Pharmaceutical Dosage Forms and Drug Delivery Systems

Howard C. Ansel

Nicholas G. Popovich

Loyd V. Allen, Jr.

SIXTH EDITION

I am a Pharmacist

- *I am a specialist in medications*

  I supply medicines and pharmaceuticals to those who need them.

  I prepare and compound special dosage forms.

  I control the storage and preservation of all medications in my care.

- *I am a custodian of medical information*

  My library is a ready source of drug knowledge.

  My files contain thousands of specific drug names and tens of thousands of facts about them.

  My records include the medication and health history of entire families.

  My journals and meetings report advances in pharmacy from around the world.

- *I am a companion of the physician*

  I am a partner in the case of every patient who takes any kind of medication.

  I am a consultant on the merits of different therapeutic agents.

  I am the connecting link between physician and patient and the final check on the safety of medicines.

- *I am a counselor to the patient*

  I help the patient understand the proper use of prescription medication.

  I assist in the patient's choice of nonprescription drugs or in the decision to consult a physician.

  I advise the patient on matters of prescription storage and potency.

- *I am a guardian of the public health*

  My pharmacy is a center for health-care information.

  I encourage and promote sound personal health practices.

  My services are available to all at all times.

- *This is my calling* ◆ *This is my pride*

Pharmaceutical Dosage Forms and Drug Delivery Systems

Howard C. Ansel, Ph.D.
Panoz Professor of Pharmacy, Department of Pharmaceutics, College of Pharmacy
The University of Georgia

Nicholas G. Popovich, Ph.D.
Professor and Head, Department of Pharmacy Practice, School of Pharmacy and Pharmacal Sciences
Purdue University

Loyd V. Allen, Jr., Ph.D.
Professor and Chair, Department of Medicinal Chemistry and Pharmaceutics, College of Pharmacy
The University of Oklahoma

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Dosage Form Design: Biopharmaceutic Considerations

As discussed in the previous chapter, the biologic response to a drug is the result of an interaction between the drug substance and functionally important cell receptors or enzyme systems. The response is due to an alteration in the biologic processes that were present prior to the drug's administration. The magnitude of the response is related to the concentration of the drug achieved at the site of its action. This drug concentration depends upon the dosage of the drug administered, the extent of its absorption and distribution to the site, and the rate and extent of its elimination from the body. The physical and chemical constitution of the drug substance—particularly its lipid solubility, degree of ionization, and molecular size—determines to a great extent its ability to effect its biological activity. The area of study embracing this relationship between the physical, chemical, and biological sciences as they apply to drugs, dosage forms, and to drug action has been given the descriptive term *biopharmaceutics*.

In general, for a drug to exert its biologic effect, it must be transported by the body fluids, traverse the required biologic membrane barriers, escape widespread distribution to unwanted areas, endure metabolic attack, penetrate in adequate concentration to the sites of action, and interact in a specific fashion, causing an alteration of cellular function. A simplified diagram of this complex series of events between a drug's administration and its elimination is presented in Figure 3–1.

The absorption, distribution, biotransformation (metabolism), and elimination of a drug from the body are dynamic processes that continue from the time a drug is taken until all of the drug has been removed from the body. The *rates* at which these processes occur affect the onset, intensity, and the duration of the drug's activity within the body. The area of study which elucidates the time course of drug concentration in the blood and tissues is termed *pharmacokinetics*. It is the study of the kinetics of absorption, distribution, metabolism and excretion (ADME) of drugs and their corresponding pharmacologic, therapeutic, or toxic response in animals and man. Further, since one drug may alter the absorption, distribution, metabolism or excretion of another drug, pharmacokinetics also may be applied in the study of interactions between drugs.

Once a drug is administered and drug absorption begins, the drug does not remain in a single body location, but rather is distributed throughout the body until its ultimate elimination. For instance, following the oral administration of a drug and its entry into the gastrointestinal tract, a portion of the drug is absorbed into the circulatory system from which it is distributed to the various other body fluids, tissues, and organs. From these sites the drug may return to the circulatory system and be excreted through the kidney as such or the drug may be metabolized by the liver or other cellular sites and be excreted as metabolites. As shown in Figure 3–1, drugs administered by intravenous injection are placed directly into the circulatory system, thereby avoiding the absorption process which is required from all other routes of administration for systemic effects.

The various body locations to which a drug travels may be viewed as separate compartments, each containing some fraction of the administered dose of drug. The transfer of drug from the blood to other body locations is generally a rapid process and is reversible; that is, the drug may diffuse back into the circulation. The drug in the blood therefore exists in equilibrium with the drug in the other compartments. However, in this equilibrium state, the concentration of the drug in the blood may be quite different (greater or lesser) than the concentration of the drug in the other compartments. This is due

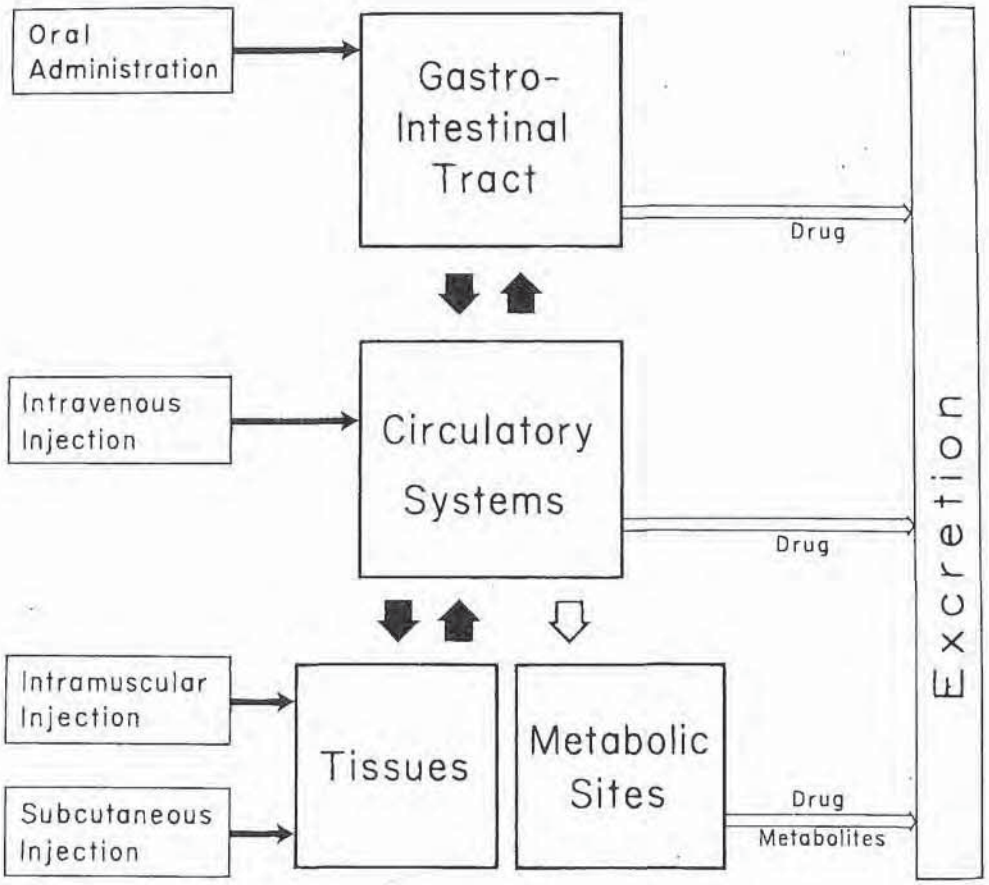

Fig. 3–1. *Schematic representation of events of absorption, metabolism, and excretion of drugs after their administration by various routes.*

largely to the physiochemical properties of the drug and its resultant ability to leave the blood and traverse the biological membranes. Certain drugs may leave the circulatory system rapidly and completely, whereas other drugs may do so slowly and with difficulty. A number of drugs become bound to blood proteins, particularly the albumins, and only a small fraction of the drug administered may actually be found at locations outside of the circulatory system at a given time. The transfer of drug from one compartment to another is mathematically associated with a specific rate constant describing that particular transfer. Generally, the rate of transfer of a drug from one compartment to another is proportional to the concentration of the drug in the compartment from which it exits; the greater the concentration, the greater is the amount of drug transfer.

Metabolism is the major process by which foreign substances, including drugs are eliminated from the body. In the process of metabolism a drug substance may be biotransformed into pharmacologically active or inactive metabolites. Often, both the drug substance and its metabolite(s) are active and exert pharmacologic effects. For example, the antianxiety drug prazepam (Centrax) metabolizes, in part, to oxazepam (Serax), which also has antianxiety effects. In some instances a pharmacologically inactive drug (termed a *prodrug*) may be administered for the known effects of its active metabolites. Dipivefrin, for example, is a prodrug of epinephrine formed by the esterification of epinephrine and pivalic acid. This enhances the lipophilic character of the drug, and as a consequence its penetration into the anterior chamber of the eye is 17 times that of epinephrine. Within the eye,

dipivefrin HCl is converted by enzymatic hydrolysis to epinephrine.

The metabolism of a drug to inactive products is usually an irreversible process which culminates in the excretion of the drug from the body, usually via the urine. The pharmacokineticist may calculate an elimination rate constant (termed k_{el}) for a drug to describe its rate of elimination from the body. The term *elimination* refers to both metabolism and excretion. For drugs which are administered intravenously, and therefore involve no absorption process, the task is much less complex than for drugs administered orally or by other routes. In the latter instances, drug absorption and drug elimination are occurring simultaneously but at different rates.

General Principles of Drug Absorption

Before an administered drug can arrive at its site of action in effective concentrations, it must surmount a number of barriers. These barriers are chiefly a succession of biologic membranes such as those of the gastrointestinal epithelium, lungs, blood, and brain. Body membranes are generally classified as three main types: (a) those composed of several layers of cells, as the skin; (b) those composed of a single layer of cells, as the intestinal epithelium; and (c) those of less than one cell in thickness, as the membrane of a single cell. In most instances a drug substance must pass more than one of these membrane types before it reaches its site of action. For instance, a drug taken orally must first traverse the gastrointestinal membranes (stomach, small and large intestine), gain entrance into the general circulation, pass to the organ or tissue with which it has affinity, gain entrance into that tissue, and then enter into its individual cells.

Although the chemistry of body membranes differs one from another, the membranes may be viewed in general as a bimolecular lipoid (fat-containing) layer attached on both sides to a protein layer. Drugs are thought to penetrate these biologic membranes in two general ways: (1) by passive diffusion and (2) through specialized transport mechanisms. Within each of these main categories, more clearly defined processes have been ascribed to drug transfer.

Passive Diffusion

The term *passive diffusion* is used to describe the passage of (drug) molecules through a membrane which behaves inertly in that it does not actively participate in the process. Drugs absorbed according to this method are said to be *passively absorbed.* The absorption process is driven by the concentration gradient (i.e., the differences in concentration) existing across the membrane, with the passage of drug molecules occurring primarily from the side of high drug concentration. Most drugs pass through biologic membranes by diffusion.

Passive diffusion is described by *Fick's first law,* which states that the rate of diffusion or transport across a membrane (dc/dt) is proportional to the difference in drug concentration on both sides of the membrane:

$$-\frac{dc}{dt} = P(C_1 - C_2)$$

in which C_1 and C_2 refer to the drug concentrations on each side of the membrane and P is a permeability coefficient or constant. The term C_1 is customarily used to represent the compartment with the greater concentration of drug and thus the transport of drug proceeds from compartment one (e.g., absorption site) to compartment two (e.g., blood).

Because the concentration of drug at the site of absorption (C_1) is usually much greater than on the other side of the membrane, due to the rapid dilution of the drug in the blood and its subsequent distribution to the tissues, for practical purposes the value of $C_1 - C_2$ may be taken simply as that of C_1 and the equation written in the standard form for a first order rate equation:

$$-\frac{dc}{dt} = PC_1$$

The gastrointestinal absorption of most drugs from solution occurs in this manner in accordance with *first order kinetics* in which the rate is dependent upon drug concentration, i.e., doubling the dose doubles the transfer rate. The magnitude of the permeability constant, depends on the diffusion coefficient of the drug, the thickness and area of the absorbing membrane, and the permeability of the membrane to the particular drug.

Because of the lipoid nature of the cell membrane, it is highly permeable to lipid soluble substances. The rate of diffusion of a drug across the membrane depends not only upon its concentra-

tion but also upon the relative extent of its affinity for lipid and rejection of water (a high lipid partition coefficient). The greater its affinity for lipid and the more hydrophobic it is, the faster will be its rate of penetration into the lipid-rich membrane. Erythromycin base, for example, possesses a higher partition coefficient than other erythromycin compounds, e.g., estolate, gluceptate. Consequently, the base is the preferred agent for the topical treatment of acne where penetration into the skin is desired.

Because biologic cells are also permeated by water and lipid-insoluble substances, it is thought that the membrane also contains water-filled pores or channels that permit the passage of these types of substances. As water passes in bulk across a porous membrane, any dissolved solute molecularly small enough to traverse the pores passes in by *filtration*. Aqueous pores vary in size from membrane to membrane and thus in their individual permeability characteristics for certain drugs and other substances.

The majority of drugs today are weak organic acids or bases. Knowledge of their individual ionization or dissociation characteristics is important, because their absorption is governed to a large extent by their degrees of ionization as they are presented to the membrane barriers. Cell membranes are more permeable to the unionized forms of drugs than to their ionized forms, mainly because of the greater lipid solubility of the unionized forms and to the highly charged nature of the cell membrane which results in the binding or repelling of the ionized drug and thereby decreases cell penetration. Also, ions become hydrated through association with water molecules, resulting in larger particles than the undissociated molecule and again decreased penetrating capability.

The degree of a drug's ionization depends both on the pH of the solution in which it is presented to the biologic membrane and on the pK_a, or dissociation constant, of the drug (whether an acid or base). The concept of pK_a is derived from the Henderson-Hasselbalch equation and is:

For an acid:

$$pH = pK_a + \log \frac{\text{ionized conc. (salt)}}{\text{unionized conc. (acid)}}$$

For a base:

$$pH = pK_a + \log \frac{\text{unionized conc. (base)}}{\text{ionized conc. (salt)}}$$

Since the pH of body fluids varies (stomach, ≈ pH 1; lumen of the intestine, ≈ pH 6.6; blood plasma, ≈ pH 7.4), the absorption of a drug from various body fluids will differ and may dictate to some extent the type of dosage form and the route of administration preferred for a given drug.

By rearranging the equation for an acid:

$$pK_a - pH = \log \frac{\text{unionized concentration (acid)}}{\text{ionized concentration (salt)}}$$

one can theoretically determine the relative extent to which a drug remains unionized under various conditions of pH. This is particularly useful when applied to conditions of body fluids. For instance, if a weak acid having a pK_a of 4 is assumed to be in an environment of gastric juice with a pH of 1, the left side of the equation would yield the number 3, which would mean that the ratio of unionized to ionized drug particles would be about 1000 to 1, and gastric absorption would be excellent. At the pH of plasma the reverse would be true, and in the blood the drug would be largely in the ionized form. Table 3–1 presents the effect of pH on the ionization of weak electrolytes, and Table 3–2 offers some representative pK_a values of common drug substances.

From the equation and from Table 3–1, it may be seen that a drug substance is half ionized at

Table 3–1. The Effect of pH on the Ionization of Weak Electrolytes*

	% Unionized	
pK_a-pH	*If Weak Acid*	*If Weak Base*
−3.0	0.100	99.9
−2.0	0.990	99.0
−1.0	9.09	90.9
−0.7	16.6	83.4
−0.5	24.0	76.0
−0.2	38.7	61.3
0	50.0	50.0
+0.2	61.3	38.7
+0.5	76.0	24.0
+0.7	83.4	16.6
+1.0	90.9	9.09
+2.0	99.0	0.99
+3.0	99.9	0.100

* From Doluisio, J.T., and Swintosky, J.V.; *Amer. J. Pharm., 137*:149, 1965.

Table 3–2. pK
Drugs

Acids:

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Table 3–2. pK_a Values for Some Acidic and Basic Drugs

		pK_a
Acids:	Acetylsalicylic acid	3.5
	Barbital	7.9
	Benzylpenicillin	2.8
	Boric acid	9.2
	Dicoumarol	5.7
	Phenobarbital	7.4
	Phenytoin	8.3
	Sulfanilamide	10.4
	Theophylline	9.0
	Thiopental	7.6
	Tolbutamide	5.5
	Warfarin	4.8
Bases:	Amphetamine	9.8
	Apomorphine	7.0
	Atropine	9.7
	Caffeine	0.8
	Chlordiazepoxide	4.6
	Cocaine	8.5
	Codeine	7.9
	Guanethidine	11.8
	Morphine	7.9
	Procaine	9.0
	Quinine	8.4
	Reserpine	6.6

a pH value which is equal to its pK_a. Thus pK_a may be defined as the pH at which a drug is 50% ionized. For example, phenobarbital has a pK_a value of about 7.4, and in plasma (pH 7.4) it is present as ionized and unionized forms in equal amounts. However, a drug substance cannot reach the blood plasma for distribution throughout the body unless it is placed there directly through intravenous injection or is favorably absorbed from a site along its route of entry, as the gastrointestional tract, and allowed to pass into the general circulation. Utilizing Table 3–2 it may be easily seen that phenobarbital, a weak acid, with a pK_a of 7.4 would be largely undissociated in the gastric environment of pH 1, and would likely be well absorbed. A drug may enter the circulation rapidly and at high concentrations if membrane penetration is easily accomplished or at a low rate and low level if the drug is not readily absorbed from its route of entry. The pH of the drug's current environment influences the rate and the degree of its further distribution, since it becomes more or less unionized and therefore more or less lipid-penetrating under some condition of pH than under another. If an unionized molecule is able to diffuse through the lipid barrier and remain unionized in the new environment, it may return to its former location or go on to a new one. However, if in the new environment it is greatly ionized due to the influence of the pH of the second fluid, it likely will be unable to cross the membrane with its former ability. Thus a concentration gradient of a drug usually is reached at equilibrium on each side of a membrane due to different degrees of ionization occurring on each side. *A summary of the concepts of dissociation/ionization is found in the accompanying Physical Pharmacy Capsule.*

It is often desirable for pharmaceutical scientists to make structural modifications in organic drugs and thereby favorably alter their lipid solubility, partition coefficients, and dissociation constants while maintaining the same basic pharmacologic activity. These efforts frequently result in increased absorption, better therapeutic response, and lower dosage.

Specialized Transport Mechanisms

In contrast to the passive transfer of drugs and other substances across a biologic membrane, certain substances, including some drugs and biologic metabolites, are conducted across a membrane through one of several postulated *specialized transport* mechanisms. This type of transfer seems to account for those substances, many naturally occurring as amino acids and glucose, that are too lipid-insoluble to dissolve in the boundary and too large to flow or filter through the pores. This type of transport is thought to involve membrane components that may be enzymes or some other type of agent capable of forming a complex with the drug (or other agent) at the surface membrane, after which the complex moves across the membrane where the drug is released, with the carrier returning to the original surface. Figure 3–2 presents the simplified scheme of this process. Specialized transport may be differentiated from passive transfer in that the former process may become "saturated" as the amount of carrier present for a given substance becomes completely bound with that substance resulting in a delay in the "ferrying" or transport process. Other features of specialized transport include the specificity by a carrier for a particular type of chemical structure so that if two substances are transported by the same mechanism one will competitively inhibit the transport of the other. Further, the transport mechanism is inhibited in general by substances that interfere with cell metabolism. The term *ac-*

Dissociation Constants

Among the physicochemical characteristics of interest is the extent of dissociation/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/ionization is, in many cases, highly dependent on the pH of the medium containing the drug. In formulation, often the vehicle is adjusted to a certain pH in order to obtain a certain level of ionization of the drug for solubility and stability purposes. In the pharmacokinetic area, the extent of ionization of a drug is an important affector of its extent of absorption, distribution, and elimination. For the practicing pharmacist, it is important in predicting precipitation in admixtures and in the calculating of the solubility of drugs at certain pH values. The following discussion will present only a brief summary of dissociation/ionization concepts.

The dissociation of a weak acid in water is given by the 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 defined as

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

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?

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

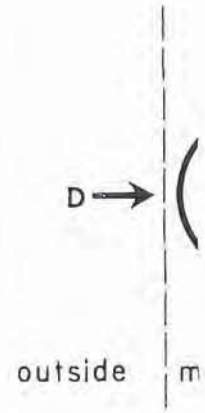

Fig. 3–2. *Active tra*
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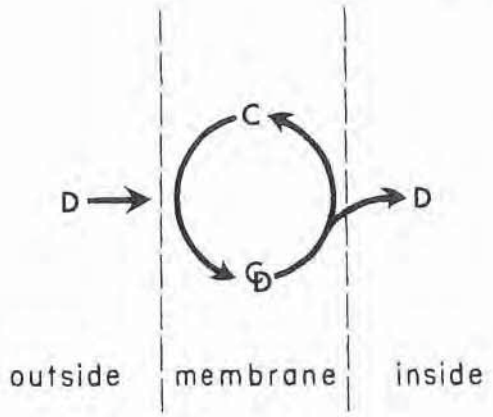

Fig. 3–2. *Active transport mechanism. D represents a drug molecule; C represents the carrier in the membrane. (After O'Reilly, W.J.: Aust. J. Pharm., 47:568, 1966.)*

tive transport, as a subclassification of specialized transport, denotes a process with the additional feature of the solute or drug being moved across the membrane against a concentration gradient, that is, from a solution of lower concentration to one of a higher concentration or, if the solute is an ion, against an electrochemical potential gradient. In contrast to active transport, *facilitated diffusion* is a specialized transport mechanism having all of the above characteristics except that the solute is not transferred against a concentration gradient and may attain the same concentration inside the cell as that on the outside.

Many body nutrients, as sugars and amino acids, are transported across the membranes of the gastrointestinal tract by carrier processes. Certain vitamins, as thiamine, niacin, riboflavin and vitamin B_6, and drug substances as methyldopa and 5-fluorouracil, require active transport mechanisms for their absorption.

Investigations of intestinal transport have often utilized *in situ* (at the site) or *in vivo* (in the body) animal models or *ex vivo* (outside the body) transport models; however, recently cell culture models of human small-intestine absorptive cells have become available to investigate transport across intestinal epithelium.[1] Both passive and transport-mediated studies have been conducted to investigate mechanisms as well as rates of transport.

Dissolution and Drug Absorption

In order for a drug to be absorbed, it must first be dissolved in the fluid at the absorption site. For instance, a drug administered orally in tablet or capsule form cannot be absorbed until the drug particles are dissolved by the fluids at some point within the gastrointestinal tract. In instances in which the solubility of a drug is dependent upon either an acidic or basic medium, the drug would be dissolved in the stomach or intestines respectively (Fig. 3–3). The process by which a drug particle dissolves is termed *dissolution.*

As a drug particle undergoes dissolution, the drug molecules on the surface are the first to enter into solution creating a saturated layer of drug-solution which envelops the surface of the solid drug particle. This layer of solution is referred to as the *diffusion layer*. From this diffusion layer, the drug molecules pass throughout the dissolving fluid and make contact with the biologic membranes and absorption ensues. As the molecules of drug continue to leave the diffusion layer, the layer is replenished with dissolved drug from the surface of the drug particle and the process of absorption continues.

