11 Transdermal Drug Delivery Systems

OBJECTIVES

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

1. Explain the physical–chemical properties of drugs that determine their ability to be incorporated into a transdermal dosage form
2. Describe physiological factors of the skin that influence percutaneous absorption
3. Define a chemical permeation enhancer and describe physical methods used to facilitate the percutaneous absorption of drugs
4. Differentiate between the various types of systems used for transdermal delivery
5. List the advantages and the disadvantages of transdermal delivery of drugs compared to other forms of drug delivery
6. Provide examples of drugs that are delivered transdermally, and list precautions associated with their use
7. Describe important counseling information to share with a patient prescribed a drug to be administered in a transdermal drug delivery system

Transdermal drug delivery systems (TDDSs) facilitate the passage of therapeutic quantities of drug substances through the skin and into the general circulation for their systemic effects. In 1965, Stoughton first conceived of the *percutaneous absorption* of drug substances (1). The first transdermal system, Transderm Scop (Baxter), was approved by the U.S. Food and Drug Administration (FDA) in 1979 for prevention of nausea and vomiting associated with travel, particularly at sea.

Evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug and/or its metabolites in the urine, and clinical response of the patient to the therapy. With transdermal drug delivery, the blood concentration needed to achieve therapeutic efficacy may be determined by comparative analysis of the patient's response to drug blood levels. For transdermal drug delivery, it is considered ideal for the drug to migrate through the skin to the underlying blood supply without buildup in the dermal layers (2). This is in direct contrast to the types of topical dosage forms discussed in the previous chapter, in which drug residence in the skin, the target organ, is desired.

As discussed in the previous chapter, the skin is composed of the stratum corneum (the outer layer), the living epidermis, and the dermis, which together provide the skin's barrier layers to penetration by external agents (see Fig. 10.6). The film that covers the stratum corneum is composed of sebum and sweat, but because of its varied composition and lack of continuity, it is not a significant factor in drug penetration, nor are the hair follicles and sweat and sebaceous gland ducts, which constitute only a minor proportion of the skin's surface.

Percutaneous absorption of a drug generally results from direct penetration of the drug through the stratum corneum, a 10- to 15-mm-thick layer of flat, partially desiccated nonliving tissue (3,4). The stratum corneum is composed of approximately 40% protein (mainly keratin) and 40% water, with the balance being lipid, principally as triglycerides, free fatty acids, cholesterol, and phospholipids. The lipid content is concentrated in the extracellular phase of the stratum corneum and forms to a large extent the membrane surrounding the cells. Because a drug's major route of penetration is through the intercellular channels, the lipid component is considered an important determinant in the first step of absorption (5). Once through the stratum corneum, drug molecules may pass through the deeper epidermal tissues and into the dermis. When the drug reaches the vascularized dermal layer, it becomes available for absorption into the general circulation.

The stratum corneum, being keratinized tissue, behaves as a semipermeable artificial membrane, and drug molecules penetrate by passive diffusion. It is the major rate-limiting barrier to transdermal drug transport (6). Over most of the body, the stratum corneum has 15 to 25 layers of flattened corneocytes with an overall thickness of about 10 mm (6). The rate of drug movement across this layer depends on its concentration in the vehicle, its aqueous solubility, and the oil–water partition coefficient between the stratum corneum and the vehicle (7). Substances with both aqueous and lipid solubility characteristics are good candidates for diffusion through the stratum corneum, epidermis, and dermis.

FACTORS AFFECTING PERCUTANEOUS ABSORPTION

Not all drug substances are suitable for transdermal delivery. Among the factors playing a part in percutaneous absorption are the physical and chemical properties of the drug, including its molecular weight, solubility, partitioning coefficient and dissociation constant (pK_a), the nature of the carrier vehicle, and the condition of the skin. Although general statements applicable to all possible combinations of drug, vehicle, and skin condition are difficult to draw, most research findings may be summarized as follows (2–11):

1. Drug concentration is an important factor. Generally, the amount of drug percutaneously absorbed per unit of surface area per time interval increases with an increase in the concentration of the drug in the TDDS.
2. The larger the area of application (the larger the TDDS), the more drug is absorbed.
3. The drug should have a greater physicochemical attraction to the skin than to the vehicle so that the drug will leave the vehicle in favor of the skin. Some solubility of the drug in both lipid and water is thought to be essential for effective percutaneous absorption. In essence, the aqueous solubility of a drug determines the concentration presented to the absorption site, and the partition coefficient influences the rate of transport across the absorption site. Generally, drugs penetrate the skin better in their unionized form. Nonpolar drugs tend to cross the cell barrier through the lipid-rich regions (transcellular route), whereas the polar drugs favor transport between cells (intercellular route) (6). For example, erythromycin base demonstrates better percutaneous absorption than does erythromycin ethyl succinate.
4. Drugs with molecular weights of 100 to 800 and adequate lipid and aqueous solubility can permeate skin. The ideal molecular weight of a drug for transdermal drug delivery is believed to be 400 or less.
5. Hydration of the skin generally favors percutaneous absorption. The TDDS acts as an occlusive moisture barrier through which sweat cannot pass, increasing skin hydration.
6. Percutaneous absorption appears to be greater when the TDDS is applied to a site with a thin horny layer than with a thick one.
7. Generally, the longer the medicated application is permitted to remain in contact with the skin, the greater is the total drug absorption.

These general statements apply to skin in the normal state. Skin that is abraded or cut permits drugs to gain direct access to the subcutaneous tissues and the capillary network, defeating the function of the TDDS.

PERCUTANEOUS ABSORPTION ENHANCERS

There is great interest among pharmaceutical scientists to develop chemical permeation enhancers and physical methods that can increase percutaneous absorption of therapeutic agents.

Chemical Enhancers

By definition, a chemical skin penetration enhancer *increases skin permeability by reversibly damaging or altering the physicochemical nature of the stratum corneum to reduce its diffusional resistance* (12). Among the alterations are increased hydration of the stratum corneum, a change in the structure of the lipids and lipoproteins in the intercellular channels through solvent action or denaturation, or both (4,13–17).

Some drugs have an inherent capacity to permeate the skin without chemical enhancers. However, when this is not the case, chemical permeation enhancers may render an otherwise impenetrable substance useful in transdermal drug delivery (17). More than 275 chemical compounds have been cited in the literature as skin penetration enhancers; they include acetone, azone, dimethylacetamide, dimethylformamide, dimethyl sulfoxide, ethanol, oleic acid, polyethylene glycol, propylene glycol, and sodium lauryl sulfate (13–15). The selection of a permeation enhancer should be based not only on its efficacy in enhancing skin permeation but also on its dermal toxicity (low) and its physicochemical and biologic compatibility with the system's other components (16).

Iontophoresis and Sonophoresis

In addition to chemical means, some physical methods are being used to enhance transdermal drug delivery and penetration, namely, iontophoresis and sonophoresis (6,15,18–23).

Iontophoresis is delivery of a charged chemical compound across the skin membrane using an electrical field. A number of drugs have been the subject of iontophoretic studies; they include lidocaine (18); dexamethasone; amino acids, peptides, and insulin (19,20); verapamil (6); and propranolol (21). There is particular interest to develop alternative routes for delivery of biologically active peptides. At present, these agents are delivered by injection because of their rapid metabolism and poor absorption after oral delivery. They are also poorly absorbed by the transdermal route because of their large molecular size and ionic character and the general impenetrability of the skin (20). However, iontophoresis-enhanced transdermal delivery has shown some promise as a means of peptide and protein administration.

Sonophoresis, or high-frequency ultrasound, is also being studied as a means to enhance transdermal drug delivery (22,23). Among the agents examined are hydrocortisone, lidocaine, and salicylic acid in such formulations as gels, creams, and lotions. It is thought that high-frequency ultrasound can influence the integrity of the stratum corneum and thus affect its penetrability.

PERCUTANEOUS ABSORPTION MODELS

Skin permeability and percutaneous absorption have been the subject of numerous studies to define the underlying principles and to optimize transdermal drug delivery. Although many experimental methods and models have been used, they tend to fall into one of two categories, in vivo or in vitro.

In Vivo Studies

In vivo skin penetration studies may be undertaken for one or more of the following purposes (24):

1. To verify and quantify the cutaneous bioavailability of a topically applied drug
2. To verify and quantify the systemic bioavailability of a transdermal drug
3. To establish bioequivalence of different topical formulations of the same drug substance

4. To determine the incidence and degree of systemic toxicologic risk following topical application of a specific drug or drug product
5. To relate resultant blood levels of drug in human to systemic therapeutic effects

The most relevant studies are performed in humans; however, animal models may be used insofar as they may be effective as predictors of human response. Animal models include the weanling pig, rhesus monkey, and hairless mouse or rat (24,25). Biologic samples used in drug penetration and drug absorption studies include skin sections, venous blood from the application site, blood from the systemic circulation, and excreta (urine, feces, and expired air) (24–28).

In Vitro Studies

Skin permeation may be tested in vitro using various skin tissues (human or animal whole skin, dermis, or epidermis) in a diffusion cell (29). In vitro penetration studies using human skin are limited because of difficulties of procurement, storage, expense, and variation in permeation (30). Excised animal skins may also vary in quality and permeation. Animal skins are much more permeable than human skin. One alternative that has been shown to be effective is shed snakeskin (*Elaphe obsoleta*, black rat snake), which is nonliving, pure stratum corneum, hairless, and similar to human skin but slightly less permeable (30,31). Also, the product Living Skin Equivalent Testskin (Organogenesis, Inc.) was developed as an alternative for dermal absorption studies. The material is an organotypic coculture of human dermal fibroblasts in a collagen-containing matrix and a stratified epidermis composed of human epidermal keratinocytes. The material may be used in cell culture studies or in standard diffusion cells.

Diffusion cell systems are employed in vitro to quantify the release rates of drugs from topical preparations (32). In these systems, skin membranes or synthetic membranes may be employed as barriers to the flow of drug and vehicle to simulate the biologic system. The typical diffusion cell has two chambers, one on each side of the test diffusion membrane (Figs. 11.1 to 11.3). A temperature-controlled solution of the drug is placed in one chamber and a receptor solution in the other chamber. When skin is used as the test membrane, it separates the two solutions. Drug diffusion through the skin may be determined by periodic sampling and assay of the drug content in the receptor solution. The skin may also be analyzed for drug content to show permeation rates and/or retention in the skin (29).

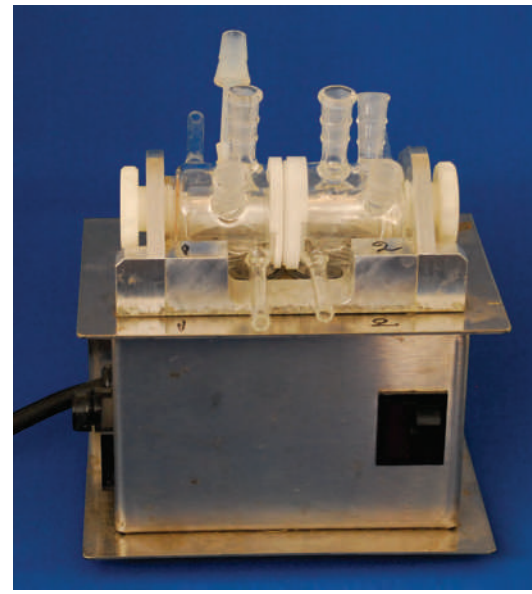

FIGURE 11.1 Typical side-by-side diffusion cell setup used for permeability/diffusion studies. A membrane or skin can be placed in the holder in the center. There are three ports on each side for sampling; one can be used to insert an electrode for iontophoresis studies. Each half cell has an inlet and outlet for constant temperature water to circulate.

The *United States Pharmacopeia* (USP) describes the apparatus and procedure to determine dissolution (release) of medication from a transdermal delivery system and provides an acceptance table to which the product must conform to meet the monograph standard for a given article (33). Commercial systems use transdermal diffusion cells and automatic sampling systems to determine the release rates of drugs from transdermal systems (34). In USP 35/NF 30, there were two official transdermal systems, that is, clonidine and nicotine.

FIGURE 11.2 Typical Franz diffusion cell. The donor cell is on top, and the upper and lower chambers are separated by either a membrane or skin. A solution or semisolid containing the drug is placed in the upper cell and a receiver solution in the lower cell. The angle tube on the right is for sampling and fluid replacement. The two ports on the left consist of an inlet and outlet where constant temperature water can be circulated.

FIGURE 11.3 A microdiffusion cell for working with very low quantities of drugs and solutions.

DESIGN FEATURES OF TRANSDERMAL DRUG DELIVERY SYSTEMS

TDDSs (also often called transdermal patches) are designed to support the passage of drug substances from the surface of the skin through its various layers and into the systemic circulation. Examples of the configuration and composition of TDDSs are described in the text, presented in Table 11.1 and shown in Figures 11.4 to 11.7. Figures 11.8 to 11.10 depict the manufacture of TDDSs. Technically, TDDSs may be categorized into two types, monolithic and membrane-controlled systems.

Monolithic systems incorporate a drug matrix layer between the backing and the frontal layers (Fig. 11.4). The drug matrix layer is composed of a polymeric material in which the drug is dispersed. The polymer matrix controls the rate at which the drug is released for percutaneous absorption. The matrix may be of two types, either with or without an excess of drug with regard to its equilibrium solubility and steady-state concentration gradient at the stratum corneum (21,35). In types having no excess, drug is available to maintain the saturation of the stratum corneum only as long as the level of drug in the device exceeds the solubility limit of the stratum corneum. As the concentration of drug in the device diminishes below the skin's saturation limit, the transport of drug from device to skin declines (35). In systems with excess drug in the matrix, a drug reserve is present to ensure continued saturation at the stratum corneum. In these instances, the rate of drug decline is less than in the type having no reserve.

In the preparation of monolithic systems, the drug and the polymer are dissolved or blended together, cast as the matrix, and dried (21). The gelled matrix may be produced in sheet or cylindrical form, with

Table 11.1 EXAMPLES OF TRANSDERMAL DRUG DELIVERY SYSTEMS (40–44,47–51)

THERAPEUTIC AGENT	TDDS	DESIGN, CONTENTS	COMMENTS
Clonidine	Catapres-TTS (Boehringer Ingelheim)	Four-layer patch: (*a*) backing of pigmented polyester film; (*b*) reservoir of clonidine, mineral oil, polyisobutylene, colloidal silicon dioxide; (*c*) microporous polypropylene membrane–controlling rate of delivery; (*d*) adhesive formulation of agents	Transdermal therapeutic system to deliver therapeutic dose of antihypertensive drug at constant rate for 7 days. TDDS generally applied to hairless or shaven area of upper arm or torso
Estradiol	Estraderm (Novartis)	Four-layer patch: (*a*) transparent polyester film; (*b*) reservoir of estradiol, alcohol gelled with hydroxypropyl cellulose; (*c*) ethylene–vinyl acetate copolymer membrane; (*d*) adhesive formulation of light mineral oil, polyisobutylene	Transdermal system to release 17b-estradiol continuously. Patch is generally applied to the trunk, including abdomen and buttocks, alternating sites, twice weekly over a 3-week cycle with dosage frequency adjusted as required.
	Vivelle (Novartis)	Three-layer patch: (*a*) translucent ethylene vinyl alcohol copolymer film; (*b*) estradiol in matrix of medical adhesive of polyisobutylene, ethylene–vinyl acetate copolymer; (*c*) polyester release liner, removed prior to application	Use and application similar to Estraderm TDDS
	Climara (Bayer healthcare)	Three-layer system: (*a*) translucent polyethylene film, (*b*) acrylate adhesive matrix containing estradiol, (*c*) protective liner of siliconized or fluoropolymer-coated polyester film, removed prior to use	Use and application similar to Estraderm TDDS. System may be applied weekly.
Fentanyl	Duragesic (Janssen)	Four-layer patch: (*a*) backing layer of polyester film, (*b*) reservoir of fentanyl, alcohol gelled with hydroxyethyl cellulose, (*c*) rate-controlling ethylene–vinyl acetate copolymer membrane, (*d*) fentanyl- containing silicone adhesive	Transdermal therapeutic system providing continuous 72-h systemic delivery of potent opioid analgesic; indicated in patients with chronic pain requiring opioid analgesia
Nicotine	Habitrol (Basel Pharm)	Multilayer round patch: (*a*) aluminized backing film; (*b*) pressure-sensitive acrylate adhesive; (*c*) methacrylic acid copolymer solution of nicotine dispersed in pad of nonwoven viscose, cotton; (*d*) acrylate adhesive layer; (*e*) protective aluminized release liner that overlies adhesive layer, removed prior to use	Transdermal therapeutic systems providing continuous release, systemic delivery of nicotine to aid smoking cessation. Patches vary somewhat in nicotine content and dosing schedules.
	Nicoderm CQ (Glaxo SmithKline)	Multilayer rectangular patch: (*a*) occlusive backing of polyethylene, aluminum, polyester, ethylene–vinyl acetate copolymer; (*b*) reservoir of nicotine in ethylene–vinyl acetate copolymer matrix; (*c*) rate-controlling polyethylene membrane; (*d*) polyisobutylene adhesive; (*e*) protective liner, removed prior to application	

(*Continued*)

Table 11.1 EXAMPLES OF TRANSDERMAL DRUG DELIVERY SYSTEMS (40–44,47–51) (Continued)

THERAPEUTIC AGENT	TDDS	DESIGN, CONTENTS	COMMENTS
	Nicotrol (Pharmacia)	Multilayer rectangular patch: (*a*) outer backing of laminated polyester film; (*b*) rate-controlling adhesive, nonwoven material, nicotine; (*c*) disposable liner, removed prior to use	
	Prostep (Wyeth)	Multilayer round patch: (*a*) beige foam tape, acrylate adhesive; (*b*) backing foil, gelatin, low-density polyethylene coating; (*c*) nicotine gel matrix; (*d*) protective foil with well; (*e*) release liner, removed prior to use	
Nitroglycerin	Deponit (UCB)	Three-layer system: (*a*) covering foil; (*b*) nitroglycerin matrix with polyisobutylene adhesive, plasticizer, release membrane; (*c*) protective foil, removed before use	
Nitroglycerin	Nitro-Dur (Key)	Nitroglycerin in gel-like matrix of glycerin water, lactose, polyvinyl alcohol, povidone, sodium citrate sealed in polyester, foil, polyethylene laminate	
Nitroglycerin	Transderm-Nitro (Summit)	Four-layer patch: (*a*) backing layer of aluminized plastic; (*b*) reservoir of nitroglycerin adsorbed on lactose, colloidal silicon dioxide, silicone medical fluid; (*c*) ethylene–vinyl acetate copolymer membrane; (*d*) silicone adhesive	
Scopolamine	Transderm Scop (Baxter)	Four-layer patch: (*a*) backing layer of aluminized polyester film; (*b*) reservoir of scopolamine, mineral oil, polyisobutylene; (*c*) microporous polypropylene membrane for rate delivery of scopolamine; (*d*) adhesive of polyisobutylene, mineral oil, scopolamine	Continuous release of drug over 3 d to prevent nausea and vomiting of motion sickness. Patch is placed behind the ear. For repeated administration, first patch is removed and second placed behind the other ear. Also approved to prevent nausea of certain anesthetics and analgesics used in surgery
Testosterone	Testoderm (Alza)	Three-layer patch: (*a*) backing layer of PET; (*b*) matrix film layer of testosterone, ethylene–vinyl acetate copolymer; (*c*) adhesive strips of polyisobutylene, colloidal silicon dioxide	Patch is placed on scrotum in treatment of testosterone deficiency.
	Androderm (Watson)	Five-layer patch: (*a*) backing film of ethylene–vinyl acetate copolymer, polyester laminate; (*b*) reservoir of testosterone, alcohol, glycerin, glyceryl monooleate, methyl laurate gelled with acrylic acid copolymer; (*c*) microporous polyethylene membrane; (*d*) acrylic adhesive; (*e*) adhesive polyester laminate	Patch is placed on back, abdomen, upper arms, or thighs for treatment of testosterone deficiency.

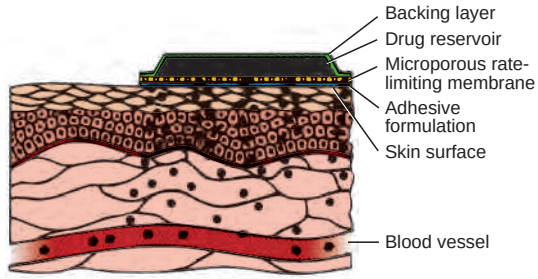

FIGURE 11.4 Four-layer therapeutic transdermal system showing the continuous and controlled amount of medication released from the system, permeating the skin, and entering the systemic circulation.

individual dosage units cut and assembled between the backing and frontal layers. Most TDDSs are designed to contain an excess of drug and thus have drug-releasing capacity beyond the time frame recommended for replacement. This ensures continuous drug availability and absorption as used TDDSs are replaced on schedule with fresh ones.

Membrane-controlled transdermal systems are designed to contain a drug reservoir, or pouch, usually in liquid or gel form; a rate-controlling membrane; and backing, adhesive, and protecting layers (Fig. 11.5). Transderm-Nitro (Summit) and Transderm Scop (Baxter) are examples of this technology. Membrane-controlled systems have the advantage over monolithic systems in that as long as the drug solution in the reservoir remains saturated, the release rate of drug through the controlling membrane remains constant (21,22). In membrane systems, a small quantity of drug is frequently placed in the adhesive layer to initiate prompt drug absorption and pharmacotherapeutic effects on skin placement. Membrane-controlled systems may be prepared by preconstructing the delivery unit, filling the drug reservoir, and sealing or by lamination, a continuous process of construction, dosing, and sealing (Figs. 11.8 to 11.10).

In summary, either the drug delivery device or the skin may serve as the rate-controlling mechanism. If the drug is delivered to the stratum corneum at a rate less than the absorption capacity, the *device* is the controlling factor; if the drug is delivered to the skin area to saturation, the *skin* is the controlling factor. Thus, the rate of drug transport in all TDDSs, monolithic and membrane, is controlled by either artificial or natural (skin) membranes.

TDDSs may be constructed of a number of layers, including (*a*) an occlusive backing membrane to protect the system from environmental entry and from loss of drug from the system or moisture from the skin; (*b*) a drug reservoir or matrix system to store and release the drug at the skin site; (*c*) a release liner, which is removed before application and enables drug release; and (*d*) an adhesive layer to maintain contact with the skin after application. Two types of adhesive layers, the peripheral adhesive and the face adhesive,

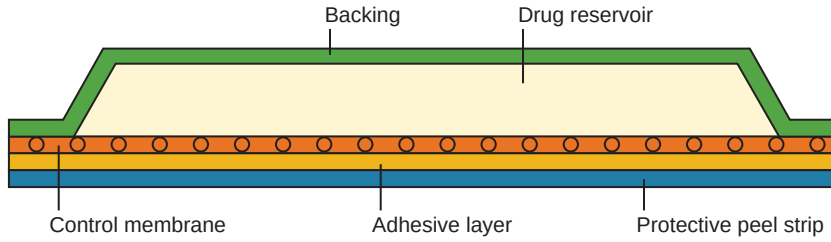

FIGURE 11.5 The Transderm-Nitro Transdermal Therapeutic System (Summit). The patch delivers nitroglycerin through the skin directly into the blood stream for 24 hours. Transderm-Nitro is used to treat and prevent angina. The system consists of a water-resistant backing layer, a reservoir of nitroglycerin, followed by a semipermeable membrane to control precisely and predictably the release of medicine, and an adhesive layer to hold the system onto the skin. The adhesive layer also contains an initial priming dose of nitroglycerin to ensure prompt release and absorption of the medication. (Courtesy of Summit Pharmaceuticals, Novartis.)

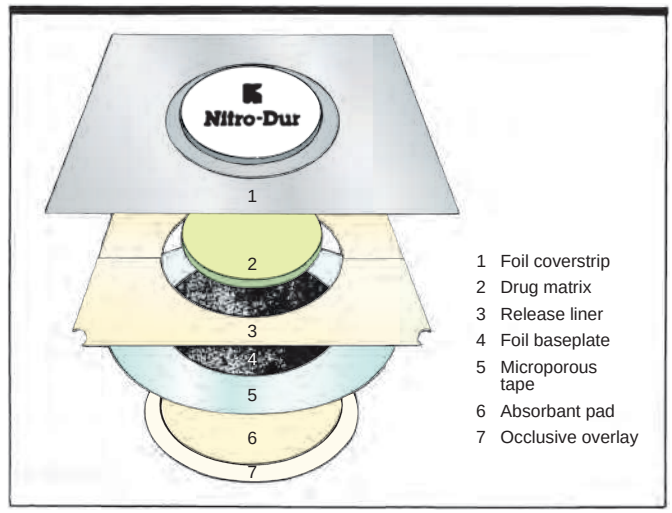

FIGURE 11.6 Nitro-Dur Transdermal Infusion System: Construction of the product. (Courtesy of Key Pharmaceuticals.)

can be used. The peripheral adhesive contains adhesive around the outer edge of the TDDS, usually in a wide strip surrounding the active drug portion. The face adhesive, which covers the entire face of the TDDS, is very common. TDDSs are packaged in individual sealed packets to preserve and protect them until use.

The backing layer must be occlusive to retain skin moisture and hydrate the site of application, enabling increased drug penetration. Preferred backing materials are approximately 2 to 3 mm thick and have a low moisture vapor transmission rate, less than about 20 g/m^2 in 24 hours (36). Transparent or pigmented films of polypropylene, polyethylene, and polyolefin are in use in TDDSs as backing liners.

The adhesive layer must be pressure sensitive, providing the ability to adhere to the skin with minimal pressure and remain in place for the intended period of wear. The adhesive should be nonirritating, allow easy peel-off after use, permit unimpeded drug flux to the skin, and be compatible with all other system components. The adhesive material is usually safety tested for skin compatibility, including tests for irritation, sensitivity, and cytotoxicity (37). In some TDDSs, the adhesive layer contains the drug. Polybutyl acrylate is commonly used as the adhesive in TDDSs. The drug release membranes are commonly made of polyethylene, with microporous structures of varying pore sizes to fit the desired specifications of the particular transdermal system.

Included among the design objectives of TDDSs are the following (2,8,35,38,39):

1. Deliver the drug to the skin for percutaneous absorption at therapeutic levels at an optimal rate
2. Contain medicinal agents having the necessary physicochemical characteristics to

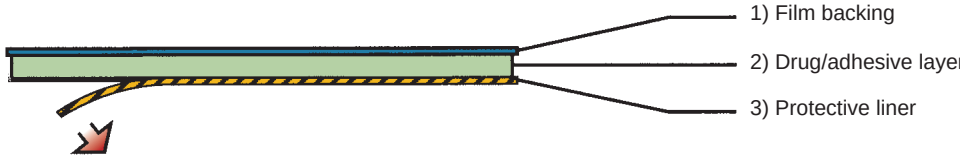

FIGURE 11.7 Two-layer TDDS, showing removal of the protective liner prior to application.

FIGURE 11.8 Pilot-scale manufacture of transdermal patches. (Courtesy of Elan Corporation, plc.)

release from the system and partition into the stratum corneum
3. Occlude the skin to ensure one-way flux of the drug into the stratum corneum
4. Have a therapeutic advantage over other dosage forms and drug delivery systems

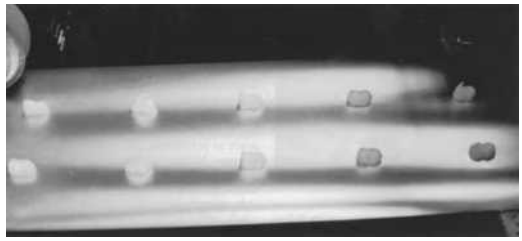

FIGURE 11.9 Measured dose for reservoir, placed on web prior to sealing into the transdermal delivery system. (Courtesy of CIBA Pharmaceutical Company.)

FIGURE 11.10 Equipment used in cutting and packaging transdermal drug delivery patches. (Courtesy of Schering Laboratories.)

5. Not irritate or sensitize the skin
6. Adhere well to the patient's skin and have size, appearance, and site placement that encourage acceptance

ADVANTAGES AND DISADVANTAGES OF TDDSs

Among the advantages of TDDSs are the following:

1. They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH, enzymatic activity, and drug interactions with food, drink, and other orally administered drugs.
2. They can substitute for oral administration of medication when that route is unsuitable, as with vomiting and diarrhea.
3. They avoid the *first-pass effect*, that is, the initial pass of a drug substance through the systemic and portal circulation following gastrointestinal absorption, possibly avoiding the deactivation by digestive and liver enzymes.
4. They are noninvasive, avoiding the inconvenience of parenteral therapy.
5. They provide extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration.
6. The activity of drugs having a short half-life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.

7. Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.
8. They are easily and rapidly identified in emergencies (e.g., unresponsive, unconscious, or comatose patient) because of their physical presence, features, and identifying markings.

The disadvantages of TDDSs are as follows:

1. Only relatively potent drugs are suitable candidates for transdermal delivery because of the natural limits of drug entry imposed by the skin's impermeability.
2. Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.

EXAMPLES OF TRANSDERMAL DRUG DELIVERY SYSTEMS

The following sections briefly describe some of the TDDSs in use. Table 11.1 describes the specific design components of representative examples of these systems.

Transdermal Scopolamine

As noted at the outset of this chapter, transdermal scopolamine was the first TDDS to receive FDA approval. Scopolamine, a belladonna alkaloid, is used to prevent travel-related motion sickness and the nausea and vomiting that result from the use of certain anesthetics and analgesics used in surgery.

The Transderm Scop system is a circular flat patch 0.2 mm thick and 2.5 cm^2 in area (40). It is a four-layer system described in Table 11.1. The TDDS contains 1.5 mg of scopolamine and is designed to deliver approximately 1 mg of scopolamine at an approximately constant rate to the systemic circulation over the 3-day lifetime of the system. An initial priming dose of 200 mg of scopolamine in the adhesive layer of the system saturates the skin binding sites and rapidly brings the plasma concentration to the required steady-state level. The continuous release of scopolamine through the rate-controlling microporous membrane maintains the plasma level constant. The rate of release is less than the skin's capability for absorption, so the membrane, not the skin, controls the delivery of the drug into the circulation.

The patch is worn in a hairless area behind the ear. Because of the small size of the patch, the system is unobtrusive, convenient, and well accepted by the patient. The TDDS is applied at least 4 hours before the antinausea effect is required. Only one disk should be worn at a time and may be kept in place for up to 3 days. If continued treatment is required, a fresh disk is placed behind the other ear and the other removed. The most common side effects are dryness of the mouth and drowsiness. Particularly in the geriatric population, use also may interfere with orientation, cognition, and memory. The TDDS is not intended for use in children and should be used with caution during pregnancy.

Transdermal Nitroglycerin

A number of nitroglycerin-containing TDDSs have been developed, including Minitran (3 M Pharmaceuticals), Nitro-Dur (Key), Transderm-Nitro (Summit), and Nitrodisc (Roberts). The design of each of these systems is briefly described in Table 11.1. Each of these products maintains nitroglycerin drug delivery for 24 hours after application. Tolerance, however, is a major factor limiting the effectiveness of these systems when used continuously for more than 12 hours per day. Hence, an appropriate dosing schedule would include a daily "patch on" period of 12 to 14 hours and a "patch off" period of 10 to 12 hours.

Nitroglycerin is used widely in the prophylactic treatment of angina. It has a relatively low dose, short plasma half-life, high peak plasma levels, and inherent side effects when taken sublingually, a popular route. It is rapidly metabolized by the liver when taken orally; this first-pass effect is bypassed by the transdermal route.

The various nitroglycerin TDDSs control the rate of drug delivery through a membrane

and/or controlled release from the matrix or reservoir. When a TDDS is applied to the skin, nitroglycerin is absorbed continuously, resulting in active drug reaching the target organs (heart, extremities) before inactivation by the liver. Only a portion of the total nitroglycerin in the system is delivered over the usual 24-hour use period; the remainder serves as the thermodynamic energy source to release the drug and remains in the system. For example, in the Deponit TDDS (UCB), only 15% of the nitroglycerin content is delivered after 12 hours of use (41).

The rate of drug release depends on the system. In the Transderm-Nitro system, nitroglycerin 0.02 mg is delivered per hour for every square centimeter of patch, whereas in the Deponit system, each square centimeter delivers approximately 0.013 mg of nitroglycerin per hour (41,42). Systems of various surface areas and nitroglycerin content are provided to accommodate individual patients' requirements. Because of different release rates, these systems cannot be used interchangeably by a patient.

The Nitro-Dur matrix is in a highly kinetic equilibrium state (43). Dissolved nitroglycerin molecules are constantly exchanging with adsorbed nitroglycerin molecules bound to the surfaces of the suspended lactose crystals. Sufficient nitroglycerin is adsorbed to the lactose in each matrix to maintain nitroglycerin in the fluid phase (aqueous glycerol) at a stable but saturated level (5 mg nitroglycerin/cm^2 matrix). When the matrix is applied to the skin, nitroglycerin molecules migrate by diffusion from solution in the matrix to solution in the skin. To make up for the molecules lost to the body, the equilibrium in the matrix shifts such that more molecules of nitroglycerin leave the crystals than are adsorbed from solution. When balance is restored, the solution is again saturated. Thus, the crystals of lactose act as a reservoir of drug to maintain drug saturation in the fluid phase. The Nitro-Dur matrix in turn acts as a saturated reservoir for diffusive drug input through the skin (43).

Not all nitroglycerin systems have the same construction. For example, the Transderm-Nitro TDDS is a four-layer drug pouch system, as described in Table 11.1 and depicted in Figure 11.5, whereas the Deponit TDDS is a thin two-layer matrix system resembling that shown in Figure 11.7.

Patients should be given explicit instructions regarding the use of Nitroglycerin Transdermal Systems. Generally, these TDDSs are placed on the chest, back, upper arms, or shoulders (Fig. 11.11). The site should be free of hair, clean, and dry so that the patch adheres without difficulty. The use of the extremities below the knee or elbow is discouraged, as are the areas that are abraded or have lesions or cuts. The patient should understand that physical exercise and elevated ambient temperatures, such as in a sauna, may increase the absorption of nitroglycerin.

Transdermal Clonidine

The first transdermal system for hypertension, Catapres-TTS (clonidine *t*ransdermal-*t*herapeutic*s*ystem, Boehringer Ingelheim), was marketed in 1985. Clonidine lends itself to transdermal delivery because of its lipid solubility, high volume of distribution, and therapeutic effectiveness in low plasma

FIGURE 11.11 A Nitroglycerin Transdermal System that will deliver 0.4 mg per hour (18 cm^2) at a constant and predetermined rate through the skin directly into the bloodstream.

concentrations. The TDDS provides controlled release of clonidine for 7 days. The product is a four-layer patch as described in Table 11.1.

Catapres-TTS is available in several sizes, with the amount of drug released proportional to the patch size. To ensure constant release over the 7-day use period, the drug content is greater than the total amount of drug delivered. The energy of drug release derives from the concentration gradient between a saturated solution of drug in the TDDS and the much lower concentration prevailing in the skin. Clonidine flows in the direction of lower concentration at a constant rate controlled by a membrane (44).

The system is applied to a hairless area of intact skin on the upper outer arm or chest. After application, clonidine in the adhesive layer saturates the skin site. Then clonidine from the reservoir begins to flow through the rate-controlling membrane and the skin to the systemic circulation. Therapeutic plasma clonidine levels are achieved 2 to 3 days after initial application. Application of a new system to a fresh skin site at weekly intervals maintains therapeutic plasma concentrations. If the patch is removed and not replaced with a new system, therapeutic plasma clonidine levels will persist for about 8 hours and then decline slowly over several days. Over this period, blood pressure returns gradually to pretreatment levels. If the patient has local skin irritation before 7 days of use, the system may be removed and replaced with a new one applied on a fresh skin site (44).

Transdermal Nicotine

Nicotine TDDSs are used as adjuncts (e.g., along with counseling) in smoking cessation programs. They have been shown to be an effective aid in quitting smoking when used according to product-recommended strategies (45). In a blinded study, users of nicotine TDDSs are more than twice as likely to quit smoking as individuals wearing a placebo patch (45). Example products include Nicoderm CQ (GlaxoSmithKline), Nicotrol (Pharmacia), and Prostep (Wyeth).

The nicotine TDDSs provide sustained blood levels of nicotine as nicotine replacement therapy to help the patient establish and sustain remission from smoking (46). Motivation to quit smoking is enhanced through the reduction of withdrawal symptoms and by partially satisfying the nicotine craving and desired sensory feelings provided by smoking (46).

The commercially available patches contain 7 to 21 mg of nicotine for daily application during the course of treatment ranging from about 6 to 12 weeks. Different treatment regimens are used for light versus heavy smokers. Examples of nicotine TDDSs are described in Table 11.1. A nicotine TDDS usually is applied to the arm or upper front torso, with patients advised not to smoke when wearing the system. The TDDS is replaced daily, with sites alternated. Some of the nicotine replacement programs provide a gradual reduction in nicotine dosage (patch strength) during the treatment program. Used TDDSs should be discarded properly because the retained nicotine is poisonous to children and pets.

Transdermal Estradiol

The estrogen estradiol has been developed for transdermal delivery. The Estraderm (Novartis) TDDS delivers 17β-estradiol through a rate-limiting membrane continuously upon application to intact skin (47). Two systems (10 or 20 cm^2) provide delivery of 0.05 or 0.1 mg estradiol per day. Estraderm is a four-layer TDDS as described in Table 11.1.

Estradiol is indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause, female hypogonadism, female castration, primary ovarian failure, and atrophic conditions caused by deficient endogenous estrogen production, such as atrophic vaginitis and kraurosis vulvae.

Orally administered estradiol is rapidly metabolized by the liver to estrone and its conjugates, giving rise to higher circulating levels of estrone than estradiol. In contrast, the skin metabolizes estradiol only to a small extent. Therefore, transdermal

administration produces therapeutic serum levels of estradiol with lower circulating levels of estrone and estrone conjugates than does oral therapy and requires a smaller total dose. Research results show that postmenopausal women receiving either transdermal or oral therapy will obtain the desired therapeutic effects, that is, lower gonadotropin levels, lower percentages of vaginal parabasal cells, decreased excretion of calcium, and lower ratio of calcium to creatinine, from both dosage forms. Studies have also demonstrated that systemic side effects from oral estrogens can be reduced by using the transdermal dosage form. Because estradiol has a short half-life (about 1 hour), transdermal administration allows a rapid decline in blood levels after the transdermal system is removed, as in a cycling regimen (47).

Therapy is usually administered on a cycling schedule (3 weeks of therapy followed by 1 week without), especially in women who have not undergone a hysterectomy. The transdermal system is applied to a clean, dry area of the skin on the trunk of the body, either the abdomen or upper quadrant of the buttocks. The patch should not be applied to the waistline because tight clothing may damage or dislodge it.

The Vivelle (Novartis) and Climara (Bayer Healthcare) estradiol TDDSs are two-layer matrix systems described in Table 11.1 and resembling that shown in Figure 11.7. The estradiol is contained in the adhesive layer (48,49). These systems are used in the same general manner as Estraderm TDDS; however, some of these systems are applied every 7 days.

Climara Pro Transdermal System (Bayer Healthcare) contains both estradiol and levonorgestrel in an adhesive-based matrix transdermal patch. The 22-cm^2 patch contains 4.5 mg estradiol and 11.39 mg of levonorgestrel; it delivers a daily dose of 0.045 mg of estradiol and 0.015 mg of levonorgestrel.

Transdermal Contraceptive System

The Ortho Evra (norelgestromin, ethinyl estradiol; Ortho-McNeil) Transdermal System is a combination contraceptive patch with a contact surface area of 20 cm^2; it contains 6 mg of norelgestromin and 0.75 mg of ethyl estradiol. It is released at a rate of norelgestromin 150 mg and ethinyl estradiol 20 mg into the blood stream every 24 hours.

The Ortho Evra is a thin matrix-type transdermal contraceptive patch consisting of three layers, including a two-ply backing layer composed of beige flexible film of low-density polyethylene and a polyester inner ply. The middle layer contains polyisobutylene and polybutene adhesive, crospovidone, nonwoven polyester fabric, and lauryl lactate as inactive components; the norelgestromin and ethinyl estradiol are in this layer. The third layer is the release liner that protects the adhesive layer during storage and is removed just prior to application. It is a transparent polyethylene terephthalate (PET) film with a polydimethylsiloxane coating on the side that is in contact with the middle layer.

Transdermal Testosterone

The testosterone transdermal systems Testoderm (Alza) and Androderm (Watson) are available with various delivery rates as hormone replacement therapy in men who have an absence or deficiency of testosterone (50,51).

The Testoderm TDDS is a two-layer system as described in Table 11.1. For optimal absorption, it is applied to clean, dry scrotal skin that has been dry shaved. Scrotal skin is reported to be at least five times as permeable to testosterone as other skin sites (50). The TDDS is placed on the scrotum by stretching the scrotal skin with one hand and pressing the adhesive side of the TDDS against the skin with the other hand, holding it in place for about 10 seconds. The TDDS is applied daily, usually in the morning to mimic endogenous testosterone release (52). Optimum serum levels are reached within 2 to 4 hours after application. The patch is worn 22 to 24 hours daily for 6 to 8 weeks.

The Androderm TDDS is designed to be applied nightly to a clean, dry, unabraded area of the skin of the back, abdomen, upper arms, or thighs. It should not be applied to

the scrotum (51). The five-layer system is described in Table 11.1.

Transdermal Methylphenidate

Transdermal methylphenidate (Daytrana, Shire) is an adhesive-based matrix transdermal system applied to intact skin. The methylphenidate is dispersed in acrylic adhesive that is dispersed in a silicone adhesive. The composition per unit area is identical in all dosage strengths, and the total dose delivered is dependent on the patch size and wear time. It is available as 10-, 15-, 20-, and 30-mg patches nominally delivering the indicated dose over a 9-hour period. The 10-mg patch actually contains 27.5 mg of the drug, the 15-mg patch contains 41.3 mg, the 20-mg patch contains 55 mg, and the 30-mg patch contains 82.5 mg of the drug. After 9 hours, the patch is to be removed, folded in on itself (adhesive to adhesive), and appropriately discarded (52). There is a dose titration schedule that should be followed initially until the individualized final dosage and wear time are determined.

Usually, methylphenidate is indicated for attention deficit hyperactivity disorder in children. The advantage of the transdermal patch is that it can be applied in the morning 2 hours prior to the time the effect is needed, that is, at school, and removed later in the day after school earlier than the 9-hour limit. This obviates the need for oral medication to be administered during the day and trips to the school nurse's office.

Other Transdermal Therapeutic Systems

Other transdermal therapeutic systems include the Oxytrol (oxybutynin chloride transdermal system, Watson), and additional drugs under study for use in TDDSs include diltiazem, isosorbide dinitrate, propranolol, nifedipine, mepindolol, and verapamil (cardiovascular agents); levonorgestrel with estradiol for hormonal contraception; physostigmine and xanomeline for Alzheimer disease therapy; naltrexone and methadone for substance addiction; buspirone for anxiety; bupropion for smoking cessation; and papaverine for male impotence.

GENERAL CLINICAL CONSIDERATIONS IN THE USE OF TDDSs

The patient should be advised of the following general guidelines along with product-specific instructions in the use of TDDSs (53,54):

1. Percutaneous absorption may vary with the site of application. The preferred general application site is stated in the package insert for each product. The patient should be advised of the importance of using the recommended site and rotating locations within that site. Rotating locations is important to allow the skin beneath a patch to regain its normal permeability after being occluded and to prevent skin irritation. Skin sites may be reused after a week.
2. TDDSs should be applied to clean, dry skin that is relatively free of hair and not oily, irritated, inflamed, broken, or callused. Wet or moist skin can accelerate drug permeation beyond the intended rate. Oily skin can impair adhesion of the patch. If hair is present at the intended site, it should be carefully cut; it should not be wet-shaved nor should a depilatory agent be used, since the latter can remove the outermost layers of the stratum corneum and affect the rate and extent of drug permeation.
3. Use of skin lotion should be avoided at the application site because lotions affect skin hydration and can alter the partition coefficient between the drug and the skin.
4. TDDSs should not be physically altered by cutting (as in an attempt to reduce the dose) since this destroys the integrity of the system.
5. A TDDS should be removed from its protective package, with care not to tear or cut into the unit. The protective backing should be removed to expose the adhesive layer with care not to touch the adhesive surface (which sometimes contains drug) to the fingertips. The TDDS should be pressed firmly against the skin site with the heel of the hand for about 10 seconds to ensure uniform contact and adhesion.

6. A TDDS should be placed at a site that will not subject it to being rubbed off by clothing or movement (as the belt line). TDDSs generally may be left on when showering, bathing, or swimming. Should a TDDS prematurely dislodge, an attempt may be made to reapply it or it may be replaced with a fresh system, the replacement being worn for a full period before it is replaced.
7. A TDDS should be worn for the full period stated in the product's instructions. Following that period, it should be removed and replaced with a fresh system as directed.
8. The patient or caregiver should be instructed to cleanse the hands thoroughly before and after applying a TDDS. Care should be taken not to rub the eyes or touch the mouth during handling of the system.
9. If the patient exhibits sensitivity or intolerance to a TDDS or if undue skin irritation results, the patient should seek reevaluation.
10. Upon removal, a used TDDS should be folded in half with the adhesive layer together so that it cannot be reused. The used patch, which contains residual drug, should be placed in the replacement patch's pouch and discarded in a manner safe to children and pets.

