Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems

TENTH EDITION

Loyd V. Allen, Jr.
Howard C. Ansel

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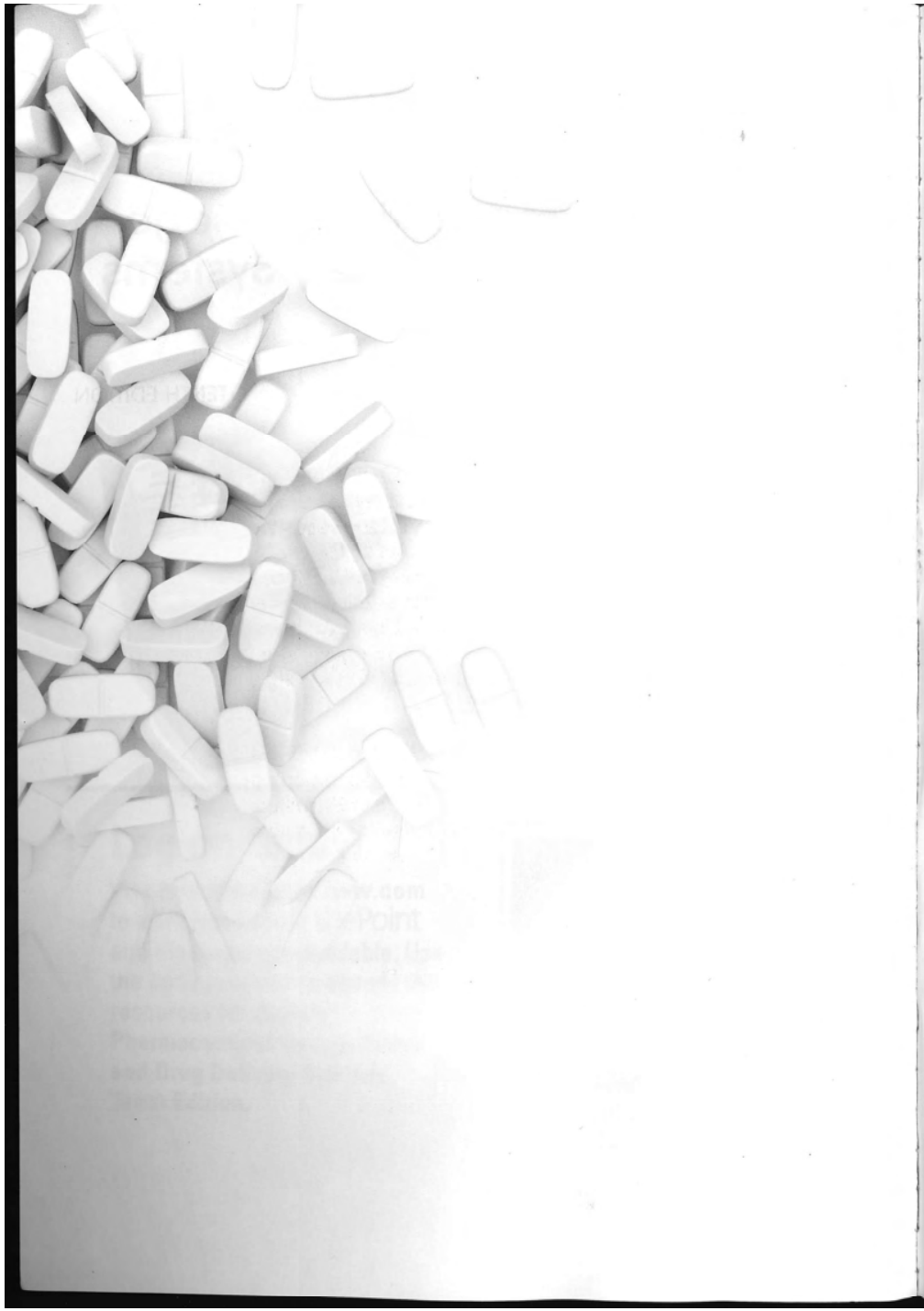

ANSEL'S PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS

TENTH EDITION

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

Howard C. Ansel, PhD
Professor and Dean Emeritus
College of Pharmacy
The University of Georgia
Athens, Georgia

Wolters Kluwer
Health
Philadelphia • Baltimore • New York • London
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Editor: Sirkka Howes
Product Development Editor: Jenn Verbiar
Production Project Manager: Priscilla Crater
Design Coordinator: Holly Reid McLaughlin
Manufacturing Coordinator: Margie Orzech
Compositor: SPi Global

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Preface

The purpose of this text is to introduce pharmacy students to the principles, practices, and technologies applied in the preparation of pharmaceutical dosage forms and drug delivery systems. An integrated presentation is used in this textbook to demonstrate the interrelationships between pharmaceutical and biopharmaceutical principles, product design, formulation, manufacture, compounding, and the clinical application of the various dosage forms in patient care. Regulations and standards governing the manufacturing and compounding of pharmaceuticals are also presented.

As has been the hallmark of this textbook since its first edition more than 40 years ago, each chapter is written at a level consistent with the requirements of students being introduced to this area of study. Because this textbook often is used early in the professional curriculum, it contains important introductory topics, such as the historical development of drugs and pharmacy, the role of the pharmacist in contemporary practice, standards of the United States Pharmacopeia–National Formulary, systems and techniques of pharmaceutical measurement, pharmaceutical and biopharmaceutical principles applicable to drug product development, current good manufacturing practice and current good compounding practice standards, and the regulatory process by which manufactured pharmaceuticals are approved for marketing by the federal Food and Drug Administration.

The detailed presentation of each dosage form includes physical, physicochemical, and clinical discussions. The new activities at the end of each chapter are designed to provide opportunities for creative thought and application of the content.

CONTINUING FEATURES IN THIS EDITION

The tenth edition presents another significant rewrite of some of the sections of the previous edition and many updated and new figures. We have retained the eight divisions, containing 20 chapters, based upon traditional pharmaceutical pedagogy. This allows the systematic presentation of dosage forms according to their physical form and characteristics. The "Physical Pharmacy Capsules" introduced in the sixth edition continue to emphasize important underlying pharmaceutical principles.