If the process of dissolution for a given drug particle is rapid, or if the drug is administered as a solution and remains present in the body as such, the rate at which the drug becomes absorbed would be primarily dependent upon its ability to traverse the membrane barrier. However, if the rate of dissolution for a drug particle

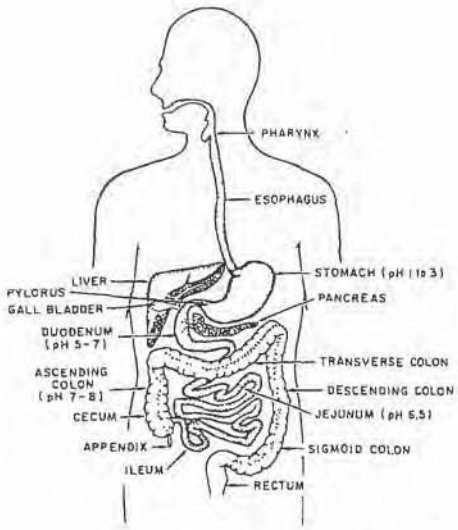

Fig. 3–3. *Anatomical diagram showing the digestive system including the locations involved in drug absorption and their respective pHs.*

is slow, as may be due to the physiochemical characteristics of the drug substance or the dosage form, the dissolution process itself would be a rate-limiting step in the absorption process. Slowly soluble drugs such as digoxin, may not only be absorbed at a slow rate, they may be incompletely absorbed, or, in some cases largely unabsorbed following oral administration, due to the natural limitation of time that they may remain within the stomach or the intestinal tract. Thus, poorly soluble drugs or poorly formulated drug products may result in a drug's incomplete absorption and its passage, unchanged, out of the system via the feces.

Under normal circumstances a drug may be expected to remain in the stomach for 2 to 4 hours (*gastric emptying time*) and in the small intestines for 4 to 10 hours, although there is substantial variation between people, and even in the same person on different occasions. Various techniques have been used to determine gastric emptying time and the gastrointestinal passage of drug from various oral dosage forms, including the tracking of dosage forms labeled with gamma-emitting radionuclides through gamma scintigraphy.[2,3] The gastric emptying time for a drug is most rapid with a fasting stomach, becoming slower as the food content is increased. Changes in gastric emptying time and/or in intestinal motility can affect drug transit time and thus the opportunity for drug dissolution and absorption.

These changes can be effected by drugs the patient may be taking. Certain drugs with anticholinergic properties, e.g., dicyclomine HCl, amitriptyline HCl, have the ability to slow down gastric emptying. This can enhance the rate of absorption of drugs normally absorbed from the stomach, and reduce the rate of absorption of drugs that are primarily absorbed from the small intestine. Alternatively, drugs which enhance gastric motility, e.g., laxatives, may cause some drugs to move so quickly through the gastrointestinal system and past their absorptive site at such a rate to reduce the amount of drug actually absorbed. This effect has been demonstrated with digoxin, whose absorption is significantly decreased by accelerating gastrointestinal motility.

The aging process itself may also influence gastrointestinal absorption. In the elderly, gastric acidity, the number of absorptive cells, intestinal blood flow, the rate of gastric emptying and intestinal motility are all decreased. It appears, however, that drugs for which absorption is dependent upon passive processes are not affected by these factors as much as those that are dependent upon active transport mechanisms, e.g., calcium, iron, thiamine, sugars. A decrease in gastric emptying time would be advantageous for those drugs that are absorbed from the stomach but disadvantageous for those drugs which are prone to acid degradation, e.g., penicillins, erythromycin, or inactivated by stomach enzymes, e.g., L-dopa.

The dissolution of a substance may be described by the modified Noyes-Whitney equation:

$$\frac{dc}{dt} = kS(c_s - c_t)$$

in which dc/dt is the rate of dissolution, k is the dissolution rate constant, S is the surface area of the dissolving solid, c_s is the saturation concentration of drug in the diffusion layer (which may be approximated by the maximum solubility of the drug in the solvent since the diffusion layer is considered saturated), and c_t is the concentration of the drug in the dissolution medium at time t ($c_s - c_t$ is the concentration gradient). The rate of dissolution is governed by the rate of diffusion of solute molecules through the diffusion layer into the body of the solution. The equation reveals that the dissolution rate of a drug may be increased by increasing the surface area (reducing the particle size) of the drug, by increasing the solubility of the drug in the diffusion layer, and by factors embodied in the dissolution rate constant, k, including the intensity of agitation of the solvent and the diffusion coefficient of the dissolving drug. For a given drug, the diffusion coefficient and usually the concentration of the drug in the diffusion layer will increase with increasing temperature. Also, increasing the rate of agitation of the dissolving medium will increase the rate of dissolution. A reduction in the viscosity of the solvent employed is another means which may be used to enhance the dissolution rate of a drug. Changes in the pH or the nature of the solvent which influence the solubility of the drug may be used to advantage in increasing dissolution rate. Effervescent, buffered aspirin tablet formulations use some of these principles to their advantage. Due to the alkaline adjuvants in the tablet, the solubility of the aspirin is enhanced within the diffusional

layer and the evolution of carbon dioxide agitates the solvent system, i.e., gastric juices. Consequently, the rate of aspirin absorbed into the bloodstream is faster than that achieved from a conventional aspirin tablet formulation. If this dosage form is acceptable to the patient, it provides a quicker means for the patient to gain relief from a troublesome headache. Many manufacturers will utilize a particular amorphous, crystalline, salt or ester form of a drug that will exhibit the solubility characteristics needed to achieve the desired dissolution characteristics when administered. Some of these factors which affect drug dissolution briefly are discussed in the following paragraphs, whereas others will be discussed in succeeding chapters in which they are relevant.

It is important to remember that the chemical and physical characteristics of a drug substance that can affect drug/drug product safety, efficacy, and stability must be carefully defined by appropriate standards in an application for FDA approval and then substained and controlled throughout product manufacture.

Surface Area

When a drug particle is reduced to a larger number of smaller particles, the total surface area created is increased. For drug substances that are poorly or slowly soluble, this generally results in an increase in the *rate* of dissolution. The actual solubility of a pure drug remains the same.

Increased therapeutic response to orally administered drugs due to smaller particle size has been reported for a number of drugs, among them theophylline, a xanthine derivative used to treat bronchial asthma; griseofulvin, an antibiotic with antifungal activity; sulfisoxazole, an anti-infective sulfonamide, and nitrofurantoin, a urinary anti-infective drug. To achieve increased surface area, pharmaceutical manufacturers frequently use *micronized* powders in their solid dosage form products. Micronized powders consist of drug particles reduced in size to about 5 microns and smaller. The use of micronized drugs is not confined to oral preparations. For example, ophthalmic ointments and topical ointments utilize micronized drugs for their preferred release characteristics and nonirritating quality after application.

Due to the different rates and degrees of absorption obtainable from drugs of various particle size, it is conceivable that products of the same drug substance prepared by two or more reliable pharmaceutical manufacturers may result in different degrees of therapeutic response in the same individual. A classic example of this occurs with phenytoin sodium capsules where there are two distinct forms. The first is the rapid-release type, i.e., Prompt Phenytoin Sodium Capsules, USP, and the second is the slow-dissolution type, i.e., Extended Phenytoin Sodium Capsules, USP. The former has a dissolution rate of not less than 85% in 30 minutes and is recommended for patient use 3 to 4 times per day. The latter has a slower dissolution rate, e.g., 15 to 35% in 30 minutes, which lends itself for use in patients who could be dosed less frequently. Because of such differences in formulation for a number of drugs and drug products, it is generally advisable for a person to continue taking the same brand of medication, provided it produces the desired therapeutic effect. Patients who are stabilized on one brand of drug should not be switched to another unless necessary. However, when a change is necessary, appropriate blood or plasma concentrations of the drug should be monitored until the patient is stabilized on the new product.

Occasionally, a rapid rate of drug absorption is not desired in a pharmaceutical preparation. Research pharmacists, in providing sustained rather than rapid action in certain preparations, may employ agents of varying particle size to provide a controlled dissolution and absorption process. *Summaries of the physical chemical principles of particle size reduction and the relation of particle size to surface area, dissolution, and solubility may be found in the accompanying Physical Pharmacy Capsules.*

Crystal or Amorphous Drug Form

Solid drug materials may occur as pure crystalline substances of definite identifiable shape or as amorphous particles without definite structure. The amorphous or crystalline character of a drug substance may be of considerable importance to its ease of formulation and handling, its chemical stability, and, as has been recently shown, even its biological activity. Certain medicinal agents may be produced to exist in either a crystalline or an amorphous state. Since the amorphous form of a chemical is usually more soluble than the crystalline form, different extents of drug absorption may result with consequent differences in the degree of pharmacologic activity obtained from each. Experiences with two antibiotic substances, novobiocin and chlor-

Particle Size, Surface Area and Dissolution Rate

Particle size has an effect on dissolution rate and solubility. As shown in the Noyes-Whitney equation:

$$\frac{dC}{dT} = kS(C_s - C_t)$$

where dC/dT is the rate of dissolution (concentration with respect to time),
k is the dissolution rate constant
S is the surface area of the particles,
C_s is the concentration of the drug in the immediate proximity of the dissolving particle, i.e., the solubility of the drug,
C_t is the concentration of the drug in the bulk fluid.

It is evident that the "C_s" cannot be significantly changed, the "C_t" is often under sink conditions (an amount of the drug is used that is less than 20% of its solubility) and "k" comprises many factors such as agitation, temperature. This leaves the "S," surface area, as a factor that can affect the rate of dissolution.

An increase in the surface area of a drug will, within reason, increase the dissolution rate. Circumstances when it may decrease the rate would include a decrease in the "effective surface area," i.e., a condition in which the dissolving fluid would not be able to "wet" the particles. Wetting is the first step in the dissolution process. This can be demonstrated by visualizing a 0.75 inch diameter by ¼ inch thick tablet. The surface area of the tablet can be increased by drilling a series of $\frac{1}{16}$ inch holes in the tablet. However, even though the surface area has been increased, the dissolution fluid, i.e., water, would not necessarily be able to penetrate into the new holes due to surface tension, etc., and displace the air. Adsorbed air and other factors can decrease the effective surface area of a dosage form, including powders. This is the reason that particle size reduction does not always result in an increase in dissolution rate. One can also visualize a powder that has been comminuted to a very fine state of subdivision and when it is placed in a beaker of water, the powder floats due to the entrapped and adsorbed air. The "effective surface area" is not the same as the actual "surface area" of the resulting powder.

amphenicol palmitate, have revealed that these materials are essentially inactive when administered in crystalline form, but when they are administered in the amorphous form, absorption from the gastrointestinal tract proceeds rapidly with good therapeutic response. In other instances, crystalline forms of drugs may be used because of greater stability than the corresponding amorphous forms. For example, the crystalline forms of Penicillin G as either the potassium or sodium salt are considerably more stable than the analogous amorphous forms. Thus, in formulation work involving Penicillin G, the crystalline forms are preferred and result in excellent therapeutic response.

The hormonal substance insulin presents another striking example of the different degree of activity that may result from the use of different physical forms of the same medicinal agent. Insulin is the active principle of the pancreas gland and is vital to the body's metabolism of glucose. The hormone is produced by two means. The first is by extraction procedures from either beef or pork pancreas. The second process involves a biosynthetic process with strains of *Escherichia coli*, i.e., recombinant DNA. Insulin is used by man as replacement therapy, by injection, when his body's production of the hormone is insufficient. Insulin is a protein, which, when combined with zinc in the presence of acetate buffer, forms an extremely insoluble zinc-insulin complex. Depending upon the pH of the acetate buffer solution, the complex may be an amorphous precipitate or a crystalline material. Each type is produced commercially to take advantage of their unique absorption characteristics.

The amorphous form, referred to as *semilente insulin* or Prompt Insulin Zinc Suspension, USP, is rapidly absorbed upon intramuscular or subcutaneous (under the skin) injection. The larger

Particle Size and Solubility

In addition to dissolution rate, surface area 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
r is the radius of the small particles.

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

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

$$r = 9.238 \times 10^{-6}\ \text{cm or } 0.09238\mu$$

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

crystalline material, called *ultralente insulin* or Extended Insulin Zinc Suspension, USP, is more slowly absorbed with a resultant longer duration of action. By combining the two types in various proportions, a physician is able to provide his patients with intermediate acting insulin of varying degrees of onset and duration of action. A physical mixture of 70% of the crystalline form and 30% of the amorphous form, called *lente insulin* or Insulin Zinc Suspension, USP, is commercially available and provides an intermediate acting insulin preparation that meets the requirements of many diabetics.

Some medicinal chemicals that exist in crystalline form are capable of forming different types of crystals, depending upon the conditions (temperature, solvent, time) under which crystallization is induced. This property, whereby a single chemical substance may exist in more than one crystalline form, is known as "polymorphism." It is known that only one form of a pure drug substance is stable at a given temperature and pressure with the other forms, called metastable forms, converting in time to the stable crystalline form. It is therefore not unusual for a metastable form of a medicinal agent to change form even when present in a completed pharmaceutical preparation, although the time required for a complete change may exceed the normal shelf-life of the product itself. However, from a pharmaceutical point of view, any change in the crystal structure of a medicinal agent may critically affect the stability and even the therapeutic efficacy of the product in which the conversion takes place.

The various polymorphic forms of the same chemical generally differ in many physical properties, including their solubility and dissolution characteristics, which are of prime importance to the rate and extent of drug absorption into the body's system. These differences are manifest so long as the drug is in the solid state. Once solution is effected, the different forms are indistinguishable one from another. Therefore, differences in drug action, pharmaceutically and therapeutically, can be expected from polymorphs contained in solid dosage forms as well as in liquid suspension. The use of metastable forms generally results in higher solubility and dissolution rates than the respective stable crys-

tal forms of the same drug. If all other factors remain constant, more rapid and complete drug absorption will likely result from the metastable forms than from the stable form of the same drug. On the other hand, the stable polymorph is generally more resistant to chemical degradation and because of its lower solubility is frequently preferred in pharmaceutical suspensions of insoluble drugs. If metastable forms are employed in the preparation of suspensions, their gradual conversion to the stable form may be accompanied by an alteration in the consistency of the suspension itself, thereby affecting its permanency. In all instances, the advantages of the metastable crystalline forms in terms of increased physiologic availability of the drug must be balanced against the increased product stability when stable polymorphs are employed. Sulfur and cortisone acetate are two examples of drugs that exist in more than one crystalline form and are frequently prepared in pharmaceutical suspensions. In fact, cortisone acetate is reported to exist in at least five different crystalline forms. It is possible for the commercial products of two manufacturers to differ in stability and in the therapeutic effect, depending upon the crystalline form of the drug used in the formulation.

Salt Forms

The dissolution rate of a salt form of a drug is generally quite different from that of the parent compound. Sodium and potassium salts of weak organic acids and hydrochloride salts of weak organic bases dissolve much more readily than do the respective free acids or bases. The result is a more rapid saturation of the diffusion layer surrounding the dissolving particle and the consequent more rapid diffusion of the drug to the absorption sites.

Numerous examples could be cited to demonstrate the increased rate of drug dissolution due to the use of the salt form of the drug rather than the free acid or base, but the following will suffice: the addition of the ethylenediamine moiety to theophylline increases the water solubility of theophylline 5-fold. The use of the ethylenediamine salt of theophylline has allowed the development of oral aqueous solutions of theophylline and diminished the need to use hydroalcoholic mixtures, e.g., elixirs.

Other Factors

The *state of hydration* of a drug molecule can affect its solubility and pattern of absorption. Usually the anhydrous form of an organic molecule is more readily soluble than the hydrated form. This characteristic was demonstrated with the drug ampicillin, when the anhydrous form was shown to have a greater rate of solubility than the trihydrate form.[4] It was also shown that the rate of absorption for the anyhdrous form was greater than that for the trihydrate form of the drug.

Once swallowed, a drug is placed in the gastrointestinal tract where its solubility can be affected not only by the pH of the environment, but by the normal components of the tract and the foodstuffs which may be present. A drug may interact with one of the other agents present to form a chemical complex which may result in reduced drug solubility and decreased drug absorption. The classic example of this complexation phenomenon is that which occurs between tetracycline analogues and certain cations, e.g., calcium, magnesium, aluminum, resulting in a decreased absorption of the tetracycline derivative. Also, if the drug becomes *ad*sorbed onto insoluble material in the tract, its availability for absorption may be correspondingly reduced.

Bioavailability and Bioequivalence

The term *bioavailability* describes the *rate* and *extent* to which an active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action. The term *bioequivalence* refers to the *comparison* of bioavailabilities of different formulations, drug products, or batches of the same drug product.

The availability to the biologic system of a drug substance formulated into a pharmaceutical product is integral to the goals of dosage form design and paramount to the effectiveness of the medication. The study of a drug's bioavailability depends upon the drug's absorption or entry into the systemic circulation, and studying the pharmacokinetic profile of the drug or its metabolite(s) over time in the appropriate biologic system, e.g., blood, plasma, urine. Graphically, bioavailability of a drug is portrayed by a concentration-time curve of the administered drug in an appropriate tissue system, e.g., plasma (Fig. 3–4). Bioavailability data are used to determine: (1) the amount or proportion of drug absorbed from a formulation or dosage form; (2) the rate at which the drug was absorbed; (3) the duration of the drug's presence in the biologic fluid or tissue; and, when correlated

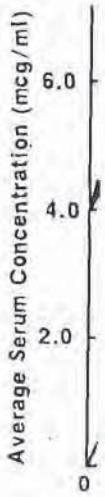

Fig. 3–4. *Serum conc*
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FDA Bioavailabilit Requirements[5]

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become confused or upset if dispensed an alternate product that differs in color, flavor, shape, or packaging from that to which he or she has become accustomed. Switching between products can generate concern, and thus pharmacists need to be prudent in both initial product selection and in product interchange.

Routes of Drug Administration

Drugs may be administered by a variety of dosage forms and routes of administration, as presented in Tables 3–5 and 3–6. One of the fundamental considerations in dosage form design is whether the drug is intended for local or systemic effects. *Local* effects are achieved from direct application of the drug to the desired site of action, such as the eye, nose, or skin. *Systemic* effects result from the entrance of the drug into the circulatory system and its subsequent transport to the cellular site of its action. For systemic effects, a drug may be placed directly into the blood stream via intravenous injection or absorbed into the venous circulation following oral, or other routes of administration.

Table 3–5. Routes of Drug Administration

Term	*Site*
oral	mouth
peroral (per os[1])	gastrointestinal tract via mouth
sublingual	under the tongue
parenteral	other than the gastrointestinal tract (by injection)
intravenous	vein
intraarterial	artery
intracardiac	heart
intraspinal or intrathecal	spine
intraosseous	bone
intraarticular	joint
intrasynovial	joint-fluid area
intracutaneous or intradermal	skin
subcutaneous	beneath the skin
intramuscular	muscle
epicutaneous (topical)	skin surface
transdermal	skin surface
conjunctival	conjunctiva
intraocular	eye
intranasal	nose
aural	ear
intrarespiratory	lung
rectal	rectum
vaginal	vagina
urethral	urethra

[1] The abbreviation "p.o." is commonly employed on prescriptions to indicate to be swallowed.

Table 3–6. Dosage Form/Drug Delivery System Application

Route of Administration	*Primary Dosage Forms*
oral	tablets capsules solutions syrups elixirs suspensions magmas gels powders
sublingual	tablets troches or lozenges
parenteral	solutions suspensions
epicutaneous/ transdermal	ointments creams infusion pumps pastes plasters powders aerosols lotions transdermal patches, discs, solutions
conjunctival	contact lens inserts ointments
intraocular/ intraaural	solutions suspensions
intranasal	solutions sprays inhalants ointments
intrarespiratory	aerosols
rectal	solutions ointments suppositories
vaginal	solutions ointments emulsion foams tablets inserts, suppositories, sponge
urethral	solutions suppositories

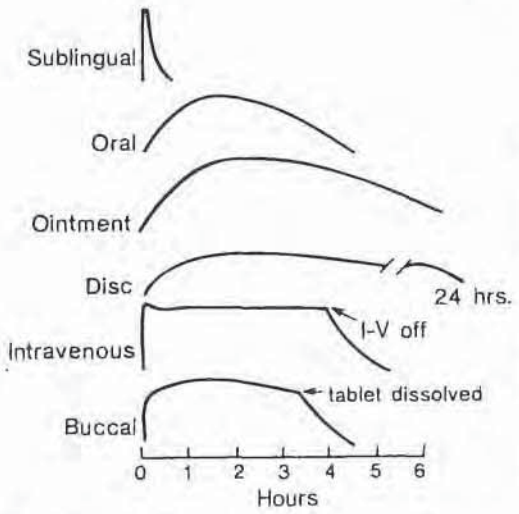

Fig. 3–11. *Blood-level curves of nitroglycerin following administration of dosage forms by various routes. (From Abrams, J.: Nitroglycerin and Long-Acting Nitrates in Clinical Practice.* The American Journal of Medicine, *Proceedings of a Symposium: First North American Conference on Nitroglycerin Therapy, June 27, 1983. Reprinted with Permission.)*

An individual drug substance may be formulated into multiple dosage forms which result in different drug absorption rates and times of onset, peak, and duration of action. This is demonstrated by Figure 3–11 and Table 3–7, for the drug nitroglycerin in various dosage forms. The sublingual, intravenous, and buccal forms present extremely rapid onsets of action whereas the oral (swallowed), topical ointment and topical disc present slower onsets of action but greater durations of action. The disc provides the longest duration of action, up to 24 hours following application of a single patch to the skin. The transdermal nitroglycerin disc allows a single daily dose, whereas the other forms require multiple dosing to maintain drug levels within the therapeutic window.

The difference in drug absorption between dosage forms is a function of the formulation and the route of administration. For example, a problem associated with the oral administration of a drug is that once absorbed through the lumen of the gastrointestinal tract into the portal vein, the drug may pass directly to the liver and undergo the *first-pass effect*. In essence a portion or all of the drug may be metabolized by the liver. Consequently, as the drug is extracted by the liver, its bioavailability to the body is decreased. Thus, the bioavailable fraction is determined by the fraction of drug that is absorbed from the gastrointestinal tract and the fraction that escapes metabolism during its first pass through the liver. The bioavailable fraction (f) is the product of these two fractions as follows:

f = Fraction of drug absorbed

× Fraction escaping first-pass metabolism

The bioavailability is lowest, then, for those drugs that undergo a significant first-pass effect. For these drugs, a hepatic extraction ratio, or the fraction of drug metabolized, E, is calculated. The fraction of drug that enters the system circulation and is ultimately available to exert its effect then is equal to the quantity $(1 - E)$. Table 3–8 lists some drugs according to their pharmacologic class that undergo a significant first-pass effect when administered by the oral route.

To compensate for this marked effect, the drug manufacturer may consider other routes of drug administration, e.g., intravenous, intramuscular, sublingual, that avoid the first-pass effect. With these routes there will be a corresponding decrease in the dosage required when compared to oral administration.

Table 3–7. Dosage and Kinetics of Nitroglycerin in Various Dosage Forms[1]

Nitroglycerin, Dosage Form	*Usual Recommended Dosage (mg)*	*Onset of Action (Minutes)*	*Peak Action (Minutes)*	*Duration (Minutes/hours)*
Sublingual	0.3–0.8	2–5	4–8	10–30 minutes
Buccal	1–3	2–5	4–10	30–300 minutes[Δ]
Oral	6.5–19.5	20–45	45–120	2–6 hours[Ω]
Ointment (2%)	½–2 inches	15–60	30–120	3–8 hours
Discs	5–10	30–60	60–180	Up to 24 hours

[Δ] Effect persists so long as tablet is intact.

[Ω] Some short-term dosing studies have demonstrated effects to 8 hours.

[1] From Abrams, J.: Nitroglycerin and Long-Acting Nitrates in Clinical Practice. *The American Journal of Medicine,* Proceedings of a Symposium: First North American Conference of Nitroglycerin Therapy, June 27, 1983, p. 88.

Table 3–8. Examples of Drugs that Undergo Significant Liver Metabolism and Exhibit Low Bioavailability when Administered by First-pass Routes

Drug Class	*Examples*
Analgesics	Aspirin, meperidine, pentazocine, propoxyphene
Antianginal	Nitroglycerin
Antiarrhythmics	Lidocaine
Beta-adrenergic blockers	Labetolol, metoprolol, propranolol
Calcium channel blockers	Verapamil
Sympathomimetic amines	Isoproterenol
Tricyclic antidepressants	Desipramine, imipramine, nortriptyline

Another consideration centers around the metabolites themselves, and whether they are pharmacologically active or inactive. If they are inactive, a larger oral dose will be required to attain the desired therapeutic effect when compared to a lower dosage in a nonfirst-pass effect route. The classic example of drug that exhibits this effect is propranolol. If, on the other hand, the metabolites are the active species, the oral dosage must be carefully tailored to the desired therapeutic effect. First-pass metabolism in this case will result in a quicker therapeutic response than that achieved by a nonfirst-pass effect route.