PATCHES (NOT SYSTEMS)

The Lidoderm (lidocaine; Endo) 5% patch consists of an adhesive material containing 5% lidocaine, which is applied to a nonwoven polyester felt backing and covered with a PET film release liner. The release liner is removed just prior to application. The patch is 10 × 14 cm, and each patch contains 700 mg of lidocaine in an aqueous base. The base contains dihydroxyaluminum aminoacetate, disodium edentate, gelatin, glycerin, kaolin, methylparaben, polyacrylic acid, polyvinyl alcohol, propylene glycol, propylparaben, sodium carboxymethylcellulose, sodium polyacrylate,D-sorbitol, tartaric acid, and urea. This product is indicated to treat postherpetic neuralgia. The patch is applied to intact skin to cover the most painful area. Depending upon the directions for use, the patient can apply up to three patches, only once for up to 12 hours within a 24-hour period. This patch may be cut with scissors into a smaller size prior to the removal of the release liner. The patient should wash his/her hands prior to and after handling the lidocaine patch and should avoid eye contact. After removal, the patch should be immediately disposed of, and in such a way to avoid accidental exposure to children and animals.

TAPES

A tape is a dosage form that is suitable for delivering drugs to the skin. It consists of a drug that is impregnated into a flexible, durable woven fabric or extruded synthetic material that is coated with an adhesive agent. Typically, the drug is present in the dry state. The adhesive layer is designed to retain the tape securely in place without the aid of additional bandaging. Tapes are not designed to control the release rate of the drug-like transdermal patches. The active drug content is expressed as an amount per surface area with respect to the tape surface exposed to the skin. The use of an occlusive dressing over the tape enhances the rate and extent of delivery of the drug to deeper layers of the skin and may result in greater systemic absorption of the drug.

For administration, a portion of the tape slightly larger than the area to be treated is cut and removed from the backing paper. It should not be applied to folds in the skin but rather to a smooth skin surface. It should be applied to dry skin.

PHARMACEUTICS  CASE STUDY

SUBJECTIVE INFORMATION

Working at a large transdermal drug delivery company, you have been given the responsibility of developing an analgesic drug delivery system for use in patients with moderate to severe chronic pain. After development of several prototypes, one is selected that delivers the drug at a rapid rate for the first 12 hours, then at a zero-order rate over the next 36 hours. In clinical trials, however, patients who tended to sweat excessively had to use a new patch about every 6 to 12 hours, as the previous patch would not adhere. They were instructed that if the patch would not adhere after repeated attempts to reapply it, it was to be removed and a new patch applied. These patients had central nervous system depression and respiratory depression as compared to patients who could use a single patch over the 48-hour period. The patients who had to replace the patch early also had blood levels in the toxic range for the drug.

OBJECTIVE INFORMATION

The release rate of the TDDS was designed to provide a rapid onset of action by providing a high rate of drug transfer after application of the patch from the drug in the adhesive. This high rate of drug flux occurred with repeated application of each new patch. The analgesic drug is highly lipophilic, and a very low dose (microgram range) is all that is required.

ASSESSMENT

There was an initial loading dose of the drug in the adhesive layer and a combination of penetration enhancers in the matrix of the TDDS, including alcohol. The lipophilic nature of the drug apparently resulted in a depot effect of the drug in the fatty tissue of the skin. The drug rapidly moved from the adhesive layer and was followed by the movement of active drug in solution in the alcohol and other penetration enhancers. After the alcohol was depleted in the TDDS matrix, the flux of drug slowed to a near-zero-order release.

PLAN

Available options include changing the formulation and adding a label caution statement. Changing the formulation would require extensive changes and new in vitro, animal, and clinical studies. A labeling statement could warn against application of a new patch for a preselected time period, such as approximately 12 hours after removal of a patch that would not adhere if it had been applied for less than 24 hours. This would allow for a depletion of the drug buildup in the skin.

CLINICAL  CASE STUDY

A.R. is a 20-year-old BF who comes into the pharmacy with concerns because she has missed the last two birth control tablets in the 2nd week of her cycle. She says, "It's so hard to remember to take the pill every night." She is a student at a local junior college, and her irregular work schedule seems to be the major contributing factor to her lack of adherence. She expresses concern about the possibility of becoming pregnant and asks for your advice.

CLINICAL CASE STUDY CONT.

PMH: Noncontributory

SH: (+) Smoker (~1 PPD)
Exercises 3 days per week

FH: Father (+) DM type 2
Grandmother (+) ovarian cancer

MEDS: Ibuprofen 400 mg po prn cramps
Ortho Tri-Cyclen 1 tablet po qd

PHARMACEUTICAL CARE PLAN

S: Lack of adherence to birth control pill regimen

O: Smoker
Grandmother (+) ovarian cancer
Father (+) DM type 2

A: A.R. is a 20-year-old BF with a history of lack of adherence to her oral contraceptive regimen. She is a student with an irregular schedule. A.R. smokes about a pack of cigarettes per day and has a family history of diabetes mellitus and ovarian cancer.

P: 1. Suggest to the patient that she contact her physician to change her prescription from an oral contraceptive tablet to a transdermal birth control patch, Ortho Evra.

2. Assuming that the physician concurs and prescribes Ortho Evra, inform the patient that the patch is applied once a week for 3 consecutive weeks, followed by 1 week that is patch free. This should help her compliance because she will have to remember to change the patch only once weekly. However, it will be good to have her write a reminder down somewhere to change the patch on the same day each week. She should not write the date on the patch. It is important for A.R. to know that she should remove the old patch before applying the new patch.

3. When changing over from her oral contraceptive tablet to the TDDS, she should understand to apply the first patch on the first day of her menstrual period. The patch can be applied to her abdomen, buttocks, upper torso (front or back, except the breasts), and upper outer arm. The patient can rotate the placement of the patch to a different location each week. However, this is not necessary.

4. The patch is to be applied to clean, dry skin. There should be no body lotion or oils on the skin where the patch will be applied. A.R. can shower, bathe, exercise, and swim while the patch is in place. If the patch gets loose or falls off <24 hours after application, the patient can reapply it or get a replacement patch at the pharmacy. If a replacement patch is applied, the patient must replace it with the next patch on the original patch change day. However, if it is beyond 24 hours since the initial application of that patch, the patient must start her cycle all over. That is, the patient will start a new 4-week cycle with a new patch change day. In that case, the patient must use backup contraceptive measures, such as condom, spermicide, or diaphragm, for the 1st week.

CLINICAL CASE STUDY CONT.

5. The patient should be made aware that smoking increases her risk of heart problems, such as blood clots, stroke, and heart attacks, when using a hormonal contraceptive product. A.R. should be encouraged to quit smoking. If the patient agrees that she would like to quit, be prepared to suggest a local wellness program where she can get help and support. Most importantly, to have an opportunity to quit smoking, she has to make a firm commitment to want to stop smoking.

6. Monitoring: Because the patient has a family history of ovarian cancer, she should be strongly encouraged to have annual Pap smears. In addition, the patient should be advised to continue to exercise regularly and increase her frequency to 4 or 5 days per week. An increase in exercise and a well-balanced diet will be advantageous in the prevention of diabetes mellitus type 2, as her family demonstrates a history of this disease.

APPLYING THE PRINCIPLES AND CONCEPTS

Group Activities

1. Compare and contrast transdermal drug delivery to other forms of drug delivery.
2. Compare and contrast the official USP monographs of the clonidine transdermal system and the nicotine transdermal system.
3. Describe special handling, storage, and disposal precautions a patient must take when using a transdermal delivery system.
4. List five counseling points for proper administration of a transdermal nitroglycerin system.
5. Create a listing of conceivable ways a consumer/patient might misuse a TDDS.

Individual Activities

1. Create a table of six transdermal products including amount of active ingredient(s), indication, contraindication, adverse effects/precautions, and dosage.
2. Generate a listing of drugs whose physical–chemical characteristics make them a candidate for incorporation into a transdermal dosage form.
3. From the primary literature, find a clinical drug study demonstrating a comparison between a transdermal delivery system and another route of delivery for the drug in terms of clinical effectiveness, and determine which delivery system would be preferred in terms of patient acceptance, patient adherence, bioequivalence, and cost. Explain the rationale for your decision.

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SECTION V

SUPPOSITORIES, INSERTS, AND STICKS

12 Suppositories, Inserts, and Sticks

OBJECTIVES

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

1. Compare and contrast various suppository, insert, and stick dosage forms in terms of physical appearance, size, and shape
2. Describe the advantages and disadvantages of suppository, insert, and stick drug delivery versus oral drug delivery
3. Identify and explain physiologic factors that influence the drug absorption from rectal suppository and vaginal/urethral insert administration
4. Identify and explain the physicochemical factors of the drug and suppository/insert base as these influence absorption
5. Compare and contrast the various classes of suppository/insert/stick bases.
6. Describe the three methods of suppository/insert/stick preparation
7. Generate a listing of key counseling points a pharmacist should share with the patient prescribed a drug in a suppository/insert/stick drug delivery system

SUPPOSITORIES

The use of rectal suppositories has been documented since the civilization of Ancient Egypt, but in modern society, suppositories have not gained the level of acceptability, respect, and usage as most other dosage forms. However, much work has been conducted in recent years as evidenced by the literature citations; in the past 50 years, there have been over 4,000 citations in Medline (1). Even though much work has been done in Europe, in the United States and elsewhere, there continues to be a tendency away from rectal delivery for routine administration of drugs. Urethral administration of suppositories has become more acceptable with urethral suppositories in the treatment of male erectile dysfunction (Muse-Vivus).

Suppositories are used more routinely in southern European countries and in Latin American countries, as compared to northern European and Anglo-Saxon countries. In the United States, less than 1% of drugs are formulated as suppositories; in Germany, it may be as high as 5% (2). In the past 5 to 10 years in the United States, progesterone vaginal inserts have become much more widely used by postmenopausal women. Hormone replacement therapy in postmenopausal women using bioidentical hormones, or those that are identical to those hormones produced by the body as compared to synthetic or semisynthetic hormones, is more popular in the treatment of postmenopausal symptoms (flushing, night sweats, mood swings, etc.) (3).

Although suppositories are not very popular as a mode of administering drugs, this

dosage form will probably always have a place in medicine. Suppositories generally have been employed for three reasons, to

1. promote defecation
2. introduce drugs into the body
3. treat anorectal diseases

Rectal administration is not often the first route of choice; but it becomes a good alternative when the oral route is inadvisable. Relatively low cost and lack of technical difficulties make rectal drug administration attractive when compared to parenteral therapy. The downside of rectal administration includes the esthetics and stigma of violating the patient's dignity; these, along with potential rectal irritation due to frequent administration and difficulty in titrating a correct dose due to limited strengths of commercial suppositories, pose some challenges.

In treating hospice patients, rectally administered medications are essential in palliative medicine. Properly selected drugs and suppository vehicles can enhance the quality of life of these patients. A suppository is also an excellent dosage form for those patients to whom one does not want to administer numerous injections daily. They are also a dosage form that can be administered to avoid nausea and vomiting caused by certain medications upon oral administration, and it is a dosage form that can often result in a fast onset of action (4). Compounding pharmacists often view suppositories as a way to meet individual patient needs when other routes of administration are not really appropriate. This is especially true for pediatric and hospice patients (4).

Definitions

A suppository is a solid dosage form in which one or more APIs are dispersed in a suitable base and molded or otherwise formed into a suitable shape for insertion into the rectum to provide local or systemic effect. Suppositories are solid dosage forms intended for insertion into body orifices where they melt, soften, or dissolve and exert local or systemic effects. The derivation of the word *suppository* is from the Latin *supponere*, meaning "to place under," as derived from *sub* (under) and *ponere* (to place) (4). Thus, suppositories are meant both linguistically and therapeutically to be placed under the body, as into the rectum.

An insert is a solid dosage form that is inserted into a naturally occurring (nonsurgical) body cavity other than the mouth or rectum, including the vagina and urethra.

Medication sticks are a convenient form for administering topical drugs. Their development is interesting because it involves the history of cosmetics, which parallels human history.

Suppository, Insert, and Stick Shapes

Suppositories have various shapes and weights; the shape and size of a suppository must be such that it can be easily inserted into the intended orifice without causing undue distension, and once inserted, it must be retained for the appropriate period. Rectal suppositories are inserted with the fingers, but certain vaginal inserts (and tablets prepared by compression) may be inserted high in the tract with the aid of an appliance.

Rectal suppositories are usually about 32 mm (1.5 inch) long, are cylindrical, and have one or both ends tapered. Some rectal suppositories are shaped like a bullet, a torpedo, or the little finger. Depending on the density of the base and the medicaments in the suppository, the weight may vary. Adult rectal suppositories weigh about 2 g when cocoa butter (theobroma oil) is employed as the base. Rectal suppositories for use by infants and children are about half the weight and size of the adult suppositories and assume a more pencil-like shape.

Vaginal inserts, formerly called *suppositories or pessaries*, are usually globular, oviform, or cone shaped and weigh about 5 g when cocoa butter is the base. However, depending on the base and the manufacturer's product, the weights of vaginal inserts may vary widely.

Urethral inserts, also called *bougies*, are slender, pencil-shaped suppositories

intended for insertion into the male or female urethra. Male urethral suppositories may be 3 to 6 mm in diameter and approximately 140 mm long, although this may vary. When cocoa butter is employed as the base, these suppositories weigh about 4 g. Female urethral suppositories are about half the length and weight of the male urethral suppository, being about 70 mm long and weighing about 2 g when made of cocoa butter.

Medication sticks are cylindrical in shape and generally range from 5 to 25 g. They are generally packaged in an applicator tube for topical administration, and the applicator can be adjusted to continually expose new, fresh stick from inside the tube.

USES AND APPLICATIONS

Examples of commonly used official suppositories and inserts are presented in Figure 12.1 and Tables 12.1, 12.2, and 12.3. It is now well accepted that many active ingredients can be administered rectally and achieve therapeutic blood levels. Some medications are best administered by this route, while others can be if needed.

Suppositories containing drugs such as aspirin and opiates for pain, ergotamine tartrate for treating migraine headaches, and many other drugs for other uses are commonly used as suppositories. These drugs are intended to be absorbed into the general circulation to provide systemic drug effects. Other examples of suppositories given for systemic results include diazepam, metronidazole, progesterone, aminophylline, morphine, prochlorperazine, chlorpromazine, thiethylperazine, indomethacin, diclofenac, ketoprofen, naproxen, and ondansetron.

The advantages of rectal administration include the following:

1. First-pass effect: Avoiding, at least partially, the first-pass effect that may result in higher blood levels for those drugs subject to extensive first-pass metabolism upon oral administration.
2. Drug stability: Avoiding the breakdown of certain drugs that are susceptible to gastric degradation.

A

B

FIGURE 12.1 **A:** Close-up of a commercial rectal suppository. (Courtesy of Paddock Laboratories.) **B:** A variety of commercial rectal suppositories.

Table 12.1 EXAMPLES OF RECTAL SUPPOSITORIES

SUPPOSITORY	COMMERCIAL PRODUCT	ACTIVE CONSTITUENT	TYPE OF EFFECT	CATEGORY AND COMMENTS
Bisacodyl	Dulcolax (Boehringer-Ingelheim)	10 mg	Local	Cathartic. Base: hydrogenated vegetable oil
Hydrocortisone	Anusol-HC (Salix)	25 mg	Local	Pruritus ani, inflamed hemorrhoids, other inflammatory conditions of the anorectum. Base: hydrogenated glycerides
Hydromorphone	Dilaudid (Purdue Pharma)	3 mg	Systemic	Analgesic. Base: cocoa butter with silicon dioxide
Indomethacin	Indocin (Iroko)	50 mg	Systemic	Anti-inflammatory: Base: polyethylene glycols
Mesalamine	Canasa (Axcan Scandipharm)	500 mg	Local	Anti-inflammatory. Base: hard fat
Promethazine HCl	Phenergan (Wyeth)	12.5, 25 mg	Systemic	Antihistamine, antiemetic, sedative: used to manage allergic conditions; preoperative or postoperative sedation or nausea and vomiting; motion sickness. Base: cocoa butter, white wax

3. Large dose drugs: Ability to administer somewhat larger doses of drugs than using oral administration.
4. Irritating drugs: Ability to administer drugs that may have an irritating effect on the oral or gastrointestinal mucosa when administered orally.
5. Unpleasant tasting or smelling drugs: Ability to administer unpleasant tasting or smelling drugs whose oral administration is limited.
6. In children, the rectal route is especially useful. An ill child may refuse oral medication and may fear injections.
7. In patients experiencing nausea and vomiting or when the patient is unconscious.
8. The presence of disease of the upper gastrointestinal tract that may interfere with drug absorption.
9. Objectionable taste or odor of a drug (especially important in children).
10. Achievement of a rapid drug effect systemically (as an alternate to injection).

Rectal administration provides for a rapid, and in many cases, extensive absorption of the active ingredient. The rapidity, intensity, and duration of action are three parameters

Table 12.2 EXAMPLES OF VAGINAL INSERTS AND TABLETS

PRODUCT (MANUFACTURER)	ACTIVE CONSTITUENTS	CATEGORY AND COMMENTS
Cleocin inserts (Pfizer)	Clindamycin phosphate 100 mg	Bacterial vaginosis
Monistat 7 inserts (Personal products)	Miconazole nitrate 100 mg	Antifungal for local vulvovaginal candidiasis (moniliasis)
Semicid vaginal contraceptive inserts (Whitehall-Robins)	Nonoxynol-9 100 mg	Nonsystemic reversible birth control
Encare contraceptive inserts (Thomson Medical)	Nonoxynol-9 100 mg	Nonsystemic reversible birth control

Table 12.3 OFFICIAL SUPPOSITORIES AND INSERTS IN THE USP

Acetaminophen
Aminophylline
Aspirin
Bisacodyl
Chlorpromazine
Ergotamine tartrate and caffeine
Glycerin
Indomethacin
Miconazole nitrate vaginal
Morphine sulfate
Nystatin vaginal
Oxymorphone hydrochloride
Prochlorperazine
Progesterone vaginal
Promethazine hydrochloride
Thiethylperazine maleate

that must be considered during formulation for rectal administration and, in many cases, can be altered to meet the needs of the individual patient.

The disadvantages of suppositories and the reasons given for the infrequent use of suppositories include the following.

1. A perceived lack of flexibility regarding dosage of commercially available suppositories resulting in underuse and a lack of availability.
2. If suppositories are made on demand, they may be expensive.
3. Suppositories as a dosage form are safe, but they exhibit variable effectiveness, depending upon many factors to be discussed later, including the pathology of the anorectal lesions.
4. Different formulations of a drug with a narrow therapeutic margin, such as aminophylline, cannot be interchanged without risk of toxicity.
5. The "bullet-shaped" suppository after insertion can leave the anorectal site and ascend to the rectosigmoid and descending colon. Hence, one may consider that suppositories with this shape possibly should not be used at bedtime.
6. Defecation may interrupt the absorption process of the drug; this may especially occur if the drug is irritating.
7. The absorbing surface area of the rectum is much smaller than that of the small intestine.
8. The fluid content of the rectum is much less than that of the small intestine, which may affect dissolution rate, etc.
9. There is the possibility of degradation of some drugs by the microflora present in the rectum.
10. The dose of a drug required for rectal administration may be greater than or less than the dose of the same drug given orally. This can be dependent upon such factors as the constitution and condition of the patient, the physicochemical nature of the drug, and its ability to traverse the physiologic barriers to absorption, and the nature of the suppository vehicle and its capacity to release the drug and make it available for absorption.
11. The factors that affect the rectal absorption of a drug administered in the form of a suppository may be divided into two main groups: (*a*) anatomic and physiologic factors and (*b*) physicochemical factors of the drug and the base.

Local Action

Once inserted, the suppository base melts, softens, or dissolves, distributing its medicaments to the tissues of the region. These medicaments may be intended for retention within the cavity for local effects, or they may be intended to be absorbed for systemic effects. Rectal suppositories intended for local action are most frequently used to relieve constipation or the pain, irritation, itching, and inflammation associated with hemorrhoids or other anorectal conditions. Antihemorrhoidal suppositories frequently contain a number of components, including local anesthetics, vasoconstrictors, astringents, analgesics, soothing emollients, and protective agents. A popular laxative, glycerin suppositories promote laxation by local irritation of the mucous membranes, probably

by the dehydrating effect of the glycerin on those membranes. Vaginal suppositories or inserts intended for local effects are employed mainly as contraceptives, as antiseptics in feminine hygiene, and as specific agents to combat an invading pathogen. Most commonly, the drugs used are nonoxynol 9 for contraception, trichomonacides to combat vaginitis caused by *Trichomonas vaginalis*, antifungals to treat *Candida* (*Monilia*) *albicans*, and anti-infectives/antibiotics directed at other microorganisms. Urethral suppositories may be antibacterial or a local anesthetic preparative for a urethral examination.

Sticks are commonly used for local effect and include hydration/emollient, antibacterial, sunscreen, antipruritic, and other uses.

Systemic Action

For systemic effects, the mucous membranes of the rectum and vagina permit the absorption of many soluble drugs. Although the rectum is used frequently as the site for the systemic absorption of drugs, the vagina is not as frequently used for this purpose.

Examples of drugs administered rectally in the form of suppositories for their systemic effects include (*a*) prochlorperazine and chlorpromazine for the relief of nausea and vomiting and as a tranquilizer; (*b*) morphine and oxymorphone for opioid analgesia; (*c*) ergotamine tartrate for the relief of migraine syndrome; (*d*) indomethacin, a nonsteroidal anti-inflammatory analgesic and antipyretic; and (*e*) ondansetron for the relief of nausea and vomiting.

SOME FACTORS OF DRUG ABSORPTION FROM RECTAL SUPPOSITORIES

The dose of a drug administered rectally may be greater than or less than the dose of the same drug given orally, depending on such factors as the constitution of the patient, the physicochemical nature of the drug and its ability to traverse the physiologic barriers to absorption, and the nature of the suppository vehicle and its capacity to release the drug and make it available for absorption.

Table 12.4 EXAMPLES OF DRUGS WITH DIFFERENT OPTIMAL ROUTES OF ADMINISTRATION

Absorbed better rectally than orally	Sodium salicylate
	Chloral hydrate
	Methylene blue
	Atropine, morphine
Absorbed better orally than rectally	Iodides
	Tetracycline hydrochloride
	Sodium penicillin G
Oral and rectal absorptions comparable	Sulfanilamide in a glycerinated gelatin base
	Prednisone

From Allen Jr LV. Suppositories. London: Pharmaceutical Press, 2008:52.

Table 12.4 contains a list of some drugs that are absorbed better rectally as compared to orally, some that are absorbed better orally as compared to rectally, and some cases where the oral and rectal doses are comparable. In some cases, the doses are different, for example, lincomycin, chloral hydrate requires four times the dose rectally as compared to orally and empirically, phenytoin requires about three times the dose rectally as compared to orally.

Physiological Factors and Drug Effect

Among the physiologic factors that affect drug absorption from the rectum are the circulation route, colonic contents, and the pH and lack of buffering capacity of the rectal fluids.

Circulation Route

Unlike drugs absorbed after oral administration, drugs absorbed rectally can bypass the portal circulation during their first pass into the general circulation. This enables drugs that are otherwise destroyed in the liver to exert systemic effects. The lower hemorrhoidal veins surrounding the colon receive the absorbed drug and initiate its circulation throughout the body, bypassing the liver. Lymphatic circulation also assists in the absorption of rectally administered drugs.

pH and Lack of Buffering Capacity of the Rectal Fluids

The pH of the rectal fluid is generally in the range of 7.2 to 7.4, and it has negligible buffer capacity. The form in which the drug is administered will not generally be chemically changed by the rectal environment; therefore, the pH of the medium may be determined by the characteristics of the drug.

Rectal. The last few inches of the large intestine constitute the rectum, terminating at the anus. The rectum contains three types of hemorrhoidal veins:

- superior hemorrhoidal vein
- middle hemorrhoidal vein
- inferior hemorrhoidal vein

These veins act by transporting the active principle absorbed in the rectum to the blood system either directly by means of iliac veins and the vena cava (inferior and middle hemorrhoidal veins) or indirectly by means of the portal vein and the liver (superior hemorrhoidal vein).

The three hemorrhoidal veins are linked by an anastomosis network. Since it is not really possible to predict the position or exact location of the suppository in the rectum, it is not really possible to predict exactly which way the active principle will be transported. It may be preferably by one pathway or another or a combination. However, it is generally accepted that at least 50% to 70% of the active ingredients administered rectally take the direct pathway, thus bypassing the liver and avoiding the first-pass effect. There is also the possibility of absorption into the lymphatic vessels that should not be dismissed, but may be minimal.

Vaginal. The vagina is a specialized organ whose primary function is reproduction. It is a highly elastic muscular tube, located between the urethra and the rectum. It has three tissue layers: epithelial tissue, loose connective tissue, and muscle tissue. The upper, middle, and lower vaginal sections have separate blood supplies. Branches of the uterine arteries supply blood to the upper vagina; the inferior vesical arteries supply blood to the middle portion of the vagina, and the hemorrhoidal and internal pudendal arteries feed into the lower vagina. Blood is returned through the venous plexus to the hemorrhoidal, pudendal, and uterine veins and then to the hypogastric veins. The pH of the vagina is in the range of about 4 to 4.5. It is moistened and cleansed daily by secretions that also serve to lubricate the vaginal tract. Normal vaginal discharge consists of about 1.5 g of vaginal fluid daily. This fluid occurs as an odorless, clear or white, and viscous or sticky fluid. This normal physiologic fluid consists of endocervical mucus, serum transudate from vaginal capillary beds, endogenous vaginal flora, and epithelial cells.

Urethra. The urethral epithelium begins as transitional cells as it exits the bladder. Further along the urethra, there are stratified columnar cells, then stratified squamous cells near the external meatus (exit hole). There are small mucus-secreting urethral glands that help protect the epithelium from the corrosive urine. The female urethra is supplied by blood vessels called the internal pudendal and vaginal arteries. The male urethra is supplied by the inferior vesical and middle rectal arteries. The veins follow these blood vessels. The nerve supply is via the pudendal nerve.

Colonic Content

When systemic effects are desired from the administration of a medicated suppository, greater absorption may be expected from a rectum that is void than from one that is distended with fecal matter. A drug will obviously have greater opportunity to make contact with the absorbing surface of the rectum and colon in the absence of fecal matter. Therefore, when deemed desirable, an evacuant enema may be administered and allowed to act before the administration of a suppository of a drug to be absorbed. Other conditions such as diarrhea, colonic obstruction due to tumorous growths, and tissue dehydration can all influence the rate and degree of drug absorption from the rectal site.

Physicochemical Factors and Drug Effect

Physicochemical factors include such properties as the relative solubility of the drug in lipid and in water and the particle size of a

dispersed drug. Physicochemical factors of the base include its ability to melt, soften, or dissolve at body temperature, its ability to release the drug substance, and its hydrophilic or hydrophobic character.

Lipid–Water Solubility

The lipid–water partition coefficient of a drug (discussed in Chapter 4) is an important consideration in the selection of the suppository base and in anticipating drug release from that base. A lipophilic drug that is distributed in a fatty suppository base in low concentration has less tendency to escape to the surrounding aqueous fluids than a hydrophilic substance in a fatty base. Water-soluble bases—for example, polyethylene glycols—that dissolve in the anorectal fluids release for absorption water-soluble and oil-soluble drugs. Naturally, the more drug a base contains, the more drug will be available for absorption. However, if the concentration of a drug in the intestinal lumen is above a particular amount, which varies with the drug, the rate of absorption is not changed by a further increase in the concentration of the drug.

Particle Size

For undissolved drugs in a suppository, the size of the drug particle will influence its rate of dissolution and its availability for absorption. As indicated many times previously, the smaller the particle, the greater the surface area, the more readily the dissolution of the particle, and the greater the chance for rapid absorption.

Whenever the active principle has a limited water solubility, the use of finely divided products (high specific surface area) often leads to an appreciable absorption improvement. Here, as well as in oral medication absorption, the rate of absorption is influenced by the solubilization rate, which in turn is related to the particle size of the active principle.

It is preferable to avoid a too fine particle size because of the high increase of the viscosity of the melted excipient that can result from the use of excessively small particles and possible difficulties in flow during production.

SUPPOSITORY BASES

Analogous to the ointment bases, suppository bases play an important role in the release of the medication they hold and, therefore, in the availability of the drug. Of course, one of the first requisites for a suppository base is that it should remain solid at room temperature but soften, melt, or dissolve readily at body temperature so that the drug is fully available soon after insertion. Certain bases are more efficient in drug release than others. For instance, cocoa butter (theobroma oil) melts quickly at body temperature, but because it is immiscible with body fluids, fat-soluble drugs tend to remain in the oil and have little tendency to enter the aqueous physiologic fluids. For water-soluble drugs in cocoa butter, the reverse is usually true and good release results. Fat-soluble drugs seem to be released more readily from bases of glycerinated gelatin or polyethylene glycol, both of which dissolve slowly in body fluids. When irritation or inflammation is to be relieved, as in the treatment of anorectal disorders, cocoa butter appears to be the superior base because of its emollient or soothing, spreading action.

Nature of the Base

As previously discussed, the base must be capable of melting, softening, or dissolving to release its drug for absorption. If the base interacts with the drug to inhibit its release, drug absorption will be impaired or even prevented. Also, if the base irritates the mucous membranes of the rectum, it may initiate a colonic response and prompt a bowel movement, eliminating the prospect of complete drug release and absorption.

Because of the possibility of chemical and/or physical interactions between the medicinal agent and the suppository base, which may affect the stability and/or bioavailability of the drug, the absence of any drug interaction between the two agents should be ascertained before or during formulation.

Long-acting or slow-release suppositories have also been prepared. Morphine sulfate in slow-release suppositories is prepared in a base that includes a material such as alginic

acid, which will prolong the release of the drug over several hours (5,6).

Classification of Bases

For most purposes, it is convenient to classify suppository bases according to their physical characteristics into two main categories and a third miscellaneous group: (*a*) fatty or oleaginous bases, (*b*) water-soluble or water-miscible bases, and (*c*) miscellaneous bases, generally combinations of lipophilic and hydrophilic substances.

A suppository base should be physically and chemically stable, nonirritating, nontoxic, nonsensitizing, chemically and physiologically inert, compatible with a variety of drugs, stable during storage, and esthetically acceptable (free from objectionable odor and a pleasing appearance). It should contract slightly on cooling to release itself from the mold with requiring mold lubricants, has wetting and emulsifying properties, has a high water number, and can be manufactured by molding by hand, machine, compression, or extrusion. It should melt or dissolve in rectal fluids and should not bind or otherwise interfere with the release or absorption of drug substances.

Other desirable characteristics depend upon the drugs to be added. For example, bases with higher melting points can be used to incorporate drugs that generally lower the melting points of the base (e.g., camphor, chloral hydrate, menthol, phenol, thymol, and volatile oils) or to formulate suppositories for use in tropical climates. Bases with lower melting points can be used when adding materials that will raise the melting points or when adding large amounts of solids. Examples of different types of suppository bases and their melting ranges are shown in Table 12.5. Additional characteristics of importance in selecting a suppository base can include the following: acid value, iodine value, saponification value, and hydroxyl value (7).

Fatty or Oleaginous Bases

Fatty bases are perhaps the most frequently employed suppository bases, principally because cocoa butter is a member of this group of substances. Among the other fatty or oleaginous materials used in suppository bases are many hydrogenated fatty acids of vegetable oils, such as palm kernel oil and cottonseed oil. Also, fat-based compounds containing compounds of glycerin with the higher–molecular-weight fatty acids, such as palmitic and stearic acids, may be found in fatty bases. Such compounds, such as glyceryl monostearate and glyceryl monopalmitate, are examples of this type of agent. The bases in many commercial products employ varied combinations of these types of materials to achieve the desired hardness under conditions of shipment and storage and the desired quality of submitting to the temperature of the body to release their medicaments. Some bases are prepared with the fatty materials emulsified or with an emulsifying agent

Table 12.5 MELTING RANGES OF SOME SUPPOSITORY BASES

BASE	COMPOSITION	MELTING RANGE (°C)
Cocoa butter	Mixed triglycerides of oleic, palmitic, stearic acids	34–35
Fattibase	Triglycerides from palm, palm kernel, and coconut oils with self-emulsifying glyceryl monostearate and polyoxyl stearate	35.5–37
Polybase	A homogeneous blend of PEGs and polysorbate 80	60–71
Suppocire OSI	Eutectic mixtures of mono-, di-, triglycerides derived from natural vegetable oils, each type having slightly different properties	33–35
Wecobee W	Triglycerides derived from coconut oil	31.7–32.8
Witepsol H15	Triglycerides of saturated fatty acids C12–C18 with varied portions of the corresponding partial glycerides	33–35

present to prompt emulsification when the suppository makes contact with the aqueous body fluids. These types of bases are arbitrarily placed in the third, or miscellaneous, group of bases.

Cocoa Butter, NF, is the fat obtained from the roasted seed of *Theobroma cacao*. At room temperature, it is a yellowish-white solid having a faint, agreeable chocolate-like odor. Chemically, it is a triglyceride (combination of glycerin and one or different fatty acids) primarily of oleopalmitostearin and oleodistearin. Because cocoa butter melts at 30°C to 36°C (86°F to 97°F), it is an ideal suppository base, melting just below body temperature and yet maintaining its solidity at usual room temperatures. However, because of its triglyceride content, cocoa butter exhibits marked *polymorphism* or existence in several crystalline forms. Because of this, when cocoa butter is hastily or carelessly melted at a temperature greatly exceeding the minimum required temperature and is then quickly chilled, the result is a metastable crystalline form (alpha crystals) with a melting point much lower than that of the original cocoa butter. In fact, the melting point may be so low that the cocoa butter will not solidify at room temperature. However, because the crystalline form is a metastable condition, there is a slow transition to the more stable *beta* form of crystals having the greater stability and a higher melting point. This transition may require several days. Consequently, if suppositories that have been prepared by melting cocoa butter for the base do not harden soon after molding, they will be useless to the patient and a loss of time, materials, and prestige to the pharmacist. Cocoa butter must be slowly and evenly melted, preferably over a bath of warm water, to avoid formation of the unstable crystalline form and ensure retention in the liquid of the more stable *beta* crystals that will constitute nuclei upon which the congealing may occur during chilling of the liquid.

Substances such as phenol and chloral hydrate have a tendency to lower the melting point of cocoa butter. If the melting point is low enough that it is not feasible to prepare a solid suppository using cocoa butter alone as the base, solidifying agents like cetyl esters wax (about 20%) or beeswax (about 4%) may be melted with the cocoa butter to compensate for the softening effect of the added substance. However, the addition of hardening agents must not be so excessive as to prevent the base from melting in the body, nor must the waxy material interfere with the therapeutic agent in any way so as to alter the efficacy of the product.

Other bases in this category include commercial products such as Fattibase (triglycerides from palm, palm kernel, and coconut oils with self-emulsifying glyceryl monostearate and polyoxyl stearate), the Wecobee bases (triglycerides derived from coconut oil), and Witepsol bases (triglycerides of saturated fatty acids C12–C18 with varied portions of the corresponding partial glycerides).

Water-Soluble and Water-Miscible Bases

The main members of this group are glycerinated gelatin and polyethylene glycols. Glycerinated gelatin suppositories may be prepared by dissolving granular gelatin (20%) in glycerin (70%) and adding water or a solution or suspension of the medication (10%). A glycerinated gelatin base is most frequently used in the preparation of vaginal suppositories, with which prolonged local action of the medicinal agent is usually desired. The glycerinated gelatin base is slower to soften and mix with the physiologic fluids than is cocoa butter and therefore provides a slower release.

Because glycerinated gelatin–based suppositories have a tendency to absorb moisture as a result of the hygroscopic nature of glycerin, they must be protected from atmospheric moisture if they are to maintain their shape and consistency. Also as a result of the hygroscopicity of the glycerin, the suppository may have a dehydrating effect and irritate the tissues upon insertion. The water in the formula for the suppositories minimizes this action; however, if necessary, the suppositories may be moistened with water prior to insertion to reduce the initial tendency of the base to draw water from the mucous membranes and irritate the tissues.

Urethral suppositories may be prepared from a glycerinated gelatin base of a formula somewhat different from the one indicated earlier. For urethral suppositories, the gelatin constitutes about 60% of the weight of the formula, the glycerin about 20%, and the medicated aqueous portion about 20%. Urethral suppositories of glycerinated gelatin are much more easily inserted than those with a cocoa butter base owing to the brittleness of cocoa butter and its rapid softening at body temperature.

Various combinations of these polyethylene glycols may be combined by fusion, using two or more of the various types to achieve a suppository base of the desired consistency and characteristics. Polyethylene glycols are polymers of ethylene oxide and water prepared to various chain lengths, molecular weights, and physical states. They are available in a number of molecular weight ranges, the most commonly used being polyethylene glycol 300, 400, 600, 1,000, 1,500, 1,540, 3,350, 4,000, 6,000, and 8,000. The numeric designations refer to the average molecular weight of each of the polymers. Polyethylene glycols having average molecular weights of 300, 400, and 600 are clear, colorless liquids. Those having average molecular weights of greater than 1,000 are waxlike white solids whose hardness increases with an increase in the molecular weight. Melting ranges, for example, polyethylene glycols, are PEG 300 (−15°C to 18°C), PEG 1000 (37°C to 40°C), PEG 3350 (54°C to 58°C), and PEG 8000 (60°C to 63°C).

Pharmacists have been called on in recent years to prepare progesterone vaginal suppositories extemporaneously. These suppositories, used in premenstrual syndrome, are commonly molded with either a polyethylene glycol base or a fatty acid base. Formulas for these suppositories are presented later in this chapter.

Polyethylene glycol suppositories do not melt at body temperature but rather dissolve slowly in the body's fluids. Therefore, the base need not be formulated to melt at body temperature. Thus, it is possible, in fact routine, to prepare suppositories from polyethylene glycol mixtures having melting points considerably higher than body temperature. This property permits a slower release of the medication from the base once the suppository has been inserted and permits convenient storage of these suppositories without need for refrigeration and without danger of their softening excessively in warm weather. Further, their solid nature permits slow insertion without fear that they will melt in the fingertips (as cocoa butter suppositories sometimes do). Because they do not melt at body temperature but mix with mucous secretions upon dissolution, polyethylene glycol–based suppositories do not leak from the orifice, as do many cocoa butter–based suppositories. Polyethylene glycol suppositories that do not contain at least 20% water should be dipped in water just before use to avoid irritation of the mucous membranes after insertion. This procedure prevents moisture being drawn from the tissues after insertion and the stinging sensation.

Poloxamers (Pluronics) are water-soluble, block copolymers with a wide range of uses. Pluronics L44, L62, L64, and F68 are potential suppository bases. The poloxamers have practically no odor or taste. An example of an aspirin suppository using a poloxamer base uses the following formula:

- Pluronic F68 6.00 g
- Pluronic L44 7.00 mL
- Aspirin 1.02 g

To prepare, the poloxamers were placed in a beaker on a water bath and heated until melted. The aspirin was added and the mixture stirred until uniform. The solution is placed in a mold and allowed to cool, and the suppositories are removed. The authors summarized that the Pluronic base aspirin suppository should be further tested in clinical situations (8).

FORMULATION VARIABLES

Formulation variables that are generally considered include (*a*) the nature and form of the active principle (esters, salts, complexes, etc.), (*b*) the physical state, particle dimensions, and the specific surface of the product, (*c*)

the solubility of the drug in various bases, (*d*) the presence or absence of adjuvants added to the active principle, (*e*) the nature and type of dosage form in which the active principle is incorporated, and (*f*) pharmaceutical procedures used in the preparation of the dosage form.

Active drugs have a number of physical characteristics. In suppositories, those of interest involve the drug's physical state, including physical state, particle size, solubility, dielectric constant, and bulk density. Some of these have been discussed in detail in other chapters.

Physical State

An active drug can be a solid, liquid, or semisolid in nature. For solids, the drug's particle size may be very important, especially if the drug is not very water soluble; the increase in surface area resulting from decreased particle size can serve to enhance its activity. For liquids, it is necessary to take up the liquid into the suppository base using one of several techniques such as forming an emulsion, adding a drying powder, or adding a suitable thickening agent when the liquid is mixed with the suppository base. For the semisolids or paste-type drugs, it can be either mixed with a solid that will serve to thicken the drug prior to mixing with the base or mixed with the base to which a thickener is added.

Particle Size

If a drug is readily soluble, the influence of particle size may be minimal. For highly water-soluble drugs, the tendency will be to dissolve and migrate to the rectal barrier. For poorly water-soluble drugs, the dissolution rate will be slower, and a reduction in particle size may increase the rate of dissolution by exposing a greater surface area. This can also be affected by the nature of the suppository base.

Solubility

Increased solubility of the active in the base can improve product homogeneity; however, it may also delay the release of the active if there is too great an affinity of the drug for the suppository vehicle.

If the active ingredient is insoluble in the base, as is the case when a "suspension" or "emulsion" is formed, this poses different problems. It is necessary to maintain homogeneity of the total mixture; this can usually be obtained by constant agitation of the mixture during processing and filling. Oftentimes, it is best to select a temperature just above the melting point of the suppository mixture where the mixture is thick but still pourable.

Viscosity

Viscosity considerations are also important in the preparation of the suppositories and the release of the drug. If the viscosity of a base is low, it may be necessary to add a suspending agent such as silica gel to ensure that the drug is uniformly dispersed until solidification occurs. When preparing the suppository, the pharmacist should stir the melt constantly and keep it at the lowest possible temperature to maintain a high viscosity. After the suppository has been administered, the release rate of the drug may be slowed if the viscosity of the base is very high. This is because the viscosity causes the drug to diffuse more slowly through the base to reach the mucosal membrane for absorption.

Brittleness

Brittle suppositories can be difficult to handle, wrap, and use. Cocoa butter suppositories are usually not brittle unless the percentage of solids present is high. In general, brittleness results when the percentage of nonbase materials exceeds about 30%. Synthetic fat bases with high stearate concentrations or those that are highly hydrogenated are typically more brittle. Shock cooling also causes fat and cocoa butter suppositories to crack. This condition can be prevented by ensuring that the temperature of the mold is as close to the temperature of the melted base as possible. Suppositories should not be placed in a freezer, which also causes shock cooling.

Volume Contraction

Bases, excipients, and active ingredients generally occupy less space at lower temperatures than at higher temperatures. When preparing a suppository, the pharmacist pours hot melt into a mold and allows the melt to cool. During this cooling process, the melt has a tendency to contract in size. This makes it easier to release the suppository from the mold, but it may also produce a cavity at the back, or open end, of the mold. Such a cavity is undesirable and can be prevented if the melt is permitted to approach its congealing temperature immediately before it is poured into the mold. It is advisable to pour a small amount of excess melt at the open end of the mold to allow for the slight contraction during cooling. Scraping with a blade or spatula dipped in warm water will remove the excess after solidification, but care must be taken not to remove the metal from the mold. The heated instrument can also be used to smooth out the back of the suppository.

Drug Release Rates

General approximate drug release rates as they relate to the drug and base characteristics are summarized as follows:

DRUG:BASE CHARACTERISTICS	APPROXIMATE DRUG RELEASE RATE
Oil-soluble drug: Oily base	Slow release; poor escaping tendency
Water-soluble drug: Oily base	Rapid release
Oil-soluble drug: Water-miscible base	Moderate release
Water-miscible drug: Water-miscible base	Moderate release; based on diffusion; all water soluble

Special Problems

Some active drugs are more difficult to incorporate in a base and require additional preparation steps. Before vegetable extracts are added, they can be moistened by levigation with a small amount of melted base. This makes it easier to distribute the active drug throughout the base.

Hard, crystalline materials can be incorporated either by pulverizing them to a fine state or by dissolving them in a small quantity of solvent, which is then taken up into the base. An aqueous solvent and a PEG base are appropriate for water-soluble materials. Alternatively, if the material is water soluble and an oily base must be used, wool fat could be used to take up the solution for incorporation into the suppository base.

When liquid ingredients are mixed with an inert powder such as starch, they become less fluid, which makes them easier to handle. The suppository produced will thus hold together better.

There are several ways of incorporating excess powder into a suppository base, depending on the base used. If the base is oil miscible, one can add a few drops of a bland oil like mineral oil. When excess powder is incorporated into water-soluble bases, the pharmacist can vary the ratio of low to high melting point ingredients. For example, since additional powders will make the suppository harder, using a higher percentage of a PEG having a low molecular weight would result in a suppository of the proper character.

A number of ingredients are incompatible with PEG bases, including benzocaine, iodochlorhydroxyquin, sulfonamides, ichthammol, aspirin, silver salts, and tannic acid. Other materials reported to have a tendency to crystallize out of PEG include sodium barbital, salicylic acid, and camphor. Polyethylene glycol–based suppositories may be irritating to some patients. Suppositories prepared with PEG should not be stored or dispensed in a polystyrene prescription vial, as the polyethylene glycol will adversely interact with polystyrene. All PEG suppositories should be dispensed in glass or cardboard containers.

Triglyceride-type bases can sometimes accept up to about 50% glycerin without much difficulty. Some solids may be dissolved in water or solidified with Aerosil prior to incorporation. Fluidextracts can be incorporated at about 35°C to 38°C into an

emulsifiable triglyceride base. Ichthammol and Peru balsam can be mixed with an equal amount of castor oil prior to incorporation. Essential oils can be incorporated without difficulty in small amounts. Larger amounts may result in lowering the melting point of the suppository, so a higher melting point suppository base may be required. Due to the volatile nature of the essential oils, they must be incorporated at the lowest possible temperature. Inert materials, such as lactose, magnesium carbonate of highly dispersed silicon dioxide, can be used to sorb the essential oils prior to incorporation. Lipophilic drugs with melting points higher than that of the base can be incorporated by suspending these drugs in polyethylene glycol 200 to 400 to a total amount of about 10%, based on the amount of triglyceride base used. Fat bloom (a whitish discoloration) that can occur on the surface of suppositories can be minimized by the addition of lecithin to the suppository base.