Other features that we have retained from the ninth edition include:

1. Enhanced considerations of dosage form design and formulation.
2. Two case studies (one pharmaceutical and one clinical) in each of the dosage form chapters (see "Explanation of the SOAP Format for Case Studies" later in the preface).
3. An update of the current good compounding practices.
4. Expanded clinical considerations in the use of the dosage forms.
5. Two glossaries in the appendices, one listing the dosage forms and one listing the pharmaceutical terms.
6. Chapter objectives that inform students what they will master in each chapter.
7. An "Applying the Principles and Concepts" section at the end of each chapter that provides faculty and students with group and individual activities for the application of the material in each chapter.

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4 Dosage Form Design: Pharmaceutical and Formulation Considerations

OBJECTIVES

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

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

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

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

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

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

THE NEED FOR DOSAGE FORMS

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

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

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

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

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

[a]Examples are of the lowest strength capsule or tablet commercially available for each listed drug.

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

GENERAL CONSIDERATIONS IN DOSAGE FORM DESIGN

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

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

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

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

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

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

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

During childhood and even adulthood, a person may have difficulty in swallowing solid dosage forms, especially uncoated tablets. For this reason, some medications are formulated as chewable tablets. Many of these tablets are comparable in texture to an after-dinner mint and break down into a pleasant-tasting creamy material. Newly available tablets dissolve in the mouth in about 10 to 15 seconds; this allows the patient to take a tablet but actually swallow a liquid. Capsules have been found by many to be more easily swallowed than whole tablets. If a capsule is moistened in the mouth before it is swallowed, it becomes slippery and readily slides down the throat with water. Also, a teaspoonful of gelatin dessert, liquid candy, or syrup placed in the mouth and partially swallowed before placing the solid dosage form in the mouth aids in swallowing them. Also, if a person has difficulty in swallowing a capsule, the contents may be emptied into a spoon, mixed with jam, honey, or other similar food to mask the taste of the medication and swallowed. There is also a device called the Pill Glide that can be used to help swallow solid dosage forms. Medications intended for the elderly are commonly formulated into oral liquids or may be extemporaneously prepared into an oral liquid by the pharmacist. In many patient-care facilities, as nursing homes, tablet-crushing devices are utilized by the nursing staff preparatory to mixing with food (as applesauce) for administration. However, certain tablets and capsules that are designed for controlled release should not be crushed or chewed, because that would interfere with their integrity and intended performance.

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

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

Preformulation Studies

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

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ingredients in the fabrication of a dosage form.

Physical Description

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

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

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

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

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

Formulation and stability difficulties arise less frequently with solid dosage forms than with liquid preparations, and for this reason, many new drugs first reach the market as tablets or dry-filled capsules. Later, when the pharmaceutical problems are resolved, a liquid form of the same drug may be marketed. This procedure is doubly advantageous, because for the most part, physicians and patients alike prefer small, generally tasteless, accurately dosed tablets or capsules to the analogous liquid forms. Therefore, marketing a drug in solid form first is more practical for the manufacturer and suits most patients. It is estimated that tablets and capsules constitute the dosage form dispensed 70% of the time by community pharmacists, with tablets dispensed twice as frequently as capsules.

Microscopic Examination

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

Heat of Vaporization

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

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

PHYSICAL PHARMACY CAPSULE **4.1**

Heat of Vaporization

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

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

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PHYSICAL PHARMACY CAPSULE 4.1 CONT.

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

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

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

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

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

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

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

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

Melting Point Depression

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

The Phase Rule

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

PHYSICAL PHARMACY CAPSULE 4.2

Melting Point Depression

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

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

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

$$\Delta T = \frac{2.303\ RTT_0}{\Delta H_f} \log N_A$$

where

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

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

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

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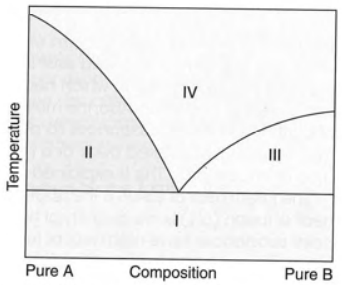
PHYSICAL PHARMACY CAPSULE 4.3

The Phase Rule

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



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

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

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

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

$$F = C - P + X$$

where

F is the number of degrees of freedom,
C is the number of components,
P is the number of phases, and
X is a variable dependent upon selected considerations of the phase diagram (1, 2, or 3).

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

EXAMPLE 1

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

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

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

EXAMPLE 2

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

PHYSICAL PHARMACY CAPSULE 4.3 CONT.

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

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

EXAMPLE 3

At the eutectic point,

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

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

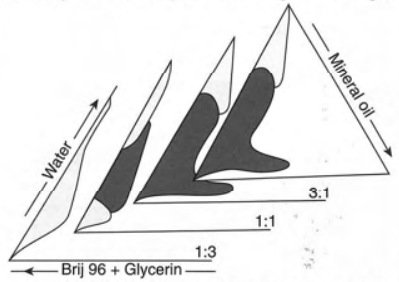
Phase diagrams are valuable for interpreting interactions between two or more components, relating not only to melting point depression and possible liquefaction at room temperature but also to the formation of solid solutions, coprecipitates, and other solid-state interactions.

PHYSICAL PHARMACY CAPSULE 4.4

Triangular (Three-Component) Phase Diagram

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

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



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

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

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Particle Size

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

Polymorphism

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

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

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

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

Solubility

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

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

PHYSICAL PHARMACY CAPSULE 4.5

Solubility and Particle Size

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

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

where

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

The equation can be used to estimate the decrease in particle size required to increase solubility. For example, a desired increase in solubility of 5% would require an increase in the S/S_0 ratio to 1.05; that is, the left term in the equation would become log 1.05. If a powder has a surface tension of 125 dynes/cm, molar volume of 45 cm^3, and temperature of 27°C, what is the particle size required to obtain the 5% increase in solubility?

$$\log 1.05 = \frac{(2)\ (125)\ (45)}{(2.303)\ (8.314\times10^{7})(300)r}$$

$$r = 9.238\times10^{-6}\ \text{cm or } 0.0238\ \mu$$

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

Solubility and Particle Size

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

Solubility and pH

Another technique, if the drug is to be formulated into a liquid product, is adjustment of the pH of the solvent to enhance solubility. However, for many drug substances, pH adjustment is not an effective means of improving solubility. Weak acidic or basic drugs may require extremes in pH that are outside accepted physiologic limits or that may cause stability problems with formulation ingredients. Adjustment of pH usually has little effect on the solubility of substances other than electrolytes. In many cases, it is desirable to use cosolvents or other techniques such as complexation, micronization, or solid dispersion to improve aqueous solubility. A review of pH is provided in Physical Pharmacy Capsule 4.6, Principles of pH. The effect of pH on solubility is illustrated in Physical Pharmacy Capsule 4.7, Solubility and pH.