One must remember also that the flow of blood through the liver can be decreased under certain conditions. Consequently, the bioavailability of those drugs that undergo a first-pass effect then would be expected to increase. For example, during cirrhosis the blood flow to the kidney is dramatically decreased and efficient hepatic extraction by enzymes responsible for a drug's metabolism also falls off. Consequently, in cirrhotic patients the dosage of drug that undergoes a first-pass effect from oral administration will have to be reduced to avoid toxicity.

Oral Route

Drugs are most frequently taken by oral administration. Although a few drugs taken orally are intended to be dissolved within the mouth, the vast majority of drugs taken orally are swallowed. Of these, most are taken for the *systemic* drug effects that result after absorption from the various surfaces along the gastrointestinal tract. A few drugs, such as antacids, are swallowed for their local action within the confines of the gastrointestinal tract.

Compared with alternate routes, the oral route is considered the most natural, uncomplicated, convenient, and safe means of administering drugs. Disadvantages of the oral route include slow drug response (when compared with parenterally administered drugs); chance of irregular absorption of drugs, depending upon such factors as constitutional make-up, the amount or type of food present within the gastrointestinal tract; and the destruction of certain drugs by the acid reaction of the stomach or by gastrointestinal enzymes.

DOSAGE FORMS APPLICABLE. Drugs are administered by the oral route in a variety of pharmaceutical forms. The most popular are tablets, capsules, suspensions, and various pharmaceutical solutions. Briefly, *tablets* are solid dosage forms prepared by compression or molding and contain medicinal substances with or without suitable diluents, disintegrants, coatings, colorants, and other pharmaceutical adjuncts. Diluents are fillers used in preparing tablets of the proper size and consistency. Disintegrants are used for the break-up or separation of the tablet's compressed ingredients. This ensures prompt exposure of drug particles to the dissolution process thereby enhancing drug absorption, as shown in Figure 3–12. Tablet coatings are of several types and for several different purposes. Some called *enteric coatings* are employed to permit safe pas-

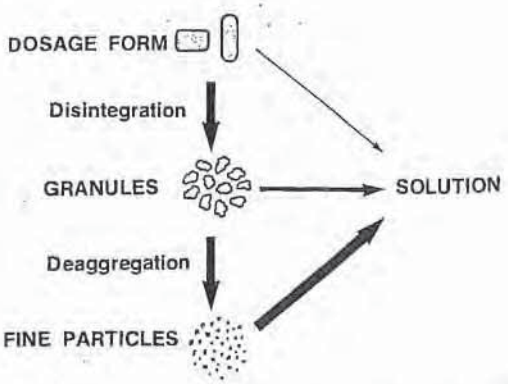

Fig. 3–12. *Schematic drawing showing disintegration of a tablet dosage form and direct availability of the contents in a capsule dosage form for dissolution and drug absorption after oral administration. (From Rowland, M., and Rozer, T.N.:* Clinical Pharmacokinetics. *2nd Ed., Philadelphia, Lea & Febiger, 1989.)*

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sage of a tablet through the acid environment of the stomach where certain drugs may be destroyed, to the more suitable juices of the intestines where tablet dissolution safely takes place. Other coatings are employed to protect the drug substance from the destructive influences of moisture, light, and air throughout their period of storage or to conceal a bad or bitter taste from the taste buds of a patient. Commercial tablets, because of their distinctive shapes, colors, and frequently employed monograms of company symbols and code numbers facilitate identification by persons trained in their use and serve as an added protection to public health.

Capsules are solid dosage forms in which the drug substance and appropriate pharmaceutical adjuncts as fillers are enclosed in either a hard or a soft "shell," generally composed of a form of gelatin. Capsules vary in size, depending upon the amount of drug to be administered, and are of distinctive shapes and colors when produced commercially. Generally, drug materials are released from capsules faster than from tablets. Capsules of gelatin, a protein, are rapidly disfigured within the gastrointestinal tract, permitting the gastric juices to permeate and reach the contents. Because unsealed capsules have been subject to tampering by unscrupulous individuals, many capsules nowadays are sealed by fusion of the two capsule shells. Also, capsule-shaped and coated tablets, called "caplets," are increasingly utilized. These are easily swallowed but their contents are sealed and protected from tampering like tablets.

Suspensions are preparations of finely divided drugs held in suspension throughout a suitable vehicle. Suspensions taken orally generally employ an aqueous vehicle, whereas those employed for other purposes may utilize a different vehicle. Suspensions of certain drugs to be used for intramuscular injection, for instance, may be maintained in a suitable oil. To be suspended, the drug particles must be insoluble in the vehicle in which they are placed. Nearly all suspensions must be shaken before use because they tend to settle. This ensures not only uniformity of the preparation but more importantly the administration of the proper dosage. Suspensions are a useful means to administer large amounts of solid drugs that would be inconveniently taken in tablet or capsule form. In addition, suspensions have the advantage over solid dosage forms in that they are presented to the body in fine particle size, ready for the dissolution process immediately upon administration. However, not all oral suspensions are intended to be dissolved and absorbed by the body. For instance, Kaolin Mixture with Pectin, an antidiarrheal preparation, contains suspended kaolin, which acts in the intestinal tract by adsorbing excessive intestinal fluid on the large surface area of its particles.

Drugs administered in aqueous solution are generally absorbed much more rapidly than those administered in solid form, because the processes of disintegration and dissolution are not required. Pharmaceutical solutions may differ in the type of solvent employed and therefore in their fluidity characteristics. Among the solutions frequently administered orally are *elixirs*, which are solutions in a sweetened hydroalcoholic vehicle and are generally more mobile than water; *syrups*, which generally utilize sucrose solutions as the sweet vehicle resulting in a viscous preparation; and *solutions* themselves, which officially are preparations in which the drug substance is dissolved predominantly in an aqueous vehicle and do not for reasons of their method of preparation (e.g., injections, which must be sterilized) fall into another category of pharmaceutical preparations.

ABSORPTION. Absorption of drugs after oral administration may occur at the various body sites between the mouth and rectum. In general, the higher up a drug is absorbed along the length of the alimentary tract, the more rapid will be its action, a desirable feature in most instances. Because of the differences in the chemical and physical nature among drug substances, a given drug may be better absorbed from the environment of one site than from another within the alimentary tract.

The oral cavity is used on certain occasions as the absorption site of certain drugs. Physically, the oral absorption of drugs is managed by allowing the drug substance to be dissolved within the oral cavity with infrequent or no swallowing until the taste of the drug has dissipated. This process is accommodated by providing the drug as extremely soluble and rapidly dissolving uncoated tablets. Drugs capable of being absorbed in the mouth present themselves to the absorbing surface in a much more concentrated form than when swallowed, since drugs become progressively more diluted with gastrointestinal secretions and contents as they pass along the alimentary tract.

Currently the oral or *sublingual* (beneath the

tongue) administration of drugs is regularly employed for only a few drugs, with nitroglycerin and certain steroid sex hormones being the best examples. Nitroglycerin, a coronary vasodilator used in the prophylaxis and treatment of angina pectoris, is available in the form of tiny tablets which are allowed to dissolve under the tongue, producing therapeutic effects in a few minutes after administration. The dose of nitroglycerin is so small (usually 400 mcg) that if it were swallowed the resulting dilute gastrointestinal concentration may not result in reliable and sufficient drug absorption. Even more important, however, is the fact that nitroglycerin is rapidly destroyed by the liver throught the *first-pass effect*. Many sex hormones have been shown to be absorbed materially better from sublingual administration than when swallowed. Although the sublingual route is probably an effective absorption route for many other drugs, it has not been extensively used, primarily because other routes have proven satisfactory and more convenient for the patient. Retaining drug substances in the mouth is unattractive because of the bitter taste of most drugs.

Drugs may be altered within the gastrointestinal tract to render them less available for absorption. This may result from the drug's interaction with or binding to some normal constituent of the gastrointestinal tract or a foodstuff or even another drug. For instance, the absorption of the tetracycline group of antibiotics is greatly interfered with by the simultaneous presence of calcium. Because of this, tetracycline drugs must not be taken with milk or other calcium-containing foods or drugs.

In some instances it is the intent of the pharmacist to prepare a formulation that releases the drug slowly over an extended period of time. There are many methods by which slow release is accomplished, including the complexation of the drug with another material, the combination of which is only slowly released from the dosage form. An example of this is the slow-release waxy matrix potassium chloride tablets. These are designed to release their contents gradually as they are shunted through the gastrointestinal tract. Because their contents are leached out gradually there is less incidence of gastric irritation. The intermingling of food and drug generally results in delayed drug absorption. Since most drugs are absorbed more effectively from the intestines than from the stomach, when rapid absorption is intended, it is generally desirable to have the drug pass from the stomach into the intestines as rapidly as possible. Therefore, gastric emptying time is an important factor in effecting drug action dependent upon intestinal absorption. Gastric emptying time may be increased by a number of factors, including the presence of fatty foods (more effect than proteins, which in turn have more effect than carbohydrates), lying on the back when bedridden (lying on the right side facilitates passage in many instances), and the presence of drugs (for example, morphine) that have a quieting effect on the movements of the gastrointestinal tract. If a drug is administered in the form of a solution, it may be expected to pass into the intestines more rapidly than drugs administered in solid form. As a rule, large volumes of water taken with medication facilitate gastric emptying and passage into the intestines.

The pH of the gastrointestinal tract increases progressively along its length from a pH of about 1 in the stomach to approximately pH 8 at the far end of the intestines. pH has a definite bearing on the degree of ionization of most drugs, and this in turn affects lipid solubility, membrane permeability and absorption. Because most drugs are absorbed by passive diffusion through the lipoid barrier, the lipid/water partition coefficient and the pK_a of the drugs are of prime importance to both their degree and site of absorption within the gastrointestinal tract. As a general rule, weak acids are largely *un*ionized in the stomach and are absorbed fairly well from this site, whereas weak bases are highly ionized in the stomach and are not significantly absorbed from the gastric surface. Alkalinization of the gastric environment by artificial means (simultaneous administration of alkaline or antacid drugs) would be expected to decrease the gastric absorption of weak acids and to increase that of weak bases. Strong acids and bases are generally poorly absorbed due to their high degrees of ionization.

The small intestine serves as the major absorption pathway for drugs because of its suitable pH and the great surface area available for drug absorption within its approximate 20-foot length extending from the pylorus at the base of the stomach to the junction with the large intestine at the cecum. The pH of the lumen of the intestine is about 6.5 (see Fig. 3–3) and both weakly acidic and weakly basic drugs are well absorbed from the intestinal surface, which behaves in the ionization and distribution of drugs between it and

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Rectal Route

Some drugs are administered rectally for their local effects and others for their systemic effects. Drugs given rectally may be administered as solutions, suppositories, or ointments. *Suppositories* are defined as solid bodies of various weights and shapes intended for introduction into a body orifice (usually rectal, vaginal, or urethral) where they soften, melt, or dissolve, release their medication, and exert their drug effects. These effects simply may be the promotion of laxation (as with glycerin suppositories), the soothing of inflamed tissues (as with various commercial suppositories used to relieve the discomfort of hemorrhoids), or the promotion of systemic effects (as antinausea or antimotion sickness). The composition of the suppository base, or carrier of the medication, can greatly influence the degree and rate of drug release and should be selected on an individual basis for each drug. The use of rectal ointments is generally limited to the treatment of local conditions. Rectal solutions are usually employed as enemas or cleansing solutions.

The rectum and the colon are capable of absorbing many soluble drugs. Rectal administration for systemic action may be preferred for those drugs destroyed or inactivated by the environments of the stomach and intestines. The administration of drugs by the rectal route may also be indicated when the oral route is precluded because of vomiting or when the patient is unconscious or incapable of swallowing drugs safely without choking. It is estimated that about 50% of a dose of drug absorbed from rectal administration is likely to bypass the liver, an important factor when considering those orally administered drugs that are rapidly destroyed in the liver by the first-pass effect. On the negative side, compared with oral administration, rectal administration of drugs is inconvenient, and the absorption of drugs from the rectum is frequently irregular and difficult to predict.

Parenteral Route

The term *parenteral* is derived from the Greek words *para*, meaning beside, and *enteron*, meaning intestine, which together indicate something done outside of the intestine and not by way of the alimentary tract. A drug administered parenterally is one injected through the hollow of a fine needle into the body at various sites and to various depths. The three primary routes of parenteral administration are subcutaneous, intramuscular (I.M.), and intravenous (I.V.) although there are others such as intracardiac and intraspinal.

Drugs destroyed or inactivated in the gastrointestinal tract or too poorly absorbed to provide satisfactory response may be parenterally administered. The parenteral route is also preferred when rapid absorption is essential, as in emergency situations. Absorption by the parenteral route is not only faster than after oral administration, but the blood levels of drug that result are far more predictable, because little is lost after subcutaneous or intramuscular injection, and virtually none by intravenous injection; this also generally permits the administration of smaller doses. The parenteral route of administration is especially useful in treating patients who are uncooperative, unconscious, or otherwise unable to accept oral medication.

One disadvantage of parenteral administration is that once the drug is injected, there is no retreat. That is, once the substance is within the tissues or is placed directly into the blood stream, removal of the drug warranted by an untoward or toxic effect or an inadvertent overdose is most difficult. By other means of administration, there is more time between drug administration and drug absorption, which becomes a safety factor by allowing for the extraction of unabsorbed drug (as by the induction of vomiting after an orally administered drug). Also, because of the strict sterility requirements for all injections, they are generally more expensive than other dosage forms and require competent trained personnel for their proper administration.

DOSAGE FORMS APPLICABLE. Pharmaceutically, injectable preparations are usually either sterile suspensions or solutions of a drug substance in water or in a suitable vegetable oil. In general, drugs in solution act more rapidly than drugs in suspension, with an aqueous vehicle providing faster action in each instance than an oleaginous vehicle. As in other instances of drug absorption, a drug must be in solution to be absorbed, and a suspended drug must first submit to the dissolution process. Also, because body fluids are aqueous, they are more receptive to drugs in an aqueous vehicle than those in an oily one. For these reasons, the rate of drug absorption can be varied in parenteral products by selective combinations of drug state and supporting vehicle. For instance, a suspension of a drug in a vegetable

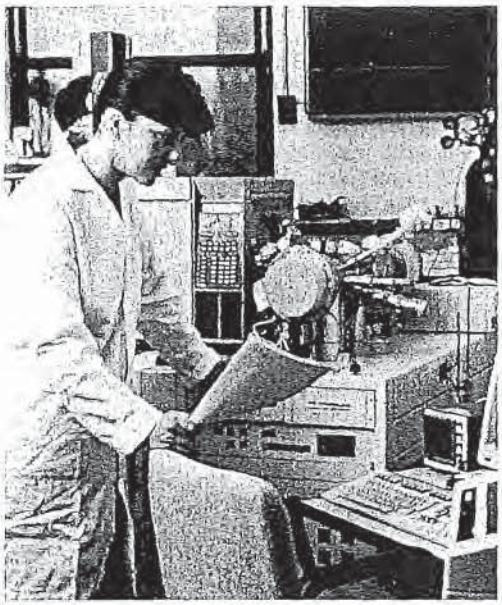

Fig. 3–19. *Computerized gas chromatography mass spectrometry used in bioanalytical studies. Consists of Hewlett Packard Gas Chromatograph (Model 5890 A) and VG Mass Spectrometer (Model UG 12-250). (Courtesy of Elan Corporation, plc.)*

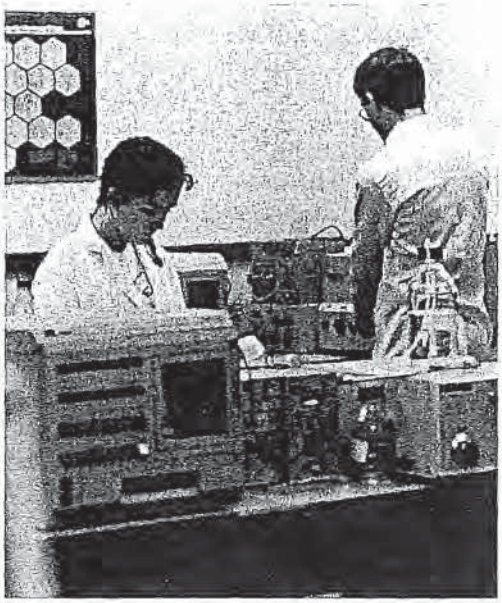

Fig. 3–20. *Assay of biological fluids using Waters HPLC (High Performance Liquid Chromatography) system consisting of (from left to right) Autosampler (Model 712 Wisp), Pump (Model M-45), Shimadzu Fluorescence Detector (Model RF-535). (Courtesy of Elan Corporation, plc.)*

the minimum effective concentration. If on the other hand this medicine is only administered every 4 hours during the waking hours, it is possible that the minimum concentration will fall below effective levels between the at-bedtime dose and the next morning dose. Consequently, the patient may awaken in the middle of the night and exhibit an asthma attack.

Patients can be monitored pharmacokinetically through appropriate plasma, serum or blood samples, and many hospital pharmacies have implemented pharmacokinetic dosing services. The intent is to maximize drug efficacy, minimize drug toxicity and keep health care costs at a minimum. Thus, for example, complications associated with overdose are controlled or drug interactions that are known to occur, e.g., smoking-theophylline, can be accommodated. In these services, for example, once the physician prescribes a certain amount of drug and monitors the clinical response, it is the clinical pharmacist who coordinates the appropriate sample time to determine drug concentration in the appropriate body fluid. After the level of drug is attained, it is the clinical pharmacist who interprets the result, and consults with the physician regarding subsequent dosages.

Pharmacokinetic research has demonstrated that the determination of a patient's dosage regimen depends on numerous factors and daily dose formulas exist for a number of drugs that must be administered on a routine maintenance schedule, e.g., digoxin, procainamide, theophylline. For certain drugs such as digoxin, which are not highly lipid soluble, it is preferable to use a patient's lean body weight (LBW) rather than total body weight (TBW) to provide a better estimate of the patient's volume of distribution. Alternatively, even though pharmacokinetic dosing formulas may exist, one must be cognizant that patient factors may be more relevant. For example, with the geriatric patient it is advisable to begin drug therapy with the lowest possible dose and increase the dosage as necessary in small increments to optimize the patient's clinical response. Then the patient should be monitored for drug efficacy and reevaluated periodically.

Examples of bioanalytical research laboratories are shown in Figures 3–19 and 3–20.

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Dosage Form Design: General Considerations, Pharmaceutic Ingredients, and Current Good Manufacturing Practice

DRUG SUBSTANCES are seldom administered alone, but rather as part of a formulation in combination with one or more nonmedical agents that serve varied and specialized pharmaceutical functions. Through selective use of these nonmedicinal agents, referred to as *pharmaceutic ingredients*, dosage forms of various types result. The pharmaceutic 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 pharmacist with the challenges of formulation and the physician with the choice of drug and drug 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 requires consideration of the physical, chemical and biological characteristics of all of the drug substances and pharmaceutic ingredients to be used in fabricating the product. The drug and pharmaceutic materials utilized 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 under appropriate measures of quality control and packaged in containers that contribute to product stability. 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 pharmaceutic ingredients, drug product formulation, and standards for good manufacturing practice.

The Need for Dosage Forms

The potent nature and low dosage of most of the drugs in use today precludes any expectation that the general public could safely obtain the appropriate dose of a drug from the bulk material. The vast majority of drug substances are administered in milligram quantities, much too small to be weighed on anything but a sensitive laboratory balance. For instance, how could the layman accurately obtain the 325 mg or 5 gr of aspirin found in the common aspirin tablet from a bulk supply of aspirin? He couldn't. 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 1/6500 the amount of aspirin in an aspirin tablet. To put it another way, 6500 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 325 mg aspirin tablet. When the dose of the drug is minute, as that for ethinyl estradiol, solid dosage forms such as tablets and capsules must be prepared with fillers or diluents so that the size of the resultant dosage unit is large enough to pick up with the fingertips.

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

1. For the protection of a drug substance from the destructive influences of atmospheric oxygen or humidity (e.g., coated tablets, sealed ampuls).
2. For the protection of a drug substance from the destructive influence of gastric acid after oral administration (e.g., enteric-coated tablets).

Table 4–1. Examples of Some Drugs with Relatively Low Usual Doses

Drug	Usual Dose, mg	Category
Lithium Carbonate	300	Antidepressant
Ferrous Sulfate	300	Hematinic
Cimetidine	300	Antiulcer
Ibuprofen	300	Antiinflammatory
Amoxicillin	250	Antibacterial
Erythromycin	250	Antibacterial
Nitrofurantoin	100	Antibacterial (urinary)
Propoxyphene HCl	65	Analgesic
Thyroid	60	Thyroid
Hydrochlorothiazide	50	Diuretic
Codeine Phosphate	30	Analgesic
Phenobarbital	30	Sedative
Chlorpromazine HCl	25	Tranquilizer
Diphenhydramine HCl	25	Antihistaminic
Morphine Sulfate	10	Narcotic analgesic
Prednisolone	5	Adrenocortical steroid
Chlorpheniramine Maleate	4	Antihistaminic
Colchicine	0.5	Gout suppressant
Nitroglycerin	0.4	Antianginal
Digoxin	0.25	Cardiotonic (maintenance)
Levothyroxine	0.1	Thyroid
Ethinyl Estradiol	0.05	Estrogen

3. To conceal the bitter, salty, or offensive taste or odor of a drug substance (e.g., capsules, coated tablets, flavored syrups).
4. To provide liquid preparations of substances that are either insoluble or unstable in the desired vehicle (e.g., suspensions).
5. To provide clear liquid dosage forms of substances (e.g., syrups, solutions).
6. To provide time-controlled drug action (e.g., various controlled-release tablets, capsules, and suspensions).
7. To provide optimal drug action from topical administration sites (e.g., ointments, creams, transdermal patches, ophthalmic, ear, and nasal preparations).
8. To provide for the insertion of a drug into one of the body's orifices (e.g., rectal or vaginal suppositories).
9. To provide for the placement of drugs directly into the bloodstream or into body tissues (e.g., injections).
10. To provide for optimal drug action through inhalation therapy (e.g., inhalants and inhalation aerosols).

General Considerations in Dosage Form Design

Before formulating a drug substance into a dosage form, it is important to predetermine the desired product type insofar as possible in order to establish the framework for product development activities. 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 and represents 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 (Table 3–6). Most commonly, a pharmaceutical 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 such therapeutic matters as: the nature of the illness, the manner in which it is generally treated, locally or through systemic action, and the age and anticipated condition of the patient.

If the medication is intended for systemic use and oral administration is desired, tablets and/or capsules are generally prepared. These dosage units 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 situation 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 the preparation of agents for motion sickness, nausea, and vomiting into tablets and skin patches 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 under 5 years of age, pharmaceutical liquids rather than solid dosage forms are preferred for oral administration. These liquids, which are generally flavored aqueous solutions, syrups or

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Fig. 4–1. *Examples of varied dosage forms of a drug substance marketed by a pharmaceutical manufacturer to meet the special requirements of the patient. (Courtesy of SmithKline Beecham)*

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. 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 an infant is in the throes of a vomiting crisis, is gagging, has a productive cough, or is simply rebellious, there may be some question as 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.