PREPARATION OF SUPPOSITORIES

Suppositories are prepared by two methods: (*a*) *molding* from a melt and (*b*) *hand rolling* and *shaping*. The method most frequently employed both on a small scale and on an industrial scale is molding.

Molding

The steps in molding include (*a*) melting the base, (*b*) incorporating any required medicaments, (*c*) pouring the melt into molds, (*d*) allowing the melt to cool and congeal into suppositories, and (*e*) removing the formed suppositories from the mold. Cocoa butter, glycerinated gelatin, polyethylene glycol, and most other bases are suitable for preparation by molding.

Suppository Molds

Commercially available molds can produce individual or large numbers of suppositories of various shapes and sizes. Individual plastic molds may be obtained to form a single suppository. Other molds, such as those most commonly found in the community pharmacy, are capable of producing 6, 12, or more suppositories in a single operation (Fig. 12.2). Industrial molds produce hundreds of suppositories from a single batch (Figs. 12.3 and 12.4).

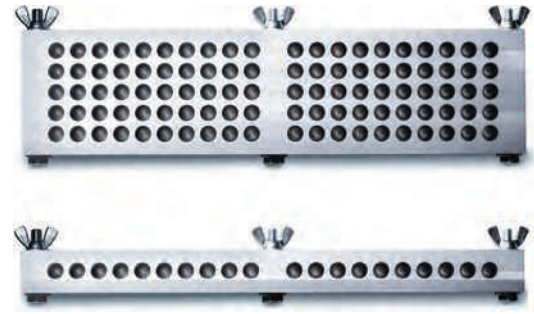

FIGURE 12.2 Partially opened mold capable of producing 50 torpedo-shaped suppositories in a single molding (Courtesy of Gallipot, Inc.).

Molds in common use today are made from stainless steel, aluminum, brass, or plastic. The molds, which separate into sections, generally longitudinally, are opened for cleaning before and after preparation of a batch of suppositories, closed when the melt is poured, and opened again to remove the cold, molded suppositories. Care must be exercised in cleaning the molds, as any scratches on the molding surfaces will take away from the desired smoothness of the suppositories. Plastic molds are especially prone to scratching.

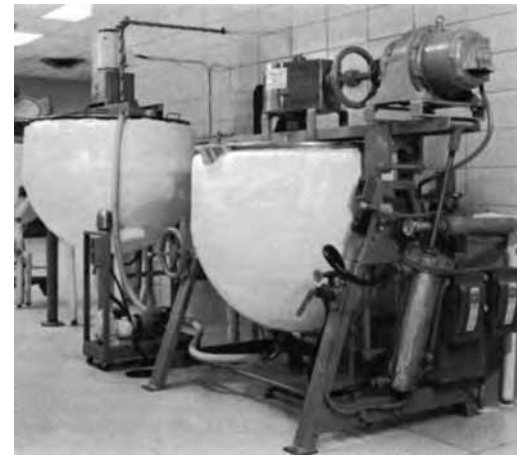

FIGURE 12.3 Large heated tanks for preparation of the melt in commercial production of suppositories by molding. (Courtesy of Wyeth-Ayerst Laboratories.)

FIGURE 12.4 Highly automated large-scale production of molded suppositories prepared and packaged in strips. (Courtesy of Paddock Laboratories.)

Although satisfactory reusable and disposable molds are commercially available for preparation of rectal, vaginal, and urethral suppositories, if necessary, temporary molds may be successfully formed by pressing heavy aluminum foil about an object having the shape of the desired suppository, then carefully removing the object and filling the shaped foil with the melt. For instance, glass stirring rods may be used to form molds for urethral suppositories, round pencils or pens may be used to form molds for rectal suppositories, and any cone-shaped object may be used to form vaginal suppositories.

Lubrication of the Mold

Depending on the formulation, suppository molds may require lubrication before the melt is poured to facilitate clean and easy removal of the molded suppositories. Lubrication is seldom necessary when the base is cocoa butter or polyethylene glycol, as these materials contract sufficiently on cooling to separate from the inner surfaces and allow easy removal. Lubrication is usually necessary with glycerinated gelatin. A thin coating of mineral oil applied with the finger to the molding surfaces usually suffices. However, no material that might irritate the mucous membranes should be employed as a mold lubricant.

Calibration of the Mold

Each individual mold is capable of holding a specific volume of material in each of its openings. Because of the difference in the densities of the materials, if the base is cocoa butter, the weight of the suppositories will differ from the weight of suppositories prepared in the same mold with a base of polyethylene glycols. Similarly, any added medicinal agent alters the density of the base, and the weight of the resulting suppository differs from that of those prepared with base material alone.

The pharmacist should calibrate each suppository mold for the usual base (generally cocoa butter and a polyethylene glycol base) so as to prepare medicated suppositories each having the proper quantity of medicaments.

The first step in calibration of a mold is to prepare molded suppositories from base material alone. After removal from the mold, the suppositories are weighed, and the total weight and average weight of each suppository are recorded (for the particular base used). To determine the volume of the mold, the suppositories are carefully melted in a calibrated beaker, and the volume of the melt is determined for the total number as well as for the average of one suppository.

Determination of the Amount of Base Required

In the prescription for medicated suppositories to be prepared extemporaneously by the pharmacist, the prescribing physician indicates the amount of medicinal substance desired in each suppository but leaves the amount of base to the discretion of the pharmacist. Generally, in preparing such prescriptions, the pharmacist calculates the amounts of materials needed for the preparation of one or two more suppositories than the number prescribed to compensate for the inevitable loss of some material and to ensure having enough material.

In determining the amount of base to be incorporated with the medicaments, the pharmacist must be certain that the required

amount of drug is provided in each suppository. Because the volume of the mold is known (from the determined volume of the melted suppositories formed from the base), the volume of the drug substances subtracted from the total volume of the mold will give the volume of base required. If the added amounts of medicaments are slight, they may be considered to be negligible, and no deduction from the total volume of base may be deemed necessary. However, if considerable quantities of other substances are to be used, the volumes of these materials are important and should be used to calculate the amount of base actually required to fill the mold. The total volume of these materials is subtracted from the volume of the mold, and the appropriate amount of base is added. Because the bases are solid at room temperature, the volume of base may be converted to weight from the density of the material. For example, if 12 mL of cocoa butter is required to fill a suppository mold and if the medicaments in the formula have a collective volume of 2.8 mL, 9.2 mL of cocoa butter will be required. By multiplying 9.2 mL times the density of cocoa butter, 0.86 g/mL, it may be calculated that 7.9 g of cocoa butter will be required. After adjusting for the preparation of an extra suppository or two, the calculated amount is weighed.

Another method for determination of the amount of base in the preparation of medicated suppositories requires the following steps: (*a*) weigh the active ingredient for the preparation of a single suppository; (*b*) dissolve it or mix it (depending on its solubility in the base) with a portion of melted base insufficient to fill one cavity of the mold and add the mixture to a cavity; (*c*) add additional melted base to the cavity to fill it completely; (*d*) allow the suppository to congeal and harden; and (*e*) remove the suppository from the mold and weigh it. The weight of the active ingredients subtracted from the weight of the suppository yields the weight of the base. This amount of base multiplied by the number of suppositories to be prepared in the mold is the total amount of base required.

A third method is to place all of the required medicaments for the preparation of the total number of suppositories (including one extra) in a calibrated beaker, add a portion of the melted base, and incorporate the drug substances. Then add sufficient melted base to reach the required volume of mixture based on the original calibration of the volume of the mold.

A summary of density calculations for molding of suppositories is found in Physical Pharmacy Capsule 12.1.

PHYSICAL PHARMACY CAPSULE 12.1

Density (Dose Replacement) Calculations for Suppositories

In preparation of suppositories, it is generally assumed that if the quantity of active drug is less than 100 mg, then the volume occupied by the powder is insignificant and need not be considered. This is usually based on a 2-g suppository weight. Obviously, if a suppository mold of less than 2 g is used, the powder volume may need to be considered.

The density factors of various bases and drugs need to be known to determine the proper weights of the ingredients to be used. Density factors relative to cocoa butter have been determined. If the density factor of a base is not known, it is simply calculated as the ratio of the blank weight of the base and cocoa butter. Density factors for a selected number of ingredients are shown in the below table.

PHYSICAL PHARMACY CAPSULE 12.1 CONT.

Alum	1.7	Morphine HCl	1.6
Aminophylline	1.1	Opium	1.4
Aspirin	1.3	Paraffin	1.0
Barbital	1.2	Peruvian balsam	1.1
Belladonna extract	1.3	Phenobarbital	1.2
Benzoic acid	1.5	Phenol	0.9
Bismuth carbonate	4.5	Potassium bromide	2.2
Bismuth salicylate	4.5	Potassium iodide	4.5
Bismuth subgallate	2.7	Procaine	1.2
Bismuth subnitrate	6.0	Quinine HCl	1.2
Boric acid	1.5	Resorcinol	1.4
Castor oil	1.0	Sodium bromide	2.3
Chloral hydrate	1.3	Spermaceti	1.0
Cocaine HCl	1.3	Sulfathiazole	1.6
Digitalis leaf	1.6	Tannic acid	1.6
Glycerin	1.6	White wax	1.0
Ichthammol	1.1	Witch hazel fluid extract	1.1
Iodoform	4.0	Zinc oxide	4.0
Menthol	0.7	Zinc sulfate	2.8

Three methods of calculating the quantity of base that the active medication will occupy and the quantities of ingredients required are illustrated here: (*a*) dosage replacement factor, (*b*) density factor, and (*c*) occupied volume methods.

Determination Of The Dosage Replacement Factor Method

$$f = \frac{[100\,(E - G)]}{[(G)(X)]} + 1$$

where

E is the weight of the pure base suppositories, and

G is the weight of suppositories with X% of the active ingredient.

Cocoa butter is arbitrarily assigned a value of 1 as the standard base. Examples of other dosage replacement factors are shown in the below table.

Balsam of peru	0.83	Phenol	0.9
Bismuth subgallate	0.37	Procaine HCl	0.8
Bismuth subnitrate	0.33	Quinine HCl	0.83
Boric acid	0.67	Resorcin	0.71
Camphor	1.49	Silver protein, mild	0.61
Castor oil	1.00	Spermaceti	1.0
Chloral hydrate	0.67	White or yellow wax	1.0
Ichthammol	0.91	Zinc oxide	0.15–0.25
Phenobarbital	0.81		

PHYSICAL PHARMACY CAPSULE 12.1 CONT.

EXAMPLE 1

Prepare a suppository containing 100 mg of phenobarbital (f = 0.81) using cocoa butter as the base. The weight of the pure cocoa butter suppository is 2.0 g. Because 100 mg of phenobarbital is to be contained in an approximately 2.0-g suppository, it will be about 5% phenobarbital. What will be the total weight of each suppository?

$$0.81 = \frac{[100(2 - G)]}{[(G)(5)] + 1} = 2.019$$

DETERMINATION OF DENSITY FACTOR METHOD

1. Determine the average blank weight, A, per mold using the suppository base of interest.
2. Weigh the quantity of suppository base necessary for 10 suppositories.
3. Weigh 1.0 g of medication. The weight of medication per suppository, B, is equal to 1 g/10 supp = 0.1 g/supp.
4. Melt the suppository base and incorporate the medication, mix, pour into molds, cool, trim, and remove from the molds.
5. Weigh the 10 suppositories and determine the average weight (C).
6. Determine the density factor as follows:

$$\text{Density factor} = \frac{B}{A - C + B}$$

where
A is the average weight of blank,
B is the weight of medication per suppository, and
C is the average weight of medicated suppository.

7. Take the weight of the medication required for each suppository and divide by the density factor of the medication to find the replacement value of the suppository base.
8. Subtract this quantity from the blank suppository weight.
9. Multiply by the number of suppositories required to obtain the quantity of base required for the prescription.
10. Multiply the weight of drug per suppository by the number of suppositories required to obtain the quantity of active drug required for the prescription.

EXAMPLE 2

Prepare 12 acetaminophen 300 mg suppositories using cocoa butter. The average weight of the cocoa butter blank is 2 g, and the average weight of the medicated suppository is 1.8 g.

$$DF = \frac{0.3}{2 - 1.8 + 0.3} = 0.6$$

From step 7: (0.3 g)/0.6 = 0.5 (the replacement value of the base)
From step 8: 2.0 – 0.5 g = 1.5 g
From step 9: 12 × 1.5 g = 18 g cocoa butter required
From step 10: 12 × 0.3 g = 3.6 g acetaminophen

DETERMINATION OF OCCUPIED VOLUME METHOD

1. Determine the average weight per mold (blank) using the designated base.
2. Weigh out enough base for 12 suppositories.

PHYSICAL PHARMACY CAPSULE 12.1 CONT.

3. Divide the density of the active drug by the density of the base to obtain a ratio.
4. Divide the total weight of active drug required for the total number of suppositories by the ratio obtained in step 3. This will give the amount of base displaced by the active drug.
5. Subtract the amount obtained in step 4 from the total weight of the prescription (number of suppositories multiplied by the weight of the blanks) to obtain the weight of base required.
6. Multiply the weight of active drug per suppository times the number of suppositories to be prepared to obtain the quantity of active drug required.

EXAMPLE 3

Prepare 10 suppositories, each containing 200 mg of a drug with a density of 3.0. The base has a density of 0.9, and a prepared blank weighs 2.0 g. Using the determination of occupied volume method, prepare the requested suppositories.

From step 1: The average weight per mold is 2.0 g.
From step 2: The quantity required for 10 suppositories is 2 × 10 g = 20 g.
From step 3: The density ratio is 3.0/0.9 = 3.3.
From step 4: The amount of suppository base displaced by the active drug is 2.0 g/3.3 = 0.6 g.
From step 5: The weight of the base required is 20 – 0.6 g = 19.4 g.
From step 6: The quantity of active drug required is 0.2 × 10 g = 2.0 g.

The required weight of the base is 19.4 g, and the weight of the active drug is 2 g.

Preparing and Pouring the Melt

Using the least possible heat, the weighed suppository base material is melted, generally over a water bath, because not a great deal of heat is required. A porcelain casserole, that is, a dish with a pouring lip and a handle, is perhaps the best utensil, because it later permits convenient pouring of the melt into the cavities of the mold. Usually, medicinal substances are incorporated into a portion of the melted base by mixing on a glass or porcelain tile with a spatula. After incorporation, this material is stirred into the remaining base, which has been allowed to cool almost to its congealing point. Any volatile materials or heat-labile substances should be incorporated at this point with thorough stirring.

The melt is poured carefully and continuously into each cavity of the mold, which has been previously equilibrated to room temperature. If any undissolved or suspended materials in the mixture are denser than the base, so that they have a tendency to settle, constant stirring, even during pouring, is required, else the last filled cavity will contain a disproportionate share of the undissolved materials. The solid materials remain suspended if the pouring is performed just above the congealing point and not when the base is too fluid. If the melt is not near the congealing point when poured, the solids may settle within each cavity of the mold to reside at the tips of the suppositories, with the result that the suppositories may be broken when removed from the mold. Alternatively, a small quantity of silica gel (about 25 mg per suppository) can be incorporated into the formula to aid in keeping the active drug suspended. In filling each suppository cavity, the pouring must be continuous to prevent *layering*, which may lead to a product easily broken on handling. To ensure a completely filled mold upon congealing, the melt is poured excessively over each opening, actually rising above the level of the mold. The excessive material may form a continuous ribbon along the top of the mold above the cavities. This use of extra suppository material prevents formation of recessed dips in the ends of the suppositories and justifies preparation of extra melt. When solidified,

the excess material is evenly scraped off of the top of the mold with a spatula warmed by dipping into a beaker of warm water; this will make a smooth surface on the back of the suppository during trimming. The filled mold is usually placed in the refrigerator to hasten hardening.

When the suppositories are hard, the mold is removed from the refrigerator and allowed to come to room temperature. Then the sections of the mold are separated, and the suppositories are dislodged, with pressure being exerted principally on their ends and only if needed on the tips. Generally, little or no pressure is required, and the suppositories simply fall out of the mold when it is opened.

An example formula for a compounded ABHR suppository used for nausea and vomiting associated with chemotherapy is:

Ativan (lorazepam)	0.5 mg
Benadryl (diphenhydramine HCl)	25 mg
Haldol (haloperidol)	0.5 mg
Reglan (metoclopramide)	10 mg
Fatty acid base	2.25 g

Melt the fatty acid base at about 50°C. Slowly and with stirring, sprinkle the powders on the surface of the melted base and mix well. Remove from heat and cool until still fluid and pourable. Pour into a suitable mold. Cool and trim, if necessary. Package and label.

Hand Rolling and Shaping

With ready availability of suppository molds of accommodating shapes and sizes, there is little requirement for today's pharmacist to shape suppositories by hand. Hand rolling and shaping is a historic part of the art of the pharmacist; a description of it may be found in the third edition of this text or in pharmacy compounding texts.

MANUFACTURING SUPPOSITORIES

Manufactured suppositories are generally prepared by the melt fusion method. Commercially automated equipment for melt fusion is available to continually produce large quantities of finished suppositories per hour. See Figures 12.3 and 12.4.

The automated equipment for preparing suppositories has provided an efficient method for manufacturing large quantities of suppositories in a relatively short time. This equipment allows for a single continuous manufacturing process. The process starts with two main components, the packaging shell material and the molten bulk drug product.

The primary packaging of suppositories in the automated process is comprised of five distinct stages. The stages include forming, dosing, cooling, sealing, and finishing. These stages are completed in a continuous process, at rates that can reach 30,000 suppositories per hour.

The forming process determines the shape and volume of the mold. It begins with two rolls of material. The film is heated between a set of dies. After the film is heated, it is transferred to the next station where it is blow molded into shape. The sides of the film are sealed as air is blown in between the heated film. The cavity is created, while the top remains open for dosing of the product.

Once the shells are formed, they move to the *dosing* station. The empty shells are aligned with the nozzles of the dosing pump, and the molten product is dosed into the empty shells. For high-speed machines, multiple cavities can be dosed at one time. This can be accomplished with an accuracy of ±0.01 g, depending on the product and equipment.

Filled shells are moved to the cooling tunnels. The cooling tunnels reduce temperature of the molten mass in the shells. This allows the product to solidify in the shells. Cooling tunnels blow chilled air around the molds. The cooling is controlled by the time the suppositories spend in the tunnels and the temperature of the tunnels.

Once the solidified suppositories leave the cooling tunnel, they move to the *sealing* area where the open top of the mold is closed. This process is accomplished by reheating the top edge of the film above the solidified suppository. After passing the shells through a series of reheating jaws, the molds move

to sealing jaws. Sealing jaws are cooled with chilled water. The cooled jaws press the plastic film together and seal them. Also, during this phase, it is possible to press the lot code and expiration date into the seal area for each individual suppository. Once the suppositories are sealed, the finishing touches can be completed.

The *finishing* of the suppositories includes perforating, notching, and cutting the molds into the appropriate count strips. The cutting of the strip length allows for the suppositories to be placed in the final cartons for distribution.

QUALITY CONTROL

Quality control procedures listed in the USP 36–NF 31 for manufactured suppositories and inserts include identification, assay, and in some cases, loss on drying, disintegration, and dissolution. Also, stability considerations in dispensing practice for suppositories include observation for excessive softening and oil stains on packaging (9). Compounded suppositories can be checked for calculations of theoretical and actual weight and weight variation, color, hardness, surface texture, and overall appearance.

PACKAGING AND STORAGE

Glycerin suppositories and glycerinated gelatin suppositories are packaged in tightly closed glass containers to prevent a change in moisture content. Suppositories prepared from a cocoa butter base are usually individually wrapped or otherwise separated in compartmented boxes to prevent contact and adhesion. Suppositories containing light-sensitive drugs are individually wrapped in an opaque material such as a metallic foil. In fact, most commercial suppositories are individually wrapped in either foil or plastic. Some are packaged in a continuous strip, separated by tearing along perforations. Suppositories are also commonly packaged in slide boxes or in plastic boxes.

Because suppositories are adversely affected by heat, it is necessary to maintain them in a cool place. Cocoa butter suppositories must be stored below 30°C (86°F) and preferably in a refrigerator (2°C to 8°C or 36°F to 46°F). Glycerinated gelatin suppositories can be stored at controlled room temperature (20°C to 25°C or 68°F to 77°F). Suppositories made from a base of polyethylene glycol may be stored at usual room temperatures.

Suppositories stored in high humidity may absorb moisture and tend to become spongy, whereas suppositories stored in places of extreme dryness may lose moisture and become brittle.

STABILITY

Pharmacists should avoid ingredients and conditions that could result in excessive physical deterioration or chemical decomposition of drug preparations, especially when compounding.

Physical Stability

Listed in Table 12.6 are the major modifications of suppository characteristics due to natural aging, as well as the causes. Physical observation can generally detect physical stability problems, including softening, hardening, drying, cracking, separation, polymorphs when melting range is affected, and one can often detect the odor of rancidity.

Chemical Stability

In working with suppositories, the majority will be anhydrous, so the presence of water is not really an issue. However, in some cases, water may be present to help incorporate the drug into the base, or it may be present as part of the hydrated form of the drug components' crystalline structure. Also, if emulsions or suspensions are incorporated into suppositories, water may be present. Last, some suppositories may be hygroscopic and absorb water from the atmosphere. Consequently, some of the issues related to instability in water will also be discussed here.

In suppositories, the following reactions and conditions can result in loss of active drug content and may not provide

Table 12.6 MAJOR CHANGES IN SUPPOSITORY CHARACTERISTICS DUE TO NATURAL AGING AND THE CAUSES

MODIFICATIONS	CAUSES	EXAMPLES
Odor	Fungal contamination	Suppositories with vegetable extracts
Color	Discoloration due to oxidation	Suppositories with tartrazine yellow aqueous solution
Shape	Incorrect temperature during storage	Suppositories with essential oils
Surface condition	Whitening	Suppositories with vegetable extracts or caffeine base suppositories
Weight	Loss of volatile substances	Suppositories with camphor, menthol, etc.

obvious visual or olfactory evidence of their occurrence; hydrolysis, epimerization, decarboxylation, dehydration, oxidation, photochemical decomposition, pH effect, solid state stability, temperature, and microbiological considerations.

Microbiological Stability

Most suppository formulations do not contain preservatives or antioxidants since water is usually excluded from the formulations. However, in the event water is present or the formulation may support the growth of microorganisms, an appropriate preservative may be indicated.

Beyond-Use Dating for Compounded Suppositories

There are numerous suppositories that are routinely compounded. The completed compounded suppositories are generally considered dry or nonaqueous and thus provide a stable dosage form as long as they are protected from moisture and heat. According to U.S.P. General Chapter <795> Pharmacy Compounding-Nonsterile, these preparations should have a beyond-use date of 25% of the time remaining on the expiration date if the compounded preparation is made using a manufactured product as the source of the active drug, or 6 months, whichever is earlier. If the product is prepared from USP/NF ingredients, a beyond-use date of 6 months is appropriate, unless evidence is available to support other dating.

If the stability of a compounded water-containing preparation is unknown and there is no other supporting data for an alternate beyond-use date, then a beyond-use date of 14 days when stored in a refrigerator can be used.

Expiration Dating for Manufactured Suppositories

To ensure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, a commercially manufactured suppository must bear an expiration date determined by appropriate stability testing. Exempt from this requirement are homeopathic drug products, allergenic extracts, and investigational new drugs providing the latter meet the standards established during preclinical and clinical studies.

As previously mentioned, excessive softening is the major indication of instability in suppositories, although some suppositories may dry out and harden or shrivel. Evidence of oil stains on packaging material should warn the pharmacist to examine individual suppositories more closely by removing any foil covering. As a general rule (although there are exceptions), suppositories should be stored in a refrigerator.

Informing and Educating the Patient

As a final step in meeting responsibility for the stability of drugs dispensed, the pharmacist is obligated to inform the patient about the proper storage conditions (e.g., in a cool, dry place—not in the bathroom) for both prescription and nonprescription products and to suggest a reasonable estimate of

the time after which the medication should be discarded. When beyond-use dates are applied, the pharmacist should emphasize to the patient that the dates are applicable only when proper storage conditions are observed. Patients should be encouraged to clean out their drug storage cabinets periodically.

RECTAL SUPPOSITORIES

Examples of rectal suppositories are presented in Table 12.1. As noted earlier, drugs like aspirin given for pain, ergotamine tartrate for treating migraine headaches, theophylline as a smooth muscle relaxant in treating asthma, and chlorpromazine and prochlorperazine, which act as antiemetics and tranquilizers, are intended to be absorbed into the general circulation to provide systemic effects. The rectal route of administration is especially useful if the patient is unwilling or unable to take medication by mouth.

Suppositories are also intended to provide local action within the perianal area. Local anesthetic suppositories are commonly employed to relieve *pruritus ani* of various causes and the pain sometimes associated with hemorrhoids. Many commercial hemorrhoidal suppositories contain a number of medicinal agents, including astringents, protectives, anesthetics, lubricants, and others, intended to relieve the discomfort of the condition. Cathartic suppositories are contact-type agents that act directly on the colonic mucosa to produce normal peristalsis. Because the contact action is restricted to the colon, the motility of the small intestine is not appreciably affected. Cathartic suppositories are more rapid acting than orally administered medication. Suppositories of bisacodyl are usually effective within 15 minutes to an hour and glycerin suppositories usually within a few minutes following insertion.

Some commercially prepared suppositories are available for both adult and pediatric use. The difference is in the shape and drug content. Pediatric suppositories are more narrow and pencil shaped than the typical bullet-shaped adult suppository. Glycerin suppositories are commonly available in each type.

A formula for glycerin suppositories is as follows:

Glycerin	91 g
Sodium stearate	9 g
Purified water	5 g
To make about	105 g

In preparation of this suppository, the glycerin is heated in a suitable container to about 50°C (120°F). Then the sodium stearate is dissolved with stirring in the hot glycerin, the purified water added, and the mixture immediately poured into the suppository mold. It is recommended that if the mold is metal, it also be heated prior to addition of the glycerin mixture. After cooling to solidification, the suppositories are removed. This formula will prepare about 50 adult suppositories. Approximately the same formulation is used in pharmaceutical and cosmetic stick products, such as deodorants and antiperspirants.

Glycerin, a hygroscopic material, contributes to the laxative effect of the suppository by drawing water from the intestine and from its irritant action on the mucous lining. The sodium stearate, a soap, is the solidifying agent and may also contribute to the laxative action. Because of the hygroscopic nature of glycerin, the suppositories attract moisture and should be maintained in tight containers, preferably at temperatures below 25°C (77°F).

URETHRAL SUPPOSITORIES

Suppositories for urethral administration tend to be thinner and tapered, often about 5 mm in diameter. They have been used in the treatment of local infections, and a much smaller urethral suppository has been introduced for the administration of alprostadil in the treatment of erectile dysfunction.

Compounding Urethral Suppositories

In addition to a urethral mold, a straw or thin glass tube can be used as the mold when preparing urethral suppositories. A

1-mL tuberculin syringe can also be used if the lower portion of the barrel is cut off (a pencil sharpener works well for this). The urethral suppository can be removed from the syringe barrel by inserting the plunger and forcing out the suppository after slight warming. A large diameter needle, attached to the syringe filled with the suppository melt, will aid in transferring the product into the 1-mL tuberculin syringe.

The MUSE (alprostadil) urethral microsuppository (Vivus, Inc.) is a single-use medicated transurethral system for the delivery of alprostadil to the male urethra. The drug is suspended in a polyethylene glycol 1450 excipient and is formed into a medicated pellet, or microsuppository, measuring 1.4 mm in diameter and 3 or 6 mm in length. Available strengths are 125, 250, 500, and 1,000 µg. The microsuppository resides in the tip of a translucent hollow applicator. It is administered by inserting the applicator tip into the urethra after urination. The pellet is delivered by depressing the applicator button. The polyethylene glycol 1450 vehicle will dissolve in the available fluid, releasing the drug for absorption. The applicator system is composed of medical grade polypropylene; each system is individually foil packaged. The MUSE microsuppository is indicated for the treatment of erectile dysfunction.

VAGINAL INSERTS

Examples of vaginal inserts (which includes vaginal tablets) are presented in Table 12.2. These preparations are employed principally to combat infections in the female genitourinary tract, to restore the vaginal mucosa to its normal state, and for contraception. The usual pathogenic organisms are *T. vaginalis*, *C.* (*Monilia*) *albicans* or other species, and *Haemophilus vaginalis*. Among the anti-infective agents in commercial vaginal preparations are nystatin, clotrimazole, butoconazole nitrate, terconazole, and miconazole (antifungals) and triple sulfas, sulfanilamide, povidone iodine, clindamycin phosphate, metronidazole, and oxytetracycline (antibacterials). Nonoxynol-9, a spermicide, is employed for vaginal contraception. Estrogenic substances such as dienestrol are found in vaginal preparations to restore the vaginal mucosa to its normal state.

The most commonly used base for vaginal inserts consists of combinations of the various molecular weight polyethylene glycols. To this base is frequently added surfactants and preservative agents, commonly the parabens. Many vaginal inserts and other types of vaginal dosage forms are buffered to an acid pH usually about 4.5, consistent with the normal vagina. This acidity discourages pathogenic organisms and provides a favorable environment for eventual recolonization by the acid-producing bacilli normally found in the vagina.

The polyethylene glycol–based vaginal suppositories are water miscible and are generally sufficiently firm for the patient to handle and insert without great difficulty. However, to make the task easier, many manufacturers provide plastic insertion devices that are used to hold the suppository or tablet for proper placement within the vagina (Fig. 12.5).

As noted earlier, pharmacists frequently are called on to prepare progesterone vaginal suppositories. Formulas for extemporaneous preparation of these suppositories have been presented in the professional literature. Micronized progesterone powder is used in

FIGURE 12.5 Dosage forms used intravaginally, including suppositories (*top* and *middle*), vaginal inserts packaged in foil (*bottom*), vaginal cream, and corresponding insert devices.

a base of polyethylene glycol, although in some formulas, cocoa butter is employed. The suppositories are prepared by adding the progesterone to a melt of the base and molding. Some representative formulas are as follows:

Rx

Progesterone, micronized	qs	qs	qs
Polyethylene glycol 400	60%	–	–
Polyethylene glycol 8000	40%	–	–
Polyethylene glycol 1000	–	75%	–
Polyethylene glycol 3350	–	25%	–
Cocoa butter	–	–	100%

The amount of progesterone per suppository usually ranges from 25 to 600 mg. The suppositories are used in treating luteal phase defect, premenstrual syndrome, luteal phase spotting, and in preparation of the endometrium for implantation.

The pharmacist should share several helpful hints with a woman who is about to use a vaginal suppository. She should first be told to read the instructions with the product. Throughout the course of therapy, the suppository should be inserted high into the vagina with the provided applicator. The patient should not discontinue therapy when the symptoms abate. Furthermore, she should notify her physician if burning, irritation, or any signs of an allergic reaction occur. When vaginal inserts (i.e., compressed tablets) are prescribed, the pharmacist should instruct the woman to dip the tablet into water quickly before insertion. Because these dosage forms are usually administered at bedtime and can be somewhat messy if formulated into an oleaginous base, the pharmacist should suggest that the woman wear a sanitary napkin to protect her nightwear and bed linens.

VAGINAL INSERTS (TABLETS)

Vaginal inserts (tablets) are widely used today as they are easy to manufacture, more stable, and less messy. They are usually ovoid and are accompanied in their packaging with a plastic inserter, a device for easy placement of the tablet within the vagina. They are prepared by tablet compression and are commonly formulated to contain lactose as the base or filler, a disintegrating agent such as starch, a dispersing agent such as polyvinylpyrrolidone, and a tablet lubricant such as magnesium stearate. They are intended to disintegrate within the vagina, releasing their medication. Examples are presented in Table 12.2.

Some vaginal inserts are capsules of gelatin-containing medication to be released intravaginally. Capsules may also be used rectally, especially to administer medication to children unwilling or unable to tolerate the drug orally. Capsule insertion into the rectum can be facilitated by first lightly wetting the capsule with water. Holes may be punched into these capsules prior to moistening and insertion to facilitate fluid movement into the capsule if desired. Drugs are absorbed from the rectum, but frequently at unpredictable rates and in varying amounts, as previously noted. Drugs that do not dissolve rapidly and that irritate mucous membranes should not be placed in direct contact with such membranes.

MEDICATION STICKS

Although cosmetics are viewed as preparations aimed at improving a person's appearance, many cosmetic preparations can serve as either medications or drug vehicle bases. Some formulations that have been introduced and improved for cosmetic use—powders, sticks, gels, solutions, suspensions, pastes, ointments, and oils—are widely used in the pharmaceutical sciences.

The medication stick, a fairly recent preparation, is used for both cosmetic and medical purposes. Examples include styptic pencils and lip balm sticks (Chapstick), which became available in the early 1940s. Today, medication sticks provide pharmacists, patients, and primary care providers with a unique, convenient, relatively stable, easy-to-prepare dosage form for the topical delivery of drugs. The use of this form will probably continue to grow.

Medication sticks are prepared similar to suppositories except that the melt is poured into the administering device, or tube. For application, the stick is pushed up from the bottom or using a screw-type device to raise the stick.

Melting bases include the bases used to prepare soft opaque and soft clear sticks. These bases, which will soften and melt at body temperatures, include cocoa butter, petrolatum, waxes, polyethylene glycols (PEGs), and the like. Active drugs can include any agent that can be applied directly to a specific skin site or over a larger area of skin to relieve such discomforts as muscle sprains and arthritis. Penetration enhancers (e.g., glycerin, propylene glycol, alcohol, and surfactants) can increase the amount of transdermal drug delivery. Using waxes, oils, or plain polymers such as PEGs alone achieves a topical effect. Melting bases can be further divided into opaque and clear. Opaque bases include waxes, oils, PEGs, and the like, whereas clear bases include sodium stearate/glycerin mixtures.

Sticks are a convenient form for administering topical medications. They come in different sizes and shapes, are readily transportable, and can be applied directly to the affected site of the body. Sticks can be easily compounded by using different materials to produce topical or systemic effects. Medications and other ingredients that have been incorporated into sticks include local anesthetics, sunscreens, oncology drugs, antivirals, and antibiotics. Sticks containing antibiotics, antivirals, and oncology agents are usually packaged in 5-g tubes, whereas sticks containing local anesthetics are usually packaged in 1- or 2-oz tubes.

The medication in a soft stick is applied by raising the stick above the tube level and simply rubbing it onto the skin, where it softens and flows easily onto the affected area. The medication usually cannot be seen on the skin. When a hard stick is applied, the tip of the stick is moistened and then touched to the affected area. The crystalline powder used to prepare the stick can leave a white residue on the skin.

Patient Counseling

When counseling a patient about the use of medication sticks, the pharmacist must take into account the active drug and the method of application. In general, the patient should be told to apply the stick only to the involved area and not to the surrounding skin. In addition, the patient should apply the medication liberally over the area but only as needed. The surface of the stick should be cleaned with a clean tissue after each use, and, to avoid transmitting infection, the product should not be shared with others.

Sample Formulations

Acyclovir Lip Balm

Acyclovir (200 mg capsules) #6
Polyethylene glycol base (Polybase) 25 g
These formulas can be modified by incorporating lidocaine, PABA, or other ingredients as needed.

Formula

1. Weigh or measure the ingredients.
2. Heat the PEG base to about 55°C.
3. Empty the acyclovir capsules into a mortar and reduce the particle size to a fine powder.
4. Add these powders to the melted base and mix thoroughly.
5. Cool to just above the melting point of the preparation, until it starts to thicken.
6. While stirring, pour into the lip balm molds or tubes.

Analgesic Medication Stick

Methyl salicylate	35 g
Menthol	15 g
Sodium stearate	13 g
Purified water	12 mL
Propylene glycol	25 g

1. Weigh or measure the ingredients.
2. Gently heat and melt the sodium stearate.
3. Mix the purified water with the propylene glycol and add to the melted sodium stearate.

4. Mix thoroughly, remove from heat, and allow the base to cool slightly.
5. Dissolve the menthol in the methyl salicylate; add this solution to the base and mix thoroughly.
6. As the preparation begins to thicken, continue to mix and pour into either 5-g or 20-g stick containers.
7. Allow to harden at room temperature.

SPECIAL TYPES OF SUPPOSITORIES

There has been a lot of work done in the development of altered release suppository dosage forms, both long-acting and slow-release suppositories (4,5). Morphine sulfate in slow-release suppositories is prepared by compounding pharmacists. The base includes a material such as alginic acid, which will prolong the release of the drug over several hours. Speeding up or slowing down the release and prolonging the action of the incorporated drug in suppositories has been investigated using various coatings, emulsions, hydrogels, layering, matrices of different substances, hollow-type suppositories, nanoparticles, osmotic release, micellar solutions, thermo-reversible liquid suppositories, xerogel suppositories, and others.

CLINICAL CONSIDERATIONS

Patients should be instructed on how to properly store the suppository, unwrap a wrapped suppository, and resolidify a melted suppository. The proper method of disposing of unused suppositories should also be discussed. They should also be counseled on the proper insertion of the suppository: whether to moisten it prior to insertion, how far to insert it, and how long to remain inactive after insertion. An example of the consultation related to administration of a suppository may be as follows:

1. Position the patient on the left side with the upper leg flexed.
2. Lubricate the suppository with a water-soluble lubricant or a small amount of water, if needed.
3. Gently insert the suppository in the rectum a finger's depth at an angle toward the umbilicus, so the suppository is placed against the rectal wall for absorption, rather than being left in the canal or pushed into a mass of stool.
4. After the finger is withdrawn, hold the buttocks together until the urge to expel has ceased.

The pharmacist should relate several helpful items of information about the proper use of suppositories. If they must be stored in the refrigerator, suppositories should be allowed to warm to room temperature before insertion. The patient should be advised to rub cocoa butter suppositories gently with the fingers to melt the surface to provide lubrication for insertion. Glycerinated gelatin or polyethylene glycol suppositories should be moistened with water to enhance lubrication. If the polyethylene glycol suppository formulation does not contain at least 20% water, dipping it into water just prior to insertion prevents moisture from being drawn from rectal tissues after insertion and decreases subsequent irritation. The shape of the suppository determines how it will be inserted. Bullet-shaped rectal suppositories should be inserted point-end first. When the patient is instructed to use one-half suppository, the patient should be told to cut the suppository in half lengthwise with a clean razor blade. Most suppositories are dispensed in paper, foil, or plastic wrappings, and the patient must be instructed to completely remove the wrapping before insertion. Depending upon the medication, purpose of the suppository, and associated factors, the administration of an enema prior to a suppository may increase the absorption of the drug. Additional information on inserting rectal suppositories and and informed consent has been published and may be useful for patient counseling (10).

PHARMACEUTICS CASE STUDY

SUBJECTIVE INFORMATION

A colleague calls you and asks for help concerning a prescription that was recently compounded. A teenaged boy with epilepsy brought in a prescription for diazepam 10 mg suppositories, and your colleague filled it using a compounded preparation that had been used in the past. However, the boy has been to the emergency room twice now with uncontrolled seizures, even after using the suppositories in an effort to bring the seizures under control. His parents have returned to the pharmacy with questions concerning the use of these suppositories. What should you tell your colleague?

OBJECTIVE INFORMATION

When questioned about the formulation for the suppositories, your colleague provides the following:

For 10 suppositories:

Diazepam powder, USP	100.0 mg
Cocoa butter	19.9 g
Mix and mold	

ASSESSMENT

The use of cocoa butter (a fatty acid base) in the formulation for diazepam suppositories may be the problem, because diazepam is a fat-soluble drug. As a result, the drug may remain dissolved in the vehicle and not be released from the dosage form rapidly enough to control the boy's seizures; the tendency for diazepam to diffuse from the lipid suppository base to the aqueous mucosal secretions is low. The use of a water-soluble base such as polyethylene glycol may be a better choice. Another possibility is to use a hollow suppository with a diazepam solution in the cavity.

PLAN

Recommend reformulation of the suppositories using polyethylene glycol as the base.

CLINICAL CASE STUDY

SUBJECTIVE INFORMATION

HPI: J.R. is a 32-year-old Hispanic female who presents to the oncology clinic for a follow-up visit 4 days after being discharged from the hospital. At that time, she received her first cycle of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy for her newly diagnosed large B-cell lymphoma. During the administration of CHOP, the patient started a regimen of two antiemetic medications, Compazine 10 mg by mouth every 6 hours as needed and lorazepam 2 mg intravenously every 6 hours as needed, to control her chemotherapy-induced nausea and vomiting (N&V). Upon discharge from the hospital, she was also given a prescription for prochlorperazine 10 mg tablets by mouth every 6 hours as needed for any N&V she might have at home. However, this morning J.R. is complaining of "feeling sick to her stomach" for the past 2 days, and she states, "Yesterday I threw up three times."She took her prochlorperazine tablets. However, twice after taking them she threw them up, and she simply "feels too nauseous now to take anything by mouth." Upon questioning, the patient denies any fever, chills, hematemesis (i.e., bloody vomitus), and diarrhea and otherwise is without complaints except for feeling "a little tired after the chemo."

CLINICAL CASE STUDY CONT.

PMH: Large B-cell lymphoma iron deficiency anemia
PSH: None
MEDS: CHOP regimen (each cycle is 21 days long):
Cyclophosphamide 750 mg/m^2 IV on day 1
Doxorubicin 50 mg/m^2 IV on day 1
Vincristine 1.4 mg/m^2 IV on day 1
100 mg po on days 1–5
Compazine 10 mg tablets po q6h prn N&V
Ferrous sulfate 325 mg tablets po tid
Tylenol 650 mg tablets po q6h prn pain
Allergies: NKDA
SH: (–) Alcohol
(–) Tobacco
(–) Illicit drugs
Pt came to the United States from Mexico 2 years ago
FH: Sister with cancer died at age 36

PHARMACEUTICAL CARE PLAN

S: Chemotherapy-induced N&V uncontrolled by prochlorperazine.

O: Vital Signs: Temp 36.0°, pulse 87, BP 117/76
Na 143, Cl 105, BUN 12, Glu 129
K 3.9, CO_2 30, Cr 0.8

A: A 32-year-old woman with chemotherapy-induced N&V uncontrolled by oral prochlorperazine. Pt is at risk for continued N&V because of the emetogenic potential of the CHOP regimen. Specifically, cyclophosphamide is associated with delayed-onset N&V that can last up to 6 or 7 days after the administration of chemotherapy. Also, J.R. has other characteristics, for example, female, less than 50 years of age, that increase her risk of N&V.

P: Because J.R. cannot take her medication by mouth, the rectal route of administration would be useful for her. Prochlorperazine is available as rectal suppositories,
and the recommended dosage for adults for N&V is 25 mg rectally twice daily. J.R. should be counseled to use her prochlorperazine suppositories as needed for N&V.
J.R. should be told that it is not necessary to store the suppositories in the refrigerator. However, they should be kept away from heat. If they are kept in the refrigerator, they should be warmed to room temperature for 5 to 10 minutes before use. Counsel J.R. on the proper administration technique. She should be instructed to remove the foil wrapping before insertion. Advise her to moisten the suppositories with some water to provide lubrication for insertion. Specific instructions are to use her finger to insert the suppository into the rectum about 1 inch and hold the suppository in place for a few moments. Afterward, the patient should thoroughly wash her hands and then resume her normal activities.
Explain to J.R. the common side effects associated with prochlorperazine use: sedation, restlessness, blurred vision, constipation, dizziness, dry mouth. Caution J.R. about performing activities that require alertness: driving a car, using machinery. Instruct J.R. to avoid alcoholic beverages and prolonged exposure to sunlight because prochlorperazine may cause skin photosensitivity.
J.R. should be monitored for resolution of her N&V. Also, monitor her for any complaint of abnormal body movements associated with long-term prochlorperazine use, such as extrapyramidal dyskinesias, tardive dyskinesia.

APPLYING THE PRINCIPLES AND CONCEPTS

Group Activities

1. Compare and contrast suppository and insert dosage forms in terms of physical appearance, size, and shape.
2. Compare and contrast pharmacist counseling directions to a patient prescribed a cocoa butter–based suppository product and a water-soluble–based suppository product.
3. Develop a listing of drugs in suppository dosage forms for inclusion into a hospital formulary system and indicate the rationale for their inclusion on the list.
4. Develop a listing of conceivable ways a patient might misuse a drug to be administered in a rectal suppository dosage form.
5. Describe special handling, storage, and disposal precautions a patient must take when prescribed a drug in a suppository dosage form.
6. Compile examples of prescriptions written for the extemporaneous preparation of a suppository delivery system.

Individual Activities

1. Create a table of six vaginal insert products including amount of active ingredient(s), indication, contraindication, adverse effects/precautions, and dosage.
2. Generate a listing of drugs whose physical–chemical characteristics make them a candidate for incorporation into a suppository dosage form.
3. List five clinical situations where the administration of a suppository or insert dosage form might be preferred over oral administration.
4. List five reasons a patient might be reluctant to use a suppository dosage form.
5. List five counseling points for proper administration of a specific rectal suppository or vaginal insert.
6. From the primary literature, locate a clinical drug study demonstrating a comparison between a rectal suppository delivery system and another route of delivery for the drug in terms of clinical effectiveness and determine which delivery system would be preferred in terms of patient acceptance, patient adherence, bioequivalence, and cost. Explain the rationale for your decision.

