taste in my mouth.” The pharmacist knows M. H. as a regular customer and decides to look up her profile to confirm that she had previously taken metronidazole. She also reviews M.H.’s past medical history.

PMH: Asthma since childhood
Vaginal yeast infections about once a year

Bacterial vaginosis in 2001
Miscarriage in 1999

SH: (+) EtOH: drinks cocktails on weekends, occasionally wine at dinner

(–) Tobacco
(–) Illicit drugs

FH: Mother (+) for breast cancer
Father (+) for hypertension and hypercholesterolemia
Brother (+) for asthma

Allergies: NKDA

Meds: Advair 250/50 1 inhalation bid
Albuterol MDI prn
Gyne-Lotrimin 3 prn yeast infections

PHARMACEUTICAL CARE PLAN

- S:** Patient has vaginal symptoms, including itching, burning, and a yellowish, malodorous discharge. Patient complains about the size of the metronidazole tablets and its metallic taste.
- O:** The gynecologist has diagnosed *trichomonal vaginitis*. Previously, the patient has been prescribed metronidazole oral tablets for bacterial vaginosis.
- A:** M.H. is a 31-year-old WF diagnosed with *trichomonal vaginitis* that is to be treated with oral metronidazole tablets. Although she is in a monogamous relationship, unprotected sex increases the risk of transmitting STDs, such as *trichomonas*. M. H.’s adherence to the metronidazole regimen is very important because untreated vaginitis may progress to urethritis and/or cystitis. Worried that the patient may not adhere to her regimen, the pharmacist considers compounding a metronidazole suspension so that the patient will not have to take the tablets and will have an easier dosage form.
- P:**
 1. The pharmacist offers the alternative of an extemporaneously prepared metronidazole suspension in lieu of the oral tablets. The patient agrees to try this option. So the pharmacist calls the patient’s physician to seek permission to change the drug delivery system.
 2. After securing permission to do so, the pharmacist decides to use metronidazole benzoate powder in lieu of metronidazole HCl, the active ingredient in the oral tablets. The benzoate form is relatively tasteless, which may also be a more suitable option for M.H. even though the metallic taste will occur from the therapy after administration.

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CLINICAL CASE STUDY CONT.

3. The first step in preparation of the suspension is a mathematical calculation to determine the equivalent dose of metronidazole benzoate. The pharmacist confirms that 200 mg of the benzoate ester is equivalent to 125 mg of the HCl salt. The prescribed dose of metronidazole HCl tablets is 250 mg tid for 7 days. Thus, the pharmacist calculates the equivalent metronidazole benzoate dose that will be 400 mg tid for 7 days.
4. After weighing the required amount of metronidazole benzoate powder, the pharmacist triturates it in a mortar and selects Ora-Plus as the suspending agent and pestle to minimize the particle size. The pharmacist Ora-Sweet as the flavoring agent. The suspension will be compounded so that the final concentration (w/v) of metronidazole benzoate will be 400 mg/5 mL. With constant mixing, the pharmacist slowly adds Ora-Plus 50 mL to the metronidazole benzoate powder to create a slurry. The resultant suspension is transferred into a graduated cylinder and diluted with enough Ora-Sweet so that the total volume of the suspension is 105 mL. Before bringing the product to final volume, the pharmacist uses some Ora-Sweet to remove as much of the slurry from the mortar as possible.

After stirring the suspension, the contents are transferred into an appropriate-sized plastic bottle, and the label with the appropriate information is affixed. The following auxiliary labels should also be affixed to the bottle:

Keep refrigerated, shake well before using, finish the entire course of therapy, avoid alcoholic beverages, and take with food.

5. When dispensing the metronidazole suspension to the patient, the pharmacist counsels and instructs M.H. M.H. should take one teaspoonful by mouth three times daily for seven consecutive days. The daily doses should be taken with food after each meal. The medication should be stored in the refrigerator when not being used, and because it is a suspension, shaken well before each dose. It is assumed that the suspension will be used up before the beyond-use date of 30 days. However, it is necessary for the pharmacist to label the product with the beyond-use date in the event that some is left over.
6. The pharmacist suggests that the medication be taken with food to help prevent stomach upset, nausea, and diarrhea. Although the benzoate form of metronidazole may help to lessen the bitter taste associated with its administration, the metallic taste may still occur after systemic absorption, and the patient should understand this. In addition, M.H. should be told about the interaction (disulfiram reaction) between metronidazole and alcohol. Alcohol must be avoided during therapy and for 72 hours after the last dose. This disulfiram reaction may result in severe flushing, headache, nausea, vomiting, or chest and abdominal pain. M.H. should also be aware that the medication may darken her urine.

CLINICAL CASE STUDY CONT.

7. Because *trichomonal vaginitis* is an STD, M.H. must be educated to take certain precautions to prevent transmission and reinfection of herself. During treatment, M.H. should refrain from sexual intercourse. The importance of practicing safe sex (e.g., condom use) should be emphasized to prevent contracting STDs and other serious infections (e.g., HIV, hepatitis). In addition, M.H.'s sexual partner should be treated with metronidazole. Although he may be asymptomatic, there is an elevated risk that he is carrying the trichomonas organism and

infecting M.H. during intercourse. Thus, with this prescription, her partner may or may not be treated. If the latter, it is important that the pharmacist tells M.H. not to share her medication with her sexual partner. She is to take a full course of therapy. If there is a primary treatment failure, it is likely that the male sexual partner will also be treated during the second course of therapy. Emphasis will be put on the importance of M.H. completing the full course of metronidazole therapy to prevent resistance, emergence, and recurrent infections.

APPLYING THE PRINCIPLES AND CONCEPTS

Group Activities

1. Discuss specific patient circumstances and therapeutic circumstances where particular liquid disperse system dosage forms would be indicated or contraindicated for use.
2. Describe the three phases of a stable emulsion.
3. Identify and describe three methods for emulsion preparation.
4. Obtain representative extemporaneous prescriptions, which result in a suspension or emulsion dosage form, and devise a procedure to compound each prescription.
5. Create a table of representative oral o/w products inclusive of active and inactive ingredients, indications and contraindications for their use, adverse effects associated with their use, dosage, and patient information.

6. Create a table of representative topical w/o and o/w products inclusive of active and inactive ingredients, indications and contraindications for their use, adverse effects associated with use, dosage, and patient information.
7. Create a table of topical gel products, which are also available as topical creams and ointments, and describe differences, which exist between the dosage forms.
8. Role-play proper counseling points a pharmacist should make when dispensing a liquid disperse system to a patient.

Individual Activities

1. Identify three desired features in a suspension, and explain how these benefit patient administration.
2. Explain the role of suspending agents when added to a dispersion medium.

APPLYING THE PRINCIPLES AND CONCEPTS (CONT.)

3. Compare and contrast the various suspending agents used in suspension dosage forms. Determine additional processes/techniques, which allow a drug to be more effectively penetrated by a given vehicle.
4. Differentiate the terms “for Oral Suspension” and “Oral Suspension,” and create a table illustrating three product examples of each.
5. List advantages of emulsifying a liquid drug over pure liquid drug for oral administration.
6. Describe the chain of events that occur after aggregation or coalescence of an emulsion.

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