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

SIXTH EDITION

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Accurate indications, adverse reactions, and dosage schedules for drugs are provided in this book, but it is possible they may change. The reader is urged to review the package information data of the manufacturers of the medications mentioned.

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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

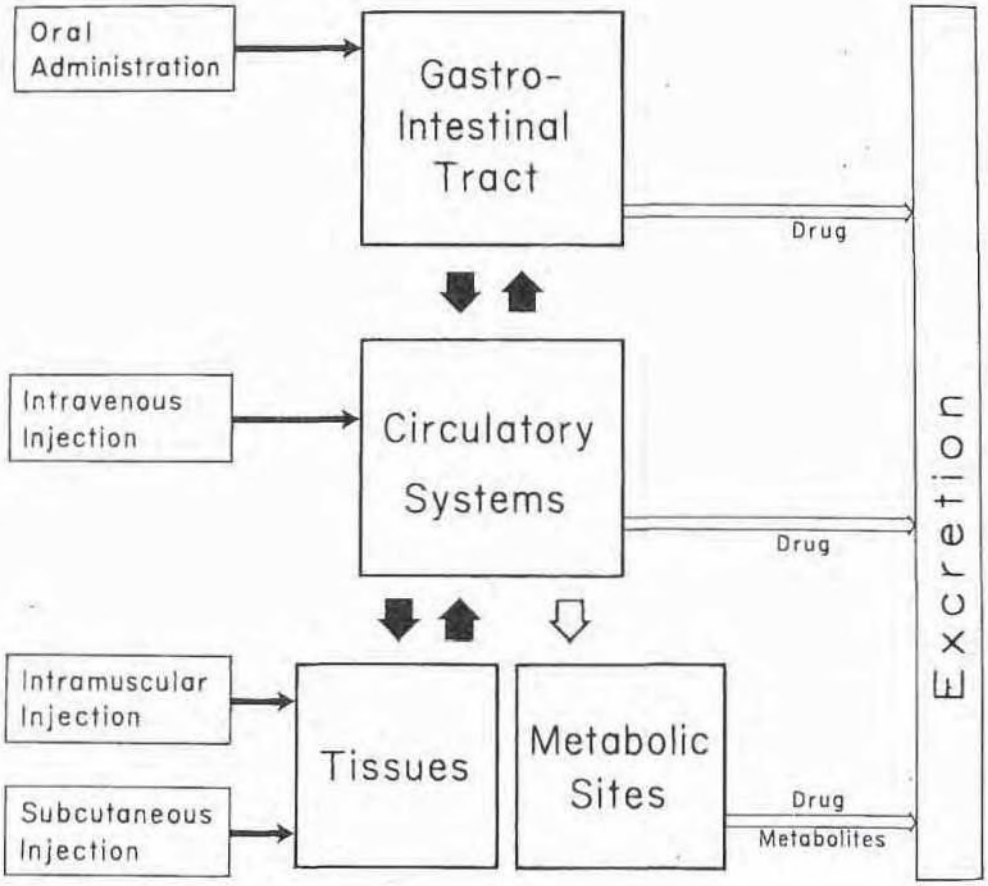

Fig. 3–1. *Schematic representation of events of absorption, metabolism, and excretion of drugs after their administration by various routes.*

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:

Bases:

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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?

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

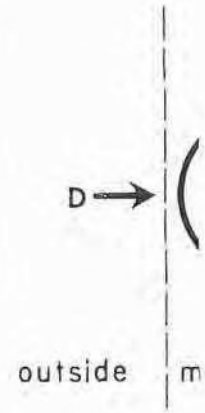

Fig. 3–2. *Active tra*
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(After O'Reilly, W.J.:

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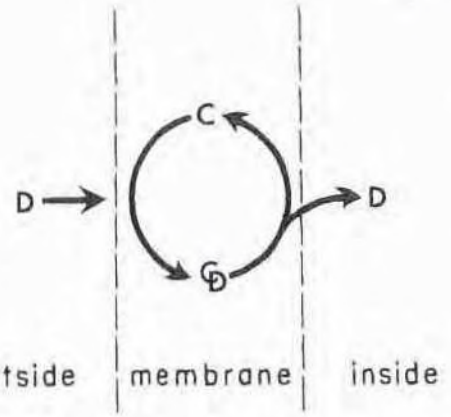

Fig. 3–2. *Active transport mechanism. D represents a drug molecule; C represents the carrier in the membrane. (After O'Reilly, W.J.: Aust. J. Pharm., 47:568, 1966.)*

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

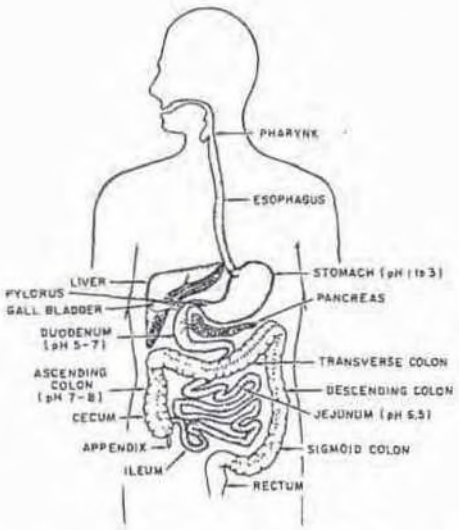

Fig. 3–3. *Anatomical diagram showing the digestive system including the locations involved in drug absorption and their respective pHs.*