During childhood and even in adult years, a person may have difficulty swallowing solid dosage forms, especially uncoated tablets. For this reason, some medications are formulated as chewable tablets that can be broken up in the mouth before swallowing. Many of these tablets are comparable in texture to an after-dinner mint and break down into a pleasant tasting, creamy material. Capsules have been found by many to be more easily swallowed than whole tablets. If a capsule is allowed to become moist in the mouth before swallowing, it becomes slippery and slides down the throat more readily with a glass of water. In instances in which a person has difficulty 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. Some older persons have difficulty in swallowing and thus tablets and capsules are frequently avoided. Medications intended for the elderly are commonly for-

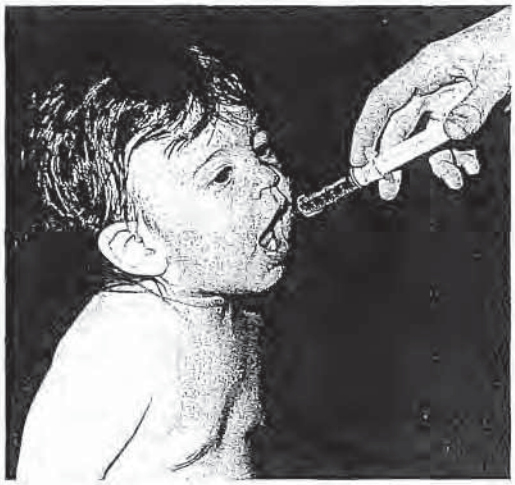


Fig. 4–2. *"Pee Dee Dose" brand of oral liquid dispenser used to administer measured volumes of liquid medication to youngsters. (Courtesy of Baxa Corporation)*

mulated into oral liquids or may be extemporaneously prepared into an oral liquid by the pharmacist.

Many patients, particularly the elderly, take multiple medications daily. The more distinctive the size, shape, and color of solid dosage forms, the easier is the proper identification of the medications. Frequent errors in taking medications among the elderly occur because of their multiple drug therapy and reduced 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 that has been gained through experience with other chemically similar drugs and through the proper utilization of the disciplines of the physical, chemical, and biologic and pharmaceutical sciences. The early stages of any new formulation involves studies to collect basic information on the physical and chemical characteristics of the drug substance to be prepared into pharmaceutical dosage forms. These basic studies comprise the *preformulation* work needed before actual product formulation begins.

Preformulation Studies

Before the formulation of a drug substance into a dosage 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 then provides the framework for the drug's combination with pharmaceutic ingredients in the fabrication of a dosage form.

Physical Description

It is important to have an understanding of the physical description of a drug substance prior to dosage form development. The majority of drug substances in use today occur as solid materials. Most of them are pure chemical compounds of either crystalline or amorphous constitution. The purity of the chemical substance is essential for its identification as well as for the evaluation of its chemical, physical, and biologic properties. *One parameter in determining chemical purity is melting point depression, the physical pharmacy concept of which is summarized in the accompanying Physical Pharmacy Capsule.* Liquid drugs are used to a much lesser extent than solid drugs; gases, even less frequently.

Among the few liquid medicinal agents in use today are the following:

Amyl nitrite, vasodilator by inhalation
Castor oil, cathartic
Clofibrate, antihyperlipidemic
Dimercaprol, antidote for arsenic, gold, and mercury poisoning
Dimethylsulfoxide, analgesic in interstitial cystitis
Ethchlorvynol, hypnotic
Glycerin, cathartic in suppository form
Mineral oil, cathartic
Nitroglycerin (as tablets), anti-anginal
Paraldehyde, sedative-hypnotic
Paramethadione, anticonvulsant
Prochlorperazine, tranquilizer and antiemetic
Propylhexedrine, vasoconstrictor by nasal inhalation
Undecylenic acid, fungistatic agent

Liquid drugs pose an interesting problem in the design of dosage forms or drug delivery systems. Many of the liquids are volatile substances and as such must be physically sealed from the atmosphere to prevent their loss. Amyl nitrite, for example, is a clear yellowish liquid that is volatile even at low temperatures and is also highly flammable. It is maintained 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

Melting Point Depression

The *melting point,* or *freezing point,* of a pure crystalline solid is defined as that temperature where the pure liquid and solid exist in equilibrium. This characteristic can be used as an indicator of purity of chemical substances (a pure substance would ordinarily be characterized by a very sharp melting peak).

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 heats of fusion and low-melting-point substances have low heats 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 as:

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

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 things are noteworthy in contributing to the extent of melting-point lowering.

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).

wets the gauze covering, producing vapors that are inhaled by the patient requiring vasodilation. Propylhexedrine provides another example of a volatile liquid drug that must be contained in a closed system to maintain its presence. 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, generally 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 period of time due to the volatilization 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 undertaking chemical modification of the drug. 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 tightly sealed glass containers. For the most part, when a liquid drug is to be administered orally and a solid dosage form is desired, two approaches are used. First, the liquid substance may be sealed in a soft gela-

tin capsule. Paramethadione (Paradione) and ethchlorvynol (Placidyl) are examples of liquid drugs commercially available in capsule form. Secondly, the liquid drug may be developed into a solid ester or salt form that will be suitable for tableting or drug encapsulating. For instance, scopolamine hydrobromide is a solid salt of the liquid drug scopolamine and is easily produced into tablets.

For certain liquid drugs, especially those employed orally in large doses or applied topically, their liquid nature may be of 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, solid materials are preferred by pharmacists in formulation work because of their ease of preparation into tablets and capsules.

Formulation and stability difficulties arise less frequently with solid dosage forms than with liquid pharmaceutical 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, when practiced, 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 also suits the majority of patients. It is estimated that tablets and capsules comprise 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 particle size range of the raw material as well as the crystal structure. Photomicrographs of the initial and subsequent batch lots of the drug substance can provide important information should problems arise in formulation processing attributable to changes in particle or crystal characteristics of the drug.

Particle Size

Certain physical and chemical properties of drug substances are affected by the particle size distribution, including drug dissolution rate, bioavailability, content uniformity, taste, texture, color, and stability. In addition, properties such as flow characteristics and sedimentation rates, among others, are also 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 product efficacy. Of special interest is the effect of particle size on the drug's absorption. Particle size has been shown to significantly influence the oral absorption profiles of certain drugs as griseofulvin, nitrofurantoin, spironolactone, and procaine penicillin.

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.

There are several methods available to evaluate particle size and distribution including sieving or screening, microscopy, sedimentation, and stream scanning. For powders in the range of approximately 44 microns and greater, sieving or screening is the most widely used method of size analysis. The difficulty with using this method early in the preformulation program is the requirement of a relatively large sample size. The main advantage of the sieve method is simplicity, both in technique and equipment requirements. Optical microscopy is frequently the first step in the determination of particle size and shape for the new drug substance. This is usually a qualitative assessment since quantitation by the microscope technique is tedious and time consuming. A key element in utilizing the microscope for particle size determination is preparation of the slide. It must be representative of the bulk of the material and be properly suspended and thoroughly dispersed in a suitable liquid phase. In order to do a quantitative particle size evaluation a minimum of 1000 of the particles should be counted.

Sedimentation techniques utilize the relationship between rate of fall of particles and their size. Techniques utilizing devices that continuously collect a settling suspension are used. These methods share the disadvantage of the microscope technique in that it is tedious to obtain the data. Also, proper dispersion, consistent sampling, temperature control, and other experimental variables must be carefully controlled in order to obtain consistent and reliable results.

Stream scanning is a valuable method for determining particle size distribution of powdered drug substances. This technique utilizes a fluid

suspension of particles which pass the sensing zone where individual particles are sized, counted, and tabulated. Sensing units may be based on light scattering or transmission, as well as conductance. Two popular units in the pharmaceutical industry for this purpose are the Coulter Counter and Hiac Counter. Both units electronically size, count, and tabulate the individual particles that pass through the sensing zone. This technique has obvious advantages in that data can be generated in a relatively short time with reasonable accuracy. Thousands of particles can be counted in seconds and used to determine the size distribution curve. All stream scanning units convert the particles to effective diameter, and therefore, have the shortcoming of not providing information relative to particle shape. Nevertheless, stream scanning methods are powerful tools and can be used for evaluation of such parameters as crystal growth in suspension formulations.

Particle size is discussed further in the next chapter.

Partition Coefficient and Dissociation Constant

As discussed in the previous chapter, in order to produce a biological response, the drug molecule must first cross a biological membrane. The biological 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 and absorption characteristics of various drugs are the basis of the pH-partition theory.

The oil/water partition coefficient is a measure of a molecule's lipophilic character; that is, its preference for the hydrophilic or lipophilic phase.

The partition coefficient should be considered in developing a drug substance into a dosage form. The partition coefficient (P) represents the ratio of the drug distribution in a two-phase system of organic solvent and aqueous phase. Using octanol-water as an example, it is defined as:

$$P = \frac{[\text{Conc. of drug in octanol}]}{[\text{Conc. of drug in water}]}$$

P is dependent 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:

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

where α equals the degree of ionization.

A summary of the concepts of solubility and distribution phenomena is found in accompanying Physical Pharmacy Capsules.

The determination of the degree of ionization or pKa value of the drug substance is an important physical-chemical characteristic relative to evaluation of possible effects on absorption from various sites of administration.

Dissociation constant or pKa is usually determined by potentiometric titration.

Polymorphism

An important factor on formulation is the crystal or amorphous form of the drug substance. Polymorphic forms usually exhibit different physical-chemical properties including melting point and solubility. The occurrence of polymorphic forms with drugs is relatively common and it has been estimated that polymorphism is exhibited by at least one-third of all organic compounds.

In addition to the polymorphic forms in which compounds may exist, they also can occur in non-crystalline or amorphous forms. The energy required for a molecule of drug to escape from a crystal is much greater than 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, chemical and physical stability, and have important implications in dosage form process functions. For example, it can be a significant factor relating to the tableting processes due to flow and compaction behaviors, among others.

Various techniques are used in determining crystal properties. The most widely used methods are hot stage microscopy, thermal analysis, infrared spectroscopy, and x-ray diffraction.

Solubility

An important physical-chemical property of a drug substance is solubility, especially aqueous system solubility. A drug must possess some aqueous solubility for therapeutic efficacy. In

Solubility and Distribution Phenomena

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 as:

$$K = C_U/C_L$$

where K is the distribution constant or partition constant,
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 broths,
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, transdermal patches),
6. study of the distribution of flavoring oil between oil and water phases of emulsions, and
7. in other applications.

The basic relationship given above 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 two immiscible layers is given by:

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

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 by:

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

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

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

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

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

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

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

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

EXAMPLE 1

At 25°C and at 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).

$U = 0.7/(0.7 + 1) = 0.41$ 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.

Solubility and Distribution Phenomena (Continued)

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

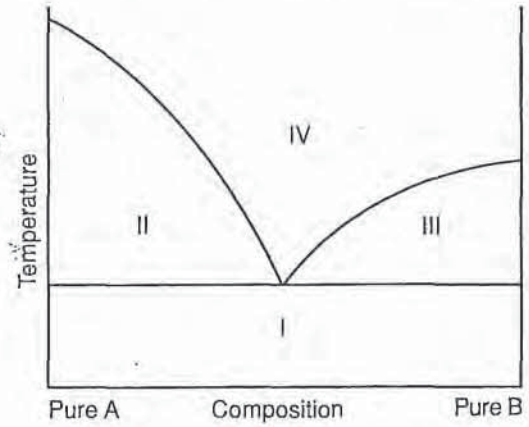
$$L_{4th} = \frac{1}{\left(\frac{0.7 \times 1}{4} + 1\right)^4} = 0.525$$

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.

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 is of 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, there are four regions, or phases, in this diagram, representing the following:

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

The Phase Rule (Continued)

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 as:

$$F = C - P + X$$

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 that need to be specified to define the phases present. The 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 by:

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

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 as:

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

In this portion of the phase diagram, it is apparent that 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 a disappearance of one of the two solid phases or the liquid phase.

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

order for a drug to enter the systemic circulation to 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 will depend on the chemical nature of the drug and the type of drug product under consideration. The chemical modification of the drug into salt or ester forms is a technique frequently used to obtain more soluble compounds. Another technique, if the drug is to be formulated into a liquid product, involves the adjustment of the pH of the solvent in which the drug is to be dissolved to enhance solubility. However, there are many

drug substances for which 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 may cause stability problems with formulation ingredients. Adjustment of pH usually has little effect on the solubility of non-electrolytes. In many cases, it is desirable to utilize co-solvents or other techniques such as complexation, micronization, or solid dispersion to improve aqueous 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 prolonged period of time until equilibrium is obtained. Chemical analysis of the drug content in solution is performed to determine degree of solubility.

Dissolution

As discussed in the previous chapter, variations in the biological 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 the absorption process. This is true for drugs administered orally in solid forms such as tablets, capsules or suspensions, as well as drugs administered intramuscularly in the form of pellets or suspensions. When the dissolution rate is the rate-limiting step, anything which 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 subsequently 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 generally 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 utilizes 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 is termed the *intrinsic dissolution rate*, and is characteristic of each solid compound and a given solvent under the fixed experimental conditions. The value is generally expressed as milligrams dissolved per minute centimeters squared ($mg/min/cm^2$). 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, an inverse relationship of particle size to dissolution is noted due to the surface properties of the drug. In these instances, surface charge and/or agglomeration results in the reduced particle size form of the drug presenting a lower effective surface area to the solvent due to incomplete wetting or agglomeration.

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

Membrane Permeability

Modern preformulation studies include an early assessment of passage of drug molecules across biological membranes.

Data obtained from the basic physical-chemical studies, specifically, pKa, solubility, and dissolution rate provide an indication of absorption expectations.

To enhance these data, a technique utilizing the "everted intestinal sac" may be used in evaluating absorption characteristics of drug substances. In this method, a piece of intestine is removed from an intact animal, everted, filled with a solution of the drug substance, and the degree and rate of passage of the drug through the membrane sac is determined. Through this method, both passive and active transport can be evaluated.

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

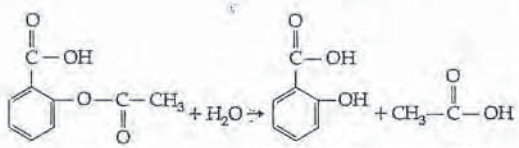
Drug Stability

One of the most important activities of preformulation work is the 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 through knowledge of the drug's chemical structure which allows the preformulation scientist to anticipate the possible degradation reactions.

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 toward 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 of different chemical constitution. 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:



The process of 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.

Another destructive process is oxidation. The oxidative process is destructive to many drug types, including aldehydes, alcohols, phenols, sugars, alkaloids, and unsaturated fats and oils.

Chemically, oxidation involves the loss of electrons from an atom or a molecule. Each electron lost is accepted by some other atom or molecule, thereby accomplishing the reduction of 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. The oxidative process frequently involves free chemical radicals, which are molecules or atoms containing one or more unpaired electrons, 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 as the process continues. The process has been described as a type of chain reaction commencing by 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 the occurrence of drug substance deterioration due to hydrolysis, oxidation, and other processes. These techniques are discussed in a later section.

Pharmaceutic Ingredients

In order to prepare a drug substance into a final dosage form, pharmaceutic ingredients are required. For example, in the preparation of pharmaceutic solutions, one or more *solvents* are utilized to dissolve the drug substance, *preservatives* may be added to prevent microbial growth, *stabilizers* may be used to prevent drug decomposition, and *colorants* and *flavorants* added to enhance product appeal. In the preparation of tablets, *diluents* or *fillers* are commonly added to increase the bulk of the formulation, *binders* to cause the adhesion of the powdered drug and pharmaceutic substances, *antiadherents* or *lubricants* to assist the smooth tableting process, *disintegrating agents* to promote tablet break-up after administration, and coatings to improve stability, control disintegration, or to enhance appearance. Ointments, creams, and suppositories achieve their characteristic features due to the pharmaceutic *bases* which are utilized. Thus, for each dosage form, the pharmaceutic ingredients

establish the primary features of the product, and contribute to the physical form, texture, stability, taste and overall appearance.

Table 4–2 presents the principal categories of pharmaceutic ingredients, with examples of some of the official and commercial agents currently used. Additional discussion of many of the pharmaceutic ingredients may be found in the chapters where they are most relevant; for example, pharmaceutic materials used in tablet and capsule formulation are discussed in Chapter 5, *Peroral Solids, Capsules, Tablets, and Controlled-Release Dosage Forms.*

The reader should also be aware of the *Hand-*

Table 4–2. Examples of Pharmaceutic Ingredients

Ingredient Type	*Definition*	*Examples*
Acidifying Agent	Used in liquid preparations to provide acidic medium for product stability.	acetic acid citric 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 borate sodium carbonate sodium hydroxide triethanolamine trolamine
Adsorbent	An agent capable of holding other molecules onto its surface by physical or chemical (chemisorption) means.	powdered cellulose activated charcoal
Aerosol Propellant	An 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	An agent which is employed to displace air in a hermetically sealed container to enhance product stability.	nitrogen
Antifungal Preservative	Used in liquid and semi-solid preparations to prevent the growth of fungi. The effectiveness of the parabens is usually enhanced when they are used in combination.	benzoic acid butylparaben ethylparaben methylparaben propylparaben sodium benzoate sodium propionate
Antimicrobial Preservative	Used in liquid and semi-solid preparations to prevent the growth of microorganisms.	benzalkonium chloride benzethonium chloride benzyl alcohol cetylpyridinium chloride chlorobutanol phenol phenylethyl alcohol phenylmercuric nitrate thimerosal

Table 4–2. Continued

Ingredient Type	*Definition*	*Examples*
Antioxidant	An agent which inhibits oxidation and thus is used to prevent the deterioration of preparations by the oxidative process.	ascorbic acid ascorbyl palmitate butylated hydroxyanisole butylated hydroxytoluene hypophophorous 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
Chelating Agent	A substance that forms stable, water soluble complexes (chelates) with metals. Chelating agents are used in some liquid pharmaceuticals as stabilizers to complex heavy metals which might promote instability. In such use they are also called *sequestering* agents.	edetate disodium edetic acid
Colorant	Used to impart color to liquid and solid (e.g., tablets and capsules) pharmaceutical 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 because of adsorbent qualities.	bentonite
Emulsifying Agent	Used to promote and maintain the dispersion of finely subdivided particles of a liquid in a vehicle in which it is immiscible. The 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 for the purpose of enclosing a drug substance or drug formulation for ease of administration.	gelatin cellulose acetate phthalate
Flavorant	Used to impart a pleasant flavor and often odor to a pharmaceutical preparation. In addition to the natural flavorants listed, many synthetic flavorants are also used.	anise oil cinnamon oil cocoa menthol orange oil peppermint oil vanillin

Table 4–2. Continued

Ingredient Type	*Definition*	*Examples*
Humectant	Used to prevent the drying out of preparations—particularly ointments and creams—due to the agent's ability to retain moisture.	glycerin propylene glycol sorbitol
Levigating Agent	A liquid used as an intervening agent to reduce the particle size of a drug powder by grinding together, usually in a mortar.	mineral oil glycerin
Ointment Base	The semisolid vehicle into which drug substances may be incorporated in preparing medicated ointments.	lanolin hydrophilic ointment polyethylene glycol ointment petrolatum hydrophilic petrolatum white ointment yellow ointment rose water ointment
Plasticizer	Used as a component of film-coating solutions to enhance the spread of the coat over tablets, beads, and granules.	diethyl phthalate glycerin
Solvent	An agent used to dissolve another pharmaceutic substance or a drug in the preparation of a solution. The solvent may be aqueous or nonaqueous (e.g., oleaginous). Cosolvents, such as water and alcohol (hydroalcoholic) and water and glycerin, may be used when needed. Solvents rendered sterile 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 the thickness or hardness of a pharmaceutical preparation, usually an ointment.	cetyl alcohol cetyl esters wax microcrystalline wax paraffin stearyl alcohol white wax yellow wax
Suppository Base	Used as a vehicle into which drug substances are incorporated in the preparation of suppositories.	cocoa butter polyethylene glycols (mixtures)
Surfactant (surface active agent)	Substances which 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 oxtoxynol 9 polysorbate 80 sodium lauryl sulfate sorbitan monopalmitate

Table 4–2. Continued

Ingredient Type	*Definition*	*Examples*
Suspending Agent	A viscosity increasing agent used to reduce the rate of sedimentation of (drug) particles dispersed throughout a vehicle in which they are not soluble. The resultant suspensions may be formulated for use orally, parenterally, ophthalmically, topically, or by other routes.	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	Agents which prevent the sticking of tablet formulation ingredients to punches and dies in a tableting machine during production.	magnesium stearate talc
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 substances used as fillers to create the desired bulk, flow properties, and compression characteristics in the preparation of tablets and capsules.	dibasic calcium phosphate kaolin lactose mannitol microcrystalline cellulose powdered cellulose precipitated calcium carbonate sorbitol starch

Table 4–2. Continued

Ingredient Type	*Definition*	*Examples*
Tablet Coating Agent	Used to coat a formed tablet for the purpose of protecting against drug decomposition by atmospheric oxygen or humidity, to provide a desired release pattern for the drug substance after administration, to mask the taste or odor of the drug substance, or for aesthetic purposes. The coating may be of various types, including sugar-coating, film coating, or enteric coating. Sugar coating is water-based and results in a thickened covering around a formed tablet. Sugar-coated tablets generally start to break up in the stomach. A film coat is a thin cover around a formed tablet or bead. Unless it is an enteric coat, the film coat will dissolve in the stomach. An enteric-coated tablet or bead will pass through the stomach and break up in the intestines. Some coatings that are water-insoluble (e.g., ethylcellulose) may be used to coat tablets and beads to slow the release of drug as they pass through 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 dosage forms to promote the disruption of the solid mass into smaller particles which are more readily dispersed or dissolved.	alginic acid carboxymethylcellulose calcium microcrystalline cellulose (e.g., Avicel) polacrilin potassium (e.g., Amberlite) sodium alginate sodium starch glycollate starch
Tablet Glidant	Agents used in tablet and capsule formulations to improve the flow properties of the powder mixture.	colloidal silica cornstarch talc
Tablet Lubricant	Substances used in tablet formulations to reduce friction during tablet compression.	calcium stearate magnesium stearate mineral oil stearic acid zinc stearate
Tablet/Capsule Opaquant	Used to render a capsule or a tablet coating opaque. May be used alone or in combination with a colorant.	titanium dioxide
Tablet Polishing Agent	Used to impart an attractive sheen to coated tablets.	carnauba wax white wax

Table 4–2. Continued

Ingredient Type	*Definition*	*Examples*
Tonicity Agent	Used to render a solution similar in osmotic characteristics to physiologic fluids. Ophthalmic, parenteral, and irrigation fluids are examples of preparations in which tonicity is a consideration.	dextrose sodium chloride
Vehicle	A carrying agent for a drug substance. They are used in formulating a variety of liquid dosage for oral and parenteral administration. Generally, oral liquids are aqueous preparations (as syrups) or hydroalcoholic (as elixirs). Parenteral 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 Bacteriostatic Water for Injection
Viscosity Increasing Agent	Used to change the consistency of a preparation to render it 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

book of Pharmaceutical Excipients,[2] which presents monographs on about 150 excipients used in pharmaceutical dosage form preparation. Included in each monograph is such information as: nonproprietary, chemical, and commercial names; empirical and chemical formulas and molecular weight; pharmaceutic specifications and chemical and physical properties; incompatibilities and interactions with other excipients and drug substances; regulatory status; and applications in pharmaceutic formulation or technology.

There is great interest nowadays in the international "harmonization" of standards applicable to pharmaceutical excipients. This is due to the fact that the pharmaceutical industry is multinational, with major companies having facilities in more than a single country, with products sold in markets worldwide, and with regulatory approval for these products generally required in each individual country. Standards for each drug substance and excipient used in pharmaceuticals are contained in pharmacopeias—or, for new agents, in an application for regulatory approval by the FDA or another nation's governing authority. The four pharmacopeias with the largest international use are the *United States Pharmacopeia/National Formulary* (USP/NF), *British Pharmacopeia* (BP), *European Pharmacopeia* (EP), and the *Japanese Pharmacopeia* (JP). Uniform standards for excipients in these and other pharmacopeias would facilitate production efficiency, enable the marketing of a single formulation of a product internationally, and enhance regulatory approval of pharmaceutical products worldwide. The goal of harmonization is an ongoing effort undertaken by corporate representatives and international regulatory authorities.

Drug Product Stability

As indicated previously, many pharmaceutic ingredients may be utilized in preparing the desired dosage form of a drug substance. Some of these agents may be used to achieve the desired physical and chemical characteristics of the product or to enhance its appearance, odor, and taste. Other substances may be used to increase the stability of the drug substance, particularly against the hydrolytic and oxidative processes. In each instance, the added pharmaceutic ingredient must be compatible with and must not detract from the stability of the drug substance in the particular dosage form prepared.

