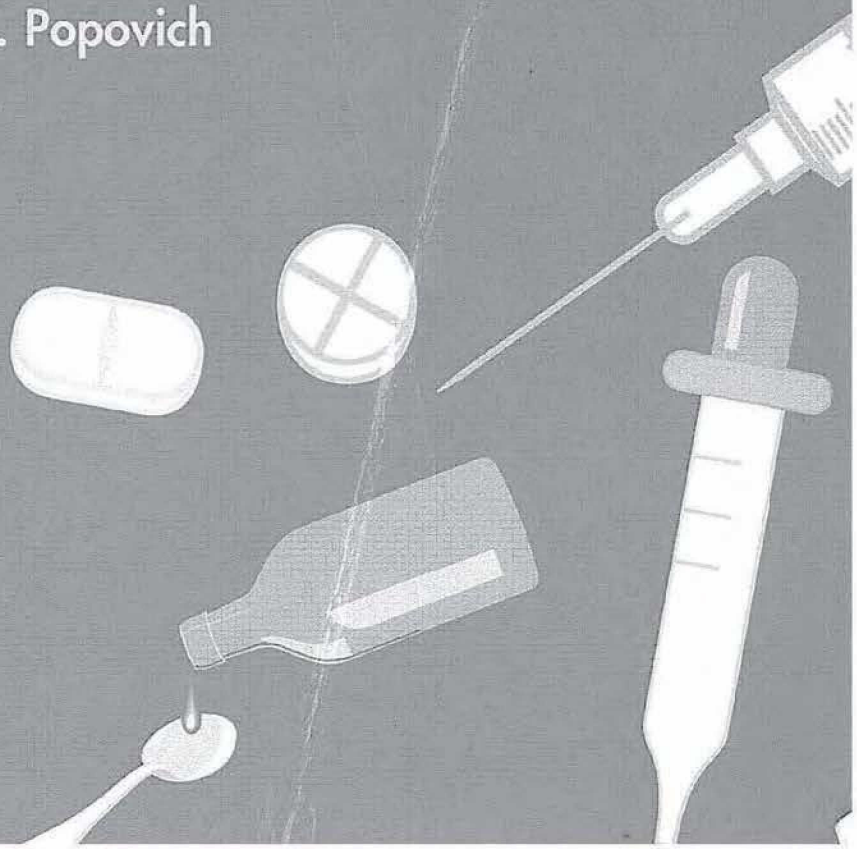
SEVENTH EDITION

PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS

Howard C. Ansel
Loyd V. Allen, Jr.
Nicholas G. Popovich



Editor: Donna Balado
Managing Editor: Jennifer Schmidt
Marketing Manager: Christine Kushner

351 West Camden Street
Baltimore, Maryland 21201–2436 USA

227 East Washington Square
Philadelphia, PA 19106

Printed in the United States of America

Library of Congress Cataloging-in-Publication Data

Ansel, Howard C., 1933–
Pharmaceutical dosage forms and drug delievery systems / Howard C. Ansel, Loyd V. Allen, Jr., Nicholas G. Popovich. — 7th ed.
p. cm.
Includes bibliographical references and index.
ISBN 0–683–30572–7
1. Drugs—Dosage forms. 2. Drug delivery systems. I. Allen, Loyd V. II. Popovich, Nicholas G. III. Title.
[DNLM: 1. Dosage Forms. 2. Drug Delivery Systems. QV 785 A618i 1999]
RS200.A57 1999
615'.1—dc21
DNLM/DLC
for Library of Congress 99–17498
CIP

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DOSAGE FORM DESIGN: BIOPHARMACEUTIC AND PHARMACOKINETIC CONSIDERATIONS

Chapter at a Glance

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 on 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 4.1.