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 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

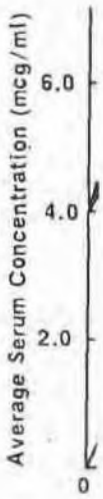

Fig. 3–4. *Serum conc*
the curve. (Courtesy of

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FDA Bioavailabilit Requirements[5]

The FDA requires
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2. *Abbreviated New*
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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

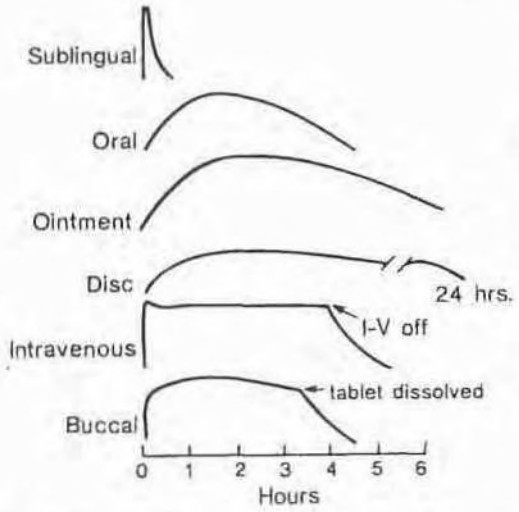

Fig. 3–11. *Blood-level curves of nitroglycerin following administration of dosage forms by various routes. (From Abrams, J.: Nitroglycerin and Long-Acting Nitrates in Clinical Practice.* The American Journal of Medicine, *Proceedings of a Symposium: First North American Conference on Nitroglycerin Therapy,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

[Π] 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-

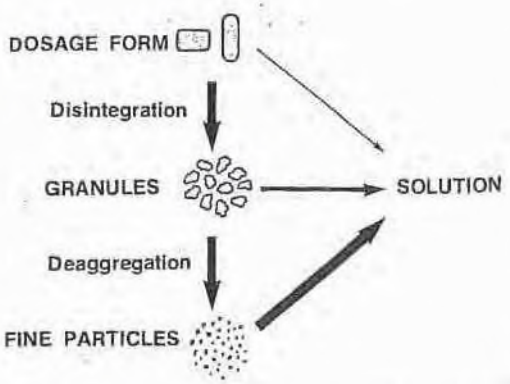

Fig. 3–12. *Schematic drawing showing disintegration of a tablet dosage form and direct availability of the contents in a capsule dosage form for dissolution and drug absorption after oral administration. (From Rowland, M., and Rozer, T.N.:* Clinical Pharmacokinetics. *2nd Ed., Philadelphia, Lea & Febiger,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

the plasma on the other side of the membrane as though its pH were about 5.3.

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.)*

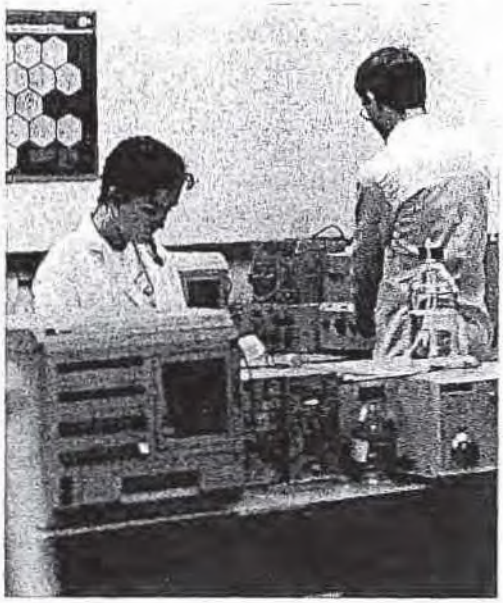

Fig. 3–20. *Assay of biological fluids using Waters HPLC (High Performance Liquid Chromatography) system consisting of (from left to right) Autosampler (Model 712 Wisp), Pump (Model M-45), Shimadzu Fluorescence Detector (Model RF-535). (Courtesy of Elan Corporation, plc.)*

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.

References

1. Cogburn, J.N., Donovan, M.G., and Schasteen: A Model of Human Small Intestinal Absorptive Cells. 1. Transport Barrier. *Pharm. Res.*, *8*:210–216, 1991.