There are several approaches to the stabilization of pharmaceutical preparations containing drugs subject to deterioration by hydrolysis. Perhaps the most obvious is the reduction, or better yet, the elimination of water from the pharmaceutical system. Even solid dosage forms containing water-labile drugs must be protected from the humidity of the atmosphere. This may be accomplished by applying a waterproof protective coating over tablets or by enclosing and maintaining the drug in tightly closed containers. It is not unusual 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 for other drugs to be administered in liquid form by suspending them in a non-aqueous vehicle rather than by 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 supplied commercially is actually a mixture of the antibiotic, suspending agents, flavorants, and colorants, which, when reconstituted by the pharmacist, remains a stable suspension or solution of the drug for the time period in which the preparation is normally consumed. Storage under refrigeration is advisable for most preparations considered unstable due to hydrolytic causes. Together with temperature, pH is a major determinant in the stability of a drug prone to hydrolytic decomposition. The hydrolysis of most drugs is dependent upon 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 the pH of 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.

Pharmaceutically, the oxidation of a susceptible drug substance is most likely to occur when it is maintained in other than the dry state in the presence of oxygen, exposed to light, or combined in formulation with other chemical agents without proper regard to their influence on the oxidation process. The oxidation of a chemical in a pharmaceutical preparation is usually attendant with an alteration in the color of that preparation. It may also result in precipitation or a change in the usual odor of a preparation.

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 more frequently used in aqueous preparations are sodium sulfite (Na_2SO_3), sodium bisulfite ($NaHSO_3$), hypophosphorous acid (H_3PO_2), and ascorbic acid. In oleaginous (oily or unctuous) preparations, alphatocopherol, butylhydroxyanisole, and ascorbyl palmitate find application.

In June 1987, FDA labeling regulations went into effect requiring a warning about possible allergic-type reactions, including anaphylaxis in the package insert for prescription drugs to which sulfites have been added to the final dosage form. 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 suffer allergic reactions from the chemicals. Many of the sulfite-sensitive persons suffer from asthma or other allergic conditions. Previous to the regulations

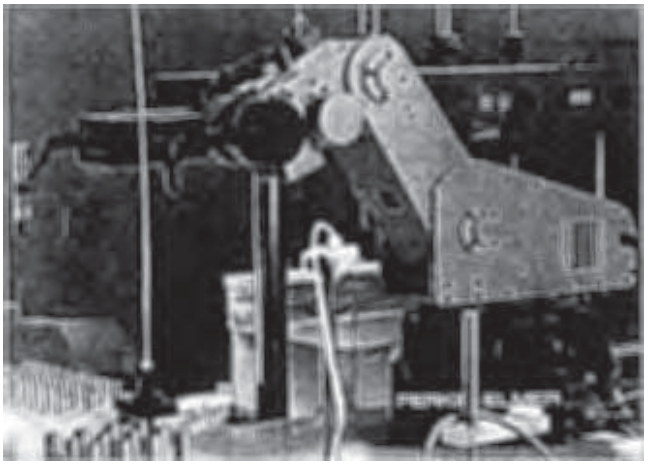


Fig. 4–12. *Robotics in laboratory use. Perkin-Elmer Robotic Arm and Perkin-Elmer Lambda 1a UV/VIS Spectrophotometer. (Courtesy of Elan Corporation, plc.)*

pling, and packaging. Figure 4–12 presents an example of the use of robotics in laboratory use. Laboratory robotics provides automation in such areas as sample preparation and handling, wet chemistry procedures, laboratory process control, and instrumental analysis.[31] Pharmaceutical applications include automated product handling in production lines and in procedures as sampling and analysis, tablet content uniformity, and dissolution testing.

Among the advantages cited for computer use and automation within the pharmaceutical industry are:[32–33]

- increased productivity reducing labor
- improved process and product quality
- reduction in operator error and levels of product rejections
- increased process yields (as from chemical synthesis of drug compounds)
- enhanced repeatability of processes
- improved operator protection due to less "hands on" activity
- automated diagnostic and alarm actions alerting of possible mechanical malfunction, process decontrol or product defect
- assist in process and product validation efforts
- assist in bookkeeping efforts
- assist in scheduling efficacy
- reduced cost per product unit

Movement toward Paperless Electronic Records

There is an effort underway by the FDA and the pharmaceutical industry to replace the traditional use of paper with electronic systems to record, transmit, and maintain needed documentation. This includes records developed by industry to support applications for drug product approvals—e.g., computer assisted new drug applications (CANDAs)—and FDA inspections for CGMP compliance.

Among the regulatory and legal issues involved in the effort toward a paperless system are the authenticity, integrity, and security of electronic records, and the electronic means of replacing conventional handwritten signatures and initials, as required on reports and documents to identify individuals having functional responsibility and operational authority.

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Peroral Solids, Capsules, Tablets, and Controlled-Release Dosage Forms

WHEN MEDICATIONS are to be administered orally in dry form, capsules and tablets are most frequently used. They are effective and provide the patient with convenience of handling, identification, and administration. From a pharmaceutic standpoint, solid dosage forms are generally more stable than are their liquid counterparts and thus are preferred for poorly stable drugs. Dry powders are taken orally (usually after mixing in water) to a much lesser extent than are capsules and tablets, but are preferred by some patients who are unable to swallow the solid dosage forms. However, most medicated powders are utilized as external applications to the skin. While the use of powders *per se* in therapeutics is limited, the use of powders in dosage form preparation is extensive. Most of the medicinal substances in use today occur in crystalline or powdered form and are blended with other powdered materials, as inert fillers and disintegrants, prior to fabrication into solid dosage forms. Powdered drugs are also frequently added to ointments, pastes, suppositories, and other dosage forms during their preparation. Similarly, granules, which are agglomerates of powdered materials prepared into larger free flowing particles, are utilized chiefly in the preparation of tablets and in dry preparations intended to be reconstituted to liquid forms prior to use by the addition of the appropriate vehicle.

Powders

As a pharmaceutical preparation, a *powder* (Latin, *pulvis*) is a mixture of finely divided drugs and/or chemicals in dry form. This should be differentiated from the general use of the term "powder" or "powdered" which is commonly used to describe the physical state of a single chemical substance or a single drug.

A powder may be a finely subdivided preparation, a coarsely comminuted product, or a product of intermediate particle size. It may be prepared from a naturally occurring dried vegetable drug, or it may be a physical admixture of two or more powdered pure chemical agents present in definite proportions. Powders may contain small proportions of liquids dispersed thoroughly and uniformly over the solid components of the mixture, or the powder may be composed entirely of solid materials.

Some powders are intended to be used internally; others, externally. Certain powders are dispensed by the pharmacist to the patient in bulk quantities; others, in divided, individually packaged portions, depending primarily on the use, dose, or potency of the powder.

The disadvantages of powders as a dosage form include the potential for patient misunderstanding of the correct method of use, the undesirability of taking bitter or unpleasant tasting drugs in this manner, the difficulty of protecting from decomposition powders containing hygroscopic, deliquescent, or aromatic materials, and the manufacturing expense required in the preparation of uniform individually wrapped doses of powders. To be of high efficacy, the powder must be a homogeneous blend of all of the components and must be of the most advantageous particle size. As noted earlier (Chapter 3), the particle size of a drug not only contributes to its rate of solubility in a glass of water or within the stomach or intestine, but also may influence its biologic availability.

Particle Size and Analysis

The particles of pharmaceutical powders may be very coarse, of the dimensions of about 10,000 microns or 10 mm, or they may be extremely fine, approaching colloidal dimensions of 1 micron or less. In order to standardize the particle size of a given powder, the USP employs descriptive terms such as "Very Coarse, Coarse, Moderately Coarse, Fine, and Very Fine," which are related to the proportion of powder that is capable of passing through the openings of standardized sieves of varying dimensions in a specified time

Table 5–1. Opening of Standard Sieves*

Sieve Number	*Sieve Opening*
2	9.5 mm
3.5	5.6 mm
4	4.75 mm
8	2.36 mm
10	2.00 mm
20	850 μm
30	600 μm
40	425 μm
50	300 μm
60	250 μm
70	212 μm
80	180 μm
100	150 μm
120	125 μm
200	75 μm
230	63 μm
270	53 μm
325	45 μm
400	38 μm

* Adapted from USP23-NF18.

period under shaking, generally in a *mechanical sieve shaker*. Table 5–1 presents the Standard Sieve Numbers and the sieve openings in each, expressed in millimeters and in micrometers. Sieves for such pharmaceutical testing and measurement are generally made of wire cloth woven from brass, bronze, or other suitable wire. They are not coated or plated.

Powders of vegetable and animal drugs are officially defined as follows:[1]

Very Coarse (or a No. 8) powder—All particles pass through a No. 8 sieve and not more than 20% through a No. 60 sieve.

Coarse (or a No. 20) powder—All particles pass through a No. 20 sieve and not more than 40% through a No. 60 sieve.

Moderately Coarse (or a No. 40) powder—All particles pass through a No. 40 sieve and not more than 40% through a No. 80 sieve.

Fine (or a No. 60) powder—All particles pass through a No. 60 sieve and not more than 40% through a No. 100 sieve.

Very Fine (or a No. 80) powder—All particles pass through a No. 80 sieve. There is no limit as to greater fineness.

The powder fineness for chemicals is defined as follows. It should be noted that there is no "Very Coarse" category.

Coarse (or a No. 20) powder—All particles pass through a No. 20 sieve and not more than 60% through a No. 40 sieve.

Moderately Coarse (or a No. 40) powder—All particles pass through a No. 40 sieve and not more than 60% through a No. 60 sieve.

Fine (or a No. 80) powder—All particles pass through a No. 80 sieve. There is no limit as to greater fineness.

Very Fine (or a No. 120) powder—All particles pass through a No. 120 sieve. There is no limit as to greater fineness.

Granules typically fall within the range of 4- to 12-sieve size, although granulations of powders prepared in the 12- to 20-sieve range are not uncommon when used in tablet making.

The purpose of particle size analysis in pharmacy is to obtain quantitative data on the size, distribution, and shapes of drug and nondrug components to be used in pharmaceutical formulations. There may be substantial differences in particle size, crystalline type, and amorphous shape within and between substances. Particle size can influence a variety of important factors:

- *Dissolution rate* of particles intended to dissolve;
- *Suspendability* of particles intended to remain undissolved but uniformly dispersed in a liquid vehicle (e.g., fine dispersions have particles of from approximately 0.5 to 10 micrometers or μm);
- *Uniform distribution* of a drug substance in a powder mixture or solid dosage form;[2]
- *Penetrability* of particles intended to be inhaled to reach a desired location within the respiratory tract (e.g., 1–5 micrometers) for deposition deep in the respiratory tract);[3] and the
- *Nongrittiness* of solid particles in dermal ointments, creams, and ophthalmic preparations (e.g., fine powders may be 50–100 micrometers in size).

A number of methods exist for the determination of particle size, including the following:

- *Sieving*, in which particles are passed by mechanical shaking through a series of sieves of known and successively smaller size and the determination of the proportion of powder passing through or being withheld on each sieve (range: from about 50 to 3360 micrometers, depending upon sieve sizes).[4]
- *Microscopy*, in which the particles are sized through the use of a calibrated grid background or other measuring device (range: 0.2 to 100 micrometers).[5,6]

Micromeritics

Micromeritics is the science of small particles; a *particle* is any unit of matter having defined physical dimensions. It is important to study particles because the majority of drug dosage forms are solids; solids are not "static" systems—the physical state of particles can be altered by physical manipulation and particle characteristics can alter therapeutic effectiveness.

Micromeritics includes a number of characteristics including particle size, particle size distribution, particle shape, angle of repose, porosity, true volume, bulk volume, apparent density and bulkiness.

PARTICLE SIZE

A number of techniques can be used for determining particle size and particle size distributions. Particle size determinations are complicated by the fact that particles are nonuniform in shape. Only two relatively simple examples will be provided for a detailed calculation of the average particle size of a powder mixture. Other methods will be generally discussed. The techniques utilized will include the microscopic method and the sieving method.

The *microscopic method* can include counting not less than 200 particles in a single plane using a calibrated ocular on a microscope. Given the following data, what is the average diameter of the particles?

Size Group of Counted Particles (μ)	Middle Value μ "d"	No. Particles Per Group "n"	*"nd"*
40–60	50	15	750
60–80	70	25	1750
80–100	90	95	8550
100–120	110	140	15400
120–140	130	80	10400
		$\Sigma n = 355$	$\Sigma nd = 36850$

$$d_{av} = \frac{\Sigma nd}{\Sigma n} = \frac{36{,}850}{355} = 103.8\ \mu$$

The *sieving method* involves using a set of U.S. Standard sieves in the size range desired. A stack of sieves is arranged in order, the powder placed in the top sieve, the stack shaken, the quantity of powder resting on each sieve weighed, and the following calculation performed.

Sieve No.	*Arithmetic Mean Opening (mm)*	*Weight Retained (G)*	*% Retained*	*% Retained × Mean Opening*
20/40	0.630	15.5	14.3	9.009
40/60	0.335	25.8	23.7	7.939
60/80	0.214	48.3	44.4	9.502
80/100	0.163	15.6	14.3	2.330
100/120	0.137	3.5	3.3	0.452
		108.7	100.0	29.232

$$d_{av} = \frac{\Sigma\ (\%\ \text{retained}) \times (\text{ave size})}{100} = \frac{29.232}{100} = 0.2923\ \text{mm}$$

Another method of particle size determination involves *sedimentation* using the "Andreasen Pipet." The Andreasen pipet is a special cylindrical container designed such that a sample can be removed from the lower portion at selected time intervals. The powder is dispersed in a nonsolvent in the Andreasen Pipet, agitated, and 20 mL samples removed over a period of time. Each 20 mL sample is dried and weighed. Using the following equation, the particle diameters can be calculated.

$$d = \frac{18\ h\eta}{(\rho_i - \rho_e)\ gt}$$

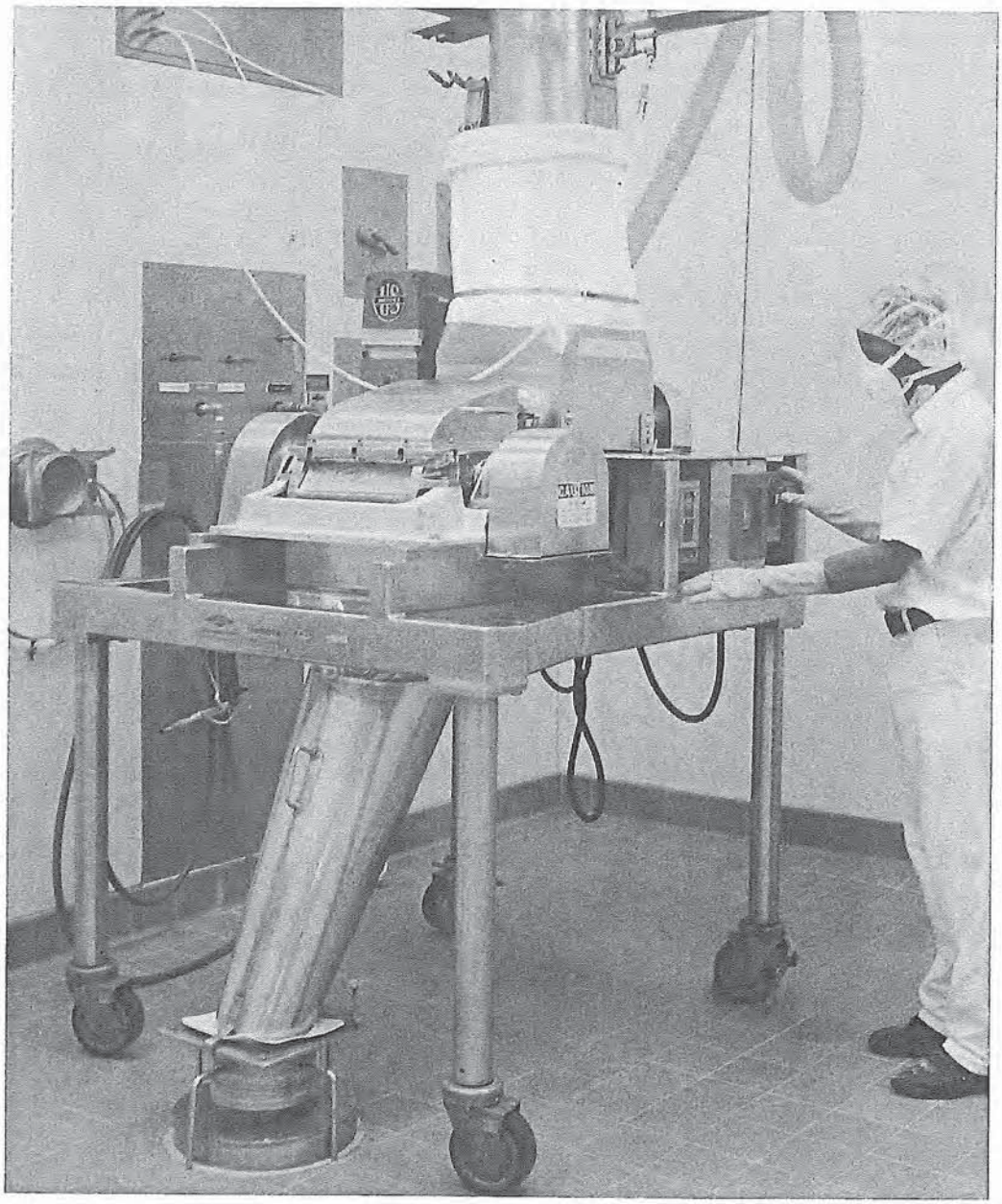

Fig. 5–47. *Frewitt Oscillator or Fitz Mill utilized in the pulverization or granulation process. (Courtesy of Eli Lilly and Company.)*

a tablet deduster. An example of this type of apparatus are shown in Figure 5–49.

Tablet Coating

Tablets are coated for a number of reasons, including the protection of the medicinal agent against destructive exposure to air and/or humidity; to mask the taste of the drug upon swallowing; to provide special characteristics of drug release (e.g., enteric coatings); and to provide aesthetics or distinction to the product.

Some tablets are coated to prevent inadvertent contact with the drug substance and the conse-

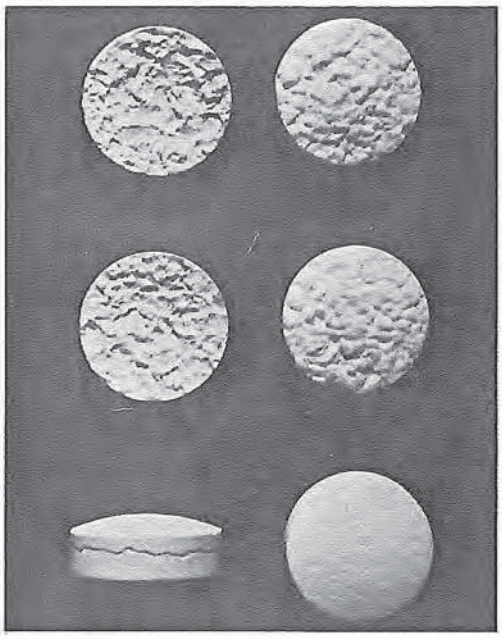

Fig. 5–48. *Tablets which have split on aging, due to conditions of manufacture or storage.*

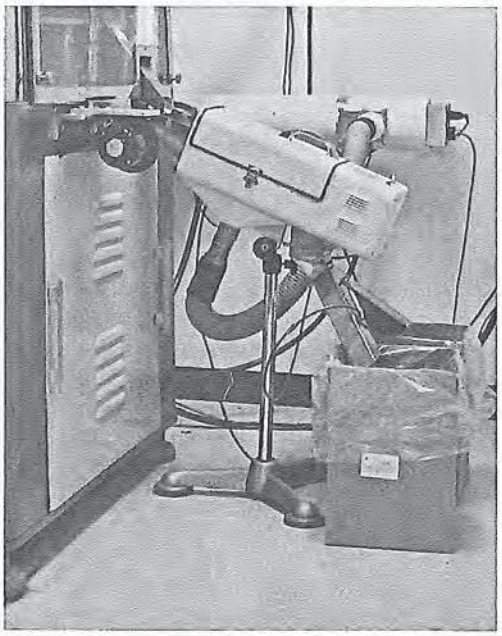

Fig. 5–49. *Model 25 Manesty Tablet Deduster. Tablets leaving tableting machine are dedusted and passed into collection containers. (Courtesy of Eli Lilly and Company.)*

quent effects of drug absorption. Proscar (finasteride, Merck) tablets, for example, are coated for just this reason. The drug is used by men in the treatment of benign prostatic hyperplasia. The labeling instructions warn that women who are pregnant or who could become pregnant should not come into contact with the drug. Drug contact can occur through the handling of broken tablets or through sexual contact, by virtue of traces of drug in semen. If finasteride is absorbed by a woman who is pregnant with a male baby, the drug has the capacity to cause abnormalities in the child's sex organs.

The general methods involved in coating tablets are as follows.

Sugarcoating Tablets

The sugarcoating of tablets may be divided into the following steps: (1) waterproofing and sealing (if needed), (2) subcoating, (3) smoothing and final rounding, (4) finishing and coloring (if desired), and (5) polishing. Generally the entire coating process is conducted in a series of mechanically operated coating pans, which are acorn-shaped vessels of galvanized iron, stainless steel, or copper partially open in the front and with diameters ranging from about 1 to 4 feet and therefore of various capacities (Figs. 5–50 and 5–51). The smaller pans are used for experimental, developmental, and pilot plant operations; the larger pans, for industrial production. The pans are fixed and operate at about a 40° angle, which permits the tablets to remain inside the pan during its revolutions yet also permits the operator to observe and handle the tablets from the open end of the pan. During each of the operations involved in the coating of tablets, the pan is rotated by a motor at moderate speeds, allowing the tablets to tumble and roll about in the pan and make contact with each other and with the coating solutions. As they rotate, the coating solution is gently poured or sprayed onto the tablets in portions, with warm air introduced to hasten the drying of the coat. Tablets may require a number of coats of material, with each coat applied only after the previous coat has dried. Tablets intended to be coated are generally compressed tablets that have been prepared to be highly convex and have as thin an edge as possible to permit the coatings to form rounded rather than angular edges.