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PHYSICAL PHARMACY CAPSULE 4.6

Principles of pH

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

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

pH is defined in terms of the hydrogen ion activity:

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

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

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

$$H^+ + H_2O = H_3O^+$$

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

$$H_2CO_3 = H^+ + HCO_3^-$$
$$HC_2H_3O_2 = H^+ + C_2H_3O_2^-$$

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

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

$$aH^+ = f_H + C_{H^+}$$

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

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

PHYSICAL PHARMACY CAPSULE 4.6 CONT.

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

THE pH SCALE

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

MEASUREMENT OF pH

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

COMBINATION ELECTRODES

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

PHYSICAL PHARMACY CAPSULE 4.7

Solubility and pH

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

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

$$HA \overset{K_a}{\leftrightarrow} H^+ + A^-$$

where K_a is the dissociation constant.

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

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

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PHYSICAL PHARMACY CAPSULE 4.7 CONT.

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

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

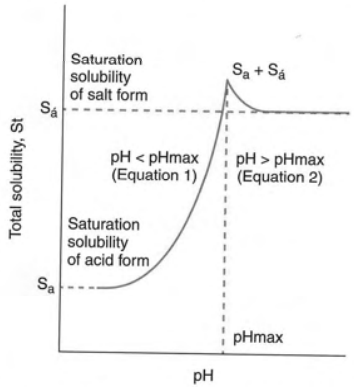
The next equation is used when above the pH_{max}:

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

where

S_a is the saturation solubility of the free acid and

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



EXAMPLE

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

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

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

$$S_T = 0.0118\left[1+\left(5.86\times10^{-6}\right)/\left(1\times10^{-6}\right)\right] = 0.0809\ molar$$

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

$$0.1053 = 0.0118\left[1+\frac{5.86\times10^{-6}}{H^+}\right]$$

$$[H^+] = 7.333\times10^{-7},\ \text{or a pH of } 6.135$$

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

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

PHYSICAL PHARMACY CAPSULE 4.7 CONT.

$$\frac{01053-0.0809}{0.0809} = 30.1\%$$

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

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

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

Dissolution

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

The dissolution rate of drugs may be increased by decreasing the drug's particle size. It may also be increased by increasing its solubility in the diffusion layer. The most effective means of obtaining higher dissolution rates is to use a highly water-soluble salt of the parent substance. Although a soluble salt of a weak acid will precipitate as the free acid in the bulk phase of an acidic solution, such as gastric fluid, it will do so in the form of fine particles with a large surface area.

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

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

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surface charge and/or agglomeration results in the reduced particle size form of the drug presenting a lower effective surface area to the solvent due to incomplete wetting or agglomeration. Fick's laws describe the relationship of diffusion and dissolution of the active drug in the dosage form and when administered in the body, as shown in Physical Pharmacy Capsule 4.8, Fick's Laws of Diffusion and the Noyes-Whitney Equation.

PHYSICAL PHARMACY CAPSULE 4.8

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

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

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

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

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

$$J = dM/(Sdt)$$

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

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

where

J is the flux of a component across a plane of unit area,
C_1 and C_2 are the concentrations in the donor and receptor compartments,
h is the membrane thickness, and
D is the diffusion coefficient (or diffusivity).

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

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

PHYSICAL PHARMACY CAPSULE 4.8 CONT.

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

The diffusion coefficients ($D \times 10^{-6}$) of various compounds in water (25°C) and other media have been determined as follows: ethanol, 12.5 cm^2/s; glycine, 10.6 cm^2/s; sodium lauryl sulfate, 6.2 cm^2/s; glucose, 6.8 cm^2/s.

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

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

where

C_1 and C_d are the concentrations in the donor compartment (g/cm^3)
and C_2 and C_r are the concentrations in the receptor compartment (g/cm^3).

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

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

or in sink conditions,

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

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

$$P = DK/h$$

EXAMPLE 1

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

h = 1 mm = 0.1 cm
$D = 4.23 \times 10^{-7}$ cm^2/s
K = 2.03
r = 2 cm, $S = \pi(2\text{ cm})^2 = 12.57$ cm^2
Cd = 0.5 mg/mL
$P = [(4.23 \times 10^{-7}\ cm^2/s)(2.03)]/0.1\ cm = 8.59 \times 10^{-6}$ cm/s
$dM/dt = (8.59 \times 10^{-6}\ cm/s)(12.57\ cm^2)(0.5\ mg/mL) = 5.40 \times 10^{-5}$ mg/s
$(5.40 \times 10^{-5}\ mg/s)(3{,}600\ s/h) = 0.19$ mg/h

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

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

where

C is the concentration of drug dissolved at time t,
D is the diffusion coefficient of the solute in solution,

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S is the surface area of the exposed solid,
V is the volume of solution,
h is the thickness of the diffusion layer.
Cs is the saturation solubility of the drug, and
C is the concentration of solute in the bulk phase at a specific time, t.

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

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

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

$$dC/dt = kSCs$$

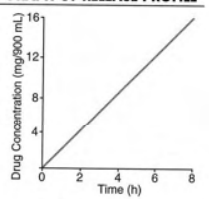
As the factors are held constant, it becomes apparent that the dissolution rate of a drug can be proportional to the surface area exposed to the dissolution medium. A number of other expressions have been derived for specific application to various situations and conditions.