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SECTION VI

LIQUID DOSAGE FORMS

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.

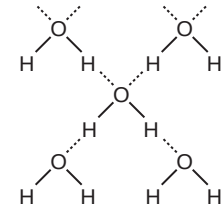
For single-solute solutions and especially for multiple-solute solutions, the pharmacist must be aware of the solubility characteristics of the solutes and the features of the common pharmaceutical solvents. Each chemical agent has its own solubility in a given solvent. For many medicinal agents, their 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.



Water

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

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, CH_2OH, COOH, NO_2, CO, NH_2, and SO_3H. 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_6H_6	1,430.0
Benzoic acid	C_6H_5COOH	275.0
Benzyl alcohol	$C_6H_5CH_2OH$	25.0
Phenol	C_6H_5OH	15.0
Pyrocatechol	$C_6H_4(OH)_2$	2.3
Pyrogallol	$C_6H_3(OH)_3$	1.7
Carbon tetrachloride	CCl_4	2,000.0
Chloroform	$CHCl_3$	200.0
Methylene chloride	CH_2Cl_2	50.0

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 resolute 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), $CH_2OH{\cdot}CHOH{\cdot}CH_2OH$

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, $CH_3CH(OH)CH_2OH$

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:

$$H - \text{resin} + M^+ + X^- + H_2O \rightarrow$$

$$M - \text{resin} + H^+ + X^- + H_2O\,(\text{pure})$$

Anion exchange:

$$\text{Resin} - NH_2 + H^+ + X^- + H_2O \rightarrow$$

$$\text{Resin} - NH_2 \cdot HX + H_2O\,(\text{pure})$$

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 µm). 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.)

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*)

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.

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:

$$(MgCO_3)_4 \cdot Mg(OH)_2 + 5H_3C_6H_5O_7 \rightarrow 5MgHC_6H_5O_7 + 4CO_2 + 6H_2O$$

(Equation 13.1)

$$3KHCO_3 + H_3C_6H_5O_7 \rightarrow K_3C_6H_5O_7 + 3CO_2 + 3H_2O$$

(Equation 13.2)

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 Scandipharm)	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 edisylate	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	Clarinex 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*)

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
H2 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

[a]A 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

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 × 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 *Cephaëlis 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.

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

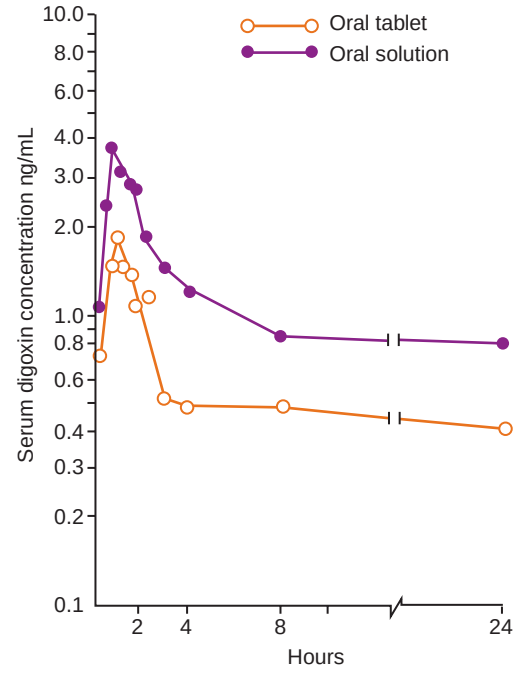


FIGURE 13.2 Serum digoxin concentrations following administration of digoxin 0.5 mg by oral tablet and elixir-like oral solution. (Adapted from Huffman DH, Azarnoff DL. Absorption of orally given digoxin preparations. JAMA 1972;222:957, with permission. Copyright © 2010 American Medical Association. 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 *Pseudomonas aeruginosa*
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 $Ca(OH)_2$ 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:

$$Ca(OH)_2 + CO_2 \rightarrow CaCO_3 + H_2O$$

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:

$$BaO_2 + H_2SO_4 \rightarrow BaSO_4 + H_2O_2$$

Another method uses electrolytic oxidation of a cold solution of concentrated sulfuric acid to form persulfuric acid, which when hydrolyzed liberates hydrogen peroxide:

$$2H_2SO_4 \rightarrow H_2S_2O_8 + H_2$$

$$H_2S_2O_8 + 2H_2O \rightarrow 2H_2SO_4 + H_2O_2$$

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.

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, antigingivitis 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 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:

FIGURE 13.4 Products for vaginal use, including solution concentrates, powder, and aerosol foam with insert device.

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:

$$I_2 + NaI \leftrightarrow NaI_3$$

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.

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 canker 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

$$2.0 = \frac{100\text{ g}}{\text{weight of an equal volume of water}}$$

$$\text{weight of an equal volume of water} = \frac{100\text{ g}}{2.0}$$

$$= 50\text{ g}$$

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:

$$\frac{27.39\ \text{g}}{1.17} = 23.41\ \text{mg, weight of equal of water}$$

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 spermatocidal 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 ($C_9H_{13}NO_2.HCl$), 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.

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*. *Magmas* 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:

$$\frac{(1\text{ ng})(1\text{ g})\left(6.02\times10^{23}\text{ molecules}\right)}{(\text{particle})\left(1\times10^{9}\right)\ (206\ \text{g})\,(\text{Mole})} = 2.923\times10^{12}\text{ molecules}$$

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.

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.

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 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.
2. The particle size of the suspensoid should remain fairly constant throughout long periods of undisturbed standing.
3. 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:

$$\frac{dx}{dt} = \frac{d^2(\rho_i - \rho_e)g}{18\eta}$$

where

dx/dt is the rate of settling,
d is the diameter of the particles,
ρ_i 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 μg (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:

$$\frac{(2.5\times10^{-4})^2\ (1.3-1.0)\ (980)}{18\times0.01} = 1.02\times10^{-4}\ \text{cm/s}$$

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:

$$\frac{(2.5\times10^{-5})^2\ (1.3-1.0)(980)}{18\times0.01} = 1.02\times10^{-6}\ \text{cm/s}$$

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:

$$\frac{\left(2.5\times10^{-5}\right)^2(1.3-1.25)(980)}{18\times4}=4.25\times10^{-10}\,\text{cm/s}$$

The smaller particle size (0.25 μm) powder will now settle at this rate:

$$\frac{\left(2.5\times10^{-5}\right)^2(1.3-1.25)(980)}{18\times4}=4.25\times10^{-10}\ \text{cm/s}$$

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,

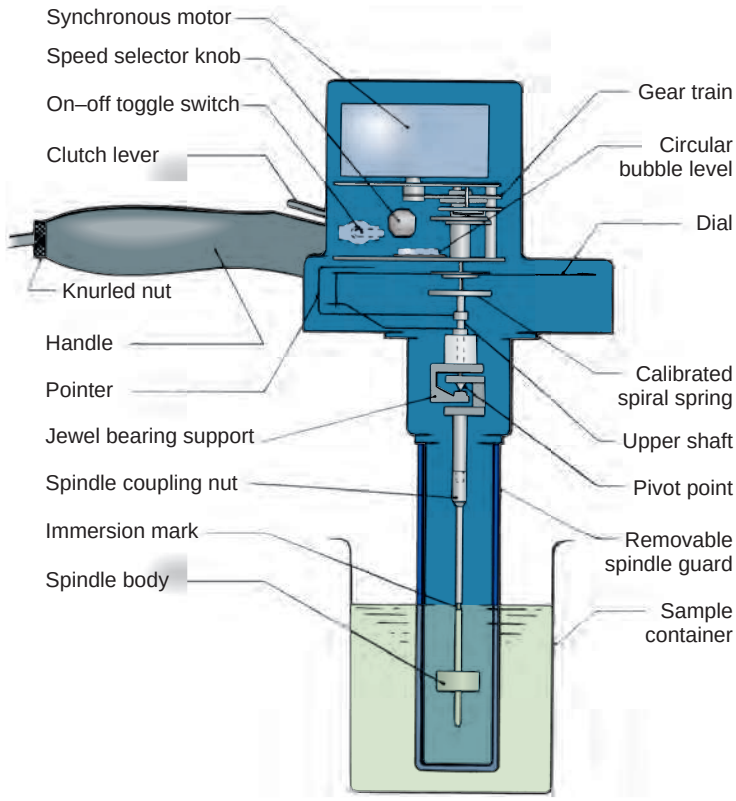


FIGURE 14.3 The Brookfield viscometer. (Courtesy of Brookfield Engineering Laboratories.)

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:

$$\eta = \frac{F}{G}$$

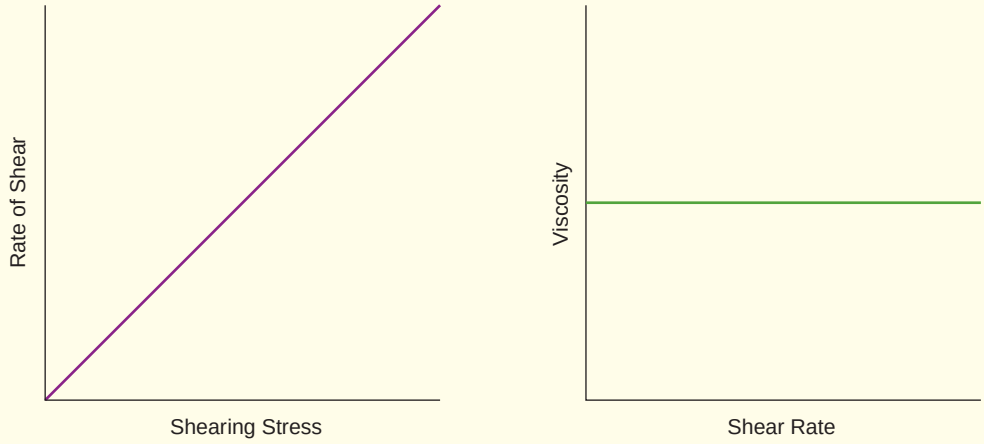
where

F = F′/A 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 cm^2 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?

$$\eta = \frac{(0.01)(1.05)(230)}{(1.0)(120)}$$

$$\eta = 0.020 \quad \text{poise} = 2.0 \text{ cP}$$

Viscosity is related to temperature; thus,

$$\eta' = Ae^{Ev/RT}$$

where

A is a constant depending on the molecular weight and molar volume of the material,
Ev 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:

$$\frac{1}{\eta} = \frac{1}{\eta}V_1 + \frac{1}{\eta}V_2$$

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)?

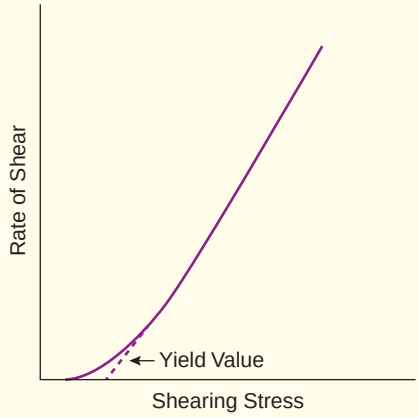
$$\frac{1}{\eta} = \frac{1(0.6)}{1.0} + \frac{1(0.4)}{3.4}$$

$$\eta = 1.4 \text{ cP}$$

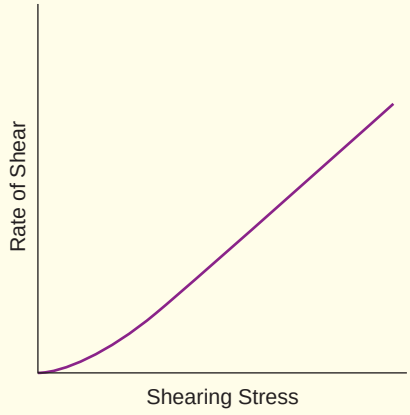
Non-Newtonian substances are those that fail to follow the Newton equation of flow. Example materials include colloidal solutions, emulsions, liquid suspensions, and ointments. There are three general types of non-Newtonian materials: plastic, pseudoplastic, and dilatant.

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.

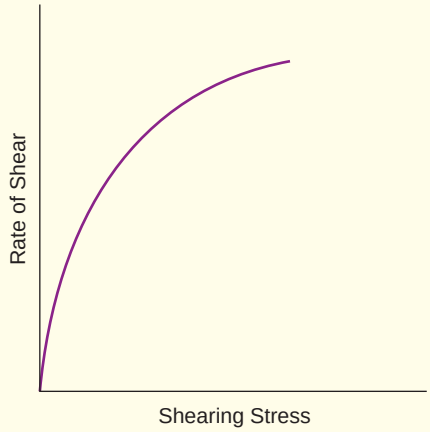
PHYSICAL PHARMACY CAPSULE 14.3 CONT.

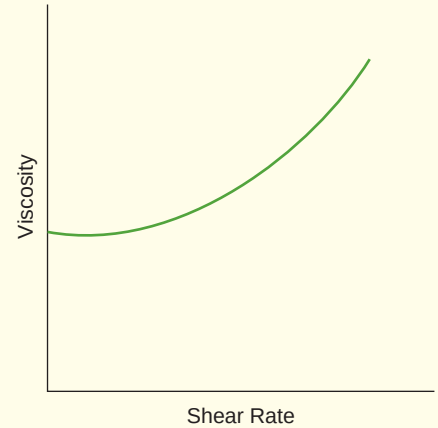


Pseudoplastic substances begin flow when a shearing stress is applied; therefore, they exhibit no yield value. With increasing shearing stress, the rate of shear increases; consequently, these materials are also called shear-thinning systems. It is postulated that this occurs as the molecules, primarily 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 tank with a liquid filling unit in the process of filling large-mouth suspension bottles is shown in Figure 14.6.

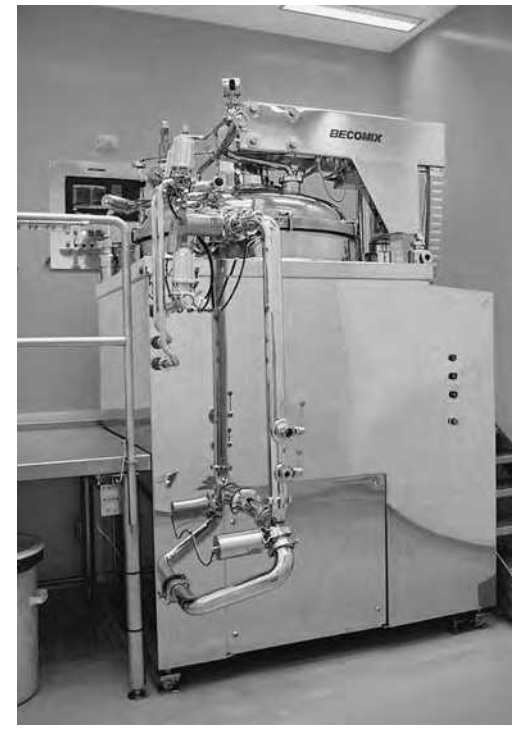


FIGURE 14.5 An industrial mixer for manufacture of disperse systems, including suspensions and emulsions. (Courtesy of Paddock Laboratories.)

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 *Escherichia coli*) 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 *Candida* (*Monilia*) *albicans*, other *Candida* spp.
Antiprotozoal			
Atovaquone	Mepron Suspension (GlaxoSmithKline)	750 mg/5 mL	Indicated for the prevention of *Pneumocystis carinii* 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 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.

FIGURE 14.7 Calibrated droppers used in the administration of pediatric medications.

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.

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

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 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.

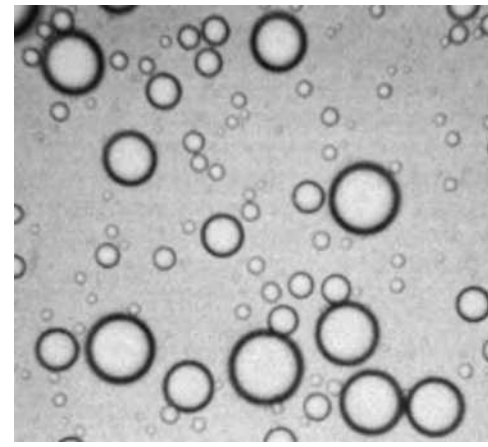


FIGURE 14.8 Mineral oil-in-water emulsion. The largest oil globule measures approximately 0.04 mm. (Courtesy of James C. Price, PhD, College of Pharmacy, University of Georgia.)

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 cm^2.
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} cm^2.
The total "A" of the 50 mL as 1-μm diameter droplets is

$$\left(7.854 \times 10^{-9}\,\text{cm}^2 / \text{droplet}\right) \times \left(9.55 \times 10^{13}\,\text{droplets}\right) = 7.5 \times 10^{5}\,\text{cm}^2$$

$$\Delta A = \frac{7.5 \times 10^{5}\,\text{cm}^2}{80\,\text{cm}^2} = 9.38 \times 10^{3}$$

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:

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

[a]ICI Americas, Wilmington, Delaware.
[b]Rohm and Haas, Philadelphia, Pennsylvania.
[c]Amerchol Corporation, Edison, New Jersey.
[d]BASF-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 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.

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

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:

$$0.75 \times 8.0 = 6.0$$

$$0.25 \times 12.0 = 3.0$$

$$\text{Total HLB} = 9.0$$

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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:

$$\frac{0.003\ cm^3}{12{,}000\ cm^2} = 2.5 \times 10^{-7}\ cm$$

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 × 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 ($8.4 \times 10^{-6} \times 6.02 \times 10^{23} = 5.0568 \times 10^{18}$ molecules).

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4. The cross-sectional area can now be calculated by dividing the surface area by the number of molecules (12,000 cm^2/5.0568 × 10^{18} × 2.373 × 10^{-15} cm^2 × 23.73 × 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

$$V_i = \frac{4}{3}\pi r^3 = \frac{4}{3}\pi\left(0.5\times10^{-4}\right)^3 = 0.524\times10^{-12}\ \text{mL}$$

To calculate the number of globules per milliliter, divide 1 mL by the volume of each globule:

$$\frac{1\ \text{mL}}{0.524\times10^{-12}\ \text{mL / globule}} = 1.91\times10^{12}\ \text{globules / mL}$$

The surface area (S) of each individual globule will be

$$S = 4\pi r^2 = 4\pi\left(0.5\times10^{-4}\right)^2 = 3.14\times10^{-8}\ \text{cm}^2$$

and the surface area of all the globules in 1 mL of oil is

$$\left(1.91\times10^{12}\right)\times\left(3.14\times10^{-8}\right) = 6\times10^{4}\ \text{cm}^2$$

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:

$$\frac{6\times10^{4}\ \text{cm}^2}{2.373\times10^{-15}\ \text{cm}^2\text{ / molecule}} = 2.528\times10^{19}\ \text{molecules}$$

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:

$$\frac{2.528\times10^{19}\ \text{molecules}}{6.02\times10^{23}\ \text{molecules / mole}} = 4.199\times10^{-5}\ \text{moles}$$

and the quantity required for 50 mL will be

$$50\ \text{mL}\times4.199\times10^{-5}\ \text{moles / mL} = 2.095\times10^{-3}\ \text{moles}$$

$$2.095\times10^{-3}\ \text{moles}\times325\ \text{g / mole} = 0.681\ \text{g, or 681 mg}$$

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 *micro*emulsion may be in the range of 100 Å (10 mμ) to 1,000 Å, whereas in a *macro*emulsion, 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

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 acacia 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 colloidals 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 gallate, 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, cetostearyl 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:

$$2NaOH + MgSO_4 \rightarrow Mg(OH)_2 + Na_2SO_4$$
$$MgO + H_2O \rightarrow Mg(OH)_2$$

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

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,

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_3H_8	C_4H_{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:

$$n_{propane} = 60 / 44.1 = 1.36$$

$$n_{isobutane} = 40 / 58.1 = 0.69$$

2. From Raoult law, determine the number of moles of each propellant.
3. From Raoult law, the partial pressure exerted by the propane is

$$P_{propane} = \left[\left(n_{propane}\right) / \left(n_{propane} + n_{isobutane}\right)\right] P_{propane}$$

$$P_{propane} = \left[(1.36) / (1.36 + 0.69)\right] 110 = 72.98\ \psi$$

4. The partial pressure exerted by the isobutane is

$$P_{isobutane} = \left[(0.69) / (1.36 + 0.69)\right] 30.4 = 10.23\ \psi$$

5. The vapor pressure exerted by both gases, P_T, is

$$P_T = 72.98 + 10.23 = 83.21\ \psi \quad \text{at } 70°F$$

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

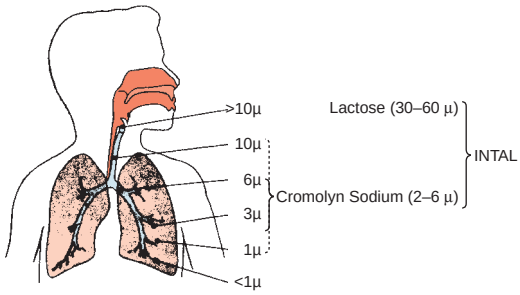

FIGURE 14.11 Relationship of INTAL (cromolyn sodium, Fisons) particle size to airway penetration. (Courtesy of Fisons Corporation.)

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 μm, 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

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_3F	11	13.4	74.7	1.485
Dichlorodifluoromethane	CCl_2F_2	12	13.4	74.1	1.485
Dichlorotetrafluoroethane	$CClF_2CClF_2$	114	21.6	38.4	1.468
Chloropentafluoroethane	$CClF_2CF_3$	115	17.5	–37.7	1.29
Monochlorodifluoromethane	CH_3CClF_2	142[b]	43.8	15.1	1.119
Difluoroethane	CH_3CHF_2	152[b]	76.4	–11.2	0.911
Octafluorocyclobutane	$CF_2CF_2CF_2CF_2$	C318	40.1	21.1	1.513

[a]Pounds per square inch absolute, equal to psig + 14.7.

[b]The 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 "b" 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.

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,

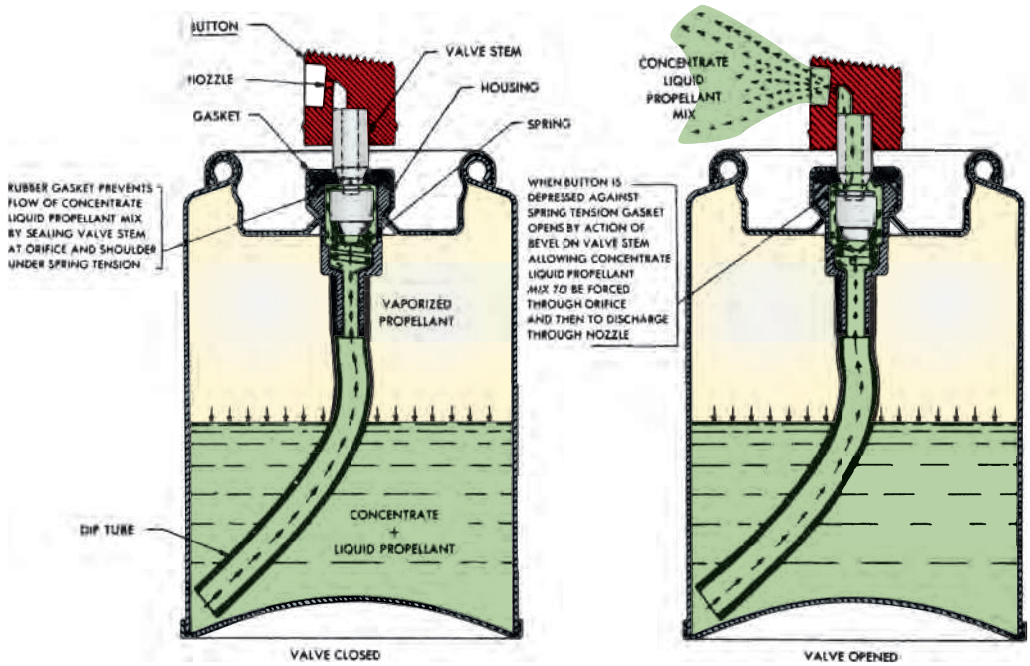

FIGURE 14.12 Cross-section sketches of contents and operation of a typical two-phase aerosol system. (Courtesy of Armstrong Laboratories, Division of Aerosol Techniques.)

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.

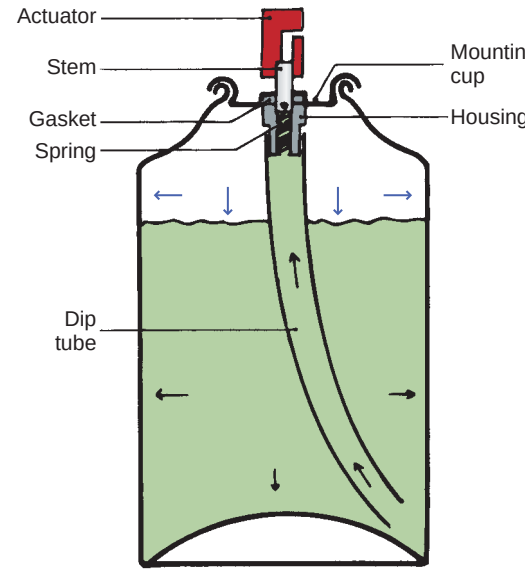

FIGURE 14.13 Valve assembly components.

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.
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, 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.

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.)

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 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.

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.)

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 (AAIPharma)	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 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.

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.)

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 vaginit*is 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.

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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SECTION VII

STERILE DOSAGE FORMS AND DELIVERY SYSTEMS

15 Parenterals

OBJECTIVES

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

1. List the advantages and disadvantages of parenteral administration
2. Define parenteral administration, and list the different parenteral methods of administration
3. Compare and contrast the risks and benefits of the various parenteral routes
4. Identify the challenges of using nonaqueous vehicles in parenteral products
5. Define osmolality and osmolarity, and explain their relationship with the tonicity of a substance
6. Compare and contrast a small-volume and a large-volume parenteral
7. Outline the different methods of sterilization for parenteral products
8. Differentiate between single- and multiple-dose packaging requirements
9. Identify the measures for proper handling and disposal of hazardous substances/chemotherapy
10. Compare and contrast total parenteral nutrition (TPN) preparations to total nutritional admixture (TNA) preparations

Considered in this chapter are important pharmaceutical dosage forms with the common characteristic of sterility, that is, they are free from contaminating microorganisms. Among these sterile dosage forms are the various small- and large-volume injectable preparations, irrigation fluids intended to bathe body wounds or surgical openings, and dialysis solutions. Biologic preparations, including vaccines, toxoids, and antitoxins, also among this group are discussed in Chapter 16. Sterility in these preparations is essential because they are placed in direct contact with the internal body fluids or tissues, where infection can easily arise. Ophthalmic preparations, which are also prepared to be sterile, are discussed separately in Chapter 17.

INJECTIONS

Injections are sterile, pyrogen-free (endotoxin units [EU] limited) preparations intended to be administered parenterally. The term *parenteral* refers to the injectable routes of administration. It derives from the Greek words *para* (outside) and *enteron* (intestine) and denotes routes of administration other than the oral route. *Pyrogens*, or bacterial endotoxins, are organic metabolic products shed from gram-negative bacteria, which can cause fever and hypotension in patients when they are in excessive amounts in intravenous (IV) injections. Pyrogens and the determination of their presence in parenteral preparations are discussed later in this chapter. In general, the parenteral routes are used when rapid drug

action is desired, as in emergencies; when the patient is uncooperative, unconscious, or unable to accept or tolerate oral medication; or when the drug itself is ineffective by other routes. With the exception of insulin injections, which are commonly *self*-administered by diabetics, most injections are administered by the physician, physician's assistant, or nurse in the course of medical treatment. Thus, injections are employed mostly in the hospital, extended care facility, clinic, and, less frequently, at home. An exception is *home health care* programs, in which health professionals pay scheduled visits to patients at home, providing needed treatment, including IV medications. These programs enable patients who do not require or are unable to pay for more expensive hospitalization to remain at home while receiving appropriate medical care. The pharmacist supplies injectable preparations to the physician and nurse as required for use in the institutional setting, clinic, office, or home health care program.

Perhaps the earliest injectable drug to receive official recognition was the hypodermic morphine solution, which appeared first in the 1874 addendum to the 1867 *British Pharmacopeia* and, in 1888, in the first edition of the *National Formulary* (*NF*) *of the United States*. Today, literally hundreds of drugs and drug products are available for parenteral administration.

Parenteral Routes of Administration

Drugs may be injected into almost any organ or area of the body, including the joints (*intra-articular*), joint fluid area (*intrasynovial*), spinal column (*intraspinal*), spinal fluid (*intrathecal*), arteries (*intra-arterial*), and, in an emergency, even the heart (*intracardiac*). However, most injections go into a vein (*intravenous, IV*), into a muscle (*intramuscular, IM*), into the skin (*intradermal, ID*; *intracutaneous*), or under the skin (*subcutaneous, SC*; *sub-Q, SQ*; *hypodermic, hypo*) (Fig. 15.1).

Intravenous Route

IV injection of drugs had its scientific origin in 1656 in the experiments of Sir Christopher Wren, architect of St Paul's Cathedral and amateur physiologist. Using a bladder and

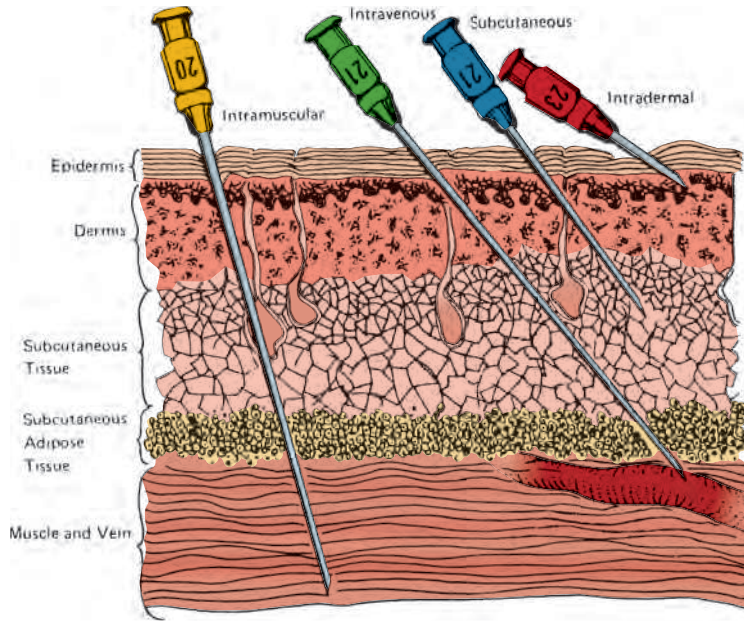

FIGURE 15.1 Routes of parenteral administration. Numbers on needles indicate gauge of the needles (outside diameter of shaft). (Reprinted with permission from Turco S, King RE. Sterile Dosage Forms: Their Preparation and Clinical Applications. 3rd Ed. Philadelphia, PA: Lea & Febiger, 1987.)

quill for a syringe and needle, he injected wine, ale, opium, and other substances into the veins of dogs and studied their effects. IV medication was first given to humans by Johann Daniel Major of Kiel in 1662 but was abandoned for a period because of thrombosis and embolism in the patients so treated. The invention of the hypodermic syringe toward the middle of the 19th century created new interest in IV techniques, and toward the turn of the 20th century, IV administration of solutions of sodium chloride and glucose became popular. Today, IV administration of drugs is a routine occurrence in the hospital, although recognized dangers are still associated with the practice. Thrombus and embolus formation may be induced by IV needles and catheters, and the possibility of particulate matter in parenteral solutions poses a concern.

IV drugs provide rapid action compared with other routes of administration, and because drug absorption is not a factor, optimum blood levels may be achieved with accuracy and immediacy not possible by other routes. In emergencies, IV administration of a drug may be lifesaving because of the placement of the drug directly into the circulation and the prompt action that ensues. On the negative side, once a drug is administered intravenously, it cannot be retrieved. In the case of an adverse reaction to the drug, for instance, the drug cannot be easily removed from the circulation, as it could, for example, by induction of vomiting after oral administration of the same drug. Furthermore, the IV dose may differ greatly from the oral dose. Thus, great care must be taken to prevent overdosing or underdosing. The beta-blocker drug class, such as metoprolol, is a perfect example of the vast differences between IV (three bolus injections of 5 mg each at about 2-minute intervals) and oral dosing (100 mg/d).

Although most superficial veins are suitable for venipuncture, the basilic and cephalic veins on the back of the hand and dorsal forearm are the best peripheral veins for IV therapy. The antecubital vein is not preferred for IV therapy because it is a point of great inflection with a high risk of extravasation. Most clinicians insert the needle with the bevel facing upward, at the most acute angle possible with the vein, to ensure that the direction of flow of the injectable is that of the flow of the blood. Strict aseptic precautions must be taken at all times to avoid the risk of infection. Not only are the injectable solutions sterile, the syringes and needles must also be sterilized, and the point of entrance must be disinfected to reduce the chance of carrying bacteria from the skin into the blood via the needle. Before injection, the health care worker must withdraw the plunger of the syringe or squeeze a special bulb found on most IV sets to ensure that the needle has been properly seated. A backflow of blood into the administration set or syringe indicates proper placement of the needle in the vein.

Both small and large volumes of drug solutions may be administered intravenously. The use of 1,000-mL containers of solutions for IV infusion is commonplace in the hospital. These solutions, containing such agents as nutrients, plasma volume expanders, electrolytes, amino acids, and other therapeutic agents, are administered through an indwelling needle or catheter by continuous infusion. The infusion or flow rate may be adjusted according to the needs of the patient. Generally, flow rates for IV fluids are expressed in milliliters per hour and range from 42 to 150 mL/h. Lower rates are used for keep open (KO, KVO) lines. For IV infusion, the needle or catheter is placed in a prominent vein of the forearm or leg and taped firmly to the patient so that it will not slip from place during infusion. The main hazard of IV infusion is thrombus formation induced by the catheter or needle touching the wall of the vein. Thrombi are most likely when the infusion solution is irritating to the biologic tissues. A *thrombus* is a blood clot formed within the blood vessel (or heart), usually because of slowing of the circulation or an alteration of the blood or vessel wall. Once such a clot circulates, it becomes an *embolus*, carried by the blood stream until it lodges in a blood vessel, obstructing it and resulting in a block or occlusion referred to as an *embolism*. Such an obstruction may be

a critical hazard to the patient, depending on the site and severity of the obstruction.

IV drugs ordinarily must be in aqueous solution; they must mix with the circulating blood and not precipitate from solution. Such an event can lead to pulmonary microcapillary occlusion and blockage of blood flow. IV fat emulsions (e.g., Intralipid, 20%, 30%, Baxter; Liposyn II, 10%, 20%, Hospira; Liposyn III, 10% to 30%, Hospira) have gained acceptance for use as a source of calories and essential fatty acids for patients requiring parenteral nutrition for extended periods, usually more than 5 days. The product contains up to 30% soybean oil emulsified with egg yolk phospholipids in a vehicle of glycerin in water for injection. The emulsion is administered via a peripheral vein or by central venous infusion.

Naturally, the IV route is used for blood transfusions, and it also serves as the point of exit for removal of blood from patients for diagnostic work and for donation.

In the late 1980s, automated IV delivery systems for intermittent self-administration of analgesics became commercially available. Patient-controlled analgesia (PCA) has been used to control the pain associated with a variety of surgical procedures, labor, sickle cell crisis, and cancer. For patients with chronic malignant pain, PCA allows a greater degree of ambulation and independence (1).

The typical PCA device includes a syringe or chamber that contains the analgesic drug and a programmable electromechanical unit. The unit, which may be compact enough to be worn on a belt or carried in a pocket (e.g., WalkMed PCA, McKinley, Wheat Ridge, CO), controls the delivery of drug by advancing a piston when the patient presses a button. The drug can be loaded into the device by a health care professional or dispensed from preloaded cartridges available from the manufacturer. The devices deliver IV bolus injections to produce rapid analgesia, along with slower infusion to produce steady-state concentrations for sustained pain control.

The advantage of the PCA is its ability to provide constant and uniform analgesia. The typical injection of an opioid into a depot muscular site may result in variable absorption, leading to unpredictable blood concentrations. Furthermore, these injections are usually given when needed and are often inadequate to treat the pain. The PCA can prevent pharmacokinetic and pharmacodynamic differences between patients from interfering with the effectiveness of analgesia. Because opioid kinetics differ greatly among patients, the rates of infusion must be tailored (2).

The PCA also permits patients to medicate themselves for breakthrough pain. It eliminates the delay between the perception of pain and receiving the medication. Furthermore, it saves nursing time. Otherwise, the nurse must check the analgesic orders given by the physician; sign out the pain reliever from a controlled, locked location; and then administer the medication to the patient.

The PCA also provides better pain control with less side effects by minimizing the variations between suboptimal pain relief and overuse of opioids. When the side effect profile of PCA patients is compared to those of patients maintained on IM opioids, nausea, sedation, and respiratory depression occur less often in the PCA group. Finally, patients accept the PCA as a favorable mode of relief, perhaps because of the sense of being in control and taking an active part in their pain relief.

PCA devices can be used for IV, SC, or epidural administration. Usually, these devices are either *demand dosing* (a fixed dose of drug is injected intermittently) or *constant-rate infusion plus demand dosing* (2). Regardless of the type used, the physician or nurse establishes the loading dose, the rate of background infusion, dose per demand, lockout interval (minimum time between demand doses), and maximum dosage over a specified time. Figure 15.2 demonstrates the LifeCare PCA Infusion System. With this device, the patient pushes a button on a pendant to deliver a prescribed quantity of the analgesic.

Intramuscular Route

IM injections of drugs provide effects that are less rapid but generally longer lasting than those obtained from IV administration (3). Aqueous or oleaginous solutions or suspensions of drug substances may be administered intramuscularly. Depending

FIGURE 15.2 LifeCare PCA Infusion System. (Courtesy of Hospira, Inc.)

on the type of preparation, absorption rates vary widely. Drugs in solution are more rapidly absorbed than those in suspension, and drugs in aqueous preparations are more rapidly absorbed than oleaginous preparations. The physical type of preparation is based on the properties of the drug itself and on the therapeutic goals.

IM injections are performed deep into the skeletal muscles. The point of injection should be as far as possible from major nerves and blood vessels. Injuries to patients from IM injection usually are related to the point at which the needle entered and where the medication was deposited. Such injuries include paralysis resulting from neural damage, abscess, cyst, embolism, hematoma, sloughing of the skin, and scarring.

In adults, the upper outer quadrant of the gluteus maximus is the most frequently used site for IM injection. In infants, the gluteal area is small and composed primarily of fat, not muscle. The muscle is poorly developed. An injection in this area may come dangerously close to the sciatic nerve, especially if the child is resisting the injection and squirming or fighting. Thus, in infants and young children, the deltoid muscles of the upper arm or the midlateral muscles of the thigh are preferred. An injection in the upper or lower portion of the deltoid would be well away from the radial nerve. The deltoid may also be used in adults, but the pain is more noticeable here than in the gluteal area. If a series of injections are to be given, the injection site is usually varied. To be certain that a blood vessel has not been entered, the clinician may aspirate slightly on the syringe following insertion of the needle to observe any blood entering the syringe. The volume of medication that may be conveniently administered by the IM route is limited, generally to a maximum of 5 mL in the gluteal region and 2 mL in the deltoid of the arm.

The Z-track technique is useful for IM injections of medications that stain the upper tissue, such as iron dextran injection, and those that irritate the tissue, such as diazepam, by sealing these medications in the lower muscle. Because of its staining qualities, iron dextran must be injected only into the muscle mass of the upper outer quadrant of the buttock. The skin is displaced laterally prior to injection, then the needle is inserted and the syringe aspirated, and the injection performed slowly and smoothly. The needle is then withdrawn and the skin released. This creates a Z pattern that blocks infiltration of medication into the SC tissue. The injection is 2 to 3 inches deep, and a 20- to 22-gauge needle is used. To reduce any further staining of the upper tissue, usually one needle is used to withdraw the iron dextran from its ampul and replaced with another for the injection.

Subcutaneous Route

The SC route may be used for injection of small amounts of medication. Injection of a drug beneath the skin is usually made in the loose interstitial tissue of the outer upper arm, the anterior thigh, or the lower abdomen. The site of injection is usually rotated when injections are frequently given, as with daily insulin injections. Prior to injection, the skin at the injection site should be thoroughly

cleansed. The maximum amount of medication that can be comfortably injected subcutaneously is about 1.3 mL, and amounts greater than 2 mL will most likely cause painful pressure. Syringes with up to 3-mL capacities and 24- to 26-gauge needles are used. These needles have cannula lengths of three-eighths of an inch to an inch. Most typically, SC insulin needles are 25 to 30 gauge with length of five-sixteenth to five-eighth of an inch. Upon insertion, if blood appears in the syringe, a new site should be selected.

Irritating drugs and those in thick suspension may produce induration, sloughing, or abscess and may be painful. Such preparations are not suitable for SC injection.

Intradermal Route

A number of substances may be effectively injected into the corium, the more vascular layer of the skin just beneath the epidermis. These substances include various agents for diagnostic determinations, desensitization, or immunization. The usual site for ID injection is the anterior forearm. A short (three-eighth of an inch) and narrow (23- to 26-gauge) needle is usually employed. The needle is inserted horizontally into the skin, with the bevel facing up. The injection is made with the bevel just disappearing into the corium. Usually, only about 0.1 mL may be administered in this manner.

Specialized Access

When it is necessary to administer repeated injections over time, it is prudent to employ devices that provide continued access and reduce pain associated with administration.

Several types of central venous catheters are used in institutions and on an outpatient basis for a variety of parenteral medications (e.g., cancer chemotherapy, long-term antibiotic therapy, TPN solutions). They can remain in place for a few days to several months. When not in use, they require heparinization to maintain patency of the catheter lumen.

The use of indwelling plastic catheters reduces the need for multiple punctures during IV therapy. Composed of polyvinyl chloride (PVC), Teflon, and polyethylene, these should be radiopaque to ensure that they are visible on radiographs. Usually, these must be removed within 48 hours after insertion. The choice of catheter depends on several factors, including length of time of the infusion, purpose of the infusion, and condition and availability of the veins. Three types of catheters are available: plain plastic, catheter over needle or catheter outside needle, and catheter inside needle.

The injection ports on Broviac and Hickman central vein catheters are not implanted subdermally. They are external usually at the abdomen after the catheter is tunneled under the abdomen and chest to access the superior vena cava. These do carry a risk of morbidity, including fracture of the catheters, entrance site infection, and catheter sepsis. Developed to overcome catheter complications, they are designed to provide repeated access to the infusion site. The delivery catheter can be placed in a vein, cavity, artery, or the central nervous system. A Huber point needle is used to inject through the skin into the rubber septum of a totally implanted central vein access device.

Official Types of Injections

According to the USP, injectable materials are separated into five general types. These may contain buffers, preservatives, and other added substances:

1. *Injection*: Liquid preparations that are drug substances or solutions thereof (e.g., Insulin Injection, USP)
2. *For injection*: Dry solids that, upon addition of suitable vehicles, yield solutions conforming in all respects to the requirements for injections (e.g., Cefuroxime for Injection, USP)
3. *Injectable emulsion*: Liquid preparation of drug substance dissolved or dispersed in a suitable emulsion medium (e.g., Propofol, USP)
4. *Injectable suspension*: Liquid preparation of solid suspended in a suitable liquid medium (e.g., Methylprednisolone Acetate Suspension, USP)
5. *For injectable suspension*: Dry solid that, upon addition of suitable vehicle, yields preparation conforming in all respects

to the requirements for *injectable suspensions* (e.g., Imipenem and Cilastatin for Injectable Suspension, USP)

The form in which the manufacturer prepares a given drug for parenteral use depends on the nature of the drug itself with respect to its physical and chemical characteristics and on certain therapeutic considerations. Generally, if a drug is unstable in solution, it may be prepared as a dry powder intended for reconstitution with a proper solvent at the time of administration, or it may be prepared as a suspension. If the drug is unstable in water, that solvent may be replaced in part or totally by a solvent in which the drug is insoluble. If the drug is insoluble in water, an injection may be prepared as an aqueous suspension or as a solution in a suitable nonaqueous solvent, such as a vegetable oil. If an aqueous solution is desired, a water-soluble salt form of the insoluble drug is frequently prepared. Aqueous or blood-miscible solutions may be injected directly into the blood stream. Blood-immiscible liquids, such as oleaginous injections and suspensions, can interrupt the normal flow of blood, and their use is generally restricted to other than IV administration. The onset and duration of action of a drug may be somewhat controlled by its chemical form, the physical state of the injection (solution or suspension), and the vehicle. Drugs that are very much soluble in body fluids generally have the most rapid absorption and onset of action. Thus, drugs in aqueous solution have a more rapid onset of action than do drugs in oleaginous solution. Drugs in aqueous suspension are also more rapid acting than drugs in oleaginous suspension because of the greater miscibility of the aqueous preparation with the body fluids after injection and the more rapid contact of the drug particles with the body fluids. Oftentimes, long action is desired to reduce the frequency of injections. These long-acting injections are called repository or depot preparations.