2. Christensen, F.N. et al.: The Use of Gamma Scintigraphy to Follow the Gastrointestinal Transit of Pharmaceutical Formulations. *J. Phar. Pharmacol. 37:* 91–95 (1985).
3. Coupe, A.J., Davis, S.S., and Wilding, I.R.: Variation in Gastrointestinal Transit of Pharmaceutical Dosage Forms in Healthy Subjects. *Pharm. Res. 8:* 360–364 (1991).
4. Poole, J.: *Curr. Therapeut. Res., 10*:292–303, 1968.
5. *Code of Federal Regulations*, Title 21, Part 320—Bioavailability and Bioequivalence Requirements.
6. Chodos, D.J., and DiSanto, A.R.: *Basics of Bioavailability*. The Upjohn Company, Kalamazoo, MI, 1973.
7. *FDA Drug Bulletin, 16*, No. 2, 1986, pp 14–15.
8. Smith, H.J.: Process of Drug Handling by the Body. *Introduction to the Principles of Drug Design*, 2nd ed., Buttersworth & Co., London, 1988.
9. Cooper, J.W.: Monitoring of Drugs and Hepatic Status. *Clinical Consult, 10*, No. 6, 1991.

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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

Fig. 4–1.
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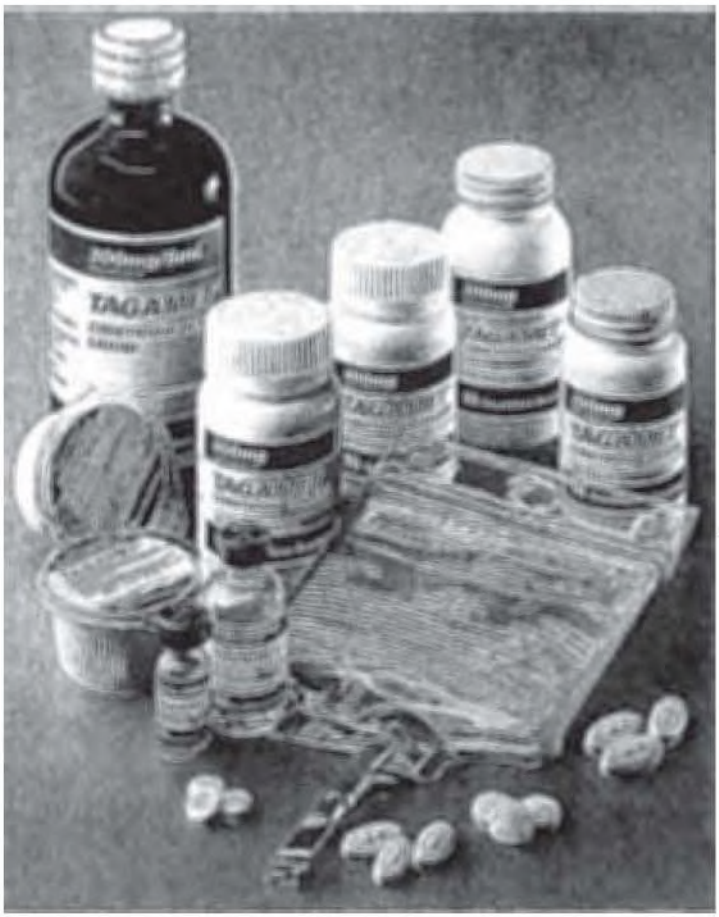

Fig. 4–1. *Examples of varied dosage forms of a drug substance marketed by a pharmaceutical manufacturer to meet the special requirements of the patient. (Courtesy of SmithKline Beecham)*

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-

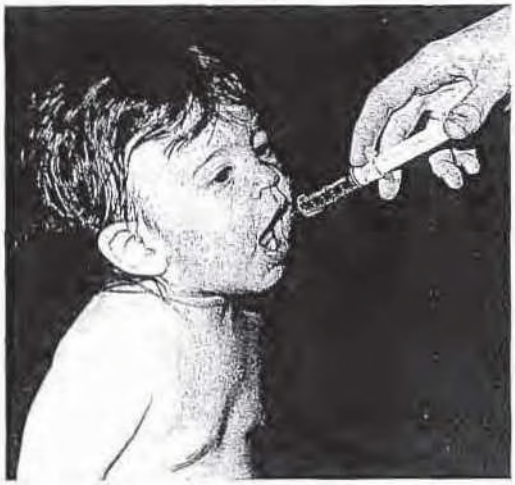

Fig. 4–2. *"Pee Dee Dose" brand of oral liquid dispenser used to administer measured volumes of liquid medication to youngsters. (Courtesy of Baxa Corporation)*

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

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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

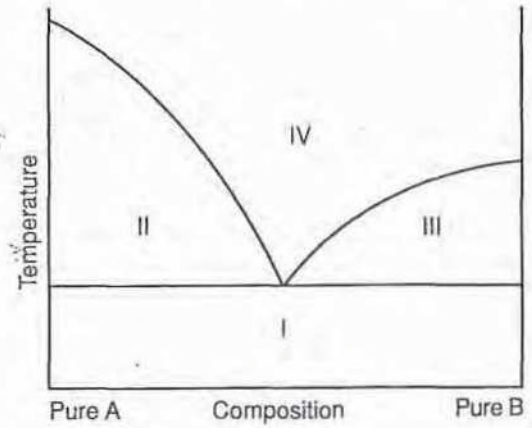
$$L_{4th} = \frac{1}{\left(\frac{0.7 \times 1}{4} + 1\right)^4} = 0.525$$

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.