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

EXAMPLE 2

The following information was obtained using the USP 32–NF 27 dissolution apparatus I. The drug is soluble at 1 g in 3 mL of water, so sink conditions were maintained; the surface area of the tablet exposed was 1.5 cm^2 (obtained by placing the tablet in a special holder exposing only one side to the dissolution medium); and the dosage form studied was a 16-mg sustained-release tablet; the release pattern should be zero order. What is the rate of release of drug?

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



In this problem, since the surface area (S) was maintained constant at 1.5 cm^2 and the solubility (Cs) of the drug is constant at 1 g in 3 mL of water, the plot of concentration versus time (t) yields a slope with a value of kSCs, or k_z, expressing the rate of release of the drug as

$$dC/dt = kSCs$$

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

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

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

Membrane Permeability

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

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

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

Partition Coefficient

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

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

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

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

where α equals the degree of ionization.

PHYSICAL PHARMACY CAPSULE 4.9

Partition Coefficient

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

$$K = C_U/C_L$$

where

K is the distribution constant or partition constant,

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

This information can be effectively used in the

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

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

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

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

where

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

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

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

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

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

where

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

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

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

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

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

EXAMPLE 1

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

PHYSICAL PHARMACY CAPSULE 4.9 CONT.

U = 0.7 / (0.7 + 1) = 0.41, the fraction of drug extracted into the upper layer
L = 1 / (0.7 + 1) = 0.59, the fraction of drug remaining in the lower layer

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

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

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

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

pK_a/Dissociation Constants

Among the physicochemical characteristics of interest is the extent of dissociation or ionization of drug substances. This is important because the extent of ionization has an important effect on the formulation and pharmacokinetic parameters of the drug. The extent of dissociation or ionization in many cases is highly dependent on the pH of the medium containing the drug. In formulation, often the vehicle is adjusted to a certain pH to obtain a certain level of ionization of the drug for solubility and stability. In the pharmacokinetic area, the extent of ionization of a drug has a strong effect on its extent of absorption, distribution, and elimination. The dissociation constant, or pK_a, is usually determined by potentiometric titration. For the practicing pharmacist, it is important in predicting precipitation in admixtures and in calculating the solubility of drugs at certain pH values. Physical Pharmacy Capsule 4.10, pK_a/Dissociation Constants, presents a brief summary of dissociation and ionization concepts.

PHYSICAL PHARMACY CAPSULE 4.10

pK_a/Dissociation Constants

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

$$HA \leftrightarrow H^+ + A^-$$
$$K_1[HA] \leftrightarrow K_2[H^+][A^-]$$

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

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

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PHYSICAL PHARMACY CAPSULE 4.10 CONT.

where K_a is the acid dissociation constant.

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

$$BH^+ \leftrightarrow H^+ + B$$

The dissociation constant is described by

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

The dissociation of a hydroxyl-containing weak base,

$$B + H_2O \leftrightarrow OH^- + BH^+$$

The dissociation constant is described by

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

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

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

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

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

Some practical applications of these equations are as follows.

EXAMPLE 1

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

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

EXAMPLE 2

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

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

Hydrates and Solvates

Many active pharmaceutical agents exist as hydrates or solvates; some are hygroscopic, deliquescent, and/or efflorescent. Hygroscopic powders are those that will tend to absorb moisture from the air. Deliquescent powders are those that will absorb moisture from the air and even liquefy. Efflorescent powders are those that may give up their water of crystallization and may even become damp and pasty. When working with these powders, extra care must be taken. Generally, the USP description of a powder will state whether it has hygroscopic, deliquescent, or efflorescent properties.

One other factor is that if a hygroscopic or deliquescent powder is being weighed on a balance, the powder may absorb moisture from the air and weigh heavier than it should. Therefore, weighings should be made quickly after opening the bulk chemical containers and then resealing them.

Solvates and hydrates must be packaged in "tight" containers to prevent the loss or gain of moisture. In fact, it is best to have all chemicals stored in "tight" containers and to keep them thoroughly closed at all times except for the short time when a weighing step is involved. Storage at the indicated temperatures is also important and to minimize any exposure to very high humidity levels. More on hydrates and solvates is presented in Physical Pharmacy Capsule 4.11, Hydrates and Solvates.

PHYSICAL PHARMACY CAPSULE 4.11

Hydrates and Solvates

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

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

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

CALCULATIONS

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

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

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

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

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

EXAMPLE:

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

2 g × 1.066 = 2.132 g of lidocaine HCl monohydrate.

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

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

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

$$X = 2.133\,g$$

Further, the USP monograph for lidocaine hydrochloride Jelly, USP states "It contains not less than 95% and not more than 105.09% of the labeled amount of lidocaine hydrochloride ($C_{14}H_{22}N_2O \cdot HCl$)." Note that this is the anhydrous form. It is important to also check the C of A for the lidocaine hydrochloride being used to determine the water content. Fortunately, most pure powders (anhydrous) generally only contain 0.2% to 0.5% moisture, which can be insignificant but need to be checked, nevertheless.

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Organic Salt Considerations

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

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

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

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

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

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

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

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

> "The titles of USP monographs for drug products and compounded preparations formulated with a salt of an acid or base use the name of the active moiety, as defined below. The strength of the product or preparation also is expressed in terms of the active moiety.
>
> An active moiety is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance without regard to the actual charged state of the molecule in vivo.
>
> For example, the active moiety of a hydrochloride salt of a base will be the free base and not the protonated form of the base. The active moiety of a metal acid salt will be the free acid.
>
> This Policy is followed by USP in naming drug products and compounded preparations that are newly recognized in the USP. Revising existing monographs to conform to this Policy is not intended, except where the USP Council of Experts determines that, for reasons such as safety, a nomenclature change is warranted."

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

PHYSICAL PHARMACY CAPSULE 4.12

Organic Salts

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

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

1. 50 µg/0.1 mL = X µg/10 mL, X = 5 mg
2. Fentanyl MW = 336.47
   Fentanyl citrate MW = 528.59
3. 336.47/5 mg = 528.59/X, X = 7.85 mg
4. Each mg of fentanyl equals 528.59/336.47 = 1.57 mg fentanyl citrate

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

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

1. Since the total salt molecule is part of the dose:
2. 30 × 35 mg = 1.05 g of diphenhydramine hydrochloride is required.