WATERPROOFING AND SEALING COATS. For tablets containing components that may absorb moisture or be adversely affected on contact with

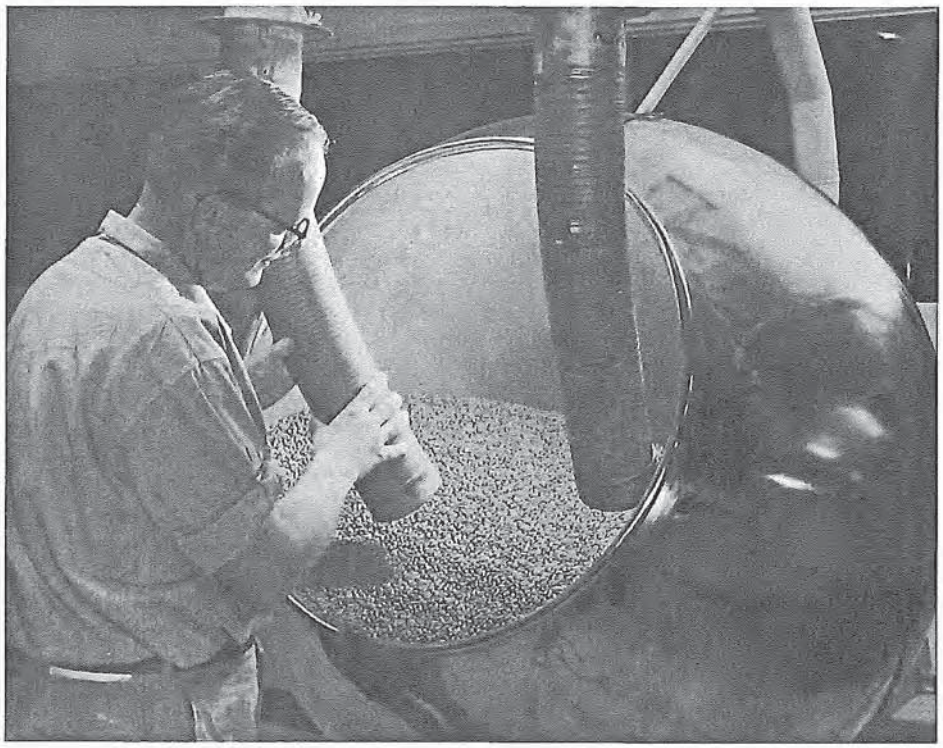

Fig. 5–50. *Tablet coating, an older style coating pan, showing the warm air supply and the exhaust. (Courtesy of Wyeth Laboratories.)*

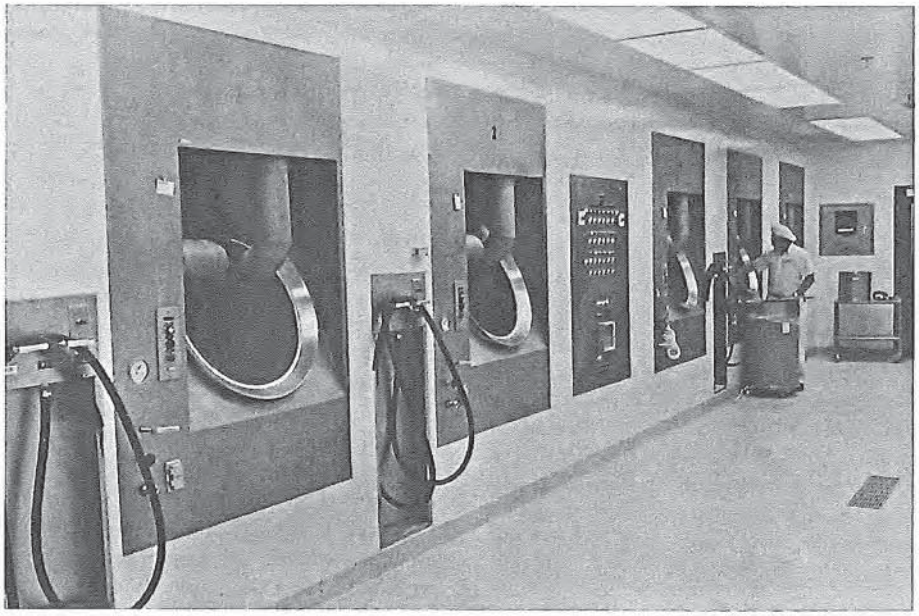

Fig. 5–51. *Modern tablet coating facility. Air and exhaust ducts to assist drying are automatically operated from central board. (Courtesy of Eli Lilly and Company.)*

moisture, a waterproofing layer or coating of a material such as shellac is placed on the compressed tablets before the subcoating application. The shellac or other waterproofing agent is applied in solution (usually alcoholic) form and is gently poured on the compressed tablets rotating in the coating pans or is sprayed on as a fine spray. Warm air is blown into the pan during the coating to hasten the drying and to prevent tablets from sticking together. A second coat of the waterproofing substance may be added to the tablets after the first coat has dried to ensure against moisture penetration into the compressed tablets.

SUBCOATING. After the waterproofing or sealing coats (if they are necessary) have been applied, the tablets are given about 3 to 5 subcoats of a sugar-based syrup for the purpose of rounding the tablets and bonding the sugar coating to the compressed tablet. In applying the subcoating, a heavy syrup generally containing gelatin or polyvinylpyrollidone (PVP), or sometimes acacia is added to the tablets as they roll in the coating pan. When the tablets are partially dry they are sprinkled with a dusting powder, which is usually a mixture of powdered sugar and starch but may also contain talc, acacia, or precipitated chalk. Warm air is applied to the rolling tablets, and when they are dry, the subcoating process is repeated and repeated again until the tablets are of the desired shape and size (Fig. 5–52). At this point, the tablets are usually removed from the coating pan, the excess powder is shaken off the tablets by gently jostling them on a cloth screen, and the coating pan is then washed to remove extraneous coating material.

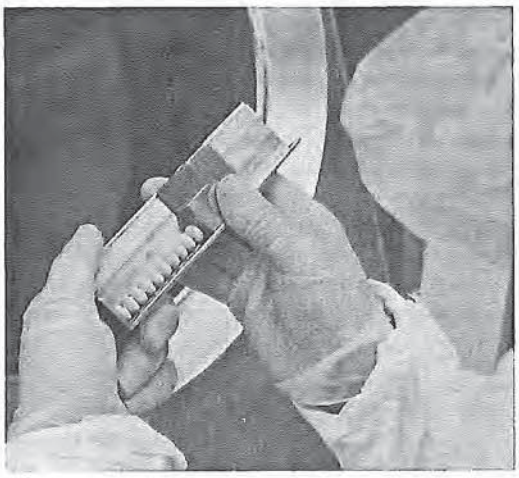

Fig. 5–52. *Tablet gauge used to measure the size of coated tablets. (Courtesy of Eli Lilly and Company.)*

SMOOTHING AND FINAL ROUNDING. After the tablets have been subcoated to the desired shape (roundness), 5 to 10 additional coatings of a very thick syrup are applied to the rolling tablets for the purpose of completing the rounding of the tablets and smoothing the coatings. This syrup may be composed of a sucrose-based simple syrup, or it may have additional components like starch and calcium carbonate. As the syrup is applied, the operator moves his hand through the rolling tablets to distribute the syrup and to prevent the sticking of the tablets to one another. A dusting powder may or may not be used between syrup applications, but warm air is generally applied to hasten the drying time of each coat. If the coating is to be colored, the suitable dye may be added to the syrup during this step of the coating process as well as during the next step.

FINISHING AND COLORING. To attain final smoothness and the appropriate color to the tablets, several coats of a thin syrup containing the desired colorant (if any) are applied. This step is usually performed in a clean pan, free from previous coating materials.

IMPRINTING. Solid dosage forms may be passed through special imprinting machines (Fig. 5–53) to impart identification codes and other distinctive symbols. By FDA regulation, effective in 1995, all solid dosage forms for human consumption, including both prescription-only and over-the-counter drug products, must be imprinted with product-specific identification codes. Some exemptions to this requirement are allowed, namely: solid dosage forms used in most clinical investigations; drugs that are extemporaneously compounded in the course of pharmacy practice; radiopharmaceutical drug products; and products that, because of their size, shape, texture or other physical characteristics, make imprinting technologically infeasible.

Code imprints, in conjunction with a product's size, shape, and color, permit the unique identification of a drug product and its manufacturer or distributor. Code imprints may contain any combination of letters and numbers, or the product's National Drug Code number, and any marks, symbols, logos, or monograms assigned by the drug company to the product. Each product's imprint must be registered with the FDA.

Technically, the imprint may be *debossed, em-*

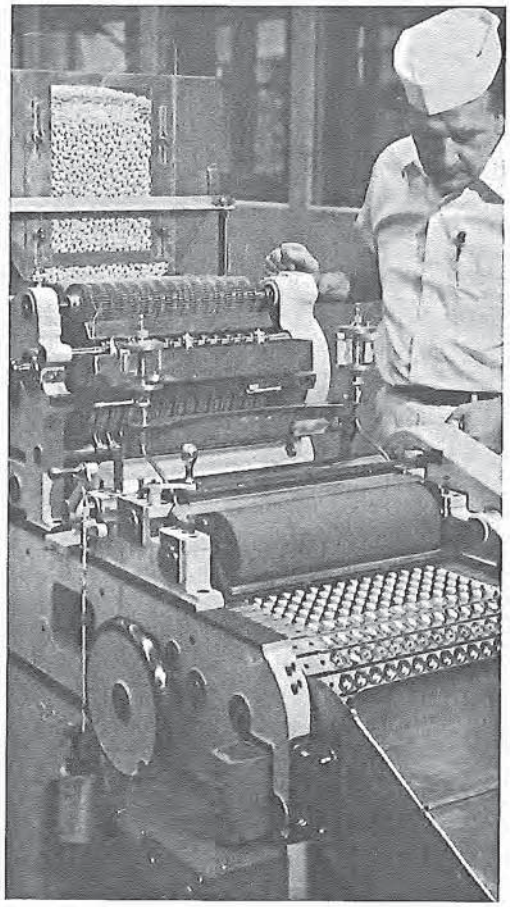

Fig. 5–53. *Branding of coated compression tablets on a Hartnett branding machine. (Courtesy of The Upjohn Company.)*

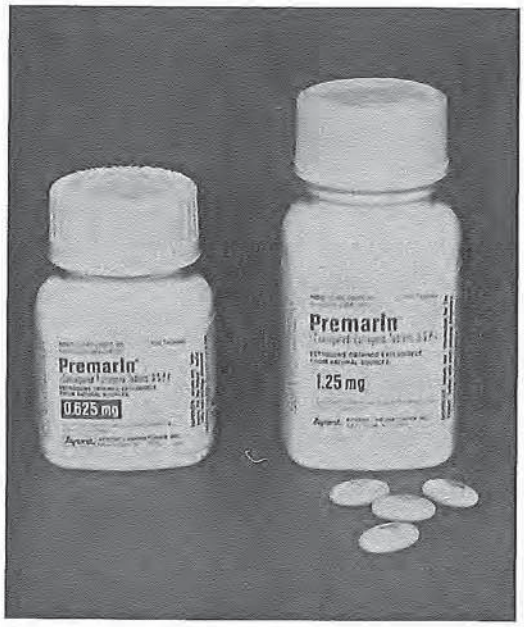

Fig. 5–54. *Example of coated, polished, and monogrammed tablets. (Courtesy of Wyeth-Ayerst Laboratories.)*

bossed, engraved, or printed on the surface with ink. *Debossed* means imprinted with a mark below the dosage form surface; *embossed* means imprinted with a mark raised above the dosage form surface; and *engraved* means imprinted with a code that is cut into the dosage form surface after it has been fabricated.

POLISHING. Coated tablets may be polished in special drum-shaped pans made by stretching a cloth fabric over a metal frame or in ordinary coating pans lined with canvas. The fabric or the canvas may be impregnated with a wax such as carnauba wax with or without the addition of beeswax and the tablets polished as they roll about in the pan. Or, the wax may be dissolved in a nonaqueous solvent such as acetone or petroleum benzin and sprayed on the rolling tablets in small amounts. After each coat has dried, the addition of a small amount of talc to the tumbling tablets contributes to their high luster (Fig. 5–54). Two or three coats of wax may be applied depending upon the desired gloss. Another method of polishing tablets simply involves placing pieces of wax in the polishing pan along with the tablets and permitting the tablets to tumble over the wax until the desired sheen is attained.

Film-Coating Tablets

As one can ascertain from the previous discussion of sugarcoating, the process is not only tedious and time-consuming, requiring the expertise of a highly skilled technician, but it also results in the preparation of coated tablets that may be twice the size and weight of the original uncoated compressed tablets. These factors are important to a manufacturer in his consideration of the expense of both packaging materials and shipping. From a patient's point of view, large tablets are not as convenient to swallow as are small tablets. Also, the coating of tablets by the application of the sugarcoating may vary slightly from batch to batch and within the batch. The film-coating process, which places a thin, skin-tight coating of a plastic-like material over the

compressed tablet, was developed to produce coated tablets having essentially the same weight, shape, and size as the originally compressed tablet. The coating is thin enough to reveal any depressed or raised monograms punched into the tablet by the tablet punches. In addition, film-coated tablets are far more resistant to destruction by abrasion than are sugar-coated tablets, and like sugar-coated tablets, the coating may be colored to make the tablets attractive and distinctive.

Film-coating solutions may be nonaqueous or aqueous. The nonaqueous solutions generally contain the following types of materials to provide the desired coating to the tablets:

1. A *film former* capable of producing smooth, thin films reproducible under conventional coating conditions and applicable to a variety of tablet shapes. Example: cellulose acetate phthalate.
2. An *alloying substance* providing water solubility or permeability to the film to ensure penetration by body fluids and therapeutic availability of the drug. Example: polyethylene glycol.
3. A *plasticizer* to produce flexibility and elasticity of the coating and thus provide durability. Example: castor oil.
4. A *surfactant* to enhance spreadability of the film during application. Example: polyoxyethylene sorbitan derivatives.
5. *Opaquants* and *colorants* to make the appearance of the coated tablets handsome and distinctive. Examples: Opaquant, titanium dioxide; colorant, F.D.&C. or D.&C. dyes.
6. *Sweeteners, flavors,* and *aromas* to enhance the acceptability of the tablet to the patient. Examples: sweeteners, saccharin; flavors and aromas, vanillin.
7. A *glossant* to provide luster to the tablets without a separate polishing operation. Example: beeswax.
8. A *volatile solvent* to allow the spread of the other components over the tablets while allowing rapid evaporation to permit an effective yet speedy operation. Example: alcohol-acetone mixture.

Tablets are film coated by the application or spraying of the film-coating solution upon the tablets in ordinary coating pans. The volatility of the solvent enables the film to adhere quickly to the surface of the tablets.

Due to both the expense of the volatile solvents used in the film-coating process and the problem of the release of these potentially toxic agents into the atmosphere, the high cost of solvent recovery systems, and their explosiveness, pharmaceutical manufacturers are favoring the use of aqueous-based film-coating solutions. One of the problems attendant to these, however, is the slow evaporation of the water-base compared to the volatile organic solvent-based film-coating solutions. One commercially available (to the pharmaceutical industry) water-based, colloidal coating dispersion, is called AQUACOAT® (FMC Corporation) and contains a 30% ethyl cellulose pseudolatex. Pseudolatex dispersions have the advantage of high solids content (for greater coating ability) and relatively low viscosity. The low viscosity allows less water to be used in the coating dispersion, resulting in a lesser requirement for water-evaporation and a reduced likelihood of water interference with the tablet formulation. In addition, the low viscosity permits greater coat penetration into the crevices of monogrammed or scored tablets. In using the pseudolatex coating dispersion, a plasticizer is incorporated to assist in the production of a denser, less-permeable film, with higher gloss and greater mechanical strength. Other aqueous systems utilized to film-coat tablets include the use of cellulosic materials as methylcellulose, hydroxypropyl cellulose, and hydroxypropyl methylcellulose.

A typical aqueous film-coating formulation contains the following:[21]

1. *Film-forming polymer* (7–18%). Examples: cellulose ether polymers as hydroxypropyl methylcellulose, hydroxypropyl cellulose, and methylcellulose.
2. *Plasticizer* (0.5–2.0%). Examples: glycerin, propylene glycol, polyethylene glycol, and dibutyl subacetate.
3. *Colorant and opacifier* (2.5–8%). Examples: FD&C or D&C Lakes and iron oxide pigments.
4. *Vehicle* (water, to make 100%).

There are some problems attendant to aqueous film-coating, including: the appearance of small amounts *(picking)* or larger amounts *(peeling)* of film fragments flaking from the tablet surface; roughness of the tablet surface due to failure of spray droplets to coalesce *(orange peel effect);* an uneven distribution of color on the tablet surface *(mottling);* filling-in of the score-line or indented logo on the tablet by the film *(bridging);* and the

disfiguration of the core tablet when subjected for too long a period of time to the coating solution (tablet *erosion*). The cause of each of these problems can be determined and rectified through appropriate changes in formulation, equipment, technique or process.[21]

Enteric Coating

The purpose of enteric coating for solid dosage forms has already been discussed. The design of an enteric coating may be based upon the transit time required for the passage of the dosage form from the stomach into the intestines. This may be accomplished through coatings of sufficient thickness to resist dissolution in the stomach. More usually, an enteric coating is based upon the pH of the environment, being designed to resist dissolution in the highly acid environment of the stomach but yielding to the less acid environment of the intestine. Some enteric coatings are designed to dissolve at pH 4.8 and greater.

Enteric coating materials may be applied to either whole compressed tablets or to drug particles or granules used in the subsequent fabrication of tablets or capsules. The coatings may be applied in multiple portions to build a thick coating or they may be applied as a thin film coat. The coating systems may be aqueous-based or organic-solvent–based so long as the coating material resists breakdown in the gastric fluid.

Among the materials used in enteric coatings are shellac, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, and cellulose acetate phthalate.

Fluid-Bed or Air Suspension Coating

This process, utilizing equipment of the type shown in Figure 5–55, involves the spray coating of pellets, beads, granules, powders, or tablets held in suspension by a column of air. The fluid bed processing equipment used is multifunctional and may be used in preparing tablet granulations as well, as noted earlier in this chapter.

In the Wurster process, named after its developer, the items to be coated are fed into a vertical cylinder and are supported by a column of air that enters from the bottom of the cylinder. Within the air stream, the solids rotate both vertically and horizontally. As the coating solution enters the system from the bottom, it is rapidly placed on the suspended, rotating solids, with rounding coats being applied in less than an hour with the assistance of warm air blasts released in the chamber.

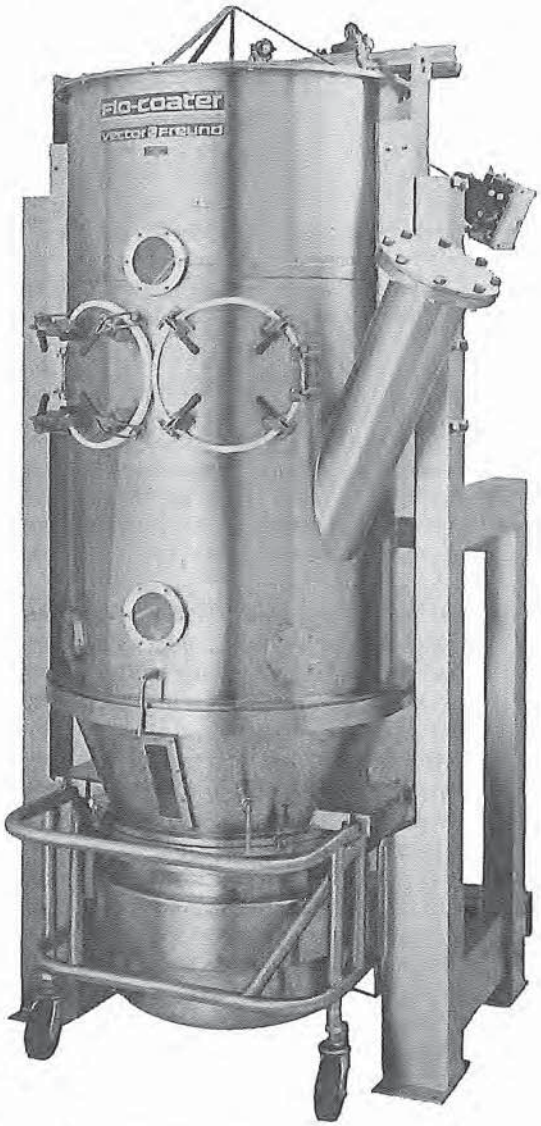

Fig. 5–55. *Vector/Freund Flo-Coater production system. A fluid bed system used in the application of coatings to beads, granules, powders, and tablets. Capacity of models ranges from 5 kg to 700 kg. (Courtesy of Vector Corporation.)*

In another type of fluidized bed system, the coating solution is sprayed downward onto the particles to be coated as they are suspended by air from below. This method is commonly referred to as the *top-spray* method. This method provided greater capacity, up to 1500 kg, than do the other air suspension coating methods.[22] Both the top-spray and bottom-spray methods

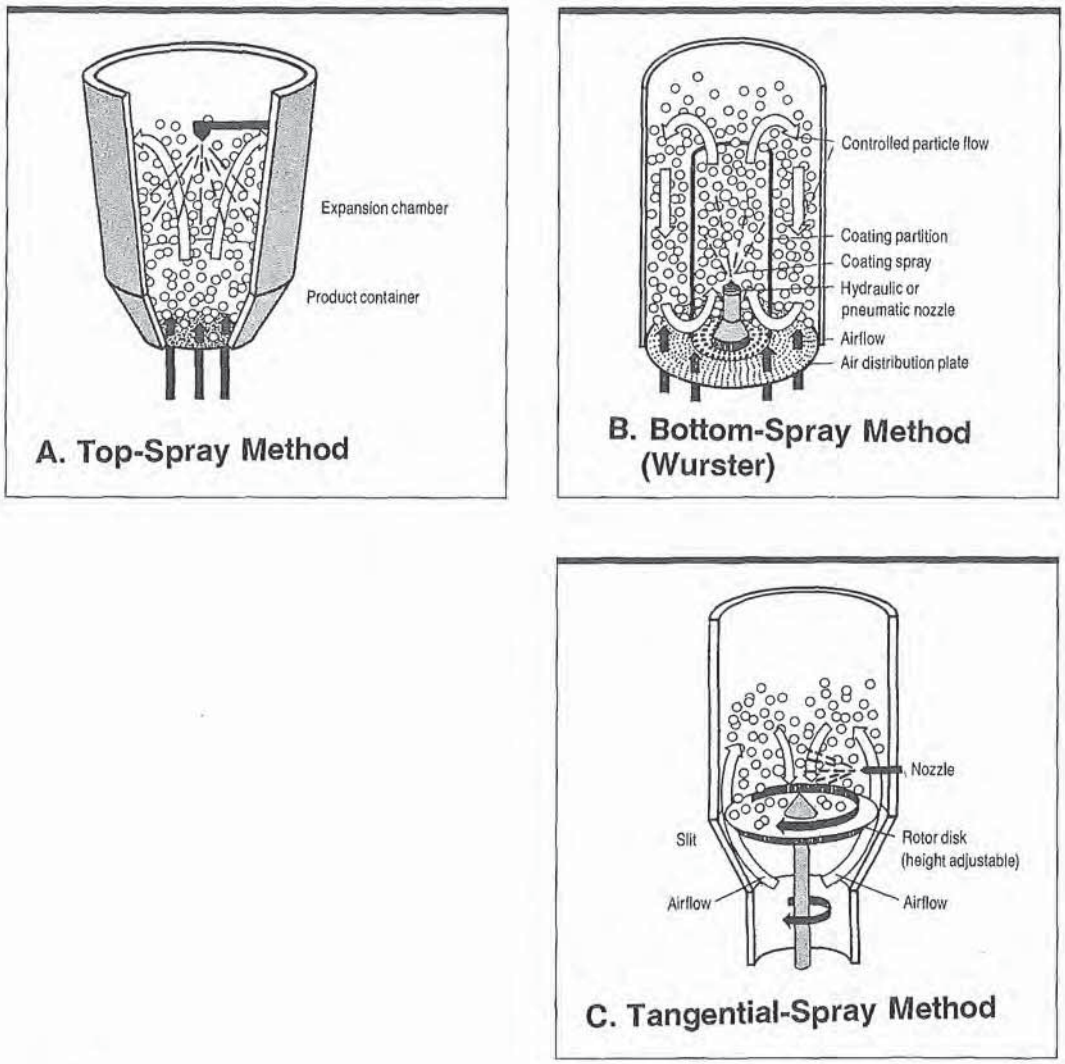

Fig. 5–56. *(A) Top-spray, (B) bottom-spray (Wurster), and (C) tangential-spray methods in the fluid-bed coating of solid particles. (Courtesy of Glatt Air Techniques, Inc.)*

may be employed using a modified apparatus used for fluidized bed granulation. A third method, the *tangential-spray technique*, is used in rotary fluid-bed coaters. The bottom-, top-, and tangential-spray methods are depicted in Figure 5–56.

The three systems are increasingly used for the application of aqueous- or organic-solvent–based polymers as film coatings. The top-spray coating method is particularly recommended for taste masking, enteric release, and barrier films on particles or tablets. The method is most effective when coatings are applied from aqueous solutions, latexes, or hotmelts.[22,23] The bottom-spray coating method is recommended for sustained-release and enteric-release products; and the tangential method for layering coatings, and for sustained-release and enteric-coated products.[23]

Among the variables requiring control in order to produce product of desired and consistent quality are: equipment used and the method of spraying (e.g., top, bottom, tangential), spray-nozzle distance from spraying bed, spray (droplet) size, spray rate, spray pressure, volume of fluidization air, batch size, method(s) and time

for drying, air temperature and moisture content in processing compartment.[23]

Compression Coating

In a manner similar to the preparation of multiple compressed tablets having an inner core and an outer shell of drug material, core tablets may be sugarcoated by compression. The coating material in the form of a granulation or a powder is compressed onto a tablet core of drug with a special tablet press. This method eliminates the time-consuming and tedious operation previously described in this section. Compression coating is an anhydrous operation and thus may be safely employed in the coating of tablets having a drug that is sensitive to moisture. The resulting coat is more uniform than the usual sugarcoating applied using pans, and less of a coating is required. Resulting tablets are lighter and smaller and are therefore easier to swallow and less expensive to package and ship.