The solutions and suspensions of drugs intended for injection are prepared in the same general manner as solutions (Chapter 13) and disperse systems (Chapter 14), with the following differences:

1. Solvents or vehicles must meet special purity and other standards ensuring their safety by injection.
2. The use of added substances, such as buffers, stabilizers, and antimicrobial preservatives, falls under specific guidelines of use and is restricted in certain parenteral products. The use of coloring agents is strictly prohibited.
3. Parenteral products are always sterilized, must meet sterility standards, and must not exceed allowable endotoxin limits (ELs).
4. Parenteral solutions must meet compendial standards for particulate matter.
5. Parenteral products must be prepared in environmentally controlled areas, under strict sanitation standards, and by personnel specially trained and clothed to maintain the sanitation standards.
6. Parenteral products are packaged in special hermetic containers of specific and high quality. Special quality control procedures are used to ensure hermetic seal and sterile condition.
7. Each container of an injection is filled to a volume in slight excess of the labeled volume to be withdrawn. This overfilling permits ease of withdrawal and administration of the labeled volumes.
8. The volume of injection permitted in multiple-dose containers is restricted, as are the types of containers (single dose or multiple dose) that may be used for certain injections.
9. Specific labeling regulations apply to injections.
10. Sterile powders intended for solution or suspension immediately prior to injection are frequently packaged as lyophilized or freeze-dried powders to permit ease of solution or suspension upon the addition of the solvent or vehicle.
11. Extemporaneously prepared parenteral preparations must be compounded in a USP <797> compliant facility.

Solvents and Vehicles for Injections

The most frequently used solvent in the large-scale manufacturer of injections is *Water for Injection, USP*. This water is purified

by distillation or by reverse osmosis and meets the same standards for the presence of total solids as does *Purified Water, USP*—that is, not more than 1 mg/100 mL Water for Injection, USP—and may not contain added substances. Although water for injection is not required to be sterile, it must be pyrogen-free. The water is intended to be used in the manufacture of injectable products to be sterilized after preparation. Water for injection should be stored in tight containers at temperatures below or above the range in which microbial growth occurs. Water for injection is intended to be used within 24 hours after collection. Naturally, the water should be collected in sterile and pyrogen-free containers. The containers are usually glass or glass lined.

Sterile Water for Injection, USP, is packaged in single-dose containers not larger than 1 L. As with water for injection, it must be pyrogen-free but does have an allowable endotoxin level, not more than 0.25 USP EU/mL. Also, it may not contain any antimicrobial agent or other added substance. This water may contain slightly more total solids than water for injection because of the leaching of solids from the glass-lined tanks during sterilization. This water is intended to be used as a solvent, vehicle, or diluent for already sterilized and packaged injectable medications. The 1-L bottles cannot be administered intravenously because they have no tonicity. Thus, they are used for reconstitution of multiple antibiotics. In use, the water is aseptically added to the vial of medication to prepare the desired injection. For instance, a suitable injection may be prepared from the dry powder Sterile Ampicillin Sodium, USP, by aseptic addition of sterile water for injection.

Bacteriostatic Water for Injection, USP, is sterile water for injection containing one or more suitable antimicrobial agents. It is packaged in prefilled syringes or in vials containing not more than 30 mL of the water. The container label must state the names and proportions of the antimicrobial agent or agents. The water is employed as a sterile vehicle in the preparation of small volumes of injectable preparations. Theoretically, presence of the bacteriostatic agent gives the flexibility for multiple-dose vials. If the first person to withdraw medication inadvertently contaminates the vial contents, the preservative will destroy the microorganism, although there has been debate on how much protection the antimicrobial agent can provide in a multiple-dose vial (4). Because of the presence of antimicrobial agents, the water must be used only in parenterals that are administered in small volumes. Its use in parenterals administered in large volume is restricted by the excessive and perhaps toxic amounts of the antimicrobial agents that would be injected along with the medication. Generally, if more than 5 mL of solvent is required, sterile water for injection rather than bacteriostatic water for injection is preferred. In using bacteriostatic water for injection, due regard must also be given to the chemical compatibility of the bacteriostatic agent or agents with the particular medicinal agent being dissolved or suspended.

USP labeling requirements demand that the label state NOT FOR USE IN NEONATES. This statement was the result of problems encountered with neonates and toxicity of the bacteriostat, that is, benzyl alcohol. This toxicity results from the high cumulative amounts (milligrams per kilogram) of benzyl alcohol and the limited detoxification capacity of the neonate liver. This solution has not been reported to cause problems in older infants, children, or adults.

Benzyl alcohol poisoning is recognized as gasping syndrome. In one study, 10 premature infants developed this clinical syndrome characterized by the development of multiorgan failure and eventually died (5). The typical clinical course included metabolic acidosis, respiratory distress requiring mechanical ventilation, central nervous system dysfunction, hyperactivity, hypotonia, depression of the sensorium, apnea, seizure, coma, intraventricular hemorrhage, hepatic and renal failure, and eventual cardiovascular collapse and death. In the study, the amount of benzyl alcohol received ranged from 99 to 234 mg/kg/d. Based on the concentration of 0.9% benzyl alcohol in the bacteriostatic water for injection and sodium

chloride injection, death resulted from as little as 11 mL/kg/d.

Following toxicity reports and the deaths of infants in the early 1980s, the FDA issued a very strong recommendation to stop the use of fluids preserved with benzyl alcohol for use in neonates as a flush solution or to reconstitute medications.

Sodium Chloride Injection, USP, is a sterile isotonic solution of sodium chloride in water for injection. It contains no antimicrobial agents but has approximately 154 mEq each of sodium and chloride ions per liter. It may be used as a sterile vehicle in solutions or suspensions of drugs for parenteral administration.

Besides its use to reconstitute medications for injection, sodium chloride injection is frequently used as a catheter or IV line flush to maintain patency. Catheters or IV lines are constantly used to infuse fluids and IV medications and draw blood for laboratory analysis, among others. Usually, 2 mL is used to flush the line after each use or every 8 hours if the line is not used.

Bacteriostatic Sodium Chloride Injection, USP, is a sterile isotonic solution of sodium chloride in water for injection. It contains one or more suitable antimicrobial agents, which must be specified on the labeling. Sodium chloride 0.9% renders the solution isotonic. For the reasons noted for bacteriostatic water for injection, this solution may not be packaged in containers larger than 30 mL. When this solution is used as a vehicle, care must be exercised to ensure compatibility of the added medicinal agent with the preservative or preservatives and with the sodium chloride.

Bacteriostatic sodium chloride injection is also used to flush a catheter or IV line to maintain its patency. When used in only small quantities for flushing lines and reconstituting medications, the amount of benzyl alcohol is negligible and safe. But in neonates, especially premature infants with very low birth weights, accumulation of benzoic acid and unmetabolized benzyl alcohol may occur as a result of liver immaturity. Because of their low physical weight, their acute illness and consequent need for medications, and the frequent use of the umbilical catheter for various purposes, these patients may receive much more flush solution relative to their body weight than adults. Thus, bacteriostatic sodium chloride injection also carries the warning NOT FOR USE IN NEONATES.

Suffice it to say that benzyl alcohol may be present in other parenteral medications, and the pharmacist must be vigilant for its inappropriate use in neonates. Generally speaking, however, the amount of benzyl alcohol received through this means is negligible compared to the amount received from flush solutions. Preferably, the medication is available in a preservative-free formulation (i.e., single-use dose), and that should be used. However, if such a formulation is not available and there is no alternative, a medication preserved with benzyl alcohol may still be used if the physician's clinical judgment is that the risk-to-benefit ratio is appropriate.

Ringer's Injection, USP, is a sterile solution of sodium chloride, potassium chloride, and calcium chloride in water for injection. The three agents are present in concentrations similar to those of physiologic fluids. Ringer's is employed as a vehicle for other drugs or alone as an electrolyte replenisher and plasma volume expander. *Lactated Ringer Injection, USP*, has different quantities of the three salts in Ringer injection, and it contains sodium lactate. This injection is a fluid and electrolyte replenisher and a systemic alkalizer.

Nonaqueous Vehicles

Although an aqueous vehicle is generally preferred for an injection, it may be precluded by the limited water solubility of a medicinal substance or its susceptibility to hydrolysis. When such physical or chemical factors limit the use of a wholly aqueous vehicle, the pharmaceutical formulator must turn to one or more nonaqueous vehicles.

The selected vehicle must be nonirritating, nontoxic in the amounts administered, and not sensitizing. Like water, it must not exert a pharmacologic activity of its own, nor may it adversely affect the activity of the medicinal agent. In addition, the physical and chemical

properties of the solvent or vehicle must be considered, evaluated, and determined to be suitable for the task at hand. Among the many considerations are the solvent's physical and chemical stability at various pH levels, viscosity, which must be such as to allow ease of injection (suitable for use in syringes); fluidity, which must be maintained over a fairly wide temperature range; boiling point, which should be sufficiently high to permit heat sterilization; miscibility with body fluids; low vapor pressure to avoid problems during heat sterilization; and constant purity or ease of purification and standardization. No single solvent is free of limitations; hence, cross-consideration and assessment of each solvent's advantages and disadvantages help the formulator determine the most appropriate solvent for a given preparation. Among the nonaqueous solvents employed in parenteral products are fixed vegetable oils, glycerin, polyethylene glycols, propylene glycol, alcohol, and a number of less often used agents, including ethyl oleate, isopropyl myristate, and dimethylacetamide. These and other nonaqueous vehicles may be used provided they are safe in the amounts administered and do not interfere with the therapeutic efficacy of the preparation or with its response to prescribed assays and tests.

The USP specifies restrictions on the fixed vegetable oils in parenteral products. For one thing, they must remain clear when cooled to 10°C (50°F) to ensure the stability and clarity of the injectable product during refrigeration. The oils must not contain mineral oil or paraffin, as these materials are not absorbed by body tissues. The fluidity of a vegetable oil generally depends on the proportion of unsaturated fatty acids, such as oleic acid, to saturated acids, such as stearic acid. Oils to be employed in injections must meet officially stated requirements of iodine number and saponification number.

Although the toxicity of vegetable oils is generally considered to be relatively low, some patients exhibit allergic reactions to specific oils. Thus, when vegetable oils are employed in parenteral products, the label must state the specific oil. The most commonly used fixed oils in injections are corn oil, cottonseed oil, peanut oil, and sesame oil. Castor oil and olive oil have been used on occasion (Physical Pharmacy Capsule 15.1).

PHYSICAL PHARMACY CAPSULE 15.1

Colligative Properties of Drugs

Drug molecules have properties that are often divided into additive, constitutive, or colligative.

Additive properties depend on the total contribution of the atoms in the molecule or on the sum of the properties of the constituents of the solution. An example is molecular weight.

Constitutive properties depend on the arrangement and, to a lesser extent, the number and kind of atoms in a molecule. Examples are refraction of light, electrical properties, and surface and interfacial properties.

Colligative properties depend primarily on the number of particles in solution. Example properties include changes in vapor pressure, boiling point, freezing point, and osmotic pressure. These values should be approximately equal for equimolar concentrations of drugs.

LOWERING OF VAPOR PRESSURE

A vapor in equilibrium with its pure liquid at a constant temperature will exert *vapor pressure*. When a solute is added to the pure liquid, it will alter the tendency of the molecules to escape the original liquid. In an ideal solution or one that is very dilute, the partial vapor pressure of one component (p_1) is proportional to the mole fraction of molecules (N_1) of that component in the mixture:

PHYSICAL PHARMACY CAPSULE 15.1 CONT.

$$p_1 = N_1 p^\circ_1$$

where p°_1 is the vapor pressure of the pure component.

EXAMPLE 1

What is the partial vapor pressure of a solution containing 50 g dextrose in 1,000 mL of water? The vapor pressure of water is given as 23.76 mm Hg.

1. (50 g dextrose)/(MW of 180) = 0.28 mol of dextrose
2. (1,000 g water)/(MW of 18) = 55.56 mol of water
3. 0.28 + 55.56 = 55.84 total moles
4. (55.56)/(55.84) = 0.995 mole fraction of water
5. p_1 = (0.995)(23.76 mm Hg) = 23.64 mm Hg

The vapor pressure of the solution is 23.64 mm Hg. The decrease in vapor pressure by the addition of the 50 g dextrose is 23.76 – 23.64 = 0.12 mm Hg.

INCREASE IN BOILING POINT

The *boiling point* of a liquid is the temperature at which the vapor pressure of the liquid comes into equilibrium with the atmospheric pressure. The vapor pressure is reduced when a nonvolatile solute is added to a solvent, so that the solution must reach a higher temperature to reestablish the equilibrium, hence an increase in the boiling point. This is described in the following equation:

$$\Delta T_b = k_b m$$

where

ΔT_b is the change in boiling point,
k_b is the molar elevation constant of water, and
m is the molality of the solute.

EXAMPLE 2

What is the boiling point elevation of a solution containing 50 g dextrose in 1,000 mL of water? The molal elevation constant of water is 0.51.

1. (50 g dextrose)/(MW of 180) = 0.28 mol of dextrose in 1,000 mL of water or 0.28-molal solution
2. ΔT_b = (0.51) (0.28) = 0.143°C

DECREASE IN FREEZING POINT

The *freezing point* of a pure liquid is the temperature at which the solid and liquid phases are in equilibrium at 1 atm. The freezing point of a solution is the temperature at which the solid phase of pure solvent and the liquid phase of solution are in equilibrium at 1 atm pressure. When a solute is added to a solvent, the decrease in freezing point is proportional to the concentration of the solute. The relationship is described by the following equation:

$$\Delta T_f = k_f m$$

where

ΔT_f is the change in freezing point,
k_f is the molal freezing point depression constant of water, and
m is the molality of the solute.

PHYSICAL PHARMACY CAPSULE 15.1 CONT.

EXAMPLE 3

What is the decrease in freezing point of a solution containing 50 g dextrose in 1,000 mL of water? The molal elevation constant of water is – 1.86°C.

1. (50 g dextrose)/(MW of 180) = 0.28 mol of dextrose in 1,000 mL of water or 0.28-mol solution
2. $\Delta T_f = (-1.86)(0.28) = -0.52°C$

OSMOTIC PRESSURE

The pressure that must be applied to a more concentrated solution to prevent the flow of pure solvent into the solution separated by a semipermeable membrane is called the *osmotic pressure*. This relationship can be expressed as follows:

$$PV = nRT$$

where

P is the pressure (atm),
V is the volume (L),
n is number of moles of solute,
R is the gas constant (0.082 L atm/mol deg), and
T is the absolute temperature (°C).

EXAMPLE 4

What is the osmotic pressure of 50 g dextrose in 1,000 mL of water at room temperature (25°C)?

1. (50 g dextrose)/(MW of 180) = 0.28 mol of dextrose
2. 273°C + 25°C = 298°C
3. Volume will be 1 L.
4. P = [(0.28)(0.082)(298)]/(1) = 6.84 atm

Deviations from reality in these ideal examples of colligative properties are explained by the use of the Van't Hoff term i, which considers that electrolytes exert more pressure than nonelectrolytes and is related to the number of ionic species present. These deviations may be caused by ionic interaction, degree of dissociation of weak electrolytes, or associations of nonelectrolytes.

MILLIEQUIVALENTS

An *equivalent weight* is the atomic weight in grams of a material divided by its valence or charge. Milliequivalents are related to equivalents, which are also considered measures of combining power, chemical activity, or chemical reactivity. Equivalency, or milliequivalency, takes into consideration the total number of ionic charges in solution and the valence of the ions. Normally, plasma contains about 155 mEq of cations and anions in solution. The number of cations is always matched by the number of anions.

A *milliequivalent* is the quantity in milligrams of a solute equal to 1/1,000 of its gram-equivalent weight. Consider the following example.

EXAMPLE 5

What is the milliequivalent weight of sodium?

1. The atomic weight of sodium is 23.
2. The valence of sodium is + 1.
3. The equivalent weight of sodium is (23 g)/(1) = 23 g.
4. The milliequivalent weight of sodium is (23 g)/1,000 = 0.023 g, or 23 mg.
5. Therefore, 1 mEq of sodium weighs 23 mg.

PHYSICAL PHARMACY CAPSULE 15.1 CONT.

Milliequivalent calculations are commonly required in pharmacy practice today. The following are some examples.

EXAMPLE 6

How many milliequivalents of potassium chloride are in a solution containing 74.5 mg/mL?

1. The atomic weight of potassium is 39 and that of chloride is 35.5. The combined molecular weight is 74.5.
2. Since the valence is 1 for both potassium and chloride, the equivalent weight for potassium chloride is 74.5 g, and the milliequivalent weight is 74.5 mg.
3. The solution contains 74.5 mg/mL, and the milliequivalent weight is 74.5 mg; therefore, there is 1 mEq/mL of potassium chloride in the solution.

EXAMPLE 7

How many milliequivalents of calcium are in 10 mL of 10% calcium chloride ($CaCl_2 \cdot 2H_2O$) solution?

1. The formula weight for calcium chloride dihydrate is 147.
2. The equivalent weight is 147/2 = 73.5, since calcium is divalent.
3. Therefore, 1 mEq of calcium chloride weighs 73.5 mg.
4. (10 mL) (10%) = 1 g, or 1,000 mg, of calcium chloride dihydrate
5. (1,000 mg)/(73.5 mg) = 13.6 mEq of calcium chloride dihydrate, which also is 13.6 mEq of calcium

EXAMPLE 8

How many milliequivalents of sodium are contained in a 1-L bag of 0.9% sodium chloride?

1. (1,000 mL) (0.009) = 9 g, or 9,000 mg
2. The formula weight for sodium chloride is 23 + 35.5 = 58.5.
3. The milliequivalent weight for sodium chloride is 58.5 mg.
4. (9,000)/(58.5) = 153.8 mEq, or 154 mEq

In these cases, since sodium chloride is monovalent, there is 154 mEq of sodium, 154 mEq of chloride, or 154 mEq of sodium chloride.

OSMOLALITY AND TONICITY

Biologic systems are compatible with solutions having similar osmotic pressures, that is, an equivalent number of dissolved species. For example, red blood cells, blood plasma, and 0.9% sodium chloride solution contain approximately the same number of solute particles per unit volume and are termed iso-osmotic and isotonic.

If solutions contain more (hypertonic) or fewer (hypotonic) dissolved species, it may be necessary to alter the composition of the solution to bring them into an acceptable range.

An osmol (Osm) is related to a mole (gram molecular weight) of the molecules or ions in solution. One mole of glucose (180 g) dissolved in 1,000 g of water has an osmolality of 1 Osm, or 1,000 mOsm/kg of water. One mole of sodium chloride (23 + 35.5 g = 58.5 g) dissolved in 1,000 g of water has an osmolality of almost 2,000 mOsm, since sodium chloride dissociates into almost two particles per molecule. In other words, a 1-molal solution of sodium chloride is equivalent to a 2-molal solution of dextrose.

Normal serum osmolality values are in the vicinity of 285 mOsm/kg (often expressed as 285 mOsm/L). Ranges may include values from about 275 to 300 mOsm/L. Pharmaceuticals should be close to this value to minimize discomfort on application to the eyes or nose or on injection.

Some solutions are iso-osmotic but not isotonic. This is because the physiology of the cell membranes must be considered. For example, the cell membrane of the red blood cell is

PHYSICAL PHARMACY CAPSULE 15.1 CONT.

not semipermeable to all drugs. It allows ammonium chloride, alcohol, boric acid, glycerin, propylene glycol, and urea to diffuse freely. In the eye, the cell membrane is semipermeable to boric acid, and a 1.9% solution of boric acid is an isotonic ophthalmic solution. But even though a 1.9% solution of boric acid is isotonic with the eye and is iso-osmotic, it is not isotonic with blood—since boric acid can freely diffuse through the red blood cells—and it may cause hemolysis.

Pharmacists are often called upon to calculate the quantity of solute that must be added to adjust a hypotonic solution of a drug to isotonic. This can be done using several methods, including L-value, sodium chloride equivalent, and cryoscopy.

One of the most frequently used methods for calculating the quantity of sodium chloride necessary to prepare an isotonic solution is the *sodium chloride equivalent method*. A sodium chloride equivalent is the amount of sodium chloride that is osmotically equivalent to 1 g of the drug. For example, the sodium chloride equivalent of ephedrine sulfate is 0.23, that is, 1 g of ephedrine sulfate is equivalent to 0.23 g of sodium chloride.

EXAMPLE 9

How much sodium chloride is required to make the following prescription isotonic?

Rx Ephedrine sulfate 2%
Sterile water, qs 30 mL
M. isoton with sodium chloride

1. (30 mL) (0.009) = 0.270 g sodium chloride is required if only sodium chloride is present in the 30 mL of solution.
2. (30 mL) (0.02) = 0.6 g ephedrine sulfate is to be present.
3. (0.6 g) (0.23) = 0.138 g is the quantity of sodium chloride represented by the ephedrine sulfate.
4. Since 0.270 g sodium chloride is required if only sodium chloride is used and the quantity of sodium chloride that is equivalent to 0.6 g of ephedrine sulfate is 0.138 g, then 0.270 g – 0.138 g = 0.132 g of sodium chloride required to render the solution isotonic.
5. Therefore, the solution requires ephedrine sulfate 0.6 g, sodium chloride 0.132 g, and sufficient sterile water to make 30 mL.

By selective employment of solvent or vehicle, a pharmacist can prepare injectable preparations as solutions or suspensions in either an aqueous or nonaqueous vehicle. For the most part, oleaginous injections are administered intramuscularly. They must not be administered intravenously, as the oil will occlude the pulmonary microcirculation. Some examples of official injections with oil as the vehicle are presented in Table 15.1.

Added Substances

The USP permits addition of suitable substances to official preparations intended for injection to increase stability or usefulness as long as the substances are not interdicted in the individual monographs, are harmless in the amounts administered, and do not interfere with the therapeutic efficacy of the preparation or with specified assays and tests. Many of these added substances are antibacterial preservatives, buffers, solubilizers, antioxidants, and other adjuncts. Agents employed solely for their coloring effect are strictly prohibited in parenteral products.

The USP requires that one or more suitable substances be added to parenteral products that are packaged in multiple-dose containers to prevent the growth of microorganisms regardless of the method of sterilization

Table 15.1 SOME INJECTIONS IN OIL

INJECTION	OIL	CATEGORY
Dimercaprol	Peanut	Antidote to arsenic, gold, and mercury poisoning
Estradiol cypionate	Cottonseed	Estrogen
Estradiol valerate	Sesame or castor	Estrogen
Fluphenazine decanoate	Sesame	Antipsychotic
Fluphenazine enanthate	Sesame	Antipsychotic
Hydroxyprogesterone caproate	Castor	Progestin
Progesterone in oil	Sesame or peanut	Progestin
Testosterone cypionate	Cottonseed	Androgen
Testosterone cypionate and estradiol cypionate	Cottonseed	Androgen and estrogen
Testosterone enanthate	Sesame	Androgen
Testosterone enanthate and estradiol valerate	Sesame	Androgen and estrogen

employed, unless otherwise directed in the individual monograph or unless the injection's active ingredients are themselves bacteriostatic. Such substances are used in concentrations that prevent the growth of or kill microorganisms. Because many of the usual preservative agents are toxic in large amounts or irritating when parenterally administered, special care must be exercised in the selection of the appropriate preservative agents. For the following preservatives, the indicated maximum limits prevail for use in a parenteral product unless otherwise directed: for agents containing mercury and the cationic surface-active compounds, 0.01%; for agents such as chlorobutanol, cresol, and phenol, 0.5%; and for sulfur dioxide as an antioxidant or for an equivalent amount of the sulfite, bisulfite, or metabisulfite of potassium or sodium, 0.2%.

In addition to the stabilizing effect of the additives, the air accompanying an injectable product is frequently replaced with an inert gas, such as nitrogen, to enhance the stability of the product by preventing a chemical reaction between oxygen and the drug.

Methods of Sterilization

The term *sterilization*, as applied to pharmaceutical preparations, means destruction of all living organisms and their spores or their complete removal from the preparation. Five general methods are used to sterilize pharmaceutical products:

1. Steam
2. Dry heat
3. Filtration
4. Gas
5. Ionizing radiation

The method is determined largely by the nature of the preparation and its ingredients. However, regardless of the method used, the resulting product must pass a test for sterility as proof of the effectiveness of the method and the performance of the equipment and personnel.

Steam Sterilization

Steam sterilization is conducted in an autoclave and employs steam under pressure. It is usually the method of choice if the product can withstand it (Fig. 15.3).

Most pharmaceutical products are adversely affected by heat and cannot be heated safely to the temperature required for dry heat sterilization (about 150°C to 170°C or 302°F to 338°F). When moisture is present, bacteria are coagulated and destroyed at a considerably lower temperature than when moisture is absent. In fact, bacterial cells with a large percentage of water are generally killed rather easily. Spores, which contain a relatively low

FIGURE 15.3 Autoclaving of IV electrolyte solutions. (Courtesy of Hospira, Inc.)

percentage of water, are comparatively difficult to destroy. The mechanism of microbial destruction in moist heat is thought to be by denaturation and coagulation of some of the organism's essential protein. It is the hot moisture in the microbial cell that permits destruction at relatively low temperature. Death by dry heat is thought to be by dehydration of the microbial cell followed by slow oxidation. Because it is not possible to raise the temperature of steam above 100°C (212°F) under atmospheric conditions, pressure is employed to achieve higher temperatures. It is the temperature, not the pressure, that destroys the microorganisms, and the application of pressure is solely to increase the temperature of the system. Time is another important factor in the destruction of microorganisms by heat. Most modern autoclaves have gauges to indicate to the operator the internal conditions of temperature and pressure and a timing device to permit the desired exposure time for the load. The usual steam pressures, the temperatures obtainable under these pressures, and the approximate length of time required for sterilization after the system reaches the indicated temperatures are as follows:

10-lb pressure (115.5°C, or 240°F) for 30 minutes
15-lb pressure (121.5°C, or 250°F) for 20 minutes
20-lb pressure (126.5°C, or 260°F) for 15 minutes

As can be seen, the greater the pressure applied, the higher the temperature obtainable and the less the time required for sterilization.

Most autoclaves routinely operate at 121°C (250°F), as measured at the steam discharge line running from the autoclave. The temperature in the chamber of the autoclave must also be reached by the interior of the load being sterilized, and this temperature must be maintained for an adequate time. The penetration time of moist heat into the load varies with the nature of the load, and the exposure time must be adjusted to account for this latent period. For example, a solution packaged in a thin-walled 50-mL ampul may reach 121°C in 6 to 8 minutes after that temperature is registered in the steam discharge line, whereas 20 minutes or longer may be required to reach that temperature within a solution packaged in a completely filled, thick-walled 1,000-mL glass bottle. An estimate of these latent periods must be added to the total time to ensure adequate exposure times. This process depends on moisture and an elevated temperature, so air is removed from the chamber as sterilization begins, because a combination of air and steam yields a lower temperature than does steam alone under the same pressure. For instance, at 15-lb pressure, the temperature of saturated steam is 121.5°C, but a mixture of equal parts of air and steam will reach only about 112°C (234°F).

In general, steam sterilization is applicable to pharmaceutical preparations and materials that can withstand the required temperatures and are penetrated but not adversely affected by moisture. In aqueous solutions, the moisture is already present, and all that is required is elevation of the temperature of the solution for the prescribed period. Thus, solutions in sealed containers, such as ampuls, are readily sterilized by this method. Sealed empty vials can be sterilized by autoclaving only if they contain a small quantity of water. Steam sterilization is also applicable to bulk solutions, glassware, surgical dressings, and instruments. It is not useful for oils, fats, oleaginous preparations, and other preparations not penetrated by moisture or for exposed powders that may be damaged by the condensed moisture.

Dry Heat Sterilization

Dry heat sterilization is usually carried out in ovens designed for this purpose. The ovens may be heated either by gas or electricity and are generally thermostatically controlled.

Because dry heat is less effective in killing microorganisms than is moist heat, higher temperatures and longer periods of exposure are required. These must be determined for each product with consideration to the size and type of product and the container and its heat distribution characteristics. In general, individual units to be sterilized should be as small as possible, and the sterilizer should be loaded so as to permit free circulation of heated air throughout the chamber. Dry heat sterilization is usually conducted at 150°C to 170°C for not <2 hours. Higher temperatures permit shorter exposure for a given article; conversely, lower temperatures require longer exposure times. For example, if a particular chemical agent melts or decomposes at 170°C but is unaffected at 140°C (284°F), the lower temperature is used, and the exposure time is increased.

Dry heat sterilization is generally employed for substances that are not effectively sterilized by moist heat. Such substances include fixed oils; glycerin; various petroleum products, such as petrolatum, liquid petrolatum (mineral oil), and paraffin; and various heat-stable powders, such as zinc oxide. Dry heat is also an effective method for sterilizing glassware and surgical instruments. Dry heat is the method of choice when dry apparatus or dry containers are required, as in the handling of packaging of dry chemicals or nonaqueous solutions.

Sterilization by Filtration

Sterilization by filtration, which depends on the physical removal of microorganisms by adsorption on the filter medium or by a sieving mechanism, is used for heat-sensitive solutions. Medicinal preparations sterilized by this method must undergo extensive validation and monitoring because the effectiveness of the filtered product can be greatly influenced by the microbial load in the solution being filtered.

Commercially available filters are produced with a variety of pore size specifications. It would be well to mention briefly one type of modern filter, the Millipore filter (Fig. 15.4). The Millipore filter is a thin plastic membrane of cellulosic esters with millions of pores per square inch. The pores are made to be extremely uniform in size and occupy approximately 80% of the membrane's volume, the remaining 20% being the filter material. This high degree of porosity permits flow rates much in excess of those of other filters having the same particle retention capability. Millipore filters are made from a variety of polymers to be suitable for filtration of almost any liquid or gas system. Also, the filters have various pore sizes, 14 to 0.025 µm, to meet the specific requirements. For comparative purposes, the period that ended the last sentence is approximately 500 µm. The smallest particle visible to the naked eye is about 40 µm, a red blood cell is about 6.5 µm, the smallest bacterium is about 0.2 µm, and a poliovirus is about 0.025 µm.

Although the pore size of a bacterial filter is of prime importance in the removal of microorganisms from a liquid, other factors, such as the electrical charge on the filter and that of the microorganism, the pH of the solution, the temperature, and the pressure or vacuum applied to the system, are also important.

The major advantages of bacterial filtration include its speed in the filtration of small quantities of solution, its ability to sterilize thermolabile materials, the relatively

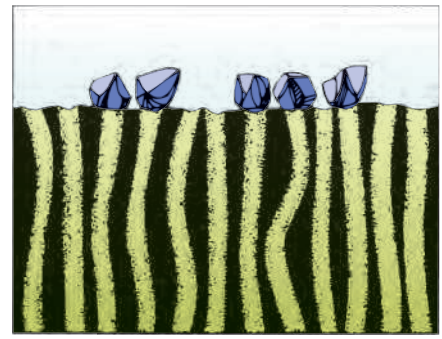

FIGURE 15.4 Membrane filters act as microporous screens that retain all particles and microorganisms larger than the rated pore size on their surface. (Courtesy of Millipore Corporation.)

FIGURE 15.5 Luer-Lok syringe adapted with a Millex Filter Unit and hypodermic needle. (Courtesy of Millipore Corporation.)

inexpensive equipment required, the development and proliferation of membrane filter technology, and the complete removal of living and dead microorganisms and other particulate matter from the solution.

The class of filter medium lends itself to more effective standardization and quality control and also gives the user greater opportunity to confirm the properties of the filter assembly before and after use. The fact that membrane filters are thin polymeric films offers many advantages but also some disadvantages compared to depth filters, such as porcelain or sintered material. Because much of the membrane surface is a void or open space, the properly assembled and sterilized filter offers the advantage of a high flow rate.

One disadvantage is that because the membrane tends to be fragile, it is essential to determine that the assembly was properly made and that the membrane was not ruptured or flawed during assembly, sterilization, or use. The housing and filter assemblies should first be validated for compatibility and integrity. This disadvantage is a circumstance not true of methods involving dry or moist heat sterilization, in which the procedures are just about guaranteed to give effective sterilization. Also, filtration of large volumes of liquids requires more time, particularly if the liquid is viscous, than, say, steam sterilization. In essence, bacterial filters are useful when heat cannot be used and also for small volumes of liquids.

Bacterial filters may be used conveniently and economically in the community pharmacy to filter extemporaneously prepared solutions (as ophthalmic solutions) that must be sterile (Figs. 15.5 and 15.6). Furthermore, the membrane filter is the method most commonly used in hospitals. Occasionally, in the past, hospitals used the autoclave (moist heat) to sterilize IV solutions, which were then unavailable commercially, for example, caffeine citrate, and many community pharmacies use autoclave sterilization for high-risk sterile compounding today.

To date, information about drug adsorption to membrane filters is limited. Several studies, however, have demonstrated that membrane filters can remove drug from solution (6–9). For example, 0.22-µm filters reduce the in vitro antimicrobial activity of amphotericin B (a colloidal suspension), while filtration of the amphotericin B through 0.85- and 0.45-µm filters did not. Butler et al. (10) demonstrated that the potency of drugs

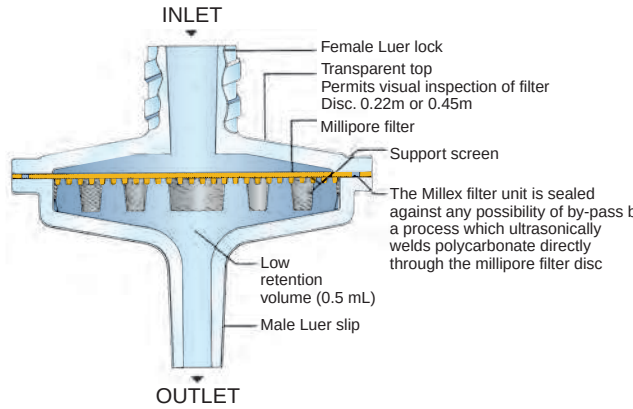

FIGURE 15.6 Cutaway showing composition of the Millex filter unit. (Courtesy of Millipore Corporation.)

administered intravenously and in small doses could be significantly reduced during in-line filtration with a filter containing a cellulose ester membrane. The literature indicates that drugs administered in low doses might present a problem of bonding to the filter. Many filters in clinical use are nitrate or acetate esters of cellulose. These compounds are polar and have residual hydroxyl groups that may adsorb drug. Hydrophobic interactions between hydrocarbon portions of drug molecules being filtered and linear cellulose molecules of filters are also thought to contribute to drug adsorption.

In general, current information suggests that little or no adsorption takes place with membrane filters. However, it is recommended that minute doses of drugs (<5 mg) should not be filtered until sufficient data demonstrate insignificant adsorption. With respect to amphotericin B, to ensure the passage of the antibiotic colloidal dispersion, the filter's mean pore diameter should be more than 1 µm.

Membrane filter media include cellulose acetate, cellulose nitrate, fluorocarbonate, acrylic polymers, polycarbonate, polyester, PVC, vinyl, nylon, polytef, and even metal membranes, and they may be reinforced or supported by an internal fabric.

Gas Sterilization

Some heat-sensitive and moisture-sensitive materials can be sterilized much better by exposure to ethylene oxide or propylene oxide gas than by other means. These gases are highly flammable when mixed with air but can be employed safely when properly diluted with an inert gas such as carbon dioxide or a suitable fluorinated hydrocarbon. Such mixtures are commercially available.

Sterilization by this process requires specialized equipment resembling an autoclave, and many combination steam autoclaves and ethylene oxide sterilizers are commercially available. Greater precautions are required for this method of sterilization than for some of the others, because the variables—for instance, time, temperature, gas concentration, and humidity—are not as firmly quantitated as those of dry heat and steam sterilization. In general, sterilization with gas is enhanced, and the exposure time required is reduced, by increasing the relative humidity of the system (to about 60%) and by increasing the exposure temperature to 50°C to 60°C. If the material being sterilized cannot tolerate either the moisture or the elevated temperature, exposure time must be increased. Generally, sterilization with ethylene oxide gas requires 4 to 16 hours of exposure. Ethylene oxide is thought to sterilize by interfering with the metabolism of the bacterial cell.

The great penetrating qualities of ethylene oxide gas make it a useful agent in certain special applications, such as sterilization of medical and surgical supplies and appliances such as catheters, needles, and plastic disposable syringes in their final plastic packaging just prior to shipment. The gas is also used to sterilize certain heat-labile enzyme preparations, certain antibiotics, and other drugs, after testing to ensure the absence of chemical reaction and other deleterious effects on the drug substance.

Sterilization by Ionizing Radiation

Techniques are available for sterilization of some types of pharmaceuticals by gamma rays and by cathode rays, but application of such techniques is limited because of the highly specialized equipment required and the effects of irradiation on the products and their containers.

The exact mechanism by which irradiation sterilizes a drug or preparation is still subject to investigation. One of the proposed theories is alteration of the chemicals within or supporting the microorganism to form deleterious new chemicals capable of destroying the cell. Another theory proposes that vital structures of the cell, such as the chromosomal nucleoprotein, are disoriented or destroyed. It is probably a combination of irradiation effects that causes the cellular destruction, which is complete and irreversible.

Validation/Verification of Sterility

Regardless of the method, pharmaceutical preparations required to be sterile must undergo tests to confirm the absence of

microorganisms. The USP contains monographs and standards for biologic indicators of sterilization. A *biologic indicator* is a characterized preparation of specific microorganisms resistant to a particular sterilization process. They may be used to monitor a sterilization cycle and/or periodically to revalidate the process. Biologic indicators are generally of two main forms. In one, spores are added to a carrier, such as a strip of filter paper, packaged to maintain physical integrity while allowing the sterilization effect. In the other, the spores are added to representative units of the product being sterilized, with assessment of sterilization based on these samples. In steam and ethylene oxide sterilization, spores of suitable strains of *Bacillus stearothermophilus* are commonly employed because of their resistance to these modes of sterilization. In dry heat, spores of *Bacillus subtilis* are commonly used. With ionizing radiation, spores of suitable strains of *Bacillus*, including *B. pumilus, B. stearothermophilus*, and *B. subtilis*, have been used.

The effectiveness of thermal sterilization has been quantified through the determination and calculation of *F value* to express the time of thermal death. *Thermal death time* is defined as the time required to kill a particular organism under specified conditions. The F_0 at a particular temperature other than 121°C is the time in minutes required to provide lethality equivalent to that provided at 121°C for a stated time.

Although heat distribution in an autoclave chamber is usually rapid, with 121°C obtained nearly instantaneously throughout the autoclave, the product being sterilized may not achieve identical conditions because of a variety of factors of heat transfer, including the thermal conductivity of the packaging components, the viscosity and density of the product, container proximity, passage of steam around containers, and other variables. F values may be computed from biologic data derived from the rate of destruction of known numbers of microorganisms, as shown in the following equation:

$$F_0 = D_{121}\left(\log A - \log B\right)$$

where

D_{121} is the time required for a one-log reduction in the microbial population exposed to a temperature of 121°C,

A is the initial microbial population, and B is the number of microorganisms that survive after a defined heating time (11).

In compounding, verification is used that involves authoritatively signed assurance and documentation that a process, procedure, or piece of equipment is functioning properly and producing the expected results. Verification may require outside laboratory testing when in-house capabilities are not adequate.

Pyrogen and Endotoxin Testing

Endotoxins are a subset of pyrogens that come from gram-negative bacteria. The terms endotoxin and lipopolysaccharide are often used interchangeably. However, to be more precise, endotoxins are the natural complex of lipopolysaccharides that occur in the outer layer of bilayered gram-negative bacterial cells, whereas lipopolysaccharides are the purified form used as a standard for quality control and research purposes.

Inadvertent administration of endotoxins to humans may result in a number of events, ranging from fever, through a cascade of pathogenic responses, to death. Responses can include irreversible and fatal septic shock, hypotension, lymphopenia, neutrophilia, and elevated levels of cortisol and C-reactive protein.

Endotoxins are potent, toxic, and very stable and are present in many pharmaceutical ingredients and on surfaces that come into contact with preparations formulated for parenteral administration. They are water soluble, will pass through 0.2-μm filters, are not destroyed by autoclaving, and are insoluble in organic solvents. Endotoxins are very difficult to eliminate in a final preparation. Therefore, procedures are directed at eliminating endotoxins during the preparation process.

The body can tolerate a certain load of endotoxins (measured as endotoxin units, or EU) without adverse results. The generally accepted EL is defined as

$$EL = K / M$$

where K is the threshold human pyrogenic dose of endotoxin per kilogram of body weight per hour, which is 5.0 EU/kg for parenteral drugs (except those administered intrathecally) and 0.2 EU/kg for the intrathecal route of administration, and where M is maximum recommended human dose per kilogram of body weight that would be administered in a single 1-hour period.

The EL, then, is equal to the threshold pyrogenic response (K in EU/kg) divided by the dose in the units by which it is administered (milliliters, units, or milligrams) per 70-kg person per hour. The delivery method (multiple or bolus doses) and other factors must also be considered.

To use the EL = K/M formula, it is necessary to know the maximum endotoxin levels established for the drugs being prepared. The table[1] included in this appendix, derived from the *United States Pharmacopeia 30–National Formulary 25* (*USP–NF*),[2] provides a handy reference. The most recent edition of that compendium should be consulted to determine if the information has been updated.

See Physical Pharmacy Capsule 15.2 for example calculations.

PHYSICAL PHARMACY CAPSULE **15.2**

Endotoxin Calculations

Allowable Endotoxin Levels in Parenteral Preparations

Pharmacists compounding high-risk sterile preparations from bulk substances must be proficient in calculating the endotoxin load for the compounded preparations. The endotoxin load in compounded sterile preparations (CSPs) can be calculated as follows:

1. Multiply the weight of the patient (in kilograms) times the allowable endotoxin units (EU) per kilogram (kg) [EU/kg] to obtain the endotoxin limit per hour for nonintrathecal or for intrathecal medication delivery.

   EU/kg × patient weight (kg) = EL per hour (nonintrathecal)
   or
   0.2 EU/kg × patient weight (kg) = EL per hour (intrathecal)

2. Obtain the required information for the calculations from *USP–NF* or a current EL table.
3. Determine the final volume of the preparation.
4. Input the information on the EL worksheet.
5. Determine the final endotoxin load.
6. Consider the route of administration, and determine if the calculated value exceeds the value in Step 1.
7. If the calculated value does not exceed the value in Step 1, the compound may be prepared.
8. If the calculated value exceeds the value in Step 1, check with the prescriber.
   The amount of endotoxin present in the sample must be less than the endotoxin release limit calculated for the given end preparation. If the endotoxin level is excessive and the parenteral has been dispensed, the patient's doctor should be notified, and the patient should be monitored for characteristic host reactions to pyrogens.

RESOURCES

1. Allen LV Jr. Quality-control analytical methods: allowable endotoxin levels in sterile preparations. Int J Pharm Compound 2004;8(6):466–467.

PHYSICAL PHARMACY CAPSULE 15.2 CONT.

2. Allen LV Jr. Quality-control analytical methods: allowable endotoxin levels in sterile preparations. Int J Pharm Compound 2004;8(6):479–485.
3. Stockton S. Endotoxin calculations. IJPC 2004;8(6):468.

EXAMPLE

1. A 158-lb patient is to receive an intrathecal infusion of morphine sulfate at a rate of 0.3 mg/h. The solution will be prepared by diluting Infumorph 200 with 0.9% sodium chloride injection to produce an infusion rate of 2 mL/h.
   A. Infumorph 200 is preservative-free morphine sulfate 10 mg/mL in 20-mL ampuls. How much Infumorph 200 and 0.9% sodium chloride injection should be used to prepare a 24-hour infusion?

      • 0.3 mg/h × 24 hours = 7.2 mg morphine sulfate
      • 7.2 mg × 1 mL/10 mg = 0.72 mL Infumorph 200
      • 2 mL/h × 24 h = 48 mL total volume
      • 48 mL – 0.72 mL = 47.28 mL 0.9% sodium chloride injection

   B. What is the endotoxin load for this preparation?

      The USP specifies a limit of 14.29 USP EU/mg of morphine sulfate in solutions for intrathecal use and a limit of 0.5 EU/mL for solutions containing 0.5 to 0.9% sodium chloride:

      • 7.2 mg × 14.29 EU/mg = 102.89 EU from morphine sulfate
      • 47.28 mL × 0.5 EU/mL = 23.64 EU from 0.9% sodium chloride injection
      • Endotoxin load = 102.89 EU + 23.64 EU = 126.53 EU
      • 126.53 EU/24 h = 5.27 EU/h

   C. Does this limit exceed the allowable EL for an intrathecal injection for this patient?

      The maximum amount of endotoxin in a solution for intrathecal administration is 0.2 EU/kg/h.
      Allowable limit: 0.2 EU/kg/h × 1 kg/2.2 lb × 158 lb = 14.36 EU/h
      The endotoxin load in the preparation does not exceed the allowable limit.

2. Epinephrine is administered subcutaneously or intramuscularly as a 1:1,000 solution and is supplied in 1-mL ampuls.
   A. What is the potential endotoxin load in a 1-mL ampul of epinephrine 1:1,000 solution?

      • The USP specifies a limit of 357 USP EU/mL of epinephrine in solutions for injection.
      • mL × 1 g/1,000 mL × 1,000 mg/g × 357 EU/mg = 357 EU

   B. What is the minimum weight (in pounds) of a patient that could receive this dose without exceeding the threshold pyrogenic dose of 5 EU/kg/h, assuming that the patient receives no more than one dose per hour?

      • 357 EU × 1 kg/5 EU × 2.2 lb/kg = 157.08 lb

3. The following is an order for a parenteral nutrition solution to be administered to a patient weighing 184 lb at a rate of 70 mL/h:

   Component Source
   • Amino acids 4% 500 mL of 8.5% amino acids injection
   • Dextrose 25% 500 mL of 70% dextrose injection
   • Sodium acetate 20 mEq 50-mL vial of 32.8% solution
   • Potassium chloride 15 mEq 25-mL vial of 14.9% solution
   • Magnesium sulfate 10 mEq 10-mL vial of 12.5% magnesium sulfate heptahydrate solution
   • Calcium gluconate 5 mEq 50-mL vial of 10% solution

PHYSICAL PHARMACY CAPSULE 15.2 CONT.