UXP XII (1942) lists about 20 tablet monographs that are all based on the "salt" form of the drug, for example, Morphine Sulfate Tablets USP contain not less than 93% and not more than 107% of the labeled amount of morphine sulfate $[(C_{17}H_{19}O_3N)_2 \cdot H_2SO_4 \cdot 5H_2O]$. The names of the monographed items in this time period were quite clear as the salt names were a part of the official name if it was to be used. For example, Barbital Tablets USP are based on the labeled amount of barbital ($C_8H_{12}N_2O_3$), but Barbital Sodium Tablets were based on the labeled amount of barbital sodium ($C_8H_{11}N_2O_3Na$).

USP XVI (1960) monograph for Amodiaquine Hydrochloride Tablets USP states "Amodiaquine Hydrochloride Tablets contain an amount of amodiaquine hydrochloride ($C_{20}H_{22}ClN_3O \cdot 2HCl \cdot 2H_2O$) equivalent to not less than 93% and not more than 107% of the labeled amount of amodiaquine base ($C_{20}H_{22}ClN_3O$)." It is evident in this monograph that the dose is calculated on the "base" form of the drug.

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

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Organic Ester Considerations

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

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

An ester is a compound of the general formula R-C-O-R1 where R and R1 may be the same or different and may be either aliphatic or aromatic. The term "aliphatic" refers to an acyclic or cyclic, saturated or unsaturated carbon compounds excluding aromatic compounds; the term "aromatic" was originally used to describe compounds that "smelled" but were later found to contain either benzene or a fused benzene rings in the structure. The term has been generalized to include aromatic heterocyclic structures.

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

$$C_2H_5OH + CH_3COOH \rightarrow CH_3CH_2 - O - CO - CH_3 + H_2O$$

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

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

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

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

PHYSICAL PHARMACY CAPSULE **4.13**

Organic Esters

Esters are quite interesting because one cannot simply look at the title and determine whether or not the drug is a salt or an ester. For example, "*acetate salts*" include calcium acetate, chlorhexidine acetate, desmopressin acetate, flecainide acetate, gonadorelin acetate, guanabenz acetate, leuprolide acetate, lysine acetate, mafenide acetate, and zinc acetate, and "*acetate esters*" include cortisone acetate, desoxycorticosterone acetate, dexamethasone acetate, fludrocortisones acetate, fluorometholone acetate, hydrocortisone acetate, isoflupredone acetate, medroxyprogesterone acetate, megestrol acetate, melengestrol acetate, methylprednisolone acetate, norethindrone acetate, paramethasone acetate, prednisolone acetate, trenbolone acetate, and betamethasone acetate.

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

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

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

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

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

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

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

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

PHYSICAL PHARMACY CAPSULE 4.13 CONT.

Potency-Designated Active Pharmaceutical Ingredients

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

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

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

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

"5.50.10 Units of Potency (Biological)"

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

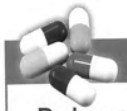
Units of biological potency defined by the World Health Organization (WHO) for International Biological Standards and International Biological Reference Preparations are termed International Units (IU). Monographs refer to the units defined by USP Reference Standards as "USP Units." For biological products,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

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

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

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

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



PHYSICAL PHARMACY CAPSULE 4.14

Potency-Designated Active Pharmaceutical Ingredients

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

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

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

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

PHYSICAL PHARMACY CAPSULE 4.14 CONT.

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

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

EXAMPLE

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

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

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

Complex Organic Molecules

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

In working with complex molecules, one must be cognizant of both the active drug constituent and the total drug formulation in which it is contained. This is true when converting a commercial product into a compounded preparation. Protein drugs are very potent and are generally used in quite low concentrations. The bulk of many manufactured products and compounded preparations may be the excipients. These excipients include the vehicle, buffers, stabilizers, and others that are often incorporated in these products. A number of different stabilizers can be used from different chemical classes and include surfactants, amino acids, polyhydric alcohols, fatty acids, proteins, antioxidants, reducing agents, and metal ions. See Physical Pharmacy Capsule 4.15, Complex Organic Molecules for further considerations.

PHYSICAL PHARMACY CAPSULE 4.15

Complex Organic Molecules

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

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

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

FACTORS

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

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

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

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

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

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

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

Specific issues relevant to large molecule drugs include the following:

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

PHYSICAL PHARMACY CAPSULE 4.15 CONT.

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

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

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

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

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

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

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

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Drug and Drug Product Stability

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

Drug Stability: Mechanisms of Degradation

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

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

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

Another destructive process is oxidation, which destroys many drug types, including aldehydes, alcohols, phenols, sugars, alkaloids, and unsaturated fats and oils. Chemically, oxidation is loss of electrons from an atom or a molecule. Each electron lost is accepted by some other atom or molecule, reducing the recipient. In inorganic chemistry, oxidation is accompanied by an increase in the positive valence of an element, for example, ferrous (+2) oxidizing to ferric (+3). In organic chemistry, oxidation is frequently considered synonymous with the loss of hydrogen (dehydrogenation) from a molecule. Oxidation frequently involves free chemical radicals, which are molecules or atoms containing one or more unpaired electrons, such as molecular (atmospheric) oxygen (•O—O•) and free hydroxyl (•OH). These radicals tend to take electrons from other chemicals, thereby oxidizing the donor.

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

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

Drug and Drug Product Stability: Kinetics and Shelf Life

Stability is the extent to which a product retains within specified limits and throughout its period of storage and use (i.e., its shelf life) the same properties and characteristics that it possessed at the time of its manufacture.

Five types of stability concern pharmacists:

1. *Chemical*: Each active ingredient retains its chemical integrity and labeled potency within the specified limits.
2. *Physical*: The original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability, are retained.
3. *Microbiologic*: Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents retain effectiveness within specified limits.
4. *Therapeutic*: The therapeutic effect remains unchanged.
5. *Toxicologic*: No significant increase in toxicity occurs.

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

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

Rate Reactions

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

PHYSICAL PHARMACY CAPSULE 4.16

Rate Reactions

ZERO-ORDER RATE REACTIONS

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

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

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

The integrated and more useful form of the equation:

$$C = -k_0 t + C_0$$

where C_0 is the initial concentration of the drug.