Irrespective of the method used in coating, all tablets are visually or electronically inspected for physical imperfections (Fig. 5–57).

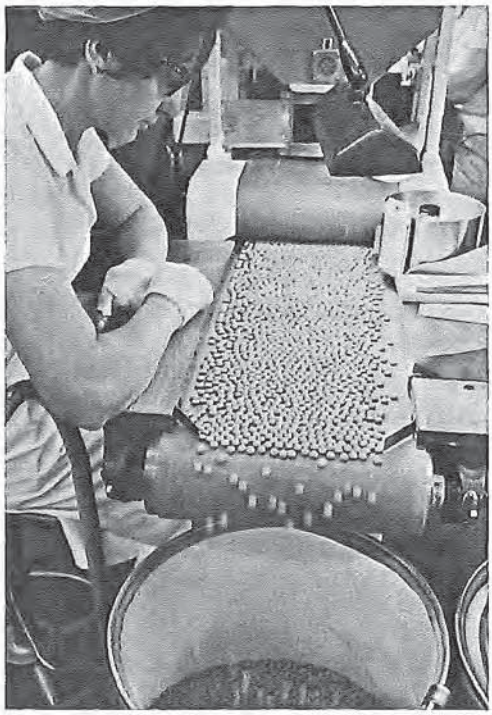

Fig. 5–57. *Checking for physical imperfections in coated tablets. (Courtesy of Smith, Kline & French.)*

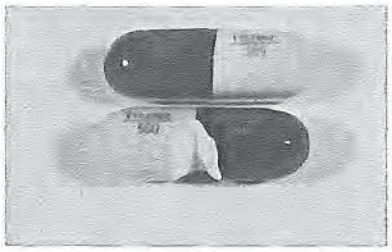

Fig. 5–58. *Cut-away view of "Gelcaps" dosage form. A gelatin-coated capsule-shaped tablet. Dosage form is more easily swallowed than a comparable tablet, smaller than an equivalent capsule, and tamper-evident. (Courtesy of McNeil Consumer Products Co.)*

Gelatin Coated Tablets

A recent innovation in tablet coating is the gelatin-coated tablet. Termed GELCAPS®, the innovator product is a gelatin-coated capsule-shaped tablet (Fig. 5–58). The use of a tablet makes the size of the product about one-third smaller than a capsule filled with an equivalent amount of powder. The gelatin coating facilitates ease of swallowing. Compared to dry-filled, unsealed capsules, GELCAPS are more tamper-resistant and tamper-evident.

Chewable Tablets

Chewable tablets are tablets which are intended to disintegrate smoothly in the mouth at a moderate rate, either with or without actual chewing. Characteristically, chewable tablets have a smooth texture upon disintegration, are pleasant tasting, and leave no bitter or unpleasant aftertaste. Mannitol, a white crystalline hexahydric alcohol, which possesses many of the characteristics desired for the excipient in chewable tablets, is widely employed for this purpose. Mannitol is about 70% as sweet as sucrose with a cool taste and mouth-feel, the latter resulting from its negative heat of solution and a moderate solubility in water. Mannitol's nonhygroscopicity also makes it an ideal excipient for the preparation of chewable tablets containing moisture-sensitive drugs. Chewable tablets are prepared by wet granulation and compression, using minimum degrees of tablet hardness. In many chewable tablet formulations, mannitol may account for 50% or more of the weight of the formulation. Sometimes, other sweetening agents, as sorbitol, lactose, dextrose and glucose, may be substituted for a portion of the mannitol. Lubricants and

binders which do not detract from the texture or desired hardness of the tablet are used in formulating chewable tablets. To enhance the appeal of the tablets, colorants and tart or fruity flavorants are commonly employed. Among the types of products prepared into chewable tablets are antacids and vitamins, analgesic and cold tablets intended for children.

The following is a formula for a typical chewable antacid tablet:[24]

	Per Tablet
Aluminum hydroxide	325.0 mg
Mannitol	812.0 mg
Sodium saccharin	0.4 mg
Sorbitol (10% w/v solution)	32.5 mg
Magnesium stearate	35.0 mg
Mint flavor concentrate	4.0 mg

Preparation: Blend the aluminum hydroxide, mannitol, and sodium saccharin. Prepare a wet granulation with the sorbitol solution. Dry at 120°F and screen through a 12-mesh screen. Add the flavor and magnesium stearate, blend, and compress into tablets.

Molded Tablets

The commercial preparation of tablets by molding has been replaced by the tablet compression process.

Official Tablets

Examples of official tablets are presented in Table 5–4.

Rate-Controlled Dosage Forms and Drug Delivery Systems

Some solid dosage forms are designed to release their medication to the body for absorption rapidly and completely, whereas other products are designed to release the drug slowly for more prolonged drug release and sustained drug action. The latter types of dosage forms are commonly referred to as *controlled-release, sustained-release, prolonged-release, timed-release, slow-release, sustained-action, prolonged-action, extended-action,* or *rate-controlled* tablets or capsules.

Although these terms have been frequently used interchangeably, the meaning of "sustained-release" and "controlled-release" are different. Sustained release describes the release of a drug substance from a dosage form or delivery system over an extended period of time. Controlled-release describes a system in which the *rate* of the drug's release is more precisely controlled compared to the sustained release product.

The term "drug delivery systems" refers to the technology utilized to present the drug to the desired body site for drug release and absorption. The modern transdermal patch, discussed in Chapter 10 is an example of a drug delivery system. The first drug delivery system developed was the *syringe,* invented in 1855, used to deliver medication by injection.

The goal of rate-controlled technology is to produce a convenient, generally self-administered dosage form that yields a constant infusion of the drug. The advantages of rate-controlled drug delivery are presented in Table 5–5.

Controlled-release dosage forms that provide sustained drug release require less frequent drug administration than ordinary dosage forms (Fig. 5–59A). This is considered an advantage in assuring patient compliance in the taking of medication. Patients required to take 1 or 2 dosage units a day are less likely to forget a dose than if they were required to take their medication 3 or 4 times a day.[25] Further, controlled-release dosage forms allow whole day coverage and help to reduce the need for the patient to be awakened for a night-time dose. Also, depending upon the medication and the dosage form, the daily cost to the patient may be less with less frequent dosage administration.

Rather than providing *sustained-release,* some solid dosage forms are designed to sequentially release two full doses of a drug. Such dosage forms also enable the patient to be maintained on the drug for longer than usual periods following the administration of a single dosage unit. These types of products are usually termed *repeat-action* tablets or capsules (Fig. 5–59B).

Many of these specialized types of dosage forms are protected by patents and have been given trademark names that help to identify both the manufacturer and the type of pharmaceutical product.

Sustained-Release Forms

Most sustained-release forms are designed so that the administration of a single dosage unit provides the immediate release of an amount of drug that promptly produces the desired therapeutic effect and gradual and continual release of additional amounts of drug to maintain this

Table 5–4. Examples of Some Official Tablets

Official Tablet	*Some Representative Commercial Products*	*Tablet Strengths Usually Available*	*Category and Comments*
Acetaminophen	Tylenol (McNeil)	325 mg	Analgesic and antipyretic
Allopurinol	Zyloprim (Burroughs Wellcome)	100 and 300 mg	Antigout; antiurolithic
Amitriptyline HCl	Elavil HCl (Stuart)	10, 25, 50, 100, and 150 mg	Antidepressant
Bisacodyl	Dulcolax (Ciba)	5 mg	Cathartic; enteric coated tablets
Carbamazepine	Tegretol (Basel)	200 mg	Anticonvulsant
Chlorambucil	Leukeran (Burroughs Wellcome)	2 mg	Antineoplastic
Chlorpheniramine Maleate	Chlor-Trimeton Maleate (Schering-Plough)	4, 8, and 12 mg	Antihistaminic; some tablets (8 and 12 mg) controlled-release
Chlorpropamide	Diabinese (Pfizer)	100 and 250 mg	Antidiabetic
Cimetidine	Tagament (SmithKline Beecham)	200 and 300 mg	Histamine H_2 receptor antagonist
Diazepam	Valium (Roche)	2, 5, and 10 mg	Sedative; skeletal muscle relaxant
Digoxin	Lanoxin (Burroughs Wellcome)	0.125, 0.25, and 0.5 mg	Cardiotonic
Dimenhydrinate	Dramamine (Upjohn)	50 mg 25 and 30 mg	Antinauseant Bronchodilator; vasoconstrictor
Furosemide	Lasix (Hoechst-Roussel)	20, 40, and 80 mg	Diuretic; antihypercalemic; antihypertensive
Griseofulvin	Fulvicin U/F (Schering)	250 and 500 mg	Antifungal
Haloperidol	Haldol (McNeil)	0.5, 1, 2, 5, 10 and 20 mg	Tranquilizer
Hydrochlorothiazide	Hydro-Diuril (Merck & Co.)	25, 50, and 100 mg	Diuretic; antihypertensive
Ibuprofen	Motrin (Upjohn)	300, 400, 600, and 800 mg	Analgesic; antipyretic
Levodopa	Larodopa (Roche)	100, 250, and 500 mg	Antidyskinetic
Levothyroxine sodium	Synthroid (Boots)	0.025, 0.05, 0.075, 0.1, 0.125, 0.15, 0.2, and 0.3 mg	Thyroid hormone
Meclizine HCl	Antivert (Roerig)	12.5, 25, and 50 mg	Antivertigo
Meperidine Hydrochloride	Demerol (Sanofi Winthrop)	50 and 100 mg	Narcotic analgesic
Meprobamate	Equanil (Wyeth-Ayerst)	200 and 400 mg	Sedative; hypnotic
Methyldopa	Aldomet (Merck & Co.)	125, 250, and 500 mg	Antihypertensive
Metronidazole	Flagyl (Searle)	250 and 500 mg	Antiamebic; antitrichomonal
Nitroglycerin	Nitrostat (Parke-Davis)	0.150, 0.3, 0.4, and 0.6 mg	Anti-anginal sublingual tablets
Penicillin V Potassium	Pen Vee (Wyeth-Ayerst)	250 and 500 mg	Antibacterial
Prednisone	Deltasone (Upjohn)	1 mg	Adrenocorticoid
Prochlorperazine Maleate	Compazine (SmithKline Beecham)	5, 10, and 25 mg	Antiemetic
Propanolol HCl	Inderal (Wyeth-Ayerst)	10, 20, 40, 60, 80, and 90 mg	Antianginal; antiarrhythmic; antihypertensive
Sulindac	Clinoril (Merck & Co.)	150 and 200 mg	Antirheumatic, antiinflammatory
Terbutaline sulfate	Brethine (Geigy)	2.5 and 5 mg	Antiasthmatic
Tolbutamide	Orinase (Upjohn)	250 and 500 mg	Antidiabetic
Warfarin Sodium	Coumadin (DuPont)	2, 2.5, 7.5, and 10 mg	Anticoagulant

Table 5–5. Advantages of Rate-Controlled Drug-Delivery Systems Over Conventional Dosage Forms

Advantage	*Explanation*
Reduction in drug blood level fluctuations	By controlling the rate of drug release, "peaks and valleys" of drug-blood or -serum levels are eliminated.
Reduction in dosing frequency	Rate-controlled products deliver more than a single dose of medication and thus are taken less often than conventional forms.
Enhanced patient convenience and compliance	With less frequency of dose administration, the patient is less apt to neglect taking a dose. There is also greater patient convenience with daytime and nighttime medication, and control of chronic illness.
Reduction in adverse side effects	Because there are seldom drug blood level peaks above the drug's therapeutic range, and into the toxic range, adverse side effects are less frequently encountered.
Reduction in health care costs i.e., economy	Although the initial cost of rate-controlled drug delivery systems is usually greater than conventional dosage forms, the average cost of treatment over an extended time period may be less. With less frequency of dosing, enhanced therapeutic benefit, and reduced side-effects, the time required of health care personnel to dispense, administer and monitor patients is reduced.

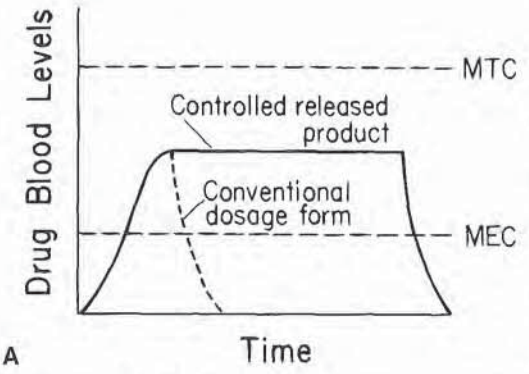

Fig. 5–59A. *Hypothetical drug blood level-time curves for a conventional solid dosage form and a controlled release product.*

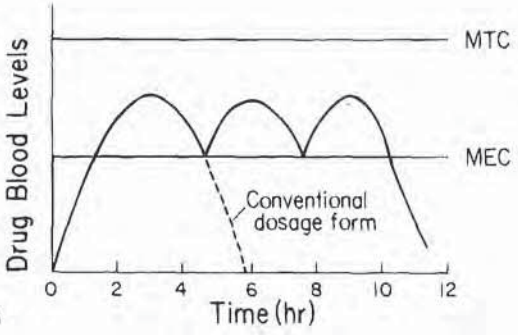

Fig. 5–59B. *Hypothetical drug blood level-time curves for a conventional solid dosage form and a multiple-action product.*

level of effect over an extended period, usually 8 to 12 hours.

In this type of dosage form, the design is based on the particular qualities of each individual drug. What may be an effective type of dosage form design for one drug may be ineffective in promoting the sustained release of another drug because of peculiar physical, chemical, and biological qualities. To maintain the constant level of drug in the system, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. For each drug, this is a highly individualized quality. In general, the drugs best suited for incorporation into a sustained release product have the following characteristics.

1. *They exhibit neither very slow nor very fast rates of absorption and excretion.* Drugs with slow rates of absorption and excretion are usually inherently long-acting and their preparation into sustained-action type dosage forms is not necessary. Similarly, a drug with a short half life, i.e., <2 hours, should not be formulated into a sustained release product because such a delivery system would require unacceptably large release rates and doses.
2. *They are uniformly absorbed from the gastrointestinal tract.* Drugs absorbed poorly or at varying and unpredictable rates are not good candidates for sustained-release products, because their drug release and therefore drug absorption will fluctuate, depending upon the position of the drug in the gastrointestinal

testinal tract and the dosage form's rate of movement within the tract.

3. *They are administered in relatively small doses.* Drugs with large single doses frequently are not suitable for the preparation of the sustained-action product because the individual dosage unit needed to maintain the extended therapeutic blood level of the drug would have to be too large for the patient to easily swallow.
4. *They possess a good margin of safety.* The most widely used measure of the margin of safety is its therapeutic index, i.e., median toxic dose, TD50/median effective dose, ED50. This index can range from one (where the effective dose produces toxic effects) to several thousand. For very "potent" drugs when therapeutic concentration is narrow, the value of the therapeutic index is very small. The larger the therapeutic index the safer the drug. Thus, those drugs which are potent in very small doses or possess very narrow or small therapeutic indices are poor candidates for formulation into controlled-release formulations because of technologic limitations of precise control over release rates.
5. *They are used in the treatment of chronic rather than acute conditions.* Drugs for acute conditions generally require more physician control of the dosage than that provided by sustained-release products.

The most common mechanisms utilized in rate-controlled pharmaceutical products are: solvent action of biologic fluids on coated drug particles, osmotic systems controlled by the diffusion of biologic fluids through a polymer, erodible systems controlled by the erosion of a polymeric matrix, diffusion systems controlled by the diffusion of the drug through a polymeric membrane or monolithic matrix, and chemical reaction or interaction between the drug substance or its pharmaceutical barrier and site-specific biologic fluids. These mechanisms are utilized in the development of dosage forms and drug delivery systems for oral and other routes of administration.

Examples of the pharmaceutical technology utilized to achieve rate-controlled and sustained release solid dosage forms are described below.

COATED BEADS OR GRANULES OR MICROENCAPSULATED DRUG. In this method a solution of the drug substance in a non-aqueous solvent such as a mixture of acetone and alcohol is coated (by pan or air-suspension coating) onto small inert non-pareil seeds or beads made of a combination of sugar and starch. In instances in which the dose of the drug is large, the starting granules of material may be composed of the drug itself. Then with some of the beads or granules remaining uncoated and intended to provide the immediately released dose of drug when taken, coats of a lipid material like beeswax or a cellulosic material like ethylcellulose are applied to the remainder (about two-thirds to three-fourths) of the granules, with some granules receiving a few coats and others many coats. Then the beads or granules of different thicknesses of coatings are blended in the desired proportions to achieve the proper blend. The coating material may be colored with a dye material so that the beads of different coating thicknesses will be darker in color and distinguishable from those having fewer coats and being lighter in color. When properly blended, the granules may be placed in capsules or tableted. The variation in the thickness of the coats and in the type of material used in the coating is reflected in the rate at which the body fluids are capable of penetrating the coating and in dissolving the drug. Naturally, the thicker the coat, the more resistant to penetration and the more delayed will be the drug release. The presence of drug granules of various coating thicknesses therefore produces the sustained drug release. The time-blood level profile is similar to that obtained with multiple dosing. An example of this type of dosage form is the *Spansule* capsule, shown in Figure 5–60.

Microencapsulation is a process by which solids, liquids, or even gases may be encapsulated into microscopic size particles through the formation of thin coatings of "wall" material around the substance being encapsulated. The process had its early origin in the late 1930s as a "clean" substitute for carbon paper and carbon ribbons as sought by the business machines industry. The ultimate development in the 1950s of reproduction paper and ribbons which contained dyes in tiny gelatin capsules released upon impact by a typewriter key or the pressure of a pen or pencil was the stimulus for the development of a host of microencapsulated materials, including drugs. Gelatin is a common wall-forming material but synthetic polymers as polyvinyl alcohol, ethylcellulose, or polyvinyl chloride have been used. The typical encapsulation process usually begins with the dissolving of the prospective wall material, say gelatin, in water. The material to be encapsulated is added and the two-phase mixture thoroughly stirred. With the material to

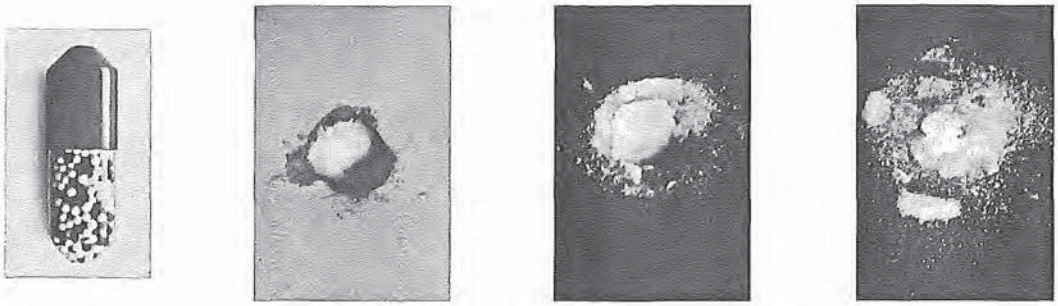

Fig. 5–60. *The* Spansule *capsule showing the hard gelatin capsule containing hundreds of tiny pellets for sustained drug release and the rupturing of one of the pellets as occurs in the gastric fluid. (Courtesy of SmithKline Beecham.)*

be encapsulated broken up to the desired particle size, a solution of a second material is added, usually acacia. This additive material is chosen to have the ability to concentrate the gelatin (polymer) into tiny liquid droplets. These droplets (coacervate) then form a film or coat around the particles of the substance to be encapsulated as a consequence of the extremely low interfacial tension of the residual water or solvent in the wall material so that a continuous, tight, film coating remains on the particle (Fig. 5–61). The final dry microcapsules are free-flowing, discrete particles of coated material. Of the total particle weight, the wall material usually represents between 2 and 20%. By varying the wall thickness of microencapsulated drug particles, their dissolution rates may be altered and sustained release obtained. An example of a drug commercially available in microencapsulated dosage form is potassium chloride as Micro-K (A. H. Robins).

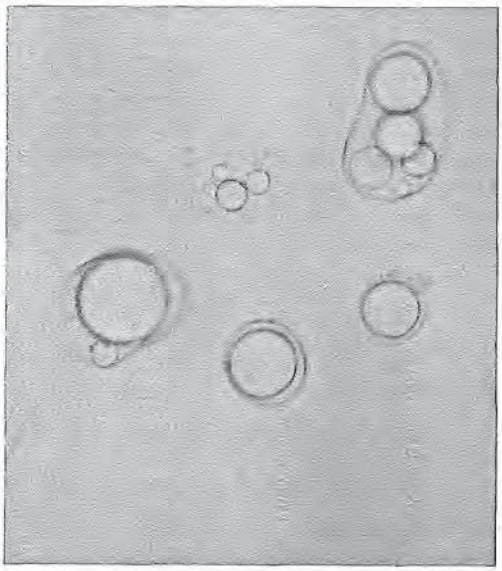

Fig. 5–61. *Microcapsules of mineral oil in a gelatin-acacia coacervate. (Photo courtesy of James C. Price, Ph.D., College of Pharmacy, The University of Georgia.)*

EMBEDDING DRUG IN SLOWLY ERODING MATRIX. By this process, the portion of the drug intended to have sustained action is combined with lipid or cellulosic material processed into granules that can be placed into capsules or tableted. When these granules are combined with granules of drug prepared without the special lipid or cellulosic excipient, the untreated portion provides the immediate drug effect, and the treated portion the prolonged effect. The treated granules slowly erode in the body fluids. The types of materials used in the preparation of the granules may be varied to achieve different rates of erosion. The product SLOW-K (Summit) is a sugar-coated tablet containing 8 mEq of potassium chloride in a wax matrix. The formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high (and irritating) localized concentrations of potassium within the gastrointestinal tract.

Two-layered tablets may be prepared from the granules, with one layer containing the untreated drug for immediate release and the other layer having the drug for sustained release. Three-layered tablets may be similarly prepared, with both outer layers containing the drug for immediate release. Some commercial tablets are prepared with an inner core containing the sustained release portion of drug and an outer shell completely enclosing the core and containing the drug portion for immediate release. Tablets prepared from the type of material described in the next method may be similarly constructed.

EMBEDDING DRUG IN INERT PLASTIC MATRIX. By this method, the drug is granulated with an inert plastic material such as polyethylene, polyvinyl acetate, or polymethacrylate, and the granulation is compressed into tablets. The drug is slowly released from the inert plastic matrix by leaching to the body fluids. The compression of the tablet creates the matrix or plastic form that retains its shape during the leaching of the drug and through its elimination from the alimentary tract. The initially released drug is present on the surfaces of the tablet or is only superficially embedded. The primary example of a dosage form of this type is the *Gradumet* (Abbott).

COMPLEX FORMATION. Certain drug substances when chemically combined with certain other chemical agents form chemical complexes that may be only slowly soluble in body fluids, depending upon the pH of the environment. This slow dissolution rate is effective to provide the sustained action of the drug.

It should be remembered that certain drug substances that are only slowly soluble in body fluids without special complexation or other treatment are inherently long acting.

ION-EXCHANGE RESINS. A solution of the cationic drug is passed through a column containing the ion-exchange resin, to which it complexes by the replacement of hydrogen atoms. The resin-drug complex is then washed and may be tableted, encapsulated, or suspended in an aqueous vehicle. The release of the drug is dependent upon the pH and the electrolyte concentration in the gastrointestinal tract. Generally, release is greater in the acidity of the stomach than the less acidic small intestine. Examples of drug products of this type include *Tussionex* suspension (hydrocodone polistirex) and *Ionamin* capsules (phentermine resin) both by Fisons.