- Potassium phosphate 15 mmol 10-mL vial of 3 mmol/mL solution
- Sterile water for injection 1,000 mL of sterile water for injection to make 1,000 mL

A. What is the endotoxin load for this solution?

- The ELs specified by the USP for each of the solutions are as follows:
- Amino acids: Endotoxin information is unavailable.
- Dextrose: 10 EU/g of dextrose in solutions containing 5% to 70% dextrose
- Sodium acetate: 3.9 EU/mEq of sodium acetate
- Potassium chloride: 8.8 EU/mEq of potassium chloride
- Magnesium sulfate: 0.09 EU/mg of magnesium sulfate
- Calcium gluconate: 0.17 EU/mg of calcium gluconate
- Potassium phosphate: 1.1 EU/mg of potassium phosphates
- Sterile water for injection: 0.25 EU/mL of sterile water
- Dextrose: 25 g/100 mL × 1,000 mL = 250 g × 10 EU/g = 2,500 EU
- Sodium acetate: 20 mEq × 3.9 EU/mEq = 78 EU
- Potassium chloride: 15 mEq × 8.8 EU/mEq = 132 EU
- Magnesium sulfate ($MgSO_4 \cdot 7H_2O$, MW = 246):
- 10 mEq × 246 mg/2 mEq = 1,230 mg × 0.09 EU/mg = 110.7 EU
- Calcium gluconate [$Ca(C_6H_{11}O_7)2$, MW = 430]:
- 5 mEq × 430 mg/2 mEq = 1,075 mg × 0.17 EU/mg = 182.75 EU
- Potassium phosphate: 15 mmol × 1 mL/3 mmol = 5 mL
- Potassium phosphates injection contains 236 mg potassium phosphate, dibasic, and 224 mg potassium phosphate, monobasic per milliliter.
- 5 mL × 236 mg K_2HPO_4/mL = 1,180 mg
- 5 mL × 224 mg KH_2PO_4/mL = 1,120 mg
- Total = 2,300 mg × 1.1 EU/mg = 2,530 EU
- In order to determine the amount of water to add, the volumes of each additive must be calculated:
- Amino acids: 4 g/100 mL × 1,000 mL = 40 g × 100 mL/8.5 g = 470.59 mL
- Dextrose: 25 g/100 mL × 1,000 mL = 250 g × 100 mL/70 g = 357.14 mL
- Sodium acetate ($NaC_2H_3O_2$, MW = 82):
- 20 mEq × 82 mg/mEq × 1 g/1,000 mg × 100 mL/32.8 g = 5 mL
- Potassium chloride (KCl, MW = 74.5):
- 15 mEq × 74.5 mg/mEq × 1 g/1,000 mg × 100 mL/14.9 g = 7.5 mL
- Magnesium sulfate: 1,230 mg × 1 g/1,000 mg × 100 mL/12.5 g = 9.84 mL
- Calcium gluconate: 1,075 mg × 1 g/1,000 mg × 100 mL/10 g = 10.75 mL
- Potassium phosphate: 5 mL
- Total volume = 865.82 mL
- Amount of water to add:
- 1,000 mL – 865.82 mL = 134.18 mL × 0.25 EU/mL = 33.54 EU
- Total endotoxin load = 5,566.99 EU (without amino acids)

B. What is the maximum amount of endotoxin that this patient may receive per hour from the parenteral nutrition solution, and does this amount exceed the limit of 5 EU/kg/h?

5,566.99 EU/1,000 mL × 70 mL/h = 389.69 EU/h from parenteral nutrition solution
5 EU/kg/h × 184 lb × 1 kg/2.2 lb = 418.18 EU/h limit for patient

The nutrition solution does not exceed the EL for this particular patient; however, since the amino acid information is not available, there is potential for the solution to exceed the limit.

USP injection monographs state a bacterial EU limit, USP EU. Thus, injections are not pyrogen- or endotoxin-free but are limited. The following are examples from the USP 35-NF 30 (12):

> Dextrose Injection: Contains not more than 0.5 USP EU/mL for injections containing less than 5% dextrose and not more than 10.0 USP EU/mL for injections containing between 5% and 70% dextrose.
> Digoxin Injection: Contains not more than 200.0 USP EU/mg of digoxin.
> Gentamicin Injection: Contains not more than 0.71 USP EU/mg of gentamicin.

Pyrogen Test. Manufacturers of water for injection may employ any suitable method for removal of pyrogens from their product. Because pyrogens are organic, one of the more common means of removing them is by oxidizing them to easily eliminated gases or to nonvolatile solids, both of which are easily separated from water by fractional distillation. Potassium permanganate is usually employed as the oxidizing agent, with its efficiency increased by addition of a small amount of barium hydroxide to impart alkalinity to the solution and to make nonvolatile barium salts of any acidic compounds that may be present. These two reagents are added to water that has been distilled several times, and distillation is repeated, the chemical-free distillate being collected under strict aseptic conditions. When properly conducted, this method results in highly pure, sterile, and pyrogen-free water. However, in each instance, the official pyrogen test must be performed to ensure the absence of these fever-producing materials.

The USP pyrogen test uses healthy rabbits that have been properly maintained in terms of environment and diet before the test. Normal, or control, temperatures are taken for each animal to be used in the test. These temperatures are used as the base for the determination of any temperature increase resulting from injection of a test solution. A given test uses rabbits whose temperatures do not differ by more than 1°C from each other and whose body temperatures are considered not to be elevated. A synopsis of the procedure of the test is as follows.

Render the syringes, needles, and glassware free from pyrogens by heating at 250°C for not less than 30 minutes or by other suitable method. Warm the product to be tested to 37°C ± 2°C.

Inject into an ear vein of each of three rabbits 10 mL of the product per kilogram of body weight, completing each injection within 10 minutes of the start of administration. Record the temperature at 30-minute intervals 1 to 3 hours subsequent to the injection.

If no rabbit shows an individual rise in temperature of 0.5°C or more, the product meets the requirements for the absence of pyrogens. If any rabbit shows an individual temperature rise of 0.5°C or more, continue the test using five other rabbits. If not more than three of the eight rabbits show individual rises in temperature of 0.5°C or more and if the sum of the eight individual maximum temperature rises does not exceed 3.3°C, the material under examination meets the requirements for the absence of pyrogens.

Endotoxin Test. An extract from the blood cells of the horseshoe crab (*Limulus polyphemus*) contains an enzyme and protein system that coagulates in the presence of low levels of lipopolysaccharides. This discovery led to the development of the *Limulus* amebocyte lysate (LAL) test for the presence of bacterial endotoxins. The Bacterial Endotoxins Test, USP, uses LAL and is considered generally more sensitive to endotoxin than the rabbit test. The FDA has endorsed it as a replacement for the rabbit test, and it is used for a number of parenteral products. The USP–NF has specific allowable endotoxin levels for various injections based on the dosage of the individual drugs to keep below a threshold level of administered endotoxins.

Some parenteral products, however, cannot be tested with LAL because the active ingredient interferes with the outcome. Such products include meperidine HCl and promethazine HCl, oxacillin sodium, sulfisoxazole, and vancomycin HCl, among others. These must be tested with the aforementioned Pyrogen Test, USP.

Because the LAL test is so sensitive for the presence of bacterial endotoxins, when the active ingredient of the small-volume parenteral can interfere with the test, a strategy to

overcome this interference is to dilute the product more than twofold. Diphenhydramine HCl, ephedrine HCl, meperidine HCl, promethazine HCl, and thiamine HCl, among others, are tested in this manner.

The Industrial Preparation of Parenteral Products

Once the formulation for a particular parenteral product is determined, including selection of the proper solvents or vehicles and additives, the production pharmacist must follow rigid aseptic procedures in preparing the products. In most manufacturing plants, the area in which parenteral products are made is maintained bacteria-free by use of ultraviolet lights; a filtered air supply; sterile manufacturing equipment, such as flasks, connecting tubes, and filters; and sterilized work clothing (Fig. 15.7).

In the preparation of parenteral solutions, the required ingredients are dissolved according to good pharmaceutical practice in water for injection, in another solvent, or in a combination of solvents. The solutions are usually filtered through a membrane until sparkling clear. After filtration, the solution is transferred as rapidly as possible and with the least possible exposure into the final containers. The product is then sterilized, preferably by autoclaving, and samples of the finished product are tested for sterility and pyrogens. If sterilization by autoclaving is impractical because of the nature of the ingredients, the individual components of the preparation that are heat or moisture labile may be sterilized by other appropriate means and added aseptically to the sterilized solvent or solution of components that can be autoclaved.

FIGURE 15.7 Sterile filling of vials. (Courtesy of Wyeth Laboratories.)

Suspensions of drugs for parenteral use may be prepared by reducing the drug to a very fine powder with a ball mill, micronizer, colloid mill, or other appropriate equipment and then suspending the material in a liquid in which it is insoluble. It is frequently necessary to sterilize separately the individual components of a suspension before combining them, as frequently the integrity of a suspension is destroyed by autoclaving. Autoclaving of a parenteral suspension may alter the viscosity of the product, affecting the suspending ability of the vehicle, or change the particle size of the suspended particles, altering both pharmaceutical and therapeutic characteristics. If a suspension remains unaltered by autoclaving, this method is generally employed to sterilize the final product. Because parenteral emulsions, which are dispersions or suspensions of a liquid throughout another liquid, are generally destroyed by autoclaving, an alternative method of sterilization must be employed for this type of injectable.

Some injections are packaged as dry solids rather than in conjunction with a solvent or vehicle because the therapeutic agent is unstable in the presence of the liquid component. These dry powders are packaged in the final container to be reconstituted, generally to a solution or less frequently a suspension. The method of sterilization of the powder may be dry heat or another appropriate method. These are examples of sterile drugs prepared and packaged *without* pharmaceutical additives such as buffers, preservatives, stabilizers, and tonicity agents:

Ampicillin sodium
Ceftizoxime sodium
Ceftazidime sodium
Cefuroxime sodium
Kanamycin sulfate
Nafcillin sodium
Penicillin G benzathine
Streptomycin sulfate
Tobramycin sulfate

Antibiotics are prepared industrially in large fermentation tanks.

Sterile drugs formulated *with* pharmaceutical additives and intended to be reconstituted prior to injection include the following:

Cyclophosphamide
Dactinomycin
Erythromycin lactobionate
Hydrocortisone sodium succinate
Mitomycin
Nafcillin sodium
Penicillin G potassium
Vinblastine sulfate

Sometimes, a liquid is packaged along with the dry powder for use at the time of reconstitution (Fig. 15.8). This liquid is sterile and may contain some of the desired pharmaceutical additives, such as the buffering agents. More frequently, the solvent or vehicle is not provided, but the label generally lists suitable solvents. Sodium chloride injection and sterile water for injection are perhaps most frequently employed to reconstitute dry-packaged injections. The dry powders are packaged in containers large enough to permit proper shaking with the liquid component when the latter is aseptically injected through the container's rubber closure during reconstitution. To facilitate dissolution, the dry powder is prevented from caking upon standing by the appropriate means, including lyophilization (Fig. 15.9). Powders so treated form a honeycomb lattice structure that is rapidly penetrated by the liquid, and solution is rapid because of the large surface area of powder exposed.

Pfizer manufactures the Mix-O-Vial, which incorporates the cover as part of the plunger. Once mixed, the small circle of plastic that covers the injection site is removed. This reduces the touch contamination potential.

The Hospira ADD-Vantage system is another example of a ready-to-mix sterile IV product designed for intermittent administration of potent drugs that do not have long-term stability in solution. With this system, antibiotics and other drugs do not have to be mixed until just prior to administration. ADD-Vantage consists of two components (Fig. 15.10): a flexible plastic IV container partially filled with diluent and a glass vial of powdered or liquid drug. The vials containing the medication and the piggybacks (50 to 250 mL of dextrose 5% in water injection, 0.45% sodium chloride solution, or 0.9% sodium chloride injection) are specially designed to be used together. The vial locks into a chamber inside the plastic container, and the drug is released by removing the stopper

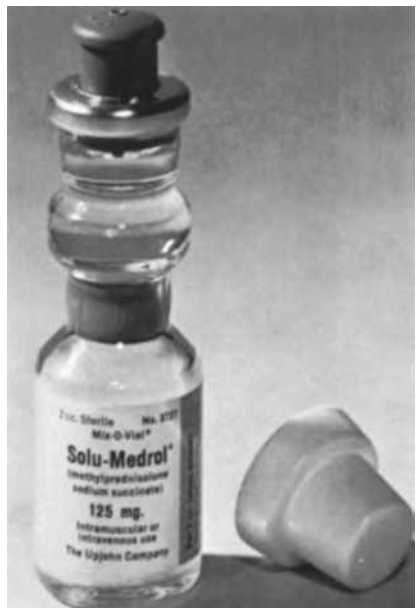

FIGURE 15.8 The Mix-O-Vial contains dry ingredients in the bottom compartment and a liquid diluent in the top, separated by a specially formulated center seal. The bottom compartment can be filled either with a liquid that is frozen and dried to make a lyophilized product or with a powder. The diluent in the top contains a preservative and sometimes one or more active ingredients. To use the vial, the dust cover is removed; pressure is applied with the thumb to the top plunger, which dislodges the center seal; and the vial is shaken well. The top of the plunger is then swabbed with a disinfectant; the syringe needle inserted through the target circle on the plunger; and the contents of the vial withdrawn into the syringe. The Mix-O-Vial offers stability of the product until it is activated, convenience, fast operation, and safety as regards the right drug with the proper diluent in the correct proportions. (Courtesy originally provided by Upjohn/Pharmacia [Now Pfizer Company].)

FIGURE 15.9 Antibiotic lyophilizers. (Courtesy of Hospira, Inc.)

FIGURE 15.10 ADD-vantage system. (Courtesy of Hospira, Inc.)

on the vial, allowing the two components to mix. This simple process is performed by external manipulation of the container, preserving the closed, sterile system.

The ADD-Vantage unit may be assembled in a number of locations. Microbiologic tests and sterility tests have been conducted at various intervals following assembly of the units under a laminar flow hood, in a pharmacy on a countertop, and in a patient's hospital room. The final admixtures were sterile, demonstrating that the ADD-Vantage unit can be aseptically assembled under the conditions tested. The assembled but not activated ADD-Vantage system can be used within 30 days of removal. Vantage system can be used within 30 days of removal of the diluent container from the outer wrapping. ADD-Vantage enables hospitals to reduce drug waste, often caused by canceled or changed prescriptions, and helps the pharmacy conserve labor and reduce material costs.

The Monovial Safety Guard (Becton Dickinson Pharmaceutical Systems) is an IV infusion system for use in preparing extemporaneous small-volume infusions using plastic minibags (Fig. 15.11). When compared to the two traditional methods of preparing small-volume infusions, that is, the transfer

FIGURE 15.11 Monovial safety guard system. (Courtesy of Becton Dickinson.)

FIGURE 15.12 Testing compatibility of rubber closures with a solution. (Courtesy of Abbott Laboratories.)

needle and vial (TFN) and syringe and vial (SYR) methods, the Monovial system performed quite favorably, saving time, using fewer materials, and costing less (13).

This system is an integrated drug transfer mechanism with a protective shield surrounding the attached transfer needle. Reconstitution and transfer of the drug into an infusion bag are accomplished safely, quickly, and with few materials. The needle is inserted into the port of the infusion bag, and the transfer set is pushed down toward the vial until it clicks. With the Monovial upright, the infusion bag is squeezed several times to transfer the fluid into the Monovial. The Monovial is shaken a few times to reconstitute the drug and inverted. Then the minibag is squeezed and released to transfer the drug back into the infusion bag. This process is repeated until the vial is empty.

Several manufacturers ship to the hospital pharmacy reconstituted IV antibiotic solutions, for example, cefazolin sodium, in the frozen state. When thawed, these nonpyrogenic solutions are stable for a finite period. Reconstituted cefazolin is stable for 48 hours at room temperature and for 10 days when refrigerated (5°C or 41°F). The product is packaged in a small plastic bag for piggyback use in IV administration.

Packaging, Labeling, and Storage of Injections

Containers for injections, including the closures, must not interact physically or chemically with the preparation so as to alter its strength or efficacy (Fig. 15.12). If the container is made of glass, it must be clear and colorless or light amber to permit inspection of its contents. The type of glass suitable for each parenteral preparation is usually stated in the individual monograph. Injections are placed either in single-dose containers or in multiple-dose containers (Figs. 15.13 to 15.15). By definition:

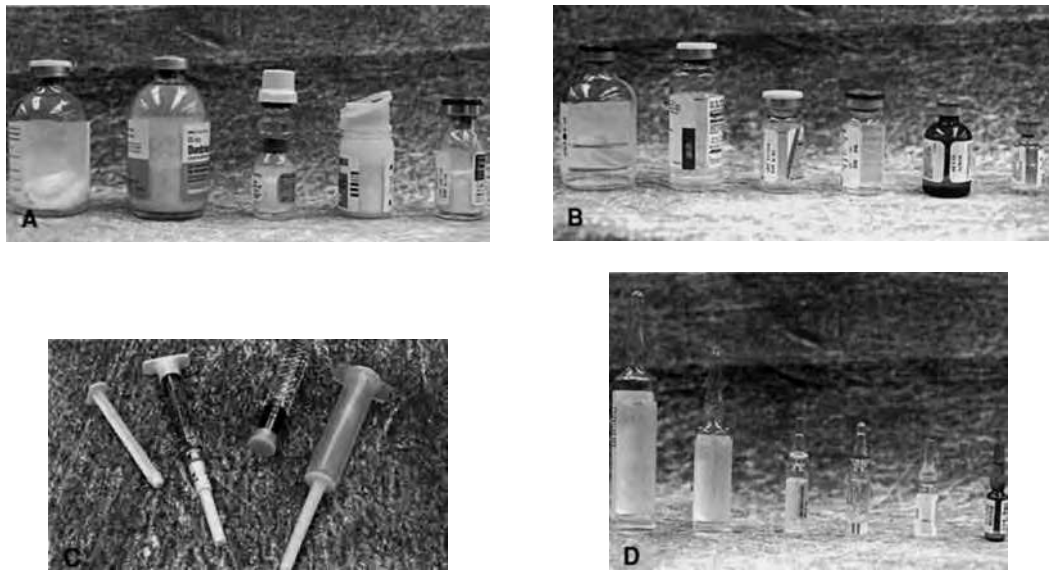

FIGURE 15.13 Packaging of injectable products. **A:** Multiple-dose vials of suspensions and dry powders. **B:** Vials for solutions, including one with light-protective glass. **C:** Unit dose, disposable syringes. **D:** Various sizes of ampuls. (Courtesy of William B. French, PhD.)

FIGURE 15.14 A typical vial for sterile injectable products, made from type I (borosilicate) glass. The rubber closure has been specially selected for compatibility with the product, desirable physical characteristics, and so on. The overseal holds the closure in place and provides ready access to the contents of the vial. (Courtesy of Hospira, Inc.)

Single-dose container: A hermetic container holding a quantity of sterile drug intended for parenteral administration as a single dose; when opened, it cannot be resealed with assurance that sterility has been maintained.
Multiple-dose container: A hermetic container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion

Single-dose containers may be ampuls or single-dose vials. Ampuls (Fig. 15.16) are

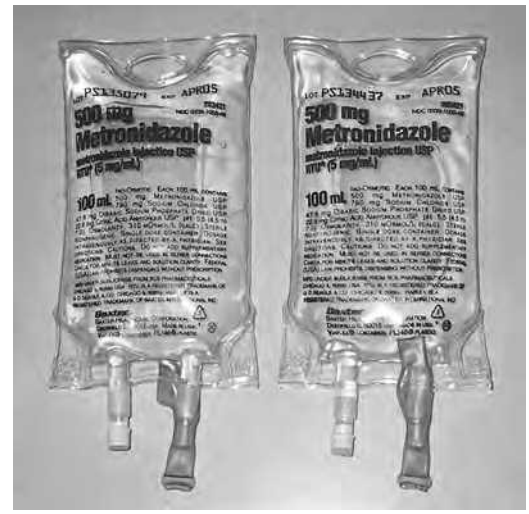

FIGURE 15.15 Two 100-mL single-dose plastic bags for IV infusion. (Courtesy of Mr Akinwale O. Onamade.)

sealed by fusion of the glass container under aseptic conditions (Fig. 15.17). The glass container is made so as to have a neck that may be easily separated from the body of the container without breaking the glass. After opening, the contents of the ampul should be withdrawn into a syringe with a 5-mm filter needle or straw apparatus. The filter needle is replaced with a regular needle. The filter

FIGURE 15.16 Ampul before filling and sealing. (Courtesy of Owens Illinois.)

FIGURE 15.17 Ampul sealing. (Courtesy of Abbott Laboratories.)

needle is used to trap any glass particles that entered the sterile solution when the neck of the ampul was broken. If a filter needle is not available, withdrawal of glass can be minimized by holding the ampul upright, tilted slightly, when inserting the needle, and avoiding the outer surface of the neck of the ampul. The needle should not be lowered to the bottom of the ampul but held slightly above to avoid drawing glass into the syringe.

Once opened, the ampul cannot be resealed, and no unused portion may be retained and used later, as the contents would have lost sterility. Some injectable products are packaged in prefilled syringes, with or without special administration devices (Figs. 15.18 to 15.20). The types of glass for parenteral product containers are described in Chapter 5. Types I, II, and III are suitable for parenteral products, with type I being the most resistant to chemical deterioration. The type of glass to be used for a particular injection is indicated in the individual monograph for that preparation.

One of the prime requisites of parenteral solutions is clarity. They should be sparkling clear and free of all particulate matter, that is, no mobile undissolved substances should be present. Such contaminants include dust, cloth fibers, glass fragments, material leached from the glass or plastic container or seal, and any other material that may find its way into the product during manufacture or administration or that develop during storage.

To keep unwanted particles out of parenteral products, a number of precautions must be taken during manufacture, storage, and use of the products. During manufacture, the parenteral solution is usually filtered just before it goes into the container. The containers are carefully selected to be

FIGURE 15.18 Disposable sterile cartridges compatible with the Carpuject holder. (Courtesy of Hospira, Inc.).

FIGURE 15.19 Carpuject, a prefilled unit dose injection system that includes a reusable, clear, plastic full-length holder. (Courtesy Abbott Hospital products division.)

chemically resistant to the solution and of the highest available quality to minimize the chances of container components leaching into the solution. It has been recognized for some time that some particulate matter in parenteral products is leached material from the glass or plastic container. Once the container is selected, it must be carefully cleaned to be free of all extraneous matter (Fig. 15.21). During container filling, extreme care must be exercised to prevent the entrance of airborne dust, lint, or other contaminants. Filtered and directed airflow in production areas reduces the likelihood of contamination. Laminar flow hoods allow for draft-free flow of clean, filtered air over the work area. These hoods are commonly found in hospitals for both manufacture and incorporation of additives into parenteral and ophthalmic products (Fig. 15.22). The personnel who manufacture parenterals must be made acutely aware of the importance of cleanliness and aseptic techniques. They are provided with uniforms of monofilament fabrics that do not shed lint. They wear face hoods, caps, gloves, and disposable shoe covers to prevent contamination (Fig. 15.23).

After the containers are filled and hermetically sealed, they are visually (Fig. 15.24) or automatically (Fig. 15.25) inspected for particulate matter. Usually, an inspector passes the filled container past a light source with a black background to observe for mobile particles. Particles of approximately 50 µm may be detected in this manner. Reflective particles, such as fragments of glass, may be visualized in smaller size, about 25 µm. Methods to detect smaller particulate matter include microscopic examination and use of sophisticated equipment such as the Coulter

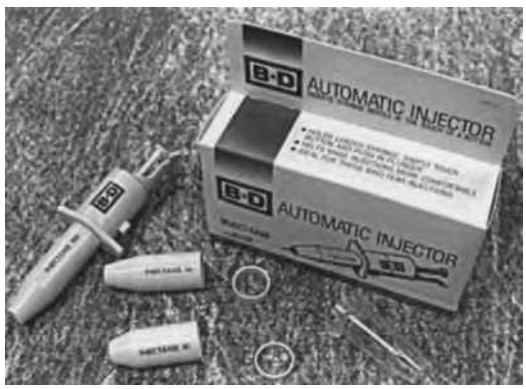

FIGURE 15.20 Inject-Ease automatically inserts the needle of an insulin syringe into the skin when activated. (Courtesy of William B. French, PhD.)

FIGURE 15.21 Filling and sealing of ampuls/vials (nonfreeze-dried preparations). (Reproduced with permission of Schering Corporation. All rights reserved.)

FIGURE 15.22 Hyperalimentation being prepared in a horizontal laminar flow hood. (Courtesy of Ms Amy Schuppert Smith.)

Counter, which electronically counts particles in samples. Having passed the inspection, the product may be labeled. However, the pharmacist should inspect each parenteral solution for evidence of particulate matter.

Although the total significance of injecting or infusing parenteral solutions containing particulate matter into a patient has not been ascertained, it is apparent that particulate matter has the potential to induce thrombi and vessel blockage, and depending on the chemical composition of the particles, it has the additional potential to introduce into the patient agents that are undesired and possibly toxic.

In formulating a single-dose parenteral product, the pharmacist must consider not only the physicochemical aspects of the drug but also the intended therapeutic use of the

FIGURE 15.23 Pharmacist preparing a parenteral admixture in a laminar flow hood. (Courtesy of Ms Amy Schuppert Smith.)

FIGURE 15.24 Semiautomatic inspection machine for parenteral products. (Reproduced with permission of Schering Corporation. All Rights reserved.)

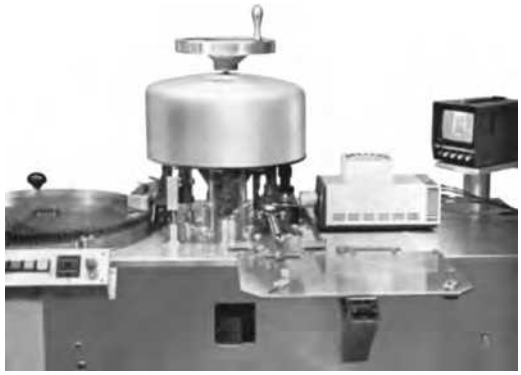

FIGURE 15.25 The Autoskan industrial automatic inspection machine, which detects particulate matter in injectables with a television camera and electronics and automatically rejects them from the production line. (Courtesy of Lakso Company.)

product. Some single-dose preparations are to be administered rapidly in small volumes, but others infuse slowly into the circulatory system over hours. Most small-volume parenterals are formulated so that a convenient amount of solution, say 0.5 to 2 mL, contains the usual dose of the drug, although larger volumes of more diluted solutions are frequently administered intravenously and intramuscularly. Generally, several strengths of injections of a given drug are marketed to permit a wider dosage selection by the physician without waste, as would be the case if only part of a given single-dose parenteral solution was administered. The large-volume single-dose preparations generally are those used to expand the blood volume or to replenish nutrients or electrolytes and are given by slow IV infusion. However, in no instance may a single-dose parenteral container permit withdrawal and administration of more than 1,000 mL. In addition, preparations intended for intraspinal, intracisternal, or peridural administration must be packaged only in single-dose containers as a precaution against contamination.

In the hospital, physicians commonly order an additional agent to be placed in a large-volume parenteral solution for infusion. The person filling such an order must be certain that aseptic conditions are employed and that the additive is compatible with the original solution (14). Care must also be exercised not to introduce particulate matter into the solution. Many pharmaceutical companies have developed special devices for aseptic transfer of pharmaceutical additives to large-volume parenterals. An ordinary sterile needle and syringe may be effectively employed to transfer solutions from one parenteral product to another by a pharmacist. However, a filtering device is employed when a transfer occurs from an ampul to a container (Fig. 15.26). Many hospital pharmacies have established well-controlled IV *additive* or *admixture* programs to ensure compatibility, safety, and efficacy of the additive and solution (14,15).

Multiple-dose containers are affixed with rubber closures to permit penetration of a hypodermic needle without removal or destruction of the closure. Upon withdrawing the needle from the container, the closure reseals and protects the contents from airborne contamination. The needle may be inserted to withdraw a portion of the prepared liquid injection, or it may be used to introduce a solvent or vehicle to a dry powder for injection. In either instance, the sterility of the injection may be maintained so long as the needle itself is sterile at the time of entry into the container. Unless otherwise indicated in the monograph, multiple-dose injectables are required to contain antibacterial preservatives. Also, unless otherwise specified, multiple-dose containers are not permitted to

FIGURE 15.26 Use of a filter syringe for aseptic addition of an ingredient to a large-volume parenteral solution. (Courtesy of Ms Amy Schuppert Smith.)

allow withdrawal of more than 30 mL to limit the number of penetrations into the closure and thus protect against loss of sterility. The limited volume also guards against an excessive amount of antibacterial preservative being inadvertently administered with the drug when unusually large doses of an injection are required, in which case a preservative-free single-dose preparation is advisable. The usual multiple-dose container contains about 10 usual doses of the injection, but the quantity may vary greatly with the individual preparation and manufacturer.

It is possible that rubber closures may contain latex, a problem for patients with latex allergies. Currently, nonlatex closures are being developed, and manufacturers will provide a list of their latex-free products.

Because it is impossible in practice to transfer the entire volume of a single-dose container or the last dose in a multiple-dose container into a hypodermic syringe, a slight excess in volume of the contents of ampuls and vials over the labeled size or volume of the package is permitted. Table 15.2 presents the recommended overages permitted by the USP to allow withdrawal and administration of the labeled volumes.

For labeling purposes, revised injectable product nomenclature became official in the USP 23 on January 1, 1995, and continues. The main points of the revised process are as follows:

I. The term *sterile* was eliminated from the titles of injectable products except appropriate monograph titles for water intended for parenteral use, such as Sterile Water for Injection, USP.
II. For established names of injectable products, all of which are suitable and intended for parenteral administration, USP, established the following criteria in determining the product's title:
   A. Liquids
      1. *Injection*: Title for liquid preparations that are drug substances or solutions thereof
      2. *Injectable suspension*: Title for liquid preparations of solids suspended in a suitable liquid medium
      3. *Injectable emulsion*: Title for liquid preparations of drug substances dissolved or dispersed in a suitable emulsion medium
   B. Solids
      1. *For injection*: Title for dry solids that, upon the addition of suitable vehicles, yield solutions conforming in all respects to the requirements for *injections*
      2. *For injectable suspension*: Title for dry solids that, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for *injectable suspensions*

Originally, to facilitate this transition to a new nomenclature, the Center for Drug Evaluation and Research encouraged parenteral drug manufacturers to place a flag, or reminder statement, on the labels of the product for 6 months, alerting practitioners to the changes. The intent was to help practitioners become familiar with the revised rules. An example of a flag is the following: FORMERLY STERILE [DRUG NAME].

In addition, the labels on containers of parenteral products must state the following:

- The name of the preparation
- For a liquid preparation, the percentage content of drug or the amount of drug in a specified volume

Table 15.2 RECOMMENDED OVERAGES FOR OFFICIAL PARENTERAL PRODUCTS IN MILLILITERS

LABELED SIZE	EXCESS VOLUME FOR MOBILE LIQUIDS	EXCESS VOLUME FOR VISCOUS LIQUIDS
0.5	0.10	0.12
1.0	0.10	0.15
2.0	0.15	0.25
5.0	0.30	0.50
10.0	0.50	0.70
20.0	0.60	0.90
30.0	0.80	1.20
50.0 or more	2.00%	3.00%

- For a dry preparation, the amount of active ingredient present and the volume of liquid to be added to prepare a solution or suspension
- The route of administration
- A statement of storage conditions and an expiration date
- The name of the manufacturer and distributor
- An identifying lot number capable of yielding the complete manufacturing history of the specific package, including all manufacturing, filling, sterilizing, and labeling operations

Injections for veterinary use are labeled so. Preparations intended to be used as dialysis, hemofiltration, or irrigation solutions should meet the requirements for injections except those relating to volume in the containers and should bear a statement indicating that the solution is not intended for use by IV infusion. Appropriately labeled containers allow a sufficient area of the container to remain free of label for its full length or circumference to permit inspection of the contents. Any injection that visual inspection reveals to contain particulate matter other than normally suspended material should be discarded.

Each individual monograph for the official injection states the type of container (single dose and/or multiple dose) permitted for the injection, the type of glass preferred for the container, exemptions if any to usual package size limitations, and any special storage instructions. Most injections prepared from chemically pure medicinal agents are stable at room temperature and may be stored without special concern or conditions. However, most biologic products—insulin injection and the various vaccines, toxoids, toxins, and related products—should be stored under refrigeration. Consult the individual monograph to find the proper storage temperature for a particular injection.

Environmental Issues

Major manufacturers, including Hospira, Inc., Baxter Healthcare, B. Braun, are shipping containers free from PVC and di-2-ethylhexylphthalate (DEHP). Some health care facilities are planning to phase out the use of PVC/DEHP products in future years. A concern, especially for male neonate patients, is that PVC bags can leach DEHP into the fluid of the container.

Another concern is the amount of plastic waste generated by PVC/DEHP containers. Hospitals for a Healthy Environment reported that hospitals produce approximately 6,600 tons of waste per day. Fifteen percent of the solid waste contains plastic. In response to the need for less plastic waste, Hospira, Inc., has launched its VISIV line of IV containers that are PVC/DEHP-free (Fig. 15.27). Also,

FIGURE 15.27 VisIV container. (Courtesy of Hospira, Inc.)

these bags do not contain any overwrap, which reduces the amount of plastic needing discarding. Advances in material science allowed incorporation of the attributes of the overwrap into the original container. In addition, the VISIV container has a sterile port. Thus, in emergency situations, the pharmacist or health care provider does not have to sterilize the port prior to administration. In addition, this new system provides thermal stability, moisture barrier properties, and inertness required for IV medication administration while avoiding leaching associated with the presence of PVC. Baxter Healthcare has introduced its Aviva line of PVC/DEHP- and latex-free IV containers for large-volume parenteral administration.

In the past, the problems associated with PVC/DEHP resulted in IV admixtures still needing preparation in glass containers. While glass containers are more expensive to prepare than PVC/DEHP containers, PVC/DEHP containers are more costly to manufacture than the non-PVC/DEHP plastic bags. In a cost-cutting environment, it is conceivable eventually most hospitals will convert to the PVC/DEHP-free containers and not carry two types of large-volume containers.

Quality Assurance for Pharmacy-Prepared Sterile Products USP <797> Expand and Update

On June 1, 2008, the revised USP Chapter <797>, Pharmaceutical Compounding-Sterile Preparations, became official (12). Unlike guidelines published by groups starting with the National Coordinating Committee for Large-Volume Parenterals in the late 1970s and, more recently, the American Society of Health-System Pharmacists (ASHP), USP <797> is enforceable by the state boards of pharmacy. Multiple state boards of pharmacy have incorporated USP <797> into their regulations. USP <797> provides the minimum practice and quality standards for CSPs. The chapter applies at all times to those who compound sterile preparations including pharmacy staff, physicians, and nurses and all locations such as hospitals, clinics, and pharmacies where sterile preparations are compounded, stored, and transported. USP <797> does not relate to the clinical administration of the CSP via its prescribed route of administration. Practitioners who compound sterile preparations must be thoroughly familiar with the chapter.

Three risk levels of CSPs are described: low-risk level, medium-risk level, and high-risk level. Risk levels are based on the potential of contaminating a low-risk-level or medium-risk-level CSP or failure to sterilize a high-risk-level CSP, which can cause harm to the patient, including death. With low-risk-level and medium-risk-level CSPs, sterile ingredients and devices are used, and sterility is maintained. High-risk-level CSPs include nonsterile components; thus, they must be sterilized before being administered. Health care professionals are responsible for determining CSP risk levels; however, any CSP with a nonsterile component is always high-risk level.

Low-risk-level CSPs include injecting sterile electrolyte solution into a large-volume IV fluid container or reconstituting a lyophilized antibiotic and then transferring the solution to a 100-mL fluid container. Compounding parenteral nutrition solutions via automated or manual methods would be considered medium-risk level as would pooling contents from multiple ampuls or vials of sterile products to provide a CSP to be administered once to multiple patients or to one patient multiple times. Sterilizing a solution made from a nonsterile bulk powder such as alum or glutamine qualifies as a high-risk level.

The immediate-use CSPs section is only for situations where there is an emergency or immediate need for the patient to receive an otherwise low-risk-level CSP. This may occur in a respiratory or cardiac arrest, emergency room, operating room, and combat zone or with the preparation of a diagnostic agent. Hazardous drugs such as chemotherapy may not be compounded as immediate use or is batch preparation or compounding based on predicted needs of CSPs. The compounding process cannot exceed 1 hour. Immediate-use CSPs are exempt from low-risk-level requirements only when all criteria noted in the chapter are met. Note that compounding

under immediate-use conditions increases the likelihood of microbial contamination and potential patient harm.

Facilities for compounding CSPs are designed and environmentally controlled to minimize airborne contamination. Primary engineering controls (PECs) such as laminar airflow workbenches, compounding aseptic isolators, compounding aseptic containment isolators (CACI), and biological safety cabinets (BSC) are PECs or sources of ISO Class 5 air quality. After initial certification, PECs should be recertified by a qualified individual at least every 6 months or whenever the device or room is relocated or altered or a major service to the facility is performed.

Exposure to hazardous drugs presents a potential health risk to compounding personnel. USP <797>. Adverse events may range from skin rashes to effects on the reproductive system and possibly cancer (16). Hazardous drugs must be compounded under conditions that protect the health care professional and other workers who may come in contact with the agents, including personnel protective equipment. Preparation shall occur in an ISO Class 5 environment such as a BSC or CACI placed in an ISO Class 7 negative pressure area (net flow of air is into the area) physically separated from other preparation areas. Closed system transfer devices (CSTDs) that prevent venting or exposure of the hazardous drug to the environment shall be used within the ISO Class 5 environment. For institutions that compound a low number of hazardous drugs, a CSTD used within a BSC or CACI in a nonnegative pressure room is acceptable. Training for personnel who compound, stock, or distribute hazardous drugs shall encompass proper storage, handling, and disposal of the drugs. Verification of appropriate hazardous drug compounding techniques shall be done on an annual basis.

Proper hand hygiene and garbing practices, personnel aseptic technique, and the disinfection of compounding surfaces are key components in minimizing the risk to patients. Direct touch is the most likely source of contamination for CSPs prepared by compounding personnel. Sterile gloves must be used, as well as disinfectants such as sterile 70% isopropyl alcohol (IPA). Repeated disinfection of gloves with IPA during the compounding process has been shown to reduce the contamination rate of pharmacy CSPs (17). Recommended frequencies are defined for cleaning and disinfecting the compounding area.

Compounding personnel must be completely trained in the theoretical and practical aspects of aseptic manipulation using audiovisual materials, professional publications, and live demonstrations. They must pass written examinations and media-fill testing before being allowed to prepare CSPs for patients. Annual media-fill testing is required for low-risk-level and medium-risk-level compounding and semiannually for high-risk-level compounding. Gloved fingertip sampling assesses competency in performing hand hygiene and garbing.

USP <797> also includes sections on establishing beyond-use dates, compounding radiopharmaceuticals and allergen extracts, characteristics of a quality assurance program, verification of compounding accuracy and sterility, finished preparation release checks and test, and elements of quality control. The appendices have useful information on required and recommended competencies, common disinfectants, and sample forms for assessing compounding personnel, cleaning, and disinfection practices.

Available Injections

Hundreds of injections of various medicinal agents are on the market. Tables 15.3 and 15.4 present some examples of those packaged in small-volume and large-volume containers, the latter for IV infusion.

SMALL-VOLUME PARENTERALS

The USP designation small-volume injection applies to an injection packaged in containers labeled as containing 100 mL or less. Table 15.3 presents some commonly employed injections given in small volume. Some of these injections are solutions, and others are suspensions.

Table 15.3 SOME INJECTIONS USUALLY PACKAGED AND ADMINISTERED IN SMALL VOLUME

INJECTION	PHYSICAL FORM	CATEGORY AND COMMENTS
Botulinum toxin type A	Powder for injection	For temporary improvement in appearance of moderate to severe glabellar lines associated with corrugator or procerus muscle activity in adult patients 65 y or younger; administered IM
Butorphanol tartrate	Solution	Opioid agonist–antagonist analgesic; administered IM or IV for relief of moderate to severe pain, as preoperative or preanesthesia medication
Chlorpromazine HCl	Solution	Antipsychotic drug with antiemetic (antidopaminergic) effects; should not be administered SQ. Injection should be IM slowly, deep into upper outer quadrant of buttocks. Avoid injecting directly into vein. IV route used ONLY for severe hiccoughs, surgery, and tetanus
Cimetidine HCl	Solution	Histamine H_2 antagonist; IM or IV for pathologic GI hypersecretory conditions or intractable ulcers
Dalteparin sodium	Solution	Sterile low molecular weight heparin for prophylaxis of deep vein thrombosis in patients at risk who are undergoing abdominal surgery. Available in a prefilled syringe; administered SQ
Dexamethasone sodium phosphate	Solution	Glucocorticoid; IM or IV for cerebral edema, unresponsive shock. Also intra-articular, intralesional, in soft tissue of joints, bursae, and ganglia
Digoxin	Solution	Cardiotonic given IM (not preferred) or IV with highly individualized and monitored dosage
Dihydroergotamine mesylate	Solution	Alpha-adrenergic blocking agent specific for migraine, IM or IV
Diphenhydramine HCl	Solution	Ethanolamine, nonselective antihistamine; IV or IM when PO impractical; indicated for type I (immediate) hypersensitivity reactions, active treatment of motion sickness
Furosemide	Solution	Loop diuretic; IM or IV slowly for edema or acute pulmonary edema
Granisetron HCl	Solution	5-HT_3 receptor antagonist for prevention of nausea and vomiting during cancer therapy, including high-dose cisplatin
Heparin sodium	Solution	Anticoagulant IV or SQ as indicated by activated partial prothrombin time or actuated coagulation time
Hydromorphone HCl	Solution	Opioid analgesic for relief of moderate to severe pain; SQ, IM, or slow IV
Ibutilide fumarate	Solution	Antiarrhythmic with predominantly class III (cardiac action potential prolongation) properties according to Vaughn Williams classification; infused IV undiluted or diluted in 50-mL diluent
Iron dextran	Solution	Hematinic agent; IV or IM for documented iron deficiency when oral administration is unsatisfactory or impossible
Isoproterenol HCl	Solution	Adrenergic (bronchodilator) given IM, SQ, or IV

(*Continued*)

Table 15.3 SOME INJECTIONS USUALLY PACKAGED AND ADMINISTERED IN SMALL VOLUME (Continued)

INJECTION	PHYSICAL FORM	CATEGORY AND COMMENTS
Ketorolac tromethamine	Solution	NSAID for <5 d of moderately severe acute pain that requires analgesia at opioid level, usually postoperatively
Lidocaine HCl	Solution	Cardiac depressant given IV as antiarrhythmic; also local anesthetic epidurally, by infiltration, and in peripheral nerve block
Magnesium sulfate	Solution	Anticonvulsant/electrolyte; IM or direct IV injection, IV infusion, other IV administration for convulsive toxemia of pregnancy, parenteral nutrition therapy, mild magnesium deficiency, and severe hypomagnesemia
Meperidine HCl	Solution	Opioid analgesic given IM, SQ, or slow continuous IV infusion
Metoclopramide monohydrochloride	Solution	Gastrointestinal stimulant; administered IM, direct IV, or slow IV admixture to prevent chemotherapy emesis
Midazolam HCl	Solution	Short-acting benzodiazepine CNS depressant; IV or IM; for preoperative sedation, anxiolysis, amnesia
Morphine sulfate	Solution	Opioid analgesic. IM, IV, and PCA
Nalbuphine HCl	Solution	Opioid agonist–antagonist analgesic; administered SQ, IM, IV for moderate to severe pain, and preoperative analgesia
Naloxone HCl	Solution	Opioid antagonist; prevents or reverses effects of opioids, including respiratory depression, sedation, hypotension; IV, IM, and SQ
Oxytocin	Solution	Oxytocic, given IM (erratic) or IV obstetrically for therapeutic induction of labor
Phenytoin sodium	Solution	Anticonvulsant; IM (erratic absorption) prophylaxis for neurosurgery or slow IV for status epilepticus
Phytonadione	Dispersion	Vitamin K (prothrombogenic) for hemorrhage. Aqueous dispersion of phytonadione, a viscous liquid
Procaine penicillin G	Suspension	Anti-infective; IM for moderately severe infections of penicillin G–sensitive microorganisms
Prochlorperazine edisylate	Solution	Antidopaminergic; IM or IV for control of severe nausea and vomiting associated with adult surgery
Propranolol HCl	Solution	Beta-adrenergic receptor blocker for hypertension. Oral dosage (tablets) is usual; IV administration is reserved for life-threatening arrhythmias and those occurring under anesthesia.
Sodium bicarbonate	Solution	Electrolyte; IV, undiluted or diluted for cardiac arrest, less urgent forms of metabolic acidosis
Sumatriptan succinate	Solution	Selective 5-hydroxytryptamine$_1$ receptor, subtype agonist, for acute migraine with or without aura. Self-administered SQ from unit-of-use syringe, *SELF-dose* unit
Verapamil HCl	Solution	Calcium channel blocker; slow IV over at least 2 min for supraventricular tachyarrhythmias

Table 15.4 REPRESENTATIVE MARKETED FROZEN, PREMIXED PRODUCTS ILLUSTRATING STABILITY DATA WHEN FROZEN AND AFTER THAWING[a]

DRUG[b]	STRENGTH	DILUENT	EXPIRATION DATING		
			FROZEN STABILITY	REFRIGERATED STABILITY	ROOM TEMPERATURE
Cefazolin sodium	1 g	Iso-osmotic in dextrose, 50 mL	24 mo	30 d	48 h
Ceftazidime sodium	1 g, 2 g	Iso-osmotic in dextrose, 50 mL	9 mo	7 d	24 h
Ceftriaxone sodium	1 g, 2 g	Iso-osmotic in dextrose, 50 mL	12 mo	21 d	48 h
Nafcillin sodium	1 g, 2 g	Iso-osmotic in dextrose, 50 mL, 100 mL	18 mo	21 d	72 h
Oxacillin sodium	1 g, 2 g	Iso-osmotic in dextrose, 50 mL	18 mo	21 d	48 h
Ticarcillin disodium and clavulanate potassium	3.1 g	Iso-osmotic in water, 100 mL	30 d	7 d	24 h
Vancomycin HCl	500 mg, 1 g	Iso-osmotic in dextrose, 100 mL	12 mo	30 d	72 h

[a]Stability information provided by Baxter Healthcare Corporation.
[b]Stability data based on packaging drug in a Galaxy® container.