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

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

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

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

If the C_0 changes, the $t_{1/2}$ changes. There is an inverse relationship between the $t_{½}$ and k.

EXAMPLE 1

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

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PHYSICAL PHARMACY CAPSULE 4.16 CONT.

$$C = -(0.5\,mg/mL/h)(72\,h) + 125\,mg/mL$$
$$C = 89\,mg/mL \text{ after } 3\,d$$
$$t_{1/2} = 1/2(125\,mg/mL)/(0.5\,mg/mL/h)$$
$$t_{1/2} = 125\,h$$

EXAMPLE 2

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

$$90\% \times 125\ mg/mL = 112.5\ mg/mL$$

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

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

FIRST-ORDER RATE REACTIONS

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

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

where

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

The integrated and more useful form of the equation:

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

where C_0 is the initial concentration of the drug.
In natural log form, the equation is

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

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

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

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

EXAMPLE 3

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

PHYSICAL PHARMACY CAPSULE 4.16 CONT.

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

EXAMPLE 4

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

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

ENERGY OF ACTIVATION: ARRHENIUS EQUATION

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

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

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

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

EXAMPLE 5

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

$$\log \frac{(0.0009)}{(0.0001)} = \frac{Ea(353 - 333)}{(2.3)(1.987)(353)(333)}$$
$$Ea = 25{,}651\ kcal/mol$$

Q_{10} Method of Shelf Life Estimation

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

Enhancing Stability of Drug Products

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

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

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

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

PHYSICAL PHARMACY CAPSULE 4.17

Buffer Capacity

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

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

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

Using the Henderson-Hasselbalch equation:

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

PHYSICAL PHARMACY CAPSULE 4.17 CONT.

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

EXAMPLE 1

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

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

EXAMPLE 2

Determine the pH of the buffer prepared as shown:

Sodium acetate 50 g
Conc. HCl 10 mL
Water qs 2 L
Helpful numbers:
pK_a acetic acid = 4.76
m.w. sodium acetate = 82.08
m.w. acetic acid = 60.05
m.w. HCl = 36.45
Conc. HCl, 44% HCl w/v

$$NaAc + HCl \rightarrow NaCl + HAc + NaAc$$
$$(0.609\ \text{mol})\ (0.121\ \text{mol})\ (0.121\ \text{mol})\ (0.121\ \text{mol})\ (0.488\ \text{mol})$$
$$HCl: \{(10\ \text{mL})[(44\ \text{g})/(100\ \text{mL})](1\ \text{mol})/(36.45\ \text{g})\} = 0.121\ \text{mol}$$
$$NaAc: \{(50\ \text{g})[(1\ \text{mol})/(82.08\ \text{g})] = 0.609\ \text{mol}\ (0.609\ \text{mol}) - (0.121\ \text{mol}) = 0.488\ \text{mol}$$
$$pH = 4.76 + \log(0.488\ \text{mol})/(0.121\ \text{mol}) = 5.367$$

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

$$\beta = \Delta B / \Delta pH$$

where

ΔB is molar concentration of acid or base added,
ΔpH is change in pH due to addition of acid or base, and
ΔpH can be determined experimentally or calculated using the Henderson-Hasselbalch equation.

EXAMPLE 3

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

$$\Delta pH = 9.5 - 8.9 = 0.6$$
$$\Delta B = 0.2\ \text{mol/L} = 0.2\ \text{M}$$
$$\beta = 0.2\ \text{M}/0.6 = 0.33\ \text{M}$$

EXAMPLE 4

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

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PHYSICAL PHARMACY CAPSULE 4.17 CONT.

H_3PO_4 : 0.02 mol + 0.002 mol = 0.022 mol
NaH_2PO_4 : 0.016 mol − 0.002 mL = 0.014 mol
pH = 2.125 + log(0.014 mol / 0.022 mol) = 1.929
ΔpH = 2.028 − 1.929 = 0.099
ΔAB = 0.002 mol / 0.3 L = 0.0067 M
β = 0.0067 M / 0.099 = 0.067 M

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

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

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

EXAMPLE 5

What is the Van Slyke buffer capacity of the buffer prepared in Example 1?
C = 0.0067 M + 0.0053 M = 0.12 M
Ka = 7.5 + 10 ^{3}
$[H^+] = 10^{-2.028} = 9.38 \times 10^{-3}$ M
$\beta = 2.3\,(0.12\text{ M})\ \{[(7.5 \times 10^{-3}\text{ M})(9.38 \times 10^{-3}\text{ M})]/[(7.5 \times 10^{-3}\text{ M})/(9.38 \times 10^{-3}\text{ M})^2]\} = 0.68\text{ M}$

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

The oxidative process is diverted and the stability of the drug is preserved by agents called *antioxidants*, which react with one or more compounds in the drug to prevent progress of the chain reaction. In general, antioxidants act by providing electrons and easily available hydrogen atoms that are accepted more readily by the free radicals than are those of the drug being protected. Various antioxidants are employed in pharmacy. Among those, most frequently used in aqueous preparations are sodium sulfite (Na_2SO_3, at high pH values), sodium bisulfite ($NaHSO_3$, at intermediate pH values), sodium metabisulfite ($Na_2S_2O_5$, at low pH values), hypophosphorous acid (H_3PO_2), and ascorbic acid. In oleaginous (oily or unctuous) preparations, alpha-tocopherol, butyl hydroxy anisole, and ascorbyl palmitate find application.

In its labeling regulations for pharmaceutical products containing sulfites, the FDA requires a warning about possible allergic-type reactions, including possible life-threatening anaphylaxis symptoms and/or asthma episodes, in susceptible persons (3). Sulfites are used as preservatives in many injectable drugs, such as antibiotics and local anesthetics. Some inhalants and ophthalmic preparations also contain sulfites, but relatively few oral drugs contain these chemicals. The purpose of the regulation is to protect the estimated 0.2% of the population who are subject to allergic reactions to the chemicals. Many sulfite-sensitive persons have asthma or other allergic conditions. Previous to the regulations dealing with prescription medication, the FDA issued regulations for the use of sulfites in food. Asthmatics and other patients who may be sulfite sensitive should be reminded to read the labels of packaged foods and medications to check for the presence of these agents. Sulfite agents covered by the regulations are potassium bisulfite, potassium metabisulfite, sodium bisulfite, sodium metabisulfite, sodium sulfite, and sulfur dioxide. The FDA permits the use of sulfites in prescription products, with the proper labeling, because there are no generally suitable substitutes for sulfites to maintain potency in certain medications. Some but not all epinephrine injections contain sulfites.