The mechanism of action of drug release from ion exchange resins may be depicted as follows.

In the stomach:

(1) Drug resinate + HCl⇌acidic resin + drug hydrochloride
(2) Resin salt + HCl⇌resin chloride + acidic drug

In the intestine:

(1) Drug resinate + NaCl⇌sodium resinate + drug hydrochloride
(2) Resin salt + NaCl⇌resin chloride + sodium salt of drug.

This system incorporates a polymer barrier coating and bead technology in addition to the ion-exchange mechanism. The initial dose comes from an uncoated portion, and the remainder from the coated beads. The coating does not dissolve, and release is controlled over a 12-hour period by ionic exchange. The drug-containing polymer particles are minute, and may be suspended to produce a liquid with controlled-release characteristics [e.g., Tussionex (Fisons)] as well as solid dosage forms.

HYDROCOLLOID SYSTEM. Hydrocolloids can play a significant role in the design of a controlled-release product. An example is the product Valrelease, a 15-mg slow-release dosage form of Valium (diazepam/Roche). Valrelease has been formulated using a unique Hydro-dynamically Balanced drug-delivery System (HBS). This dosage form was designed to achieve, in one administration, plasma concentrations of diazepam equivalent to those obtained with conventional Valium 5 mg tablets taken 3 times daily. The Hydrodynamically Balanced drug-delivery System consists of a matrix so designed that upon contact with gastric fluid, the dosage form demonstrates a bulk density of less than one and, thus, remains buoyant. Capsules and tables prepared to have this characteristic are sometimes referred to as "floating" capsules or tablets. When the Valrelease capsule shell dissolves, the outermost hydrocolloids come in contact with gastric fluid. They swell to form a boundary layer, which prevents immediate penetration of fluid into the formulation. The outer hydrocolloid boundary layer gradually erodes, with the subsequent formation of another "outer" boundary layer. This is a continuous process causing the gelatinous mass to constantly erode, while diazepam is gradually released through each layer as the fluid slowly penetrates the matrix. Valrelease remains in the stomach for a variable period of time, depending on individual physiologic characteristics. However, when Valrelease passes into the intestine, gradual release of the active drug and absorption continue.

OSMOTIC PUMP. The Oros system, developed by Alza, is an *o*ral *os*motic pump composed of a core tablet and a semi-permeable coating with a 0.4 mm diameter hole for drug exit. The hole is produced by a laser beam and the product operates on the principle of osmotic pressure (Fig. 5–62A). The semi-permeable membrane permits water to enter from the patient's stomach into the core, dissolving the drug. The pressure that is built up forces or pumps the drug solution out of the delivery orifice (Fig. 5–63).

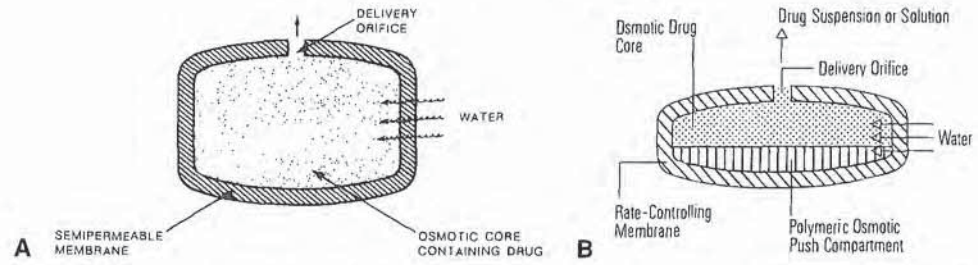

Fig. 5–62. *A, Depiction of the elementary OROS osmotic pump drug delivery system, and B, the OROS Push-Pull Osmotic System. (Courtesy of Alza Corporation.)*

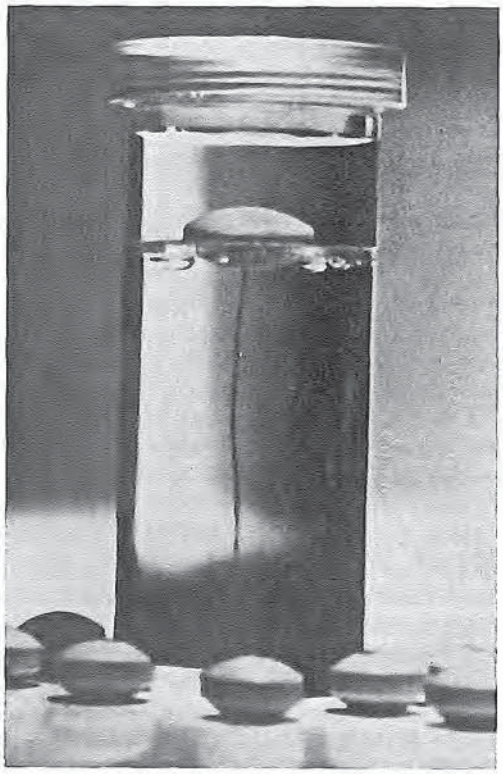

Fig. 5–63. *The OROS (Oral Osmotic) drug delivery system. A tablet core of drug is surrounded by a semipermeable membrane that is pierced by a small laser-drilled hole. After ingestion, water is drawn into the tablet from the digestive tract by osmosis. As water enters the tablet core, the drug gradually goes into solution. The solution is pushed out through the small hole at a controlled rate of about 1 to 2 drops per hour. (Courtesy of ALZA Corporation.)*

The rate of inflow of water and the outflow of drug solution are controlled by the properties of the membrane. Only the drug solution (not the undissolved drug) passes through the hole in the tablet. The rate of drug solution release is approximately one to two drops per hour. The drug-release rate is not affected by the acidity, alkalinity, or movement of the gastrointestinal tract. A currently marketed product of this type is Acutrim (CIBA Consumer).

Oros is a sophisticated oral controlled release drug delivery system in which the release rate may be controlled by changing the *surface area, the thickness* or *the nature* of the membrane and/or by changing the diameter of the drug release orifice.

The *OROS Push-Pull Osmotic System* has two layers (Fig. 5–62B) that are surrounded by a semi-permeable membrane. One layer contains the drug and the other contains a polymeric osmotic agent. When the tablet is swallowed, it draws in a few drops of water every hour across the membrane, slowly dissolving or suspending the drug, and expanding the polymeric osmotic compartment to release the drug through one or more laser-drilled holes at a controlled rate.

Other pharmaceutical companies have developed similar osmotic systems. For example, Elan Pharmaceutical has developed a system called Modas—*Multidirectional Osmotic Drug Absorption System.* Modas is an osmotic device with solubilized drug delivered through a fixed permeable membrane designed to admit moisture and excrete the soluble drug back through the same membrane at constant pressure. The drug comes out of the entire surface area of the tablet at a constant rate.

Repeat Action Forms

Some specialized tablets are prepared so that an initial dose of the drug is released from the

tablet shell and a second dose from an inner core of the tablet, which is separated from the outer shell by a slowly permeable barrier coating. Generally the barrier coating is penetrated and drug from the inner core is exposed to the body fluids some 4 to 6 hours after the swallowing of the tablet. Such a tablet permits the release of two doses of drug from a single tablet, eliminating the need for more frequent drug administration. An example of this type of dosage form is *Repetabs* (Schering). As for the sustained-action type of dosage forms, the repeat-action forms are best suited for those drugs having low dosage and employed in chronic conditions and for drugs having regular absorption patterns with fairly rapid rates of absorption and excretion.

Delayed Action Forms

The release of a drug from a dosage form may be intentionally delayed until it reaches the intestinal environment for any of several reasons. Among these may be the fact that the drug is destroyed by the gastric juices, or it may be excessively irritating to the lining of the stomach or a nauseating drug, or it may be better absorbed from the intestines than from the stomach. Capsules and tablets coated so as to remain intact in the stomach but yield their ingredients in the intestines are said to be *enteric coated*. The coating may be composed of a material that is pH dependent and breaks down in the less acidic environment of the intestine, or the coating may erode due to moisture and on a time basis coinciding with the time required for the tablet or capsule to reach the intestines. Other coatings may deteriorate due to the hydrolysis-catalyzing action of certain intestinal enzymes. Among the many agents used to enteric coat tablets and capsules are fats, fatty acids, waxes and mixtures of these, shellac, and cellulose acetate phthalate. An example of a commercially prepared brand of enteric coated tablets is *Enseals* (Lilly). A popular enteric-coated aspirin tablet is Ecotrin (SmithKline Beecham Consumer Brands).

Liposomes

In the early 1960s, research scientists noted that various phospholipids formed multilayered vesicles (sacs) when dispersed in water. These cell-like structures become known as *liposomes*. Like a biologic cell, a liposome is composed of a thin but durable membrane that surrounds an aqueous compartment, protecting it from the outside environment. Both cellular and liposome membranes are capable of regulating the transport of molecules in and out of the enclosed compartment. Thus liposomes may be used to control the passage of drugs, entrapped in the aqueous phase, through the membrane and to the intended body site for absorption or action. In recent years, drug-containing liposome systems have been developed for the delivery of drugs by various routes of administration including inhalation, ocular, injectable, dermal, and oral.

Liposomes may be constructed to have a single aqueous compartment surrounded by a lipid layer *(unilamellar)* or they may consist of concentric lipid and aqueous layers *(multilamellar)*. The structure of liposomes permits the incorporation of fat-soluble drugs in the lipid layer and water-soluble drugs in the interior aqueous compartment. Drugs encapsulated in the aqueous phase are released by slowly diffusing through the lipid membrane. Lipid-soluble drugs embedded in the lipid membrane or bound to the membrane surface are slowly released as the membrane is broken down by body fluids. Because lipids from natural sources are used to form the liposome membrane, liposomes are considered biocompatible and biodegradable.

Liposomes are produced by dispersing the lipid (usually phospholipids) phase in the drug solution. Simple mixing to vigorous agitation is applied to the system. Upon dispersion, the lipid molecules align to form the biomolecular membrane. The lipophilic ends of the lipid molecules intercalcate to form the inside of the membrane and the hydrophilic ends line up on the two outer surfaces. The membrane then wraps around, encapsulating the drug solution as the liposome is formed.

Generally, simple hand mixing of the phospholipid and aqueous phase produces a dispersion of multilamellar vesicles of large and widely mixed size. Various homogenizers and pressure flow-through devices have been utilized to achieve a more narrowly defined liposome size distribution. For use as drug carriers, liposomes should be homogeneous and reproducible in batch-to-batch production, stability, and drug release characteristics. Recently, microfluidization techniques have been used to produce liposomes of well-defined size distribution. This process involves the ultra high velocity interaction of two fluid streams in closely defined interaction. The pressures of the system, as high as 8000 psi, result in the jet interaction of the phases and lipo-

some formation rates of as high as 75%, in contrast to other mixing systems which may result in a capture of the aqueous phase between 8 to 25%.

Because of the variation in the method of preparation, the size of liposomes varies from about 0.3 to 10 microns. The size of liposomes influences both their distribution in the body and their deposition. For instance, following injection, large size liposomes can have the tendency to deposit in the lungs whereas smaller particles may concentrate in other body sites, such as the liver. Alterations in the membrane composition, the phospholipid configuration, or in the electrical charge on liposomes can also greatly influence their distribution in the body. Agents such as cholesterol and cetylphosphate have been incorporated into the phospholipid bilayers to alter the liposome's properties, changing not only the diffusion characteristics of the membrane but also the distribution of the liposome within the body following administration.

Several liposome products are under commercial development for inhalation, ocular, dermal and parenteral routes of administration. For example, liposome-based bronchodilators, delivered as nebulized and aerosolized solutions, are being designed to treat bronchospasm. Ocular delivery products containing "bioadhesive" liposomes that adhere to the eye's surface are being developed to provide lubricating eye drops and sustained effects for glaucoma medication. Liposome products for application of therapeutic agents to the skin and scalp to provide extended drug release and perhaps greater percutaneous absorption are being investigated. Liposome-based products are also being developed to target drugs to specific body organs following intravenous administration. The objective is to concentrate the drug's action at the desired body site to maximize therapeutic action and minimize toxicity. Drugs being studied include anticancer agents, antibiotics, and peptide hormones.

Other technologies for rate-controlled targeted delivery include the use of transdermal drug delivery systems, implantable (subcutaneous) drug delivery systems, ocular drug delivery systems, intravenous infusion pumps, and monoclonal antibodies which are utilized as specific carriers for drugs, enzymes, and radiopharmaceuticals in the diagnosis and treatment of disease. These technologies are discussed elsewhere in this text.

Pharmacist Monitoring of Patients Using Controlled-Release Drugs

When a patient is prescribed a controlled-release drug the attainment of the peak and therapeutic concentration of the drug might be somewhat delayed. If an immediate effect is desirable, either an intravenous dose or immediate-release dosage form of the drug would be preferable. Thus, a pharmacist when consulted about a dosing recommendation should keep this in mind as it relates to patient needs.

As mentioned earlier in this chapter variations in the bioavailability from a controlled-release product are possible so the pharmacist must be cognizant of patient complaints of unusual adverse effects or possible ineffectiveness. Therapeutic levels of the certain drugs, e.g., theophylline, must be maintained for the desired therapeutic outcome to occur and once a patient is stabilized on a controlled-release product it should not be substituted. A different product, even with an identical amount of active ingredient, could cause a marked shift in the patient's drug blood/serum level due to different release characteristics of the dosage form. Unless two controlled-release products of the same drug have demonstrated similar bioavailability and therapeutic effect they should not be used interchangeably or substituted for one another.

Packaging and Storing Tablets

Tablets are best stored in tight containers and in places of low humidity protected from extremes in temperature. Products that are especially prone to decomposition by moisture may be copackaged with a desiccant. Drugs that are adversely affected by light are packaged in light-resistant containers. With a few exceptions, solid dosage forms that are properly stored will be stable for several years or more.

In most instances of dispensing, the pharmacist is well advised to use a similar type of container as provided by the manufacturer of the product and the patient advised to maintain the drug in the container dispensed. Proper storage conditions as recommended for the particular drug should be maintained by the pharmacist and patient and expiration dates observed.

The pharmacist should be aware also that the hardness of certain tablets may change upon aging usually resulting in a decrease in the disintegration and dissolution rates of the product.

The increase in tablet hardness can frequently be attributed to the increased adhesion of the binding agent and other formulative components within the tablet. Examples of increased tablet hardening with age have been reported for a number of drugs including aluminum hydroxide, sodium salicylate and phenylbutazone.[26]

Certain tablets containing volatile drugs, as nitroglycerin, may experience the migration of the drug between tablets in the container thereby resulting in a lack of uniformity among the tablets.[27] Further, packing materials, as cotton and rayon, in contact with nitroglycerin tablets may absorb varying amounts of nitroglycerin rendering the tablets sub-potent.[28]

In 1972, the Food and Drug Administration issued a number of regulations covering the packaging, labeling, and dispensing of nitroglycerin products. These regulations include:

1. All nitroglycerin tablets must be packaged in glass containers with tightly-fitting metal screw caps.
2. No more than 100 tablets may be packaged in each container.
3. Nitroglycerin tablets must be dispensed in their original containers and bear the label–"Warning: To prevent loss of potency, keep these tablets in the original container. Close tightly immediately after use."
4. All nitroglyercin tablets should be stored at controlled room temperatures of between 59° and 86°F.

Implementation of these regulations contributed to the maintenance of better content uniformity standards for nitroglycerin tablets than had been previously achieved. However, since nitroglycerin is a volatile liquid at room temperature, some nitroglycerin is lost to the atmosphere when the containers are opened and particularly if they are not tightly closed. In a further effort to reduce the loss of nitroglycerin from tablets and to prevent the migration of the substance from tablet to tablet, pharmaceutical manufacturers of these tablets have recently been developing "stabilized" nitroglycerin tablets. The main method used is to include a small amount of a nonvolatile substance in the formulation which has the effect of reducing the vapor pressure of the nitroglycerin and thus its tendency to escape from the tablet. One such marked product is *Nitrostat* by Parke-Davis which contains polyethylene glycol as the stabilizer.

Other Solid Dosage Forms for Oral Administration

Pills

Pills are small, round, solid dosage forms containing a medicinal agent and intended to be administered orally. Although the manufacture and administration of pills was at one time quite prevalent, today pills have been replaced by compressed tablets and capsules. A procedure for the extemporaneous preparation of pills on a small-scale may be found in the first edition of this text.

Lozenges

Lozenges are disc-shaped, solid dosage forms containing a medicinal agent and generally a flavoring substance and intended to be slowly dissolved in the oral cavity for localized effects. Lozenges are frequently called *troches* and less frequently referred to as *pastilles*. Many of the commercially available lozenges have a hard candy as the base or a base of sugar and an adhesive substance such as mucilage or gum.

Commercially, lozenges may be made by compression, using a tablet machine and large, flat punches. The machine is operated at a high degree of compression to produce lozenges that are harder than ordinary tablets so that they slowly dissolve or disintegrate in the mouth. Medicinal substances that are heat stable may be prepared into a hard, sugar candy lozenge by candy-making machines that process a warm, highly concentrated, flavored syrup as the base and form the lozenges by molding and drying.

Lozenges are gaining renewed acceptance as a means to deliver a multitude of different drugs. As an example, for the treatment of oropharyngeal candidiasis a lozenge dosage form is available with either nystatin or clotrimazole (e.g. Mycelex Troche, Miles) as its active ingredient. The patient allows the lozenge (or troche) to slowly dissolve in the mouth, and the dosage form is much more convenient to the patient when compared to the necessity of swishing an oral suspension in the mouth. Further, these lozenges maintain adequate salivary levels of the antifungal drug for about 3 hours and help to promote effectiveness of therapy. Lozenge dosage forms are also available for self-care drugs, e.g., benzocaine, dextromethorphan, phenylpropanolamine, to treat acute, self-limiting conditions ranging from minor sore throat to cough

and congestion. These forms are particularly advantageous for those persons who find it difficult to swallow solid dosage forms and for young children.

Proper Administration of Peroral Dosage Forms

The dosage forms discussed in this chapter are all to be administered by mouth. The easiest way is to place the dosage form upon the tongue and swallow it with a glassful of water. Most patients will understand this method of administration and do so with water. However, some persons do not realize that these dosage forms should be taken with water and may proceed to merely swallow the tablet or the capsule. This can be dangerous because it is possible for the tablet or capsule to lodge within the esophagus. Several documented cases of esophageal ulceration in young women, for example, have occurred with the ingestion of tetracycline and tetracycline derivatives, particularly when taken just before bedtime. Thus, it is important to counsel the patient to take all oral dosage forms with at least some water. This is particularly so with those dosage forms that contain aspirin, ferrous sulfate, any nonsteroidal antiinflammatory drug (NSAID), potassium chloride and any tetracycline drug, to ensure passage of the medicine into the stomach. It is equally important to also instruct patients to take these medications no later than at least 1 hour before retiring for the evening.

Senior citizens are at an increased risk because the process of swallowing medications like those mentioned takes longer, and if they have esophageal strictures, there is the potential for these to lodge in the esophagus. Further, patients who suffer from gastroesophageal reflux disease must also be cautioned to take medicines with water and at least 1 hour before retiring. Otherwise, there is a possibility that some of the medicine may be refluxed back into the esophagus from the stomach once the patient retires for the evening.

As mentioned earlier in this chapter, certain oral dosage forms have protective coatings, e.g., enteric-coated, or may be formulated to provide delayed or continuous release of the active ingredient. The patient must be advised not to chew or crush these tablets as the amount and the rate of release of the drug may be dramatically altered. The patient should also be forewarned that they may notice remnants of these types of dosage forms in the stool. They should be told not to be concerned as the drug portion of the preparation has already been absorbed.

When a tablet can be crushed or a capsule opened to facilitate oral administration the pharmacist must keep in mind that medicines usually have an unpleasant taste. The bitter taste of the drug could be masked partially by recommending to the patient to mix the drug with applesauce, fruit juice, or carbonated beverages. However, the patient must be advised to consume the entire mixture. Otherwise the patient will not receive the total dose.

For those who experience gagging or choking when taking a solid dosage form, there is an innovative product called the Drink-A-Pill Drinking Glass. This contains a specially-designed shelf on which a tablet or capsule is placed after the glass is filled with water. When the patient drinks the content of the glass, the dosage form flows with the water into the mouth and goes right down without the gag reflex. Alternatively, if the patient simply cannot swallow the solid dosage form, the pharmacist can suggest to the prescribing physician a liquid form of the drug. If such a preparation is not available, it may be possible to extemporaneously compound the drug into a liquid vehicle. Several liquid formulations from solid dosage forms are listed in the *Handbook on Extemporaneous Formulations*. If this is not possible, the pharmacist could recommend the use of an available liquid dosage form of a different chemical compound with similar therapeutic effect.

Solid Dosage Forms for Nonoral Route of Administration

There are a few solid dosage forms which are used by routes of administration other than oral. For instance, dosage forms called *pellets* or *inserts* are implanted under the skin by special injectors or by surgical incision for the purpose of providing for the continuous release of medication. Such implants provide the patient with an economical means of obtaining long-lasting effects and obviate the need for frequent injections or oral dosage administration. Hormonal substances are most frequently administered in this manner. For example, the Norplant® system (Wyeth-Ayerst) of levonorgestrel implants provides up to five years of protection from pregnancy after subcutaneous insertion. The implants are closed capsules made of a di-

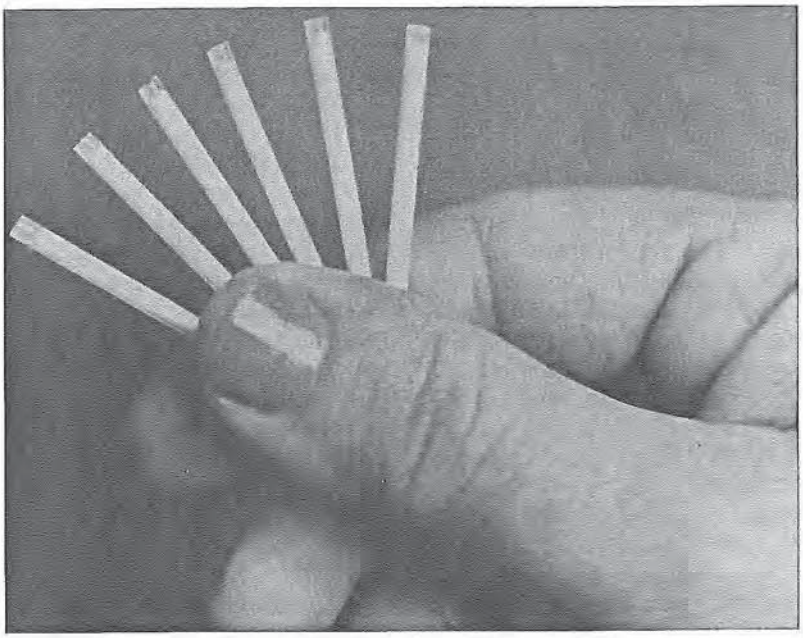

Fig. 5–64. *Norplant® System of levonorgestrel implants for the long-term (up to 5 years) prevention of pregnancy. Six implants are inserted subdermally in the midportion of the inner upper arm about 8 to 10 cm above the elbow crease. The implants are inserted in a fanlike pattern about 15 degrees apart. (Courtesy of Wyeth-Ayerst Laboratories.)*

methylsiloxane/methylvinylsiloxane copolymer containing 36 mg of the synthetic progestin levonorgestrel (Fig. 5–64). Each capsule is 2.4 mm in diameter and 34 mm in length. Six capsules are inserted in a plane beneath the skin of the upper arm by small incision and special injector. Following their term of use, the capsules are removed and may be replaced with fresh capsules.[29]

Other solid dosage forms, *vaginal tablets* or *inserts*, are specially formulated and shaped tablets intended to be placed in the vagina by special applicators, where the medication is released, generally for localized effects. Another example of a solid dosage form intended for use by means other than swallowing is a specially prepared capsule containing a micronized powder [Intal (Fisons)] intended to be released from the capsule and inhaled deep into the lungs through the use of a special inhaler-device (Spinhaler turboinhaler). These dosage forms and drug delivery systems will be discussed in subsequent chapters.

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