Premixed IV delivery systems have simplified delivery for small-volume parenterals in particular. A distinct advantage of these ready-to-use systems is that they require little or no manipulation to make them patient specific. Thus, they are a viable alternative to the traditional labor-intensive method of compounding parenteral medications from individual or multiple doses of IV medications and an appropriate parenteral solution. Since the introduction of the first ready-to-use systems in the late 1970s, the availability and variety of systems have increased (e.g., Baxter Healthcare Corporation, B. BraunMedical, Hospira) (Table 15.4).

The traditional method for preparing small-volume parenteral therapy from a partial-fill drug vial into a minibag can be labor intensive and costly in materials. The savings accrued through ready-to-use systems can be significant (18). Another key advantage of these systems is extended stability dating and reduced wastage. Doses can be put together (but not activated) in cycles, then activated just prior to use, and delivered to the nursing station by the pharmacy personnel (18).

The downside of these ready-to-use small parenteral products is that they do not offer flexibility in changing the volume or concentration of the product. This may pose a problem to the fluid-restricted patient (18). But the introduction of minibags in volumes of 100, 50, and 25 mL has helped this problem somewhat. Another disadvantage of the ready-to-use products is that some manufacturers' premixed products require thawing. Microwave use for quick thawing poses stability problems for some of these products (e.g., cefazolin). For example, before it was removed from the market, the high-energy microwave oven could cause a structural alteration of the cephalothin molecule. Another possibility was that a substance would leach from the rubber stopper when frozen ampuls of Neutral Keflin were thawed in the microwave, and oftentimes, thawing was not even, with the periphery thawed and the central portion still frozen.

General precautions (19) were once published for using a microwave to thaw frozen products. However, this practice is no longer suggested. Instead, many

hospital pharmacies use the Saf-Thaw (MMI of Mississippi, Crystal Springs). This apparatus provides a layer of conditioned air continuously circulating around the frozen product. The thawing surface facilitates recirculating the conditioned air in the unit and thereby prevents collection of unconditioned air or moisture from the room where the Saf-Thaw is operating. The frozen product is placed on the thawing surface, which is approximately 37°C (99°F), warm to the touch when the unit is in operation. Several dozen frozen products can be placed on the thawing surface at one time, depending on their size.

In years past, some manufacturers recommended warming frozen premixed products in a water bath, with a warning not to submerge the product because there was a distinct possibility that water from the bath could enter and contaminate the product. Now, manufacturers recommend that the frozen container be thawed at room temperature or in a refrigerator (e.g., for 1 hour) and prohibit the use of a water bath or microwave. Thawed floor stock is usually available for emergency orders. Generally, these are kept in refrigerators and warm up quickly (e.g., 20 minutes) to room temperature.

The ready-to-use systems have not been used much in the pediatric and neonatal population. The unique dosing and fluid requirements of these patients make these systems inappropriate. In some institutions, the unique dosing and fluid requirements of pediatric and neonate patients are addressed by making dilutions of medications to standardized concentrations, filling and capping individual syringes, and administering these doses through a syringe pump.

INSULINS

Among the most used of the small-volume injections are the various insulin preparations. Insulin, the active principle of the pancreas gland, is primarily concerned with the metabolism of carbohydrates but also influences protein and fat metabolism. Insulin facilitates the cellular uptake of glucose and its metabolism in liver, muscle, and adipose tissue. It increases the uptake of amino acids and inhibits the breakdown of fats and the production of ketones. Insulin is administered to patients with abnormal or absent pancreatic *beta* cell function to restore glucose metabolism and maintain satisfactory carbohydrate, fat, and protein metabolism. It is used in the treatment of *diabetes mellitus* that cannot be controlled satisfactorily by dietary regulation alone or by oral antidiabetic drugs. Insulin may also be used to improve the appetite and increase the weight in selected cases of nondiabetic malnutrition and is frequently added to IV infusions.

Insulin is administered by needle, pen device, and pump (Figs. 15.28 to 15.30). A system for nasal administration of insulin was introduced onto the market. However, it was withdrawn from the market due to the variability in drug delivery.

Originally, insulin was available as U-40 (i.e., 40 U/mL) and U-80 (i.e., 80 U/mL). However, confusion associated with dosing caused patient errors with injecting too much or too little of the required dosage. Ultimately, the U-100 (i.e., 100 U/mL) insulin was suggested as a replacement for the U-40 insulin, with the intention of making U-100 the single strength for in-home use by the patient. In December 1991, Eli Lilly announced that it would cease the production of U-40 insulins, and subsequently, other insulin manufacturers also decided to cease the production of this strength. Previously, the U-80 strength had been decertified. The basis for this decision was lack of demand (very low numbers of patients using this strength). Recognizing, however, that insulin under 100 U/mL might still be needed (i.e., for small children, veterinary use), Lilly markets a diluting fluid for Humalog, Humulin N, Humulin R, Humulin

FIGURE 15.28 Medi-Jector II, a jet injection device. The jet injection method uses pressure rather than a needle to provide subcutaneous distribution of medication. This device can be used with U-100 insulin or a combination of insulins and can deliver 2 to 100 units in half-unit increments. (Courtesy of Antares Pharm Inc.)

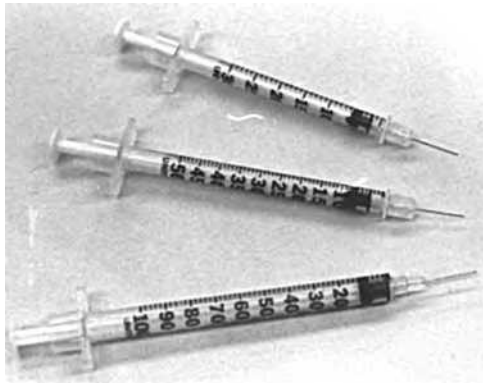

FIGURE 15.29 Insulin syringes calibrated in units. (Courtesy of William B. French, PhD.)

70/30, Humulin 50/50, and Humulin R (U-500). This fluid can be used to prepare any strength of insulin below 100 U/mL. It is not commercially available, however, and can only be secured through a direct, special order request to Eli Lilly and Co.

The diluting solutions are identical to the diluent in the insulin in every way (e.g., preservative agent, buffer, pH) except for the presence of insulin. The recommended storage condition for opened and unopened diluting solutions is controlled room temperature, 25°C (77°F). Once the diluting solutions are opened, the material can be used for a month.

Age-associated sight difficulties and the vision deterioration associated with diabetes can interfere significantly with buying and using insulin products. Therefore, packaging of insulins must make allowances for visual deficits. To facilitate identification of the proper medication at the site of purchase, the arrangement and size of the package lettering must make it easy for the insulin-dependent patient to recognize the type and concentration of the product. For example, Humulin insulins, an international symbol also appears on the cartons and bottles of all formulations of Humulin insulins. These symbols help ensure that patients with diabetes secure the correct Humulin formulation anywhere in the world. Each manufacturer of insulin has its own distinct labeling for its insulin products.

The goal of insulin therapy is to achieve tight blood glucose control by mimicking insulin secretion by the normal pancreas. Normal insulin secretion consists of two components, basal and bolus insulins. These components are mimicked by the administration of two types of insulins. Basal insulins are intermediate-acting or long-acting insulins that mimic basal secretion of insulin. This is the small amount that the pancreas secretes continuously. These products help to suppress hepatic glucose production between meals and overnight. Basal insulins provide approximately 50% of a person's daily requirements. Bolus insulins are rapid-acting or short-acting insulins that mimic the extra insulin the pancreas secretes in response to the postprandial rise of blood glucose levels. Postprandial blood glucose values contribute significantly to hemoglobin A_{1C} values and consequently to the long-term complications of diabetes if these blood glucose values are not controlled. Thus, postprandial control of blood glucose is essential for optimal management. Bolus injections are estimated to provide 10% to 20% of a patient's total daily insulin requirement at each meal.

There is no ceiling insulin dose; however, most patients will not need more than 60 to

FIGURE 15.30 Packaging of disposable sterile insulin syringes and needles. (Courtesy of William B. French, PhD.)

70 U/d. It is recommended when insulin requirements exceed 100 U/d; attempts to reduce insulin resistance should be implemented, for example, exercise, reducing dietary carbohydrate intake, and adding metformin to the patient's drug regimen.

Regular Insulin

Regular insulin is a sterile aqueous solution of insulin. Commercially, the solution was prepared from beef or pork pancreas or both. Currently, it is prepared exclusively through biosynthetic means (human insulin), discussed in the next section. The source must be stated on the labeling. In 1980, purified pork insulin (Iletin II, pork, Lilly) became available for individuals allergic to or otherwise adversely affected by the mixed pork and beef product. The first insulin developed for clinical use was amorphous. This type was then replaced by a purer zinc–insulin crystalline product that produced a clear aqueous solution. Originally, insulin injection (regular insulin) was produced at a pH of 2.8 to 3.5. This was necessary because particles formed in the vial when the pH was increased above the acid range. However, changes in manufacturing to produce insulin of greater purity have allowed for insulin injection with a neutral pH. The neutral product is more stable than the acidic product.

Regular insulin is prepared to contain 100 or 500 USP insulin units per milliliter. The labeling must state the potency in USP insulin units per milliliter and the expiration date, which must not be later than 24 months after the date of manufacture. As an added precaution against inadvertent use of the incorrect strength, the packages are color coded for strength. For instance, all insulins of the various types containing 100 U/mL have an orange code/label, and the 500 U/mL preparation has a brown code/label with diagonal white stripes. U-500 insulin is indicated for patients with a marked insulin requirement usually (more than 200 U/d) because a large dose may be administered subcutaneously in a small volume. Its effect lasts up to 24 hours, possibly due to delayed absorption of the concentration solution.

Regular insulin is a colorless to straw-colored solution, depending on its concentration; the 500 U/mL product is straw colored. It is substantially free from turbidity. A small amount of glycerin (1.4% to 1.8%) is added for stability, and 0.1% to 0.25% of either phenol or cresol is added for preservation. Insulin remains stable if stored in a cold place, preferably the refrigerator. However, because injection of cold insulin is uncomfortable, the patient may store the vial being used at room temperature (15°C to 30°C or 59°F to 86°F) for up to 28 days. Any insulin remaining in the vial after that time should be discarded. Freezing should be avoided, as this reduces potency.

The various insulin preparations differ as to their onset of action, peak of action, and duration of action (Table 15.5). Regular insulin, being a solution, is categorized as rapid acting. Insulin suspensions are slower acting. Only regular insulin may be administered intravenously; all others are normally given subcutaneously, usually 30 minutes to 2 hours before a meal so that physiologic effects will parallel absorption of glucose. The dosage is individually determined, with the usual range being 5 to 100 U. The pharmacist plays a vital role in the education of the diabetes patient, particularly in the proper use of insulin. The insulin dose should always be checked to ensure it is correct. Because it is a solution, regular insulin can be used in emergencies, such as ketoacidosis, to effect a rapid decrease in blood glucose levels. However, with the exception of diabetic ketoacidosis, it is rare for a patient to require a dose of regular insulin greater than 25 U. Previously, diabetes patients combined regular insulin with a modified insulin, such as NPH, to provide daily coverage in two injections (morning, late afternoon) or use premixed preparations. So, it was important that the patient understood how much of each to use and in what order to mix them in the syringe. Regular insulin is drawn up first into the syringe. Now, however, a patient will inject a rapid-acting insulin before meals and a long-acting insulin one time per day.

In an institutional setting, the pharmacist must make sure that written insulin orders

Table 15.5 INSULIN ACTIVITY PROFILES AND COMPATIBILITY

PREPARATION	ONSET (H)	PEAK (H)	DURATION (H)	COMPATIBLE WITH
Rapid acting				
Insulin lispro	0.25	0.5–1.0	3	Ultralente; NPH
Insulin aspart	0.25	0.5–1.0	3	None
Short acting				
Regular insulin	0.5	2–5	5–8	All
Intermediate acting				
Isophane (NPH) insulin	1–2	6–10	16–20	Regular
Insulin–zinc (Lente)	1–2	6–12	18–24	Regular, semilente
Long acting				
Insulin–zinc extended (Ultralente)	4–6	10–18	24–28	Regular, semilente
Insulin glargine	2	None	>24	None
Mixtures				
Isophane/regular insulin 70/30, 50/500.75	7–12	16–24	—	—
NPL/lispro mix 75/25	5 min	7–12	1–24	—

are correctly transcribed or transmitted. Allied health care workers have made errors in insulin dosage. Written orders for "6U" of insulin have been interpreted to mean 60 U, and an order for "4U" has been read as 4 cc. Each of these occurred because the abbreviation "U" for units was read as a zero or cc.

The patient should be instructed to rotate the site of insulin injections. Rotation of the site will help to avoid lipohypertrophy, a buildup of fibrous tissue. With continual injection into one site, the tissue becomes spongy and avascular. The avascular nature of the site perpetuates the problem because the skin becomes anesthetized and the injection is not felt. This is a particular problem with children who continue to use the same site and do not realize that the absorption of insulin from this site becomes erratic and uncontrollable. Numerous brochures from manufacturers of diabetes supplies demonstrate the appropriate rotation of insulin injection sites over the entire body.

Another problem with insulin injections is the development of lipodystrophy. Generally, this problem appears within 2 months to 2 years following the beginning of insulin therapy and occurs predominantly in women and children. Its cause has been ascribed to injection of refrigerated insulin (not giving enough time for it to warm up prior to injection), to failure to rotate the injection site, and to impurities in the insulin. The result is the formation of an SC indentation caused by wasting or atrophy of the lipid tissue. It appears that the greater purity of current insulins has significantly decreased this problem, and a marked improvement in existing atrophic areas has been demonstrated by injection of human insulin directly into or on the periphery of the atrophic areas.

Prior to use, the patient should be instructed to inspect the insulin carefully. Regular insulin, insulin glargine, and insulin detemir should appear clear, while the other insulins, which are suspensions, should appear uniformly cloudy. With the suspensions, the patient should be instructed how to prepare the insulin: The vial is rotated slowly and gently between the palms of the hands several times before the insulin is drawn into the syringe. This avoids frothing and bubble formation, which would result in an inaccurate dose. The patient should not shake the insulin vial as this may affect the insulin molecules rendering them somewhat ineffective and incorporate air in the solution/suspension resulting in an incorrect dose being measured.

Proper storage should also be encouraged. These preparations should be stored in a cool

place or a refrigerator. The patient should be warned to avoid exposing the insulin to extremes of temperature, that is, freezing, such as overnight in the car in the winter and heat, as in the glove compartment of a car in summer or in direct sunlight. If this occurs, the patient should discard the insulin and get a new bottle (20). Any bottle of insulin that appears frosted or clumped should be returned to the pharmacy where it was purchased. Finally, the patient should use the insulin in a timely fashion, not beyond the expiration date indicated on the insulin vial.

Human Insulin

Biosynthetic human insulin was the first recombinant DNA drug product to receive approval from FDA. This product, Humulin (Lilly), became available in 1983. It is produced by using a special non–disease-forming laboratory strain of *Escherichia coli* and recombinant DNA technology. A recombined plasmid DNA coding for human insulin is introduced into the bacteria, and it is then cultured by fermentation to produce the A and B chains of human insulin. These A and B chains are freed and purified individually before they are linked by the specific disulfide bridges to form human insulin. The insulin produced is chemically, physically, and immunologically equivalent to insulin derived from the human pancreas. The biosynthetic insulin is free of contamination with *E. coli* peptides and is also free of the pancreatic peptides that are present as impurities in insulin preparations extracted from animal pancreas. These latter impurities include proinsulin and proinsulin intermediates, glucagon, somatostatin, pancreatic polypeptide, and vasoactive intestinal peptide.

Pharmacokinetic studies in some normal subjects and clinical observations in patients indicate that formulations of human insulin have a slightly faster onset of action and a slightly shorter duration of action than the original purified pork insulin counterparts. Two formulations of human insulin were initially marketed: neutral regular human insulin (Humulin R, Lilly) and NPH human insulin (Humulin N, Lilly). Neutral regular human insulin consists of zinc–insulin crystals in solution. It has a rapid onset of action and a relatively short duration of action at 6 to 8 hours. NPH human insulin is an intermediate-acting turbid preparation with a slower onset of action and longer duration of action (16 to 20 hours) than regular insulin.

Human insulins should be stored as other insulins, in a cold place, preferably a refrigerator. Freezing should be avoided.

Insulin Lispro

Insulin lispro solution consists of zinc–insulin lispro crystals dissolved in a clear aqueous fluid. It is created when the amino acids at positions 28 and 29 on the insulin B chain are reversed.

Insulin lispro solution is rapidly absorbed after SC administration and demonstrates no significant differences in absorption from abdominal, deltoid, and femoral sites of injection. Its bioavailability mimics that of regular insulin. However, peak serum levels of insulin lispro occur within 0.5 to 1.5 hours and are higher, and it is shorter acting than regular insulin with a duration of 3 to 4 hours. Peak hypoglycemic effects are more pronounced with lispro insulin solution. Thus, hypoglycemia is the primary complication associated with its use. Comparative studies have demonstrated, however, that hypoglycemic episodes have been less frequent with insulin lispro than with regular insulin.

Insulin lispro solution administered within 15 minutes before meals has decreased the risk of hypoglycemic episodes and improved postprandial glucose excursions when compared to conventional regular insulin therapy. Some studies have demonstrated a greater impact on the quality of life with insulin lispro solution, and it has been shown to be more effective than regular insulin in reducing hypoglycemia associated with exercise within 3 hours after a meal. Thus, as a newer insulin, it offers more flexibility for the diabetes patient and should be added to formularies as an alternative to regular insulin.

Insulin lispro solution should be stored in a refrigerator but not in the freezer. If accidentally frozen, it should not be used. It

may be stored at room temperature for up to 28 days, but the storage temperature should be as cool as possible. Insulin lispro pens should be kept at room temperature once in use. The vial or cartridge should be kept away from direct light and heat. At the end of 28 days, any unused portion of the insulin lispro solution should be discarded.

Insulin Aspart

Insulin aspart is a recombinant, ultra–short-acting insulin using *Saccharomyces cerevisiae* (baker's yeast) as the production organism. It is homologous with regular human insulin except for a single substitution of the amino acid proline by aspartic acid in position B28. This insulin was developed to control postprandial glucose concentrations when administered 5 to 10 minutes before mealtime in a manner similar to that for insulin lispro. The dosage is individualized to the patient's needs.

Insulin aspart demonstrates pharmacokinetics very similar to those of insulin lispro solution in terms of onset of action (0.25 hours), peak effect (0.5 to 1 hour), and duration of action (3 hours). A few studies have demonstrated that patients treated with insulin aspart had better glucose control and fewer nocturnal hypoglycemic episodes than patients using insulin regular. These studies demonstrate that insulin aspart is a viable alternative therapy for patients who use insulin regularly.

Mixing insulin aspart with NPH human insulin immediately before injection may produce some attenuation in the peak concentration of the insulin aspart. However, the time to peak concentration and the total bioavailability of the insulin aspart should not be affected. When insulin aspart is mixed with NPH human insulin, the insulin aspart should be drawn up first. This combination should be injected immediately after mixing. Insulin aspart should not be mixed with crystalline zinc–insulin preparations because compatibility data are lacking.

Insulin Glulisine (APIDRA)

Insulin glulisine is a recombinant rapid-acting insulin analog that differs from human insulin by the replacement of two amino acids on the *beta*-chain at positions B3 (i.e., asparagine replaced by lysine) and B29 (i.e., lysine replaced by glutamic acid). This insulin is produced by recombinant DNA technology using a nonpathogenic strain of *E. coli* (K12). Apidra is equipotent to regular human insulin when administered intravenously. When given subcutaneously, insulin glulisine demonstrates a more rapid onset of action and shorter duration of action compared to regular insulin. It is a sterile, clear, aqueous, and colorless solution with a pH of approximately 7.3.

Insulin glulisine has the onset of action in 0.2 to 0.5 hours and reaches its peak effect in 1.6 to 1.8 hours. It has a duration of action of 3 to 4 hours. Apidra demonstrates distribution and elimination properties very similar to those of regular insulin with a volume of distribution of 13 L and a half-life of 13 minutes (IV) and 42 minutes (SubQ).

For SC administration, the dosage of insulin glulisine is individualized to the patient's need, usually 0.5 to 1.0 U/kg/d. It should be administered 15 minutes prior to a meal or within 20 minutes after a meal. Generally, it is used with a long-acting (basal) form of insulin or as a continuous basal administration via SubQ infusion pump. Fifty to seventy percent of the total daily insulin requirement may be provided by insulin glulisine when given subcutaneously in a meal-related treatment regimen. The remainder requirement can be provided by employing an intermediate-acting or a long-acting insulin. Insulin glulisine should be injected into thighs, arms, buttocks, or abdomen, with the sites rotated.

Insulin glulisine can be administered intravenously *via* infusion under medical supervision, and close monitoring of glucose levels and serum potassium levels is recommended. It should be used at concentrations of 0.05 to 1 U/mL in infusion systems using PVC bags and tubing. This insulin has been shown to be stable only in normal saline solution.

In patients with renal impairment, insulin glulisine requirements are reduced as a result of its decreased metabolism or clearance. Studies have shown that there are increased levels of circulating insulin in

renal failure patients. No dosage adjustments are required in patients with impaired hepatic function.

Insulin glulisine can only be mixed with NPH insulin, and when mixed, it should be drawn into the syringe first. It is available in a concentration of 100 U/mL in 10-mL vials and 3-mL cartridges for use in the OptiClik insulin delivery device. Unopened vials of Apidra should be stored in the refrigerator (2°C to 8°C). It should not be stored in the freezer and should be discarded if frozen. Similarly, if inadvertently exposed to extremes in temperature (i.e., heat, freezing) in the glove compartment of an automobile, for example, it should be discarded. Open (in-use) vials can be stored in the refrigerator or at room temperature of not greater than 25°C. Open, in-use cartridges inserted into the OptiClik system should not be refrigerated but kept at room temperature. Any open vials or cartridges should be discarded after 28 days. The vial or the cartridges should be protected from direct light and heat. Infusion bags for IV use are stable at room temperature for 48 hours. Apidra is stable in the infusion sets for up to 48 hours and should be discarded if exposed to temperatures greater than 37°C.

Isophane Insulin Suspension (NPH Insulin)

Isophane insulin suspension is a sterile suspension in an aqueous vehicle buffered with dibasic sodium phosphate to pH 7.1 to 7.4. It is prepared from zinc–insulin crystals modified by the addition of protamine so that the solid phase of the suspension consists of crystals of insulin, zinc, and protamine. Protamine is prepared from the sperm or the mature testes of fish belonging to the genus *Oncorhynchus* and others. As mentioned in the discussion of the aqueous insulin solutions, suspensions of insulin with a pH on the alkaline side inherently have a longer duration of action than solutions. Insulin is least soluble at pH 7.2.

The rod-shaped crystals of isophane insulin suspension should be approximately 30 µm long and the suspension free of large aggregates of crystals following moderate agitation. This is necessary for it to pass freely through the needle and for absorption of the drug to be consistent from one batch to another. When a portion of the suspension is examined microscopically, the suspended matter is largely crystalline, with only traces of amorphous material. The official injection is required to contain glycerin and phenol for stability and preservation. The specified expiration date is 24 months after the immediate container was filled by the manufacturer. The suspension is packaged in multiple-dose containers having not less than 10 mL of injection. Each milliliter contains 100 U of insulin. The suspension is best stored in a refrigerator, but freezing must be avoided.

As indicated earlier, isophane insulin suspension is an intermediate-acting preparation administered as required mainly as hormonal replacement in diabetes mellitus. The usual dose range subcutaneously is 10 to 80 U. Its effects are comparable with those of a mixture of two to three parts of regular insulin and one part of protamine zinc–insulin.

The *NPH* used in some product names stands for neutral protamine Hagedorn because the preparation is neutral (pH about 7.2), contains protamine, and was developed by Hagedorn. The term *isophane* is based on the Greek words *iso* (equal) and *phane* (appearance) and refers to the equivalent balance between the protamine and insulin.

Isophane Insulin Suspension and Regular Insulin

In years past, patients needing a rapid onset of action and intermediate duration of activity, approximately 1 day, would routinely mix isophane insulin suspension, an intermediate-acting insulin, with regular insulin, a rapid-acting insulin. Unexpected responses, such as hypoglycemic episodes, were encountered. In addition, it was fairly common for the patient to contaminate one of the vials during mixing. Subsequently, a premixed formulation of isophane insulin suspension and regular insulin became

available, and now there are two formulations. The 70/30 combination consists of 70% isophane insulin suspension and 30% regular insulin, and the 50/50 combination consists of 50% isophane insulin suspension and 50% regular insulin. These combinations are stable and absorbed as if injected separately.

Humulin 50/50 achieves a higher insulin concentration (C_{max}) and maximum glucose infusion rates with more rapid elimination than Humulin 70/30. However, as expected, the cumulative amounts of insulin absorbed (area under the curve, or AUC) and the cumulative effects over 24 hours following injection are identical. Thus, the 70/30 combination provides an initial response tempered with a more prolonged release of insulin. The 50/50 mixture is useful when a greater initial response is required and for patients who have been using extemporaneously compounded insulin mixtures in a 50/50 ratio.

The Humulin 70/30 and 50/50 premixed insulins are cloudy suspensions with a zinc content of 0.01 to 0.04 mg/100 U. These insulins are neutral in pH and phosphate buffered. *m*-Cresol and phenol are the preservatives for both combinations. Protamine sulfate is the modifying protein salt.

Patients should not attempt to change the ratio of these products by adding NPH or regular insulin. If Humulin N and Humulin R mixtures are prescribed in a different proportion, the individual insulin products should be mixed in the amounts recommended by the physician.

Humalog Mix

Humalog Mix is a manufactured premixed insulin consisting of insulin lispro and neutral protamine lispro (NPL) in a fixed ratio. Humalog Mix 50/50 consists of 50% insulin NPL suspension and 50% insulin lispro injection. Humalog Mix 75/25 contains 75% insulin NPL suspension and 25% insulin lispro injection. It is estimated that these premixed combinations are used by more than 40% of diabetes patients who inject insulin twice daily.

These fixed combinations were developed to give better control for diabetes patients who use a combination of short- and long-acting insulins. In comparison to Humulin 70/30, Humalog Mix 75/25 demonstrated lower postprandial blood glucose levels and no difference between the afternoon and overnight glucose values. Furthermore, insulin NPL suspension was developed as an alternative to combinations employing NPH insulin. NPH insulin was unstable over weeks to months when mixed with lispro insulin.

Insulin Glargine

Insulin glargine is a long-acting (up to 24 hours) basal insulin preparation intended for once-daily SC administration at bedtime in the treatment of type 1 diabetes mellitus in adults and children. It can also be used by adults with type 2 diabetes who require long-acting insulin. It is created when the amino acids at position 21 of human insulin are replaced by glycine and two arginines are added to the C terminus of the B chain.

Insulin glargine is a recombinant, human insulin analog. Formulated at a pH of 4.0, it is completely soluble at that pH. However, once it is injected into SC tissue, it is neutralized, which causes formation of microspheres. This peakless insulin begins working in 2 hours and mimics basal insulin secretion more closely than other long-acting insulins for 24 hours. This allows for once-daily dosing. Because insulin glargine provides only basal coverage, it is often used in conjunction with other insulins or oral hypoglycemic drugs. However, because of the unique release characteristics of insulin glargine, it should not be mixed with any other insulin. Differences in pH can cause clumping. If it has to be used in combination with a rapid-acting insulin, the injections must be administered separately.

The unique release characteristics of insulin glargine may help to decrease the number of required injections of long-acting insulin from twice daily to once daily. Clinical studies have demonstrated no relevant differences in insulin glargine absorption after abdominal,

deltoid, or thigh administration. For those patients requiring more than 100 U of basal insulin, the pharmacist can suggest to the diabetologist dividing the dose and injecting it at different sites or at different times.

If the patient is changing over to insulin glargine from an intermediate- or long-acting regimen, the dosage may or may not have to be adjusted. When patients are transferred from twice-daily NPH to insulin glargine once daily at bedtime, to reduce the risk of hypoglycemia, the initial dose is usually decreased by approximately 20% from the total daily dose of NPH product for the first week of treatment and then adjusted to the patient's response. However, when patients are transferred from once-daily NPH to once-daily insulin glargine, the initial dose is usually not changed.

Insulin Detemir

Insulin detemir is an intermediate- to long-acting basal insulin, which is dosed subcutaneously either once or twice daily. It is supplied as a clear neutral (pH 7.4) solution and produced by recombinant DNA in *S. cerevisiae* (i.e., baker's yeast). It is similar in structure to human insulin with the exception of a deletion of the amino acid threonine in position B30 and a C14 fatty acid chain attached to the amino acid position B29.

Insulin detemir maintains its long-acting property through slow systemic absorption. The drug molecules have strong self-association and are highly albumin bound. Insulin Detemir has an onset of action of 3 to 4 hours and a peak effect within 6 to 8 hours. The duration of action is dose dependent. At low dosages (i.e., 0.1 to 0.2 U/kg), its duration can range between 5.7 and 12.1 hours. This is the most variable dosage range. At a middle range dosage (i.e., 0.6 U/kg), its duration of action approaches 20 hours, and at high dosages (i.e., >0.6 U/kg), its duration of action is the least variable between 22 and 23 hours. The administered dose of drug, therefore, determines if this insulin should be given once or twice daily.

Detemir should not be mixed with any other insulin. Short- or rapid-acting insulin given in a separate syringe is often used as a bolus, while insulin detemir is simultaneously used as the basal insulin. The conversion from NPH to insulin detemir is 1:1 with small adjustments as needed based on glucose monitoring. This insulin should never be frozen and should be stored in a refrigerator or a cool room out of direct light. Once the vial is in use, it can be kept for up to 42 days.

Insulin Pens

Insulin pens use disposable or single-use cartridges filled with either 150 or 300 U of insulin and packaged five per box (21). These pens are available for a number of insulin types, for example, regular insulin, insulin isophane, insulin glulisine, and insulin glargine. Their ease of use and portability make them desirable for patients to administer insulin, particularly for those patients who desire to avoid the embarrassment of needle use in public.

An advantage of the pen devices is that they improve the accuracy of insulin administration when compared to the traditional vial and syringe administration. These devices allow the dose of insulin to be dialed in, or some have audible dose selectors. This feature is particularly advantageous for administering low insulin dosages (22). These devices may be ideal for children, adolescents, and patients with visual and/or physical dexterity difficulties. Just as with the handling of a suspension form of insulin, for example, Novolin 70/30 PenFill (Novo Nordisk), the patients should be instructed to roll the cartridge in their hands gently before administering it.

Adherence to dosing schedules facilitates effective patient care and helps to decrease health care costs. This is particularly important with diabetes therapy. Getting patients to adhere to insulin dosages facilitates glycemic control and provides value to the payers of health care. Lee et al. (23) demonstrated that health care costs, for example, emergency room visits, decreased hospital length of stay, and physician visits, were reduced in patients studied who switched from insulin

vials and syringes to a prefilled insulin analog pen device.

Insulin Infusion Pumps

Insulin infusion pumps allow an estimated 300,000 patients to achieve and maintain blood glucose at nearly normal levels on a *constant basis* through continuous SC insulin infusion (i.e., CSII) (24). CSII is achieved through the use of small and lightweight pumps and eliminates the need for the patient to adhere rigidly to a regimen of multiple daily injections of insulin. This provides convenience, better adherence, and control over the disease process. The main objective of pump therapy is strict control of the blood glucose level at 70 to 140 mg/dL to reduce blood glucose variations that increase the risk for micro- and macrovascular complications, for example, gangrene and diabetic retinopathy.

Early insulin infusion pumps were large, bulky bedside units, for example, AutoSyringe (Baxter, *syn*. "Big Blue Brick") used mainly in hospitals. Today, an insulin pump is of the size and weight of a personal pager, for example, 3.2 × 2.2 × 0.8 inch, and weighs between 3 to 4 ounces with battery (i.e., AA, AAA) and full cartridge. It is a plastic-encased computer device that can be worn in a pocket or bra or on a belt. A computer chip in the pump allows the patient to program the amount of insulin for the pump to release. Inside the pump, depending upon the model, a syringe reservoir will hold up to 300 U of U-100 insulin. Unlike conventional insulin therapy, which normally combines rapid-acting and intermediate-acting insulins, the infusion pump delivers either short-acting or rapid-acting insulin. Frequently, a rapid-acting insulin, such as aspart (NovoLog) or lispro (Humalog), is preferred.

CSII is generally recommended for patients more than 10 years of age. Key needs for the patient are to be technological savvy, possess an intellectual ability to manage insulin pump therapy on an independent basis, be willing and eager to start insulin pump therapy, be proficient in carbohydrate counting, understanding of the benefits and limitations of CSII, and demonstrate reasonable expectations. Usually, children need a higher degree of involvement by parents or guardians who must also be supportive of and knowledgeable about insulin pump therapy. Insulin pumps may also be useful for patients who cannot tolerate large doses of insulin or multiple daily injections.

The reservoir delivers insulin through a plastic infusion set, available in 24- or 42-inch lengths. The triggering device inserts the infusion set's flexible catheter into the SC tissue. Once the catheter is inserted, the needle is removed. Multiple safety alarms can be set to warn of a low battery, to serve as a reminder to test postprandial blood glucose, to change the infusion site, and to refill the insulin reservoir when a specified number is reached. These alarms can also signal when the infusion line is clogged or when a mechanical problem occurs with the pump. Further, pumps can be set to signal when a bolus dose has not been administered at the usual period of time. An auto-off feature can be set in the event the buttons have not been touched for a period of time, for example, 8 to 9 hours. The pump will deactivate to prevent the administration of more insulin. Most patients insert the infusion set into a body area with an adequate amount of SC fate, for example, the abdomen, thighs, and buttocks. Here, the insulin is rapidly and consistently absorbed. It is crucial that the set be inserted subcutaneously and not intramuscularly and for the patient to use an antiseptic product, for example, IV prep wipes, povidone–iodine solution, and chlorhexidine liquid, to prevent site infections. Once inserted, a hypoallergenic adhesive tape is used to secure the infusion set onto the skin a couple of inches away from the pump to prevent the catheter from being pulled from its site of insertion. Patients should understand not to place the pump where their clothing may rub against it (e.g., underwear area, waistline, a 4-inch area around the umbilicus) and to make sure to rotate the insertion site.

For optimal working efficiency, the patient should change the infusion site every 2 or 3 days or whenever blood glucose is above 240 mg/dL for two tests in a row. This may

indicate that the infusion set is not working properly.

It is very important that patients understand the necessity to monitor their blood glucose so they know to adjust their dosage of insulin. Patients should check their blood glucose level before each meal, at bedtime, and whenever they have symptoms of hypoglycemia, such as sweating, shakiness, nausea, headache, and difficulty concentrating, or symptoms of hyperglycemia, such as polyuria, polydipsia, polyphagia, nocturnal enuresis, weakness, fatigue, blurred vision, and alteration in mental status.

Infusion-site reactions include contact dermatitis and infections. Alternative adhesives or infusion sets will help resolve encountered dermatitis. Infections are more common, and prevention is the best treatment. Patients should be educated what to observe, for example, inflammation, swelling, soreness, redness, and purulent discharge, if the site becomes infected and to know to contact his/her health care provider. Patients should then be prescribed a systemic course of antibiotics. In the meantime, the infusion set should be moved to another site, or insulin may be administered manually until the infection is cured.

At night, the insulin pump can be placed on the nightstand close to the bed requiring long-enough tubing, in the bed next to the patient, or in a pajama pocket. When bathing, the patient can place the pump on the bathroom floor and allow the tubing to drape over the side of the tub. For showering, the pump can be placed in a special plastic bag and hung around the patient's neck or on the faucet handle. Typically, however, the patient will disconnect the pump, but for no more than 1 hour to allow for bathing or other activity. In addition, to provide coverage over this hour, the educated and skilled diabetes patient may administer a bolus dose of insulin prior to the time the pump is disconnected.

LARGE-VOLUME PARENTERALS

The USP designation large-volume IV solution applies to a single-dose injection intended for IV use and is packaged in containers labeled as containing more than 100 mL. Common examples of large-volume parenterals in use today are presented in Table 15.6 and are administered by IV infusion to replenish body fluids or electrolytes or to provide nutrition. They are usually administered in volumes of 100 mL to 1 L or more per day by slow IV infusion with or without a controlled-rate infusion system (Fig. 15.31). Because of the large volumes administered,

Table 15.6 SOME IV INFUSIONS THAT MAY BE ADMINISTERED IN VOLUMES OF 1 L OR MORE, ALONE OR WITH OTHER DRUGS

INJECTION	USUAL CONTENTS	CATEGORY AND COMMENTS
Amino acid	3.5%, 5%, 5.5%, 7%, 8.5%, and 10% crystalline amino acid with or without varying concentrations of electrolytes or glycerin	Fluid and nutrient replenisher
Dextrose Injection, USP	2.5%, 5%, and 10% dextrose, other strengths	Fluid and nutrient replenisher
Dextrose and Sodium Chloride Injection, USP	Dextrose 2.5%–10%; NaCl 0.11%–0.9% (19–154 mEq sodium)	Fluid, nutrient, electrolyte replenisher
Mannitol Injection, USP	5%, 10%, 15%, 20%, and 25% mannitol	Diagnostic aid in renal function; diuretic; fluid and nutrient replenisher
Ringer's Injection, USP	147 mEq sodium, 4 mEq potassium, 4.5 mEq calcium, and 156 mEq chloride per liter	Fluid and electrolyte replenisher
Lactated Ringer Injection, USP	2.7 mEq calcium, 4 mEq potassium, 130 mEq sodium, and 28 mEq lactate per liter	Systemic alkalinizer; fluid and electrolyte replenisher
Sodium Chloride Injection, USP	0.9% NaCl	Fluid and electrolyte replenisher; isotonic vehicle

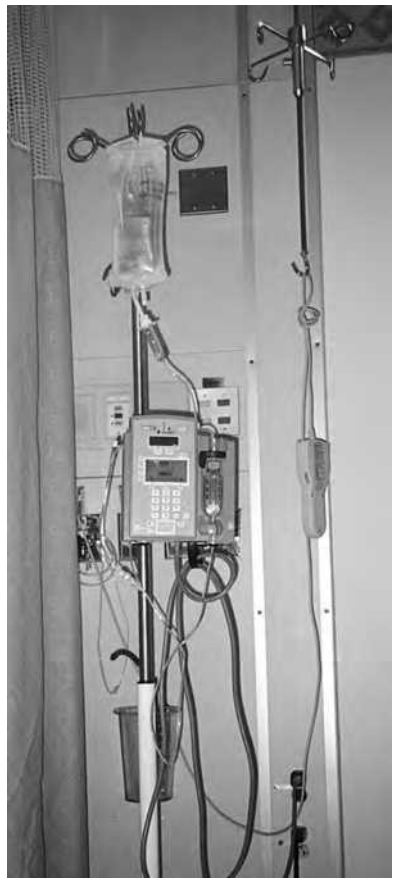

FIGURE 15.31 Accurate delivery of IV fluids and medications by use of a controlled-rate infusion system (Alaris Medical Systems) for the drug vial and a volumetric infusion pump for the IV fluids. (Courtesy of Mr Akinwale O. Onamade.)

these solutions must not contain bacteriostatic agents or other pharmaceutical additives. They are packaged in large single-dose containers (Figs. 15.32 and 15.33).

As indicated previously, electrolytes, vitamins, and antineoplastics are frequently incorporated into large-volume parenterals for coadministration to the patient. It is the responsibility of the pharmacist to understand the physical and chemical compatibilities of the additive in the solution or liquid in which it is placed. Obviously, a combination that results in formation of insoluble material or affects the efficacy or potency of the therapeutic agent of the vehicle is not acceptable. For example, deaths were associated with the administration of calcium

FIGURE 15.32 IV solution packaged in pliable plastic. (Courtesy of Ms Amy Schuppert Smith.)

and phosphate in total nutrient admixtures (TNAs) (25).

It is also important to be vigilant for incompatibilities associated with multiple infusions coadministered to a patient. A typical nursing question may be, "Can the dopamine drip be run in with the heparin drip?" To answer these questions, the pharmacist must know about parenteral therapy and be aware of incompatibilities reported in the literature. Numerous references (e.g., *Handbook on Injectable Drugs, King's Guide to Parenteral Admixtures* [King Guide Publications]) are available for sources listing and discussing parenteral incompatibilities. However, the pharmacist should use only the most current

FIGURE 15.33 Peritoneal dialysis and irrigation fluids. (Courtesy of William B. French, PhD.)

edition of these references. Whenever possible, the pharmacist should attempt to answer these important questions and explain the incompatibilities that come to his or her attention as part of the daily routine. Furthermore, the pharmacist should create a file of data and add to it from experience and the literature. Internet-accessible services (e.g., Micromedex) can also be employed to check incompatibilities. These reference the *Handbook on Injectable Drugs* and *King's Guide to Parenteral Admixtures*.

While it is impossible to chart every possible admixture incompatibility, principles can be learned and applied. For example, certain drugs are inactivated or precipitate at either high or low pH values, some drugs (e.g., sympathomimetics) encounter problems when added to IV fluids, and certain therapeutic large-volume solutions (e.g., sodium bicarbonate, urea, mannitol) should never contain additives.

Large-volume parenteral solutions are employed in *maintenance therapy* for the patient entering or recovering from surgery and for the patient who is unconscious and unable to take fluids, electrolytes, and nutrition orally. The solutions may also be used in *replacement therapy* for patients who have suffered a heavy loss of fluid and electrolytes.

Maintenance Therapy

When a patient is receiving parenteral fluids for only a few days, simple solutions providing adequate amounts of water, dextrose, and small amounts of sodium and potassium generally suffice. When patients are unable to take oral nutrition or fluids for slightly longer periods, say 3 to 6 days, solutions of higher caloric content may be used. If oral feeding must be deferred for periods of weeks or longer, TPN or TNAs must be implemented to provide all of the essential nutrients to minimize tissue breakdown and to maintain normalcy within the body. TNAs (three-in-one) include all substrates necessary for nutritional support—carbohydrates, protein, fat, electrolytes, and trace elements—mixed in a single plastic IV bag for convenient administration.

These admixtures are very useful for chemotherapy, gastrointestinal patients, and anorexic patients. The use of three-in-one admixtures in pediatrics, especially for neonates, is controversial. The concentrations of calcium, phosphorus, and necessary warm administration for pediatric TPN do not lend themselves to stable preparations. As a result, many pediatric institutions do not compound three-in-one admixtures for their patients but administer the fat emulsion separately.

When using TNA, the pharmacist must consider the order of substrate mixing, differentiate between various brands of substrate and their physicochemical properties, determine the type of plastic bag system that is most appropriate, determine how the product should be stored, and assess any potential complications. Per FDA ruling, TNAs must be filtered with a 1.2-μm filter. For example, the use of plastic bags with DEHP may result in plasticizer leaching into the solution.

In April 1994, the FDA issued a safety alert regarding the hazards of precipitation associated with parenteral nutrition (26). This was in response to two deaths and at least two other cases of respiratory distress associated with the use of three-in-one admixtures. Autopsies revealed diffuse microvascular pulmonary emboli linked to a calcium phosphate precipitate in the admixture. Consequently, the FDA safety alert recommends that a filter be used when infusing either central or peripheral parenteral nutrition admixtures. A 0.22-μm filter containing both bacterial retentive and air-eliminating filters has been recommended for use with lipid-free (two-in-one) parenteral nutrient solutions.

Lipid emulsions and three-in-one parenteral nutrient solutions can be safely filtered at a pore size of at least 1.2 μm. A problem with the lipid emulsion in a three-in-one admixture is that it obscures any precipitate. Thus, if a lipid emulsion is needed, a preferable alternative is to employ a two-in-one admixture with a lipid infused separately via a Y-site. Driscoll et al. demonstrated that certain lipid injectable emulsions packaged in plastic containers have baseline abnormal globule size distributions (GSDs) compared with those

packaged in glass containers. When used to compound TNAs, the abnormal GSD profile worsens and produces less stable TNAs than those compounded with lipid injectable emulsions packaged in glass (27).

Replacement Therapy

When the patient has undergone a heavy loss of water and electrolytes, as in severe diarrhea or vomiting, greater than usual amounts of these materials may be initially administered and then maintenance therapy provided. Patients with Crohn disease, AIDS, burns, or trauma are candidates for replacement therapy.