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

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

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

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

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

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

$$I_2 + 2Na_2S_2O_3 \rightarrow 2NaI + Na_2S_4O_6$$

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

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

Stability Testing

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

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

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

PHYSICAL PHARMACY CAPSULE 4.18

Analytical Methods and Standard Curves

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

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

SELECTION OF AN ANALYTICAL METHOD

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

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

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FACTORS INVOLVED IN METHODS SELECTION

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

SAMPLING REQUIREMENTS

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

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

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

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

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

DATA INTERPRETATION REQUIREMENTS

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

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ANALYTICAL METHODS

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

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

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

CLASSIFICATION OF ANALYTICAL AND MICROBIOLOGICAL METHODS

- Physical testing procedures
  - Melting point
  - Freezing point
  - Boiling point
  - Density
  - Refractive index
  - Optical rotation (polarimetry)
  - Thermal analysis
  - Color change
  - Precipitate formation
  - Viscosity change
- Interaction of electromagnetic radiation
  - Ultraviolet/visible spectroscopy
  - Infrared spectroscopy
  - Fluorescence/phosphorescence spectroscopy
  - Raman spectroscopy
  - X-ray spectroscopy
  - Flame emission and atomic absorption spectroscopy
  - Polarimetry
  - Refractometry
  - Interferometry
- Conductance methods
  - pH
  - Ion-selective electrodes
  - Polarography
- Immunoassay
  - Radioimmunoassay
  - Enzyme-multiplied immunoassay technique
  - Enzyme-linked immunosorbent assay
  - Fluorescent immunoassay
- Separation techniques
  - HPLC
  - GC
  - Thin-layer chromatography
  - Paper chromatography
  - Column chromatography
- Gravimetric
  - Balance
- Others
  - Osmolality
- Microbiological methods
  - Sterility testing
  - Endotoxin testing
  - Preservative effectiveness testing

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

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

CONSTRUCTION OF A STANDARD CURVE

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

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

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

When plotted on a graph, one obtains the following:

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

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

$$y = mx + b$$
$$3,895 = 259.3x + 0$$
$$x = 15.02\ \mu g/mL$$

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

Product containers, closures, and other packaging features must be considered in stability testing. For instance, tablets or capsules packaged in glass or plastic bottles require different stability test protocols from those for blister packs or strip packaging. Drugs particularly subject to hydrolysis or oxidative decomposition must be evaluated accordingly. And sterile products must meet sterility test standards to ensure protection against microbial contamination. All preservatives must be tested for effectiveness in the finished product.

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

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

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

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

Accelerated Stability Studies

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[a]For chemical entities. Adapted from Stability and Testing of New Drug Substances and Products. Available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128204.pdf. (Accessed September 28, 2012).
[b]RH, relative humidity.

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

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

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Q_{10} Method of Shelf Life Estimation

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

$$Q_{10} = e^{\{(Ea/R)[(1/T+10)-(1/T)]\}}$$

where

Ea is the energy of activation,
R is the gas constant, and
T is the absolute temperature.

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

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

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

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The equation for Q_{10} shelf life estimates is

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

where

$t_{90}T_2$ is the estimated shelf life,
$t_{90}T_1$ is the given shelf life at a given temperature, and
ΔT is the difference in the temperatures T_1 and T_2.

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

EXAMPLE 1

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

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

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

EXAMPLE 2

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

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

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

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

Prescriptions requiring extemporaneous compounding by the pharmacist do not require the extended shelf life that commercially manufactured and distributed products do because they are intended to be used immediately on receipt by the patient and used only during the immediate course of the prescribed treatment. However, these compounded prescriptions must remain stable and efficacious during the course of use, and the compounding pharmacist must employ formulative components and techniques that will result in a stable product (7).

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

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

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

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

PHARMACEUTICAL INGREDIENTS AND EXCIPIENTS

Definitions and Types

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

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

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

Table 4.3 EXAMPLES OF PHARMACEUTICAL INGREDIENTS

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

(*Continued*)

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Table 4.3 EXAMPLES OF PHARMACEUTICAL INGREDIENTS (Continued)

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

Table 4.3 EXAMPLES OF PHARMACEUTICAL INGREDIENTS (Continued)

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

(Continued)

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Table 4.3 EXAMPLES OF PHARMACEUTICAL INGREDIENTS (Continued)

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

Table 4.3 EXAMPLES OF PHARMACEUTICAL INGREDIENTS (Continued)

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

may or may not be present, it should be qualified by words such as "or" or "may also contain." If an ingredient is a trade secret, it may be omitted from the list if the list states "and other ingredients." If an ingredient is only present in a trace amount and has no functional or technical effect on the product, it does not need to be listed unless it has been shown to cause sensitivity reactions or allergic responses.

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Handbook of Pharmaceutical Excipients

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

Appearance and Palatability

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

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

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

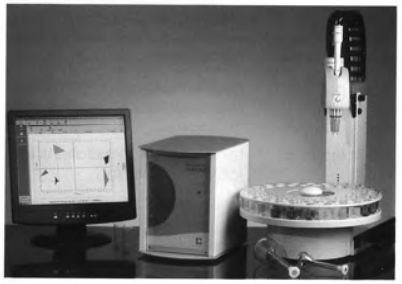

FIGURE 4.4 Electronic tongue to assist in formulation development. (Courtesy of Alpha MOS.)