Water Requirement

In normal individuals, the daily water requirement is the amount needed to replace normal and expected losses. Water is lost daily in the urine and feces and from the skin and respiration. The normal daily requirement of water for adults is about 25 to 40 mL/kg of body weight or an average of about 2 L/m^2 of body surface area (28). Nomograms for the determination of body surface area from height and weight are presented in Figure 2.10. Children and small adults need more water per pound of body weight than do larger adults; water requirements correlate more closely with body surface area than with weight, and a guideline to estimate normal daily requirement for water in these patients is as follows:

1. < 10 kg: 100 mL/kg/d
2. 10 to 20 kg: 1,000 mL + 50 mL/kg/d for weight over 10 kg
3. 20 kg to maximum of 80 kg: 1,500 mL + 20 mL/kg/d for weight over 20 kg

However, in the newborn, the volume administered in the first week or two should be about half that calculated from body surface area.

In water replacement therapy for adults, 70 mL/kg/d may be required in addition to maintenance water requirements; a badly dehydrated infant may require an even greater proportion (28). Thus, a 50-kg patient may require 3,500 mL for replacement plus 2,400 mL for maintenance. To avoid fluid overload, especially in elderly patients and those with renal or cardiovascular disorders, monitoring of blood pressure is desirable.

Because water administered intravenously as such may cause osmotic hemolysis of red blood cells and because a patient who requires water generally requires nutrition and/or electrolytes, parenteral administration of water is generally as a solution with dextrose or electrolytes with sufficient tonicity (sodium chloride equivalency) to protect the red blood cells from hemolyzing.

Electrolyte Requirement

Potassium, the primary intracellular cation, is particularly important for normal cardiac and skeletal muscle function. The usual daily intake of potassium is about 100 mEq, and the usual daily loss is about 40 mEq. Thus, any replacement therapy should include a minimum of 40 mEq plus the amount needed to replace additional losses. Potassium can be lost through excessive perspiration, repeated enemas, trauma (such as severe burns), uncontrolled diabetes, disease of the intestinal tract, surgical operation, and the use of such medications as thiazide and loop diuretics. Poorly nourished people, those using very low-calorie diet products, and victims of anorexia nervosa or acute alcoholism also may have low potassium levels (hypokalemia), because they are not taking in enough of the mineral. Symptoms of potassium loss include a weak pulse, faint heart sounds, falling blood pressure, and general weakness. Severe loss of potassium can lead to death. Too much potassium is not a good thing, either. An excess may cause diarrhea, irritability, muscle cramps, and pain. Hyperkalemia can be caused by kidney failure or excessive consumption of potassium-rich foods. Prescribed potassium supplements, potassium-sparing diuretic therapy, angiotensin-converting enzyme inhibitors (e.g., lisinopril), and the indiscriminate use of OTC salt substitutes have also been implicated to induce hyperkalemia.

In cases of severe potassium deficiency, IV electrolyte replacement is usually employed.

The pharmacist who receives a prescription for IV potassium chloride must be careful and check the amount of potassium chloride in the prescription and the infusion rate. Potassium preparations must be diluted with a suitable large-volume parenteral solution, mixed well, and given by slow IV infusion. They are not to be administered undiluted. Undiluted potassium chloride administered intravenously has resulted in fatalities.

The most commonly used concentration of potassium chloride for continuous-infusion maintenance therapy is 20 to 40 mEq/L. With a peripheral line, that concentration may increase to 60 mEq/L, and with a central line, the maximum concentration can be up to 80 mEq/L.

For intermittent potassium replacement therapy in patients with hypokalemia, the usual infusion rate is 10 mEq/h (maximum recommended rate is 20 mEq/h). Because of potassium chloride's ability to effect electrocardiographic (ECG) changes (e.g., progressive increase in height and peaking of T waves, lowering of the R wave, decreased amplitude, and ultimate disappearance of the P waves), most hospitals establish a maximum infusion rate of 10 mEq/h if the patient is not monitored by ECG. For patients monitored by ECG, the usual infusion rate is 20 mEq/h with a maximum infusion rate of 40 mEq/h, depending on the clinical condition of the patient.

For patients in need of aggressive potassium replacement, the potassium serum level should be assessed every 6 hours during the early intensive phase of therapy and once daily after normal potassium serum levels are achieved. For patients whose serum potassium is more than 2.5 mEq/L, the potassium level should be measured after the first 60 mEq is administered. For patients whose serum potassium is <2.5 mEq/L, the potassium level should be measured after the first 80 mEq is administered.

Sodium, the principal extracellular cation, is vital to maintain normal extracellular fluids. Average daily intake of sodium is 135 to 170 mEq (8 to 10 g). The body is able to conserve sodium when this ion is lost or removed from the diet. When there is sodium loss or a deficit, the daily administration of 3 to 5 g of sodium chloride (51 to 85 mEq) should prevent a negative sodium balance. A low sodium level in the body may result from excessive sweating, use of certain diuretics, or diarrhea. Fatigue, muscle weakness, apprehension, and convulsions are among the symptoms of excessive sodium loss. Sodium concentrations can increase when a person does not drink enough water, especially in hot weather, or if kidney function is impaired. Dry, sticky mucous membranes, flushed skin, elevated body temperature, lack of tears, and thirst are among the symptoms of sodium excess. Sodium has been implicated as a causative factor in about 20% of cases of high blood pressure.

Chloride, the principal anion of the extracellular fluid, is usually paired with sodium. Chloride is also important for muscle contraction, balancing the fluid levels inside and outside the cells, and maintaining the acid–base balance of the extracellular fluid. An adequate supply of chloride is necessary to prevent bicarbonate, the second most prevalent anion, from tipping the acid–base balance to the alkaline side. In 1979, a lack of chloride in a brand of infant formula caused metabolic alkalosis in babies who had been exclusively fed that formula. As a result, the Congress passed the Infant Formula Act of 1980, which spells out the nutrients that must be in formulas and establishes quality control procedures for the manufacture of these infant foods. Although other electrolytes and minerals, including calcium, magnesium, and iron, are lost from the body, they generally are not required during short-term parenteral therapy.

Caloric Requirements

Generally, patients requiring parenteral fluids are given 5% dextrose to reduce the caloric deficit that usually occurs in patients undergoing maintenance or replacement therapy. The use of dextrose also minimizes ketosis and the breakdown of protein. Basic caloric requirements may be estimated by body weight; in the fasting state, the average daily loss of body protein is approximately

80 g per day for a 70-kg man. Daily ingestion of at least 100 g of glucose reduces this loss by half.

Parenteral Nutrition

Parenteral nutrition is infusion of enough basic nutrients to achieve active tissue synthesis and growth. It is characterized by the long-term IV feeding of protein solutions containing high concentrations of dextrose (~ 20%), electrolytes, vitamins, and, in some instances, insulin. Among the components used in parenteral nutrition solutions are the following, listed in quantities commonly provided per liter of fluid. The individual components and amounts vary with the patient's needs.

Electrolytes	
Sodium	35 mEq
Potassium	30 mEq
Magnesium	5 mEq
Calcium	5 mEq
Chloride	40 mEq
Acetate	35 mEq
Phosphate	15 mM
Vitamins	
Vitamin A	3,300 USP units
Vitamin D	200 USP units
Vitamin E	10 IU
Vitamin C	200 mg
Niacin	40 mg
Vitamin B_2	3.6 mg
Vitamin B_1	6 mg
Vitamin B_6	6 mg
Pantothenic acid	15 mg
Folic acid	600 mg
Vitamin B_{12}	5 mg
Biotin	60 mg
Vitamin K	150 µg
Essential Amino Acids	
L-Isoleucine	590 mg
L-Leucine	770 mg
L-Lysine acetate	870 mg (free base 620 mg)
L-Methionine	450 mg
L-Phenylalanine	480 mg
L-Threonine	340 mg
L-Tryptophan	130 mg
L-Valine	560 mg
Nonessential Amino Acids	
L-Alanine	600 mg
L-Arginine	810 mg
L-Histidine	240 mg
L-Proline	950 mg
L-Serine	500 mg
Aminoacetic acid	1.19 g

The large proportion of dextrose increases the caloric value of the solution while keeping the volume required to be administered to a minimum. The solution is administered slowly through a large vein, such as the superior vena cava. The superior vena cava is accessed through the subclavian vein immediately beneath the clavicle and near the heart. This permits rapid dilution of the concentrated hyperalimentation fluid and minimizes the risk of tissue or cellular damage due to the hypertonicity of the solution. Generally, final concentrations of dextrose (not greater than 10%) can be given peripherally. Solutions containing more than 10% dextrose should be given via the superior vena cava.

Calcium, usually as calcium gluconate, and phosphate, usually as potassium or sodium phosphate, are frequently present in parenteral admixtures. A significant problem associated with their use is the formation of calcium phosphate, an insoluble precipitate. As mentioned earlier in this chapter, formation of calcium phosphate and deposition of its crystals in lung tissue led to the 1994 FDA safety alert (26).

Many factors have been implicated in the formation of the insoluble precipitate. Among these are the concentration of the individual ions, the salt form of the calcium, the concentration and type of amino acids, the concentration of the dextrose, the temperature and pH of the TPN, the presence of other additives (e.g., cysteine), and the order of mixing. The potential for calcium phosphate precipitation is especially challenging

for compounding neonate and pediatric TPN admixtures because of the small volume they are able to tolerate and the need for aggressive replacement therapy. Thus, pharmacists must be alert to avoid this serious compatibility problem.

Figure 15.34 demonstrates a four-station Nutrimix Macro TPN Compounder. This device can pump four nutritional solutions (dextrose, water, amino acids, fat) simultaneously to compound nutritional admixtures by gravimetric means. The user programs the volume and specific gravity of the fluid to be pumped, and the device calculates the weight of the solution that has to be transferred from the source station to the bag. The fifth load cell serves as a confirmation of the weights programmed versus weights delivered. The picture demonstrates big flexible containers and the fat emulsion in glass. Figure 15.35 demonstrates the Nutrimix Micro TPN Compounder. This automatically dispenses small-volume nutritional additives into flexible containers that already contain a base nutritional admixture. The figure depicts 10 stations of small vials. Typically, TPN Compounders are connected directly to a computer entry program, which automatically calculates the amount of each ingredient to be added and drives the compounder to deliver the required amount. These compounders, for example, Baxa Compounder, also have a bar code reader that "reads" each bottle hung on the machine, thereby reducing the chance of human error. They also deliver ingredients in a specific order to avoid incompatibilities, for example, calcium ion is delivered last, after a rinse to ensure all phosphates have been washed from the tubing.

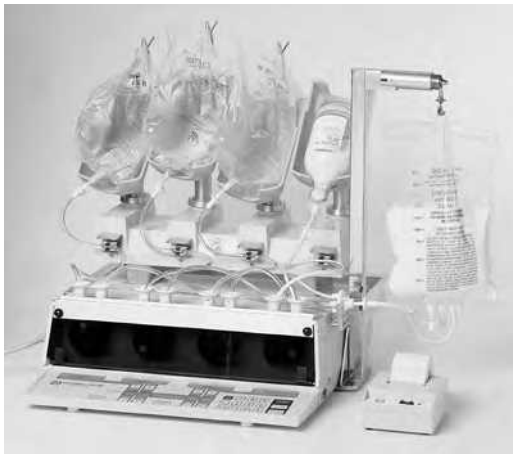

FIGURE 15.34 Nutrimix Macro TPN Compounder. (Courtesy of Abbott Laboratories.)

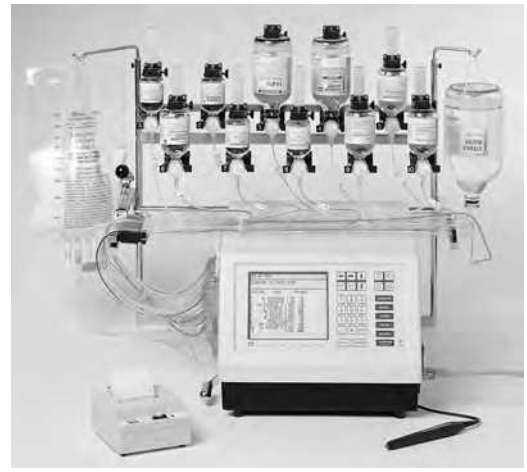

FIGURE 15.35 Nutrimix Micro TPN Compounder. (Courtesy of Abbott Laboratories.)

With the increasing use of parenteral solutions in children, including nutritional solutions, pharmacists are frequently confronted with inquiries concerning the appropriate method of parenteral drug delivery (29). A dilemma with young patients is that they often have a limited fluid capacity caused by disease (e.g., congestive heart failure, renal insufficiency) and limited vascular access. As a consequence, pharmacists are asked whether a medication can be administered along with a parenteral nutrition solution. Although this practice is to be discouraged, it may be the only way to ensure that the patient is receiving adequate nutrition as well as appropriate drug therapy. Furthermore, administering the medication with the nutritive solution, rather than interrupting the feeding to administer medication, makes rebound hypoglycemia less likely. However, the practice of administering medication through a central venous line intended for parenteral nutrition solutions is not without risks. Catheter sepsis and occlusion can result.

Formerly, 1 L of TPN was prepared at a time. However, to conserve time, a 24-hour supply is much more efficient and now the norm. Indeed, if a patient encounters a problem necessitating remake of a bag, the cost difference between one or two 1,000-mL bags and a 2,000-mL bag is not that significant. Waste should not be a consideration because the attending physician should not use the TPN to adjust minutely for a patient's need. Typically, electrolyte requirements exceed the physical compatibilities of the TPN components (e.g., calcium–phosphate compatibilities in lipid-containing TPNs), and when this occurs, the pharmacist should encourage the physician to order a separate infusion to make up the deficiency.

The following abbreviations may be used in hospitals in describing the desired order for parenteral nutrition:

CVTPN (central vein TPN)
TPN (total parenteral nutrition)
PPN (peripheral parenteral nutrition)

Enteral Nutrition

As appropriate, hospitalized and home care patients may receive their nutritional needs through *enteral* rather than *parenteral* means. Enteral nutrition products may be administered orally, via nasogastric tube, via feeding gastrostomy, or via needle–catheter jejunostomy. These products are formulated to contain a variety of vitamins, minerals, carbohydrates, proteins, fats, and caloric requirements to meet the specific needs of patients. While parenteral feeding is appropriate for short-term use in a hospital or long-term care facility or when the gastrointestinal tract is unable to absorb nutrients, enteral feeding is preferable whenever possible. It is just as effective as a source of nutrients, less expensive than parenteral feeding, and has a low potential to cause serious complications.

The defined formula diets may be monomeric or oligomeric (amino acids or short peptides and simple carbohydrates) or polymeric (complex protein and carbohydrates). Modular supplements are used for individual supplementation of protein (ProMod powder, Propac powder), carbohydrate (Moducal powder), or fat (Lipomul liquid) when formulas do not offer sufficient flexibility. For example, a physician may order a powder reconstituted as one quarter strength, half strength, or full strength for a particular patient and have the preparation administered via a nasogastric tube, a feeding gastrostomy, or a needle–catheter jejunostomy.

There is no single classification system for these products, and there are different criteria for evaluating and categorizing them. Caloric density (generally in the range of 1, 1.5, or 2 kcal/mL) influences the density of other nutrients. Protein content is also a major determinant in these products. For patients with diarrhea and cramping, high-osmolality formulas may present difficulty. Low-fat products should be suggested for patients with significant malabsorption, hyperlipidemia, or exocrine pancreatic insufficiency. Medium-chain triglycerides, while providing a useful source of energy in patients with malabsorption, do not provide essential fatty acids.

Originally, enteral feedings contained lactose and presented problems in lactase-deficient individuals. This ingredient has been eliminated from many of the nutritionally complete enteral formulas. For patients with hepatic or renal disease, the sodium and potassium content of the formulations must be considered. For patients receiving warfarin therapy, consideration should be focused on the content of vitamin K in the formulation. Although many products now have less vitamin K than before, caution is still warranted to avoid hypoprothrombinemic alterations in warfarin therapy.

Specific enteral products are selected according to the patient type they serve. For example, a requirement of <2,000 calories per day or increased protein typically applies to an elderly, bedfast patient who is not physically active. This level of support is also advocated for postsurgical patients and those with infection or fractured bones. While requiring fewer calories, these individuals still need normal nutrients, including protein. Such products as Ensure HN, Sustacal, and Osmolite HN are appropriate in this circumstance. Most persons, including those with

poor appetite or cancer, need 2,000 to 3,000 calories per day. The last category of patients is those with daily caloric needs that exceed 3,000 calories. These individuals usually have high protein losses from severe trauma, such as burns, sepsis, or multiple trauma. As in the first example, there are numerous products for these patient categories.

The pharmacist can help select these products, because they do differ in the amounts of carbohydrate, fat, protein, and fiber. Furthermore, these products differ in taste and consumer acceptability criteria, such as mouthfeel and cost. Pharmacists may encounter consumers who wish to self-administer an enteral product. If the intent is to supplement calories or protein in an otherwise healthy individual who simply wishes to ensure a balanced dietary intake, a complete formula can be recommended. However, if it is intended to help a person regain weight lost unexpectedly, the individual should be instead referred to a doctor. Sudden weight loss may indicate a serious pathologic problem requiring medical attention.

Pharmacists can also help manage the cost of these products. Composition (oligomeric or polymeric) and form (ready to use versus powder) influence cost. Generally, the polymeric products are less expensive than the oligomeric products. While powder forms may be less expensive than ready-to-use formulations, there is an indirect cost of labor required in powder preparation.

Pharmacists are often requested to provide information on how to administer medication via enteral tubes (30,31). A first inclination is to use a liquid or crush a tablet. However, there are some important considerations to be made first. The type of tubing, for example, nasoenteric tubes, which clog easily, dictates a liquid medication. Location of the enteral tube is important too. For example, quinolones should not be administered via a jejunostomy tube because these are located beyond the duodenum, the primary site of absorption for quinolones.

When considering the use of liquids, one must be cognizant that these might contain sugar, a "no-no" for the diabetes patient, or large amounts of sorbitol that could induce diarrhea. Hypertonic liquids, for example, nystatin, should be diluted with 10 to 30 mL of water to reduce cramping, vomiting, and diarrhea in the patient. Bulk-forming laxatives and cholestyramine resin should not be used because of the possibility of clogging the tubing even when prepared appropriately.

Most immediate-release tablets can be crushed and mixed with water to create a slurry for administration down an enteral tube. However, sustained-release tablets, enteric-coated tablets, or those containing carcinogenic medicines cannot be crushed and administered as a slurry. Pellets from some microencapsulated products (e.g., Cardizem CD, Effexor XR, Micro-K) can be poured down a feeding tube provided they are not crushed.

The pharmacist must also be cognizant that enteral feedings can alter the absorption of certain drugs, for example, warfarin, levothyroxine, and quinolones. So the timing of administration is critical. For a patient maintained on phenytoin, enteral feedings can reduce absorption and subsequently plasma levels by as much as 75%. Thus, enteral tube feedings should be withheld for 2 hours prior to or after phenytoin administration.

Intravenous Infusion Devices

Since the early 1970s, the use of the IV route to administer drugs has become increasingly popular. In 1989, it was estimated that about 40% of drugs and fluid used in hospitals was administered intravenously (28). This increase has affected the development and use of mechanical infusion devices. Advances in infusion technology and computer technology have resulted in devices with extremely sophisticated drug delivery capabilities (e.g., multiple-rate programming, pumps) (32). As a result, these cost-efficient devices provide greater accuracy and reliability of drug delivery than the traditional gravity-flow infusion methods. They also help reduce the fluid volume attributable to the medication infusion and decrease the need for monitoring fluid input, saving nurses' time. Furthermore, multiple-drug dosages can be administered, and incompatible drugs can be administered separately (28).

Originally, the disadvantages associated with these mechanical devices included the initial capital investment and extensive in-service education. Furthermore, the influence of infusion pump devices on the delivery of a drug was not fully recognized by clinicians. For example, intrinsic factors (e.g., operating mechanisms, flow accuracy, flow continuity, occlusion detection) and an extrinsic factor (back pressure) may have altered the rate of drug delivery and the therapeutic response of the patient.

Pumps were classified by their *mechanism of operation* (peristaltic, piston, diaphragm), *frequency or type of drug delivery* (continuous or intermittent, bolus dosing, single solution or multiple solution), or *therapeutic application* (PCA) (33). Current research focuses on the influence of drug delivery by these devices and the creation of new technologies (e.g., implantable pumps, pumps with chronobiologic applications, osmotic pressure devices, and open- or closed-loop systems) (33). Today, several features are to be considered in selecting an infusion pump system. Most important is patient safety, then convenience and versatility of the device and cost efficiency.

In terms of enhanced safety, there should be a flow check occlusion alarm system that monitors in-line resistance of incremental back pressure. Also, does the device have a flow rate calculation system that is automatic after the volume and time are selected? Does it protect against inadvertent gravity free flow? Against tampering?

In terms of greater convenience and versatility, does the infusion device possess programmed delivery? Is the system user friendly, easy to understand and use? Does it have an incremental flow rate, and what is the minimum amount that can be delivered incrementally? Some newer infusion devices can deliver 0.1 mL per hour. Does it have an automatic restart feature once an occlusion clears, and can automatic piggybacking be employed to accommodate secondary medications? What is the volume capacity? Some infusion devices can accommodate a range of volumes from 0.1 to 9,999 mL (e.g., Baxter's 6060 Multitherapy Infusion Pump, 0.1 to 999.9 mL in 0.1-mL increments or 1,000 to 9,999 mL in 1-mL increments).

In terms of cost efficiency, can the device be used with standard administration sets? For example, the Baxter Laboratories standard administration sets are compatible with the Flo-Gard 6201 Volumetric Infusion Pump. This eliminates the need for costly disposable sets and reduces the potential for waste.

ALARIS Medical Systems (http://www.alarismed.com/products/infusion_medley.shtml) markets a variety of infusion systems. One of these is the Medley System, which uses modularity, a common user interface, and the Guardrails Safety Software suite of applications, which improve medication safety by using total quality management principles for administration at the point of care. Table 15.7 lists several infusion devices used in parenteral nutrition support and features associated with each.

The Symbiq Infusion System with Hospira MedNet Software (Fig. 15.36) requires users to select an entry from the drug library for all drug delivery programs. Human factors design was incorporated to provide intuitive ease of use, accelerate staff acceptance, and reduce the risk of programming errors. Hospitals can configure the device to focus on patient needs for each care area. Wireless communication enables customers to gather infusion data remotely. Hospitals can track medication risk events and generate quality assurance reports.

SPECIAL CONSIDERATIONS ASSOCIATED WITH PARENTERAL THERAPY

Standardization of Intravenous Concentrations

Parenteral medications, including IV administration, account for twice as many errors as other methods of administration (i.e., 3% versus 1.4%) (34). Consequently, stakeholders including representatives from the ASHP, Infusion Nurses Society, the Joint Commission, National Patient Safety Foundation, Institute for Safe Medication Practices, and the USP met and called for

Table 15.7 SELECTED INFUSION DEVICES USED IN LARGE-VOLUME INFUSIONS

PUMP	MANUFACTURER	FEATURES
Colleague CX	Baxter	Micro and macro rate range, basic delivery programming, and ability to piggyback secondary medications. Pump settings include patient weight limits, air detection sensitivity, rate limits, and medication parameters. The dose calculator may be used for up to nine delivery modes. Pump includes a label library of 64 drug and therapy labels. Guardian feature gives a warning when programmed doses are not within institutional limits. This feature also displays overrides which are stored in the pump's history log for added security.[a]
Symbiq	Hospira	Simple to use and program. Allows hospitals to define soft and hard limits for up to 400 medications. Ability to track medication risk events and generate quality assurance reports. Rate accuracy of the Symbiq system is ± 5% across the entire delivery range (0.1–1,000 mL/h) allowing hospitals to meet the needs of all care areas.[b]
Plum A +	Hospira	Easy-to-read display with programming options that include automated piggyback delivery, automated concurrent delivery, programmable standby settings, multistep delivery, loading dose automation, and programmable delayed starts. Can be upgraded with Hospira MedNet Software[c]
Outlook safety infusion	B. Braun	Has DoseScan technology that allows the clinician to match the right drug to the right patient. This protects against the number one cause on IV medication errors. Outlook also has DoseGuard technology alerting the clinician when a dose limit is exceeded.[d]
Flo-Gard	Baxter	Flow check occlusion alarm (an in-line resistance display of incremental back pressure), flow rate calculation is automatic after volume and time are selected, slide clamp option offers an additional step to protect against inadvertent gravity free flow, front panel lockout protects against tampering, automatic restart once occlusion clears, automatic piggybacking of secondary medication, programmed delivery profile allows up to 10 steps, and individualizing control of infusion ramping and tapering[e]

[a]http://www.baxter.com/products/medication_management/infusion_pumps/large_volume_infusion_pumps/colleague/index.html
[b]http://www.hospira.com/Products/Symbiqinfusionsystem.aspx
[c]http://www.hospira.com/Products/plumaplusinfusionsystem.aspx
[d]http://www.bbraunusa.com/index.cfm?uuid=598A9770D0B759A1E35DC94F1D834815
[e]http://www.baxter.com/products/medication_management/infusion_pumps/large_volume_infusion_pumps/flo_gard/index.html

standardization in IV use, especially with regard to infusion concentrations and dosage units by 2012 (35).

Different health care settings use different concentrations of IV medications, which foster errors because pharmacists and health care practitioners have to recalculate and recompound medications for individual patients. Thus, this group called upon pharmaceutical manufacturers and the FDA to create products available in "ready-to-administer" form. That is, all IV medications should be available to the end user in the most readily available form, which does not have to be manipulated. Further, this group also recommended that medications, which cannot be provided in "ready-to-administer" dosage forms, be compounded exclusively in the pharmacy whenever possible.

Summit short-term goals included the development of national standards for IV medication use, requesting an expedited FDA regulatory process of new

FIGURE 15.36 A portable disposable system for infusion or irrigation therapy. (Courtesy of Hospira, Inc.)

concentrations, promoting universal use of intelligent infusion devices, and developing a business case for IV safety. Long-term goals proposed were advocating for standardized medication bar codes, establishing multidisciplinary safety training during professional schooling, developing IV safety tools and resources, exploring new methods for reporting errors and sharing lessons learned, and establishing a research agenda for IV safety.

Look-Alike Products

To prevent mix-ups in which one drug product is selected in error because of its similarity in appearance to another, storage shelves should be labeled to warn about this possibility. A recent example of a serious medication error occurred when Lupron Depot-Ped 11.25 mg (Leuprolide acetate-TAP), a 1-month gonadotropin-releasing analog used to treat central precocious puberty, was confused with Lupron Depot 3 Month. The latter is administered every 3 months to women with endometriosis or uterine leiomyomata (fibroids). The product releases its active ingredient over 3 months. Inadvertently, the second product was administered to children and caused them to receive therapy that was too low. It led attending physicians to believe that the drug therapy was a failure. One reason for the confusion was that the pharmacy staff inadvertently selected the wrong computer code during order entry, and this was repeated when, after referencing patients' drug profiles for monthly refills, the staff continued to select the 3-month dosage form instead of the monthly pediatric dosage form (36).

The manufacturer actually anticipated the problem and placed a picture of either an adult or a child to help discriminate the products. Unfortunately, price stickers were placed directly over the pictures and obscured the visual cues. To compound the problem, the products were taken to the pediatricians' offices, where the nurses administering the product also failed to note the mistake. The mistake might not have been detected except that a parent of one of the children questioned the pharmacy to ask about the increased prescription cost; Lupron Depot 3-Month costs more than Lupron Depot-Ped.

In the recent past, Heparin 10- and 10,000-U/mL vials from Baxter Laboratories were of the same size and both had blue labels, just differing in the degree of blue shading. A pharmacy technician inadvertently loaded an automated cabinet, that is, Pyxis, with the 10,000-U/mL vial instead of the 10-U/mL flush in the neonatal unit. Subsequently, the nurses pulled the drug and did not read the label. Then the catheters of several premature infants were flushed with doses 1,000 times greater than thought. The infants who received multiple doses developed bleeding and four ultimately died. The result was the 10,000-U/mL heparin product being removed from the hospital formulary and only one strength, that is, 10 U/mL is carried for a catheter flush (37). In addition, flush protocols have been rewritten to change the saline flush eliminating heparin altogether.

Adsorption of Drugs

Numerous studies have demonstrated that some drugs are adsorbed to the inner lining of IV containers and tubing or administration sets. Most often these include proteins and peptides. Some of the drugs that have been

implicated in this phenomenon include insulin and monoclonal antibodies, for example, laronidase (Aldurazyme). To obviate the adsorption phenomenon, human albumin is added. For laronidase, for example, the concentration of human albumin is 0.1% in 0.9% sodium chloride injection.

The adsorption of insulin onto glassware and tubing depends on several factors, including concentration of insulin, contact time of insulin with glass and tubing, flow rate of the infusion, and presence of negatively charged proteins (human serum albumin). Plastic IV infusion sets have reportedly removed up to 80% of a dose, but 20% to 30% is more common. The percent adsorbed is inversely proportional to the insulin concentration and will take place within 30 to 60 minutes. Because this phenomenon cannot be easily and accurately predicted, it is essential to monitor the patient.

Pharmacists must be cognizant of this phenomenon and take appropriate steps to prevent it. The significance of the loss is magnified with drugs that are used in small quantities because a small amount lost to adsorption results in a higher percentage loss of the drug delivered to the patient. One method to minimize this is to administer infusions through short lengths of small-diameter tubing made of inert plastics.

Absorption (Sorption) of Drugs

Plastic materials used for IV drug delivery may also facilitate drug absorption into the material itself. Absorption into a plastic material is most important to consider, as this phenomenon has been shown to occur in IV containers, delivery sets, syringes, filters, and other plastic apparatus, particularly associated with flexible PVC and can decrease the amount of drug delivered to the patient. This provides a hydrophobic environment for drug migration into the material. Most drug–plastic container interactions result from drug absorption by the DEHP in flexible PVC bags and tubing.

Examples of drugs lost from aqueous solutions during infusion through flexible PVC tubing include the following:

- Amiodarone HCl
- Chlorpromazine HCl
- Diazepam
- Lorazepam
- Nitroglycerin (NTG)
- Promazine HCl
- Promethazine HCl
- Thiopental sodium
- Thioridazine HCl
- Trifluoperazine HCl
- Warfarin sodium

NTG, for example, should always be prepared in glass and/or a plastic known to be compatible with it. It is adsorbed (40% to 80% of total dose) to PVC. Previously, some manufacturers packaged NTG for IV use with special non-PVC tubing to avoid loss (<5%) of the drug into the tubing during administration. However, many manufacturers have discontinued supplying NTG IV in the US market. Baxter Healthcare and Abbott Laboratories still manufacture NTG IV for injection, that is, 5 mg/mL. Baxter Healthcare, Hospira, and B. Braun market NTG premixed 100, 200, and 400 µg/mL in 250- and 500-mL glass bottles in 5% dextrose. However, the administration set, including tubing, is sold separately from the medication.

Special high-density polyethylene administration sets are recommended for NTG IV administration. Hard solid plastics, such as polyethylene and polypropylene, generally do not adsorb NTG. The amount of NTG adsorption depends on such factors as concentration, flow rate (e.g., a slow flow rate and long tubing increase the loss of NTG), surface area of the tubing, and contact time with the tubing.

IV NTG should be regulated by automatic infusion equipment (pumps, controllers) to enhance consistent dose administration. However, infusion pumps may fail to occlude the non-PVC infusion sets completely because the non-PVC tubing is stiffer than standard PVC tubing. Excessive flow at low infusion rate settings may occur, causing alarms or unregulated gravity flow when the infusion pump is stopped. This could lead to overinfusion of NTG.

Some practitioners have responded by using the PVC tubing with the NTG and working around the problem. This is justified by some in that even though a great amount of drug is lost, the amount of drug the patient receives is based on hemodynamic functions. But when the previous set is replaced, retitration of the drug is necessary. To allay this problem, several manufacturers market non–PVC-containing pump administration sets.

In similar fashion to coping with the adsorption phenomenon of drugs to IV containers and/or administration sets, pharmacists must also be cognizant of the absorption phenomenon with flexible PVC materials and take appropriate steps to prevent it. The significance of the loss is magnified with drugs that are used in small quantities because a small amount lost to absorption results in a higher percentage loss of the drug delivered to the patient.

Handling and Disposal of Chemotherapeutic Agents for Cancer

In 1982, health care personnel became aware of environmental contamination from handling cytotoxic agents. Mutagenic and allergic case reports began to emerge in the literature, and in 1985, in response, the American Society of Hospital Pharmacists (now the ASHP) published its initial technical assistance bulletin on handling cytotoxic and hazardous drugs. This was revised in 1990. In 2006, ASHP issued their Guidelines on Handling Hazardous Drugs that replaced the technical assistance bulletin (38). These guidelines provide recommendations for the safe handling of hazardous drugs, environmental and ventilation controls, personal protective equipment, work practices, and hazardous waste containment and disposal. Unlike USP <797>, this is not an enforceable document; however, practitioners should be familiar with the ASHP guidelines along with publications from OSHA and NIOSH. Appendices include use of personal protective equipment, BSCs, and isolators, reducing exposure to hazardous drugs during administration, spill kits, and treatment of workers with direct skin or eye contact with hazardous drug.

IRRIGATION AND DIALYSIS SOLUTIONS

Solutions for irrigation of body tissues and for dialysis are subject to the same stringent standards as parenteral preparations. The difference is in use. Irrigation and dialysis solutions are not injected into the vein but employed outside of the circulatory system. Because they are generally used in large volumes, they are packaged in large containers, generally of the screw cap type, which permits rapid pouring. Dialysis solutions generally appear similar to IV bags, and irrigation solutions are screw-capped or bagged, so caution is necessary to avoid selecting the wrong product.

It is important to note that hemodialysis and peritoneal dialysis procedures have the capability to enhance the plasma clearance of a drug. In instances of clearance by 30% or more, supplemental dosing may be required or dosing after dialysis should be considered. Variations in duration of dialysis, flow rates, dialysis membrane type, and whether peritoneal dialysis is continuous or intermittent, all affect the extent of drug clearance. Drugs that have been shown to be cleared from plasma by hemodialysis, for example, include acetaminophen, captopril, cefaclor, imipenem, lithium, and metformin.

Irrigation Solutions

Irrigation solutions are intended to bathe or wash wounds, surgical incisions, or body tissues. Examples are presented in Table 15.8.

Dialysis Solutions

Dialysis is separation of substances from one another in solution by taking advantage of their differing diffusibility through membranes. *Peritoneal dialysis* solutions, allowed to flow into the peritoneal cavity, are used to remove toxic substances normally excreted

Table 15.8 EXAMPLES OF IRRIGATION SOLUTIONS

SOLUTION	DESCRIPTION
Acetic Acid Irrigation, USP	0.25% solution applied topically to bladder for irrigation; pH 2.8–3.4, calculated osmolarity 42 mOsm/L; during urologic procedures, washes away blood and surgical debris while maintaining suitable conditions for tissue and permitting unobstructed view.
Neomycin and Polymyxin B Sulfates Solution for Irrigation, USP	Sterile urogenital solution contains 57 mg neomycin sulfate (40 mg neomycin) and polymyxin B sulfate 2,00,000 U/mL; topical antibacterial in continuous irrigation of bladder; pH 4.5–6; 1 mL added to 1 L 0.9% NaCl, administered via three-way catheter at 1 L/24 h (~ 40 mL/h)
Ringer Irrigation, USP	NaCl 8.6 g/L, potassium chloride 0.3 g/L, calcium chloride 0.33 g/L in purified water, in same proportions as in Ringer injection. Sterile and pyrogen-free; used topically to irrigate; must be labeled NOT FOR INJECTION; pH 5–7.5, calculated osmolarity 309 mOsm/L
Sodium Chloride Irrigation, USP	NaCl in water for injection; 77, 154 mEq/L of each sodium, chloride in 0.45% and 0.9% solutions, respectively; NaCl irrigation pH 5.3 approx.; 0.45%, 0.9% solutions calculated osmolarity 154, 308 mOsm/L, respectively. Employed topically to wash wounds and body cavities where absorption into blood not likely; also employed as enema; for simple evacuation, 150 mL; for colonic flush, 1,500 mL may be used.
Sterile Water for Irrigation, USP	Sterilized and suitably packaged. Label designations FOR IRRIGATION ONLY, NOT FOR INJECTION must appear prominently. Must not contain any antimicrobial or other added agent

by the kidney. In cases of poisoning or kidney failure, or in patients awaiting renal transplants, dialysis is an emergency lifesaving procedure. Solutions are commercially available containing dextrose as a major source of calories, vitamins, minerals, electrolytes, and amino acids or peptides as a source of nitrogen. The solutions are made to be hypertonic (with dextrose) to plasma to avoid absorption of water from the dialysis solution into the circulation.

Peritoneal dialysis uses the principles of osmosis and diffusion across the semipermeable peritoneal membrane and includes osmotic and chemical equilibration of the fluid within the peritoneal cavity with that of the extracellular compartment. The semipermeable peritoneal membrane restricts the movement of formed elements (e.g., erythrocytes) and large molecules (e.g., protein) but allows the movement of smaller molecules (e.g., electrolytes, urea, water) in both directions across the membrane according to the concentration on each side of the membrane, with net movement occurring in the direction of the concentration gradient. Intraperitoneal instillation of dialysis solutions containing physiologic concentrations of electrolytes allows for movement of water, toxic substances, and/or metabolites across the membrane in the direction of the concentration gradient, removing these substances from the body following drainage of the solution from the peritoneal cavity (i.e., outflow).

Hemodialysis is employed to remove toxins from the blood. In this method, the arterial blood is shunted through a polyethylene catheter through an artificial dialyzing membrane bathed in an electrolyte solution. Following the dialysis, the blood is returned to the body circulation through a vein.

Various dialysis solutions are available commercially, and the pharmacist may be called upon to provide them or to make adjustments in their composition.

PHARMACEUTICS CASE STUDY

SUBJECTIVE INFORMATION

You have been asked to prepare progesterone injection 200 mg/mL in sesame oil for a physician's office. How will you formulate it?

OBJECTIVE INFORMATION

Progesterone is sparingly soluble in vegetable oils, and cosolvents must be used to obtain the 200-mg/mL concentration. Hormone injections in oil sometimes contain benzyl alcohol and/or benzyl benzoate. Benzyl alcohol, in addition to being a solvent, has preservative and anesthetic properties. Benzyl benzoate can be metabolized to benzyl alcohol and benzoic acid.

ASSESSMENT

It is apparent that a cosolvent system must be used, possibly consisting of sesame oil, benzyl alcohol, and benzyl benzoate, similar to other hormone injections. The product must be sterilized and suitably packaged.

PLAN

After reviewing the literature and the formulations for other hormone in oil injections, you determine that the formula will consist of benzyl alcohol 20%, benzyl benzoate 20%, and sesame oil 60%. The progesterone will be dissolved in the solvent system and be placed in a suitable container for dry heat sterilization. The dry heat sterilization will be validated but will start with 150°C for 1 hour. After sterilization, the injection will be aseptically packaged and labeled.

CLINICAL CASE STUDY

M.N. is an 18-year-old AA female diagnosed with type 1 diabetes mellitus 3 months ago. Today she presents to the clinic for her regular checkup. Yesterday, she had her local pharmacist download her blood glucose (BG) levels for the past month from her home monitor. M.N. takes these to her physician for interpretation. M.N. tells her physician that she is "concerned about some of her BG levels, especially in the morning." She notes that her morning BG levels are usually around 160 mg/dL. She also states that she has been waking up from nightmares around 3 AM a few times every week. Three nights ago, after waking up, she checked her BG level at 3 AM, and her value was 192 mg/dL. She repeated the test to ensure that there was no error with her technique, and her reading was 188 mg/dL. Upon further questioning, the physician determines that M.N.'s knowledge of diabetes is increasing. However, the physician believes that M.N. would benefit from further education on diet and exercise. Because M.N. is newly diagnosed, the physician also wants her to review her insulin injection technique "from start to finish."

Meds: Humulin (NPH/regular) 70/30 18 U before breakfast and 9 U before dinner.

Develop a pharmaceutical care plan addressing the following problems:
Hyperglycemia at 3:00 AM, 8:00 AM
Nutrition and exercise
Insulin injection technique

CLINICAL CASE STUDY CONT.

PHARMACEUTICAL CARE PLAN

S: M.N. is seen in the clinic for a regular checkup by her primary care physician. She is concerned with some BG levels that she has recorded over the past month. She says she has had nightmares a few times every week at that time. M.N. has been compliant with her insulin regimen and has requested additional education on insulin injection technique along with nutrition and exercise information.

O: Weight: 120 lb (54.5 kg)
See graph for average BG levels for April.
Current medications:
Humulin (NPH/Regular) 70/30 18 U before breakfast and 9 U before dinner.

A:
1. M.N.'s BG is uncontrolled with hyperglycemia at 3:00 AM and 8:00 AM. Hyperglycemia at these times is most likely because the patient is without appropriate insulin coverage throughout the night. M.N. checked her BG level at 3:00 AM after awakening from a nightmare, and the level was found to be elevated. The nightmares are an indication of high BG levels during sleep.
2. M.N. would like to review appropriate insulin injection preparation and administration technique with the pharmacist.
3. M.N. is a newly diagnosed patient and would like further information regarding diet and exercise.

P:
1. Because M.N.'s BG levels at 3:00 AM and 8:00 AM have been running high, it is appropriate to adjust the dinnertime dose of insulin. With a dinnertime dose of less than 10 U, the UKPDS suggests that the dose of insulin be increased by 1 U (if particular injection dose is more than 10 U, increase it by 2 U). Therefore, M.N.'s Humulin 70/30 dose may be increased to 11 U at dinnertime to provide control during the night. M.N. should be instructed to monitor her 8:00 AM BG levels and three consecutive 3:00 AM BG levels and report these to her physician. If M.N. finds that her BG level after dinner is falling too low, she should increase her meal with one additional carbohydrate exchange.
2. The main points regarding insulin injection technique include in order:
   Roll the vial of insulin in palms to warm insulin and disperse it evenly.
   Swipe the top of the vial once with an alcohol swab.
   Swipe the body site for the injection with a different alcohol swab.
   Pull air into the syringe. The amount of air pulled in should be equal to the amount of insulin that will be needed for the injection.
   Insert the needle into the vial using the anticoring technique (demonstrated to the patient) and push the air into the vial.
   While holding onto the vial and the syringe, invert both and remove the desired dose of insulin.
   Remove the syringe from the vial.
   At injection site, gather a fold of skin.
   Insert the needle at 90 degree angle to injection site.
   Inject insulin.
   Remove the needle from skin.
   Discard the syringe in designated container for disposal.
3. Refer the patient to a registered dietitian for tailored meal planning. Some points M.N. should keep in mind:

CLINICAL CASE STUDY CONT.

Eat three scheduled meals per day. Skipping meals can cause BG to be uncontrolled.
Watch for serving sizes and control portion sizes.
Balance diet between carbohydrates, proteins, and fats.
It is important to monitor BG levels regularly.
Instruct the patient to make exercise a regular part of her day. Explain that exercise can help lower BG levels and any extra effort can be beneficial (e.g., parking further away from the store, taking the stairs instead of an elevator). Caution: Start off slowly when beginning a new exercise program. For example, the patient may begin walking 3 days per week for 20 minutes and increase as tolerated. Instruct the patient to discuss the exercise regimen with a physician.

APPLYING THE PRINCIPLES AND CONCEPTS

Group Activities

1. Prepare a chart outlining the differences in storage, administration, duration of activity, and compatibility of the different insulin products.
2. Develop an instruction sheet for health care professionals for proper use of an ampul (consider technique, reuse, Luer-Lok).
3. Review articles about parenteral and enteral nutrition and highlight the important advantages and disadvantages of each type.
4. Aseptic Technique Development:
   - Properly gown with personal protective equipment and gloves and assess hand hygiene by sampling the gloves with agar plate medium.
   - Perform media-fill testing using Soybean-Casein Digest to develop and practice aseptic technique.
   - Practice aseptic volume transfers using a solution with the addition of methylene blue to demonstrate caution needed when preparing hazardous parenteral drugs.
5. Locate the standard operational procedure from your institution's IV room and compare it to the current USP <797> standards.
6. Discuss available references needed to determine:
   - if an oral dosage form can be crushed and added to an enteral feeding
   - the availability of alternative dosage forms for use in an enteral feeding
   - if it is acceptable to deliver a drug product through an enteral feeding tube
7. Discuss common technique mistakes when preparing compounded sterile products, and discuss how these technique mistakes can be overcome and corrected.

Individual Activities

1. Summarize the five general types of injectable materials and identify which can be used directly/require reconstitution before administration: (*a*) injection, (*b*) for injection, (*c*) injectable emulsion, (*d*) injectable suspension, and (*e*) for injectable suspension.
2. Make a list of drugs that can cause electrolyte imbalance.
3. In a table, summarize the advantages and disadvantages of IV administration.
4. List examples of compounded sterile products from each risk category, that is, low, medium, and high.

APPLYING THE PRINCIPLES AND CONCEPTS (CONT.)

5. Given simulated, daily blood glucose levels, follow a diabetes diet for 1 week, and calculate your insulin requirements at each meal.
6. Review the daily requirements of electrolytes, vitamins, and essential/nonessential amino acids, and then compare these values to your daily dietary intake and the contents found within a representative daily multivitamin product.
7. Perform a primary literature search that addresses the use of standardized versus individualized TPN orders, and compare/contrast the pros/cons of each.

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