Flavoring Pharmaceuticals

The flavoring of pharmaceuticals applies primarily to liquids intended for oral administration. The 10,000 taste buds on the tongue, roof of the mouth, cheeks, and throat have 60 to 100 receptor cells each (13). These receptor cells interact with molecules dissolved in the saliva and produce a positive or negative taste sensation. Medication in liquid form comes into immediate and direct contact with these taste buds. The addition of flavoring agents to liquid medication can mask the disagreeable taste. Drugs placed in capsules or prepared as coated tablets may be easily swallowed with no contact between the drug and the taste buds. Tablets containing drugs that are not especially distasteful may remain uncoated and unflavored. Swallowing them with water usually is sufficient to avoid undesirable taste sensations. However, chewable tablets, such as certain antacid and vitamin products, usually are sweetened and flavored to improve acceptance.

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

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

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

Thus, prediction of the taste characteristics of a new drug is only speculative. However, it is soon learned and the formulation pharmacist is then put to the task of increasing the drug's palatability in the environment of other formulative agents. The selection of an appropriate flavoring agent depends on several factors, primarily the taste of the drug substance itself. Certain flavoring materials are more effective than others in masking or disguising the particular bitter, salty, sour, or otherwise undesirable taste of medicinal agents. Although individuals' tastes and flavor preferences differ, cocoa-flavored vehicles are considered effective for masking the taste of bitter drugs. Fruit or citrus flavors are frequently used to combat sour or acid-tasting drugs, and cinnamon, orange, raspberry, and other flavors have been successfully used to make preparations of salty drugs more palatable.

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

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

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

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

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

Sweetening Pharmaceuticals

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

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

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

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

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

Coloring Pharmaceuticals

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

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

Many coal tar dyes were originally used indiscriminately in foods and beverages to enhance their appeal without regard to their toxic potential. It was only after careful scrutiny that some dyes were found to be hazardous to health because of either their own chemical nature or the impurities they carried. As more dyestuffs became available, some expert guidance and regulation were needed to ensure the safety of the public. After passage of the Food and Drug Act in 1906, the U.S. Department of Agriculture established regulations by which a few colorants were *permitted* or *certified* for use in certain products. Today, the FDA regulates the use of color additives in foods, drugs, and cosmetics through the provisions of the Federal Food, Drug, and Cosmetic Act of 1938, as amended in 1960 with the Color Additive Amendments. Lists of color additives *exempt* from certification and those *subject* to certification are codified into law and regulated by the FDA (15). Certified color additives are classified according to their approved use: (*a*) FD&C color additives, which may be used in foods, drugs, and cosmetics; (*b*) D&C color additives, some of which are approved for use in drugs, some in cosmetics, and some in medical devices; and (*c*) external D&C color additives, the use of which is restricted to external parts of the body, not including the lips or any other body surface covered by mucous membrane. Each certification category has a variety of basic colors and shades for coloring pharmaceuticals. A current list of certified color additives may be found at 21CFR74 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart = 74). One may select from a variety of FD&C, D&C, and external D&C reds, yellows, oranges, greens, blues, and violets. Each is identified by category, color, and number, as for example, "D&C Yellow No. 8" and "FD&C Red No. 4." By selective combinations of the colorants, one can create distinctive colors (Table 4.4).

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

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

It should be borne in mind, however, that on an individual basis, some persons may demonstrate an allergic-type response to certain color additives and should avoid such agents accordingly.

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

Table 4.4 EXAMPLES OF COLOR FORMULATIONS

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

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

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

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

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

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

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

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

In addition to esthetics and the certification status of a dye, a formulation pharmacist must select the dyes to be used in a particular formula on the basis of their physical and chemical properties. Of prime importance is the solubility of a prospective dye in the vehicle to be used for a liquid formulation or in a solvent to be employed during a pharmaceutical process, as when the dye is sprayed on a batch of tablets. In general, most dyes are broadly grouped into those that are water soluble and those that are oil soluble; few if any dyes are both. Usually, a water-soluble dye is also adequately soluble in commonly used pharmaceutical liquids like glycerin, alcohol, and glycol ethers. Oil-soluble dyes may also be soluble to some extent in these solvents and in liquid petrolatum (mineral oil), fatty acids, fixed oils, and waxes. No great deal of solubility is required, since the concentration of dye in a given preparation is minimal.

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

Preservatives

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

Sterilization and Preservation

Although some types of pharmaceutical products, for example, ophthalmic and injectable preparations, are sterilized by physical methods (autoclaving for 20 minutes at 15 lb pressure and 121°C, dry heat at 180°C for 1 hour, or bacterial filtration) during manufacture, many of them also require an antimicrobial preservative to maintain their aseptic condition throughout storage and use. Other types of preparations that are not sterilized during their preparation but are particularly susceptible to microbial growth because of the nature of their ingredients are protected by the addition of an antimicrobial preservative. Preparations that provide excellent growth media for microbes are most aqueous preparations, especially syrups, emulsions, suspensions, and some semisolid preparations, particularly creams. Certain hydroalcoholic and most alcoholic preparations may not require the addition of a chemical preservative when the alcoholic content is sufficient to prevent microbial growth. Generally, 15% v/v alcohol will prevent microbial growth in acid media and 18% v/v in alkaline media. Most alcohol-containing pharmaceuticals, such as elixirs, spirits, and tinctures, are self-sterilizing and do not require additional preservation. The same applies to other individual pharmaceuticals that by virtue of their vehicle or other formulative agents may not permit the growth of microorganisms.

Preservative Selection

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

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

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

General Preservative Considerations

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

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

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

Mode of Action

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

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

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

For each type of preparation to be preserved, the research pharmacist must consider the influence of the preservative on the comfort of the patient. For instance, a preservative in an ophthalmic preparation must have an extremely low degree of irritant qualities, which is characteristic of chlorobutanol, benzalkonium chloride, and phenylmercuric nitrate, frequently used in ophthalmic preparations. In all instances, the preserved preparation must be biologically tested to determine its safety and efficacy and shelf-tested to determine its stability for the intended shelf life of the product.

CLINICAL CASE STUDY

SUBJECTIVE INFORMATION

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

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

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

MEDICATION RECORD

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

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

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

OBJECTIVE INFORMATION

A physical exam reveals a well-nourished, well-developed female child who appears normal for her age. BP, 92/64; HR, 74 bpm; RR, 23 rpm; and temperature of 38°C.

ASSESSMENT

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

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

PLAN

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

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APPLYING THE PRINCIPLES AND CONCEPTS

Group Activities

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

Individual Activities

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

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