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 por-

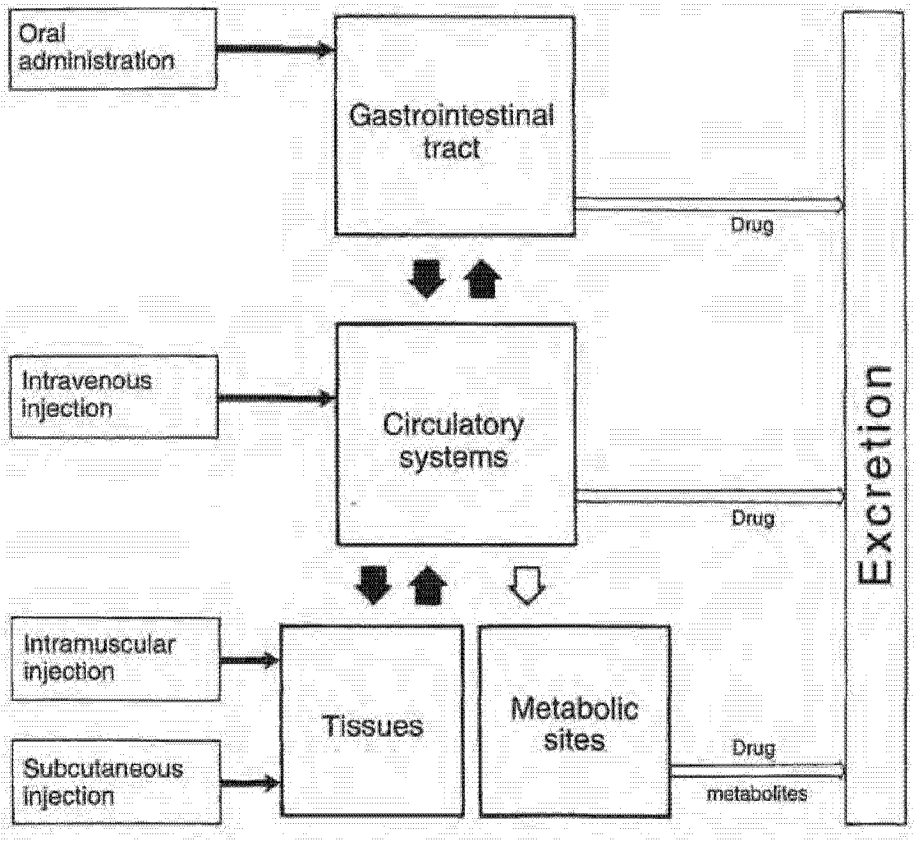


Fig. 4.1 *Schematic representation of events of absorption, metabolism, and excretion of drugs after their administration by various routes.*

tion 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 4.1, 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 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_e) for a drug to describe its rate of elimination from the body. The term *elimination* refers to both metabolism and excretion. For drugs that 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 on 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 concentration 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 4.1 presents the effect of pH on the ionization of weak electrolytes, and Table 4.2 offers some representative pK_a values of common drug substances.

From the equation and from Table 4.1, it may be seen that a drug substance is half ionized at 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. As shown in Table 4.2, 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 because 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 physical pharmacy capsule entitled "pKa/Dissociation Constants" in Chapter 3.

It is often desirable for pharmaceutical scientists to make structural modifications in organic drugs

Table 4.1. The Effect of pH on the Ionization of Weak Electrolytes* pK_a-pH % Unionized

	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	0.990
+3.0	99.9	0.100

*Reprinted with permission from Doluisio JT, Swintosky JV. Am J Pharm 1965;137:149.

Table 4.2. 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
	Sulfandamide	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

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 4.2 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 *active 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.

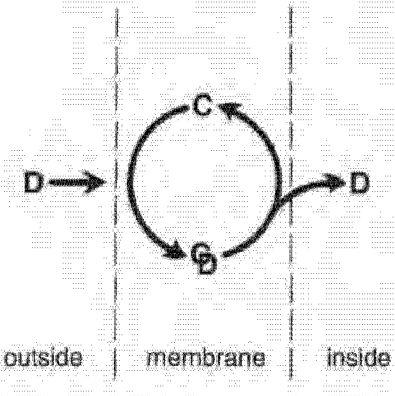


Fig. 4.2 *Active transport mechanism. D represents a drug molecule; C represents the carrier in the membrane. (Modified from O'Reilly W. Aust J Pharm 1966;47:568.)*

Dissolution and Drug Absorption

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. 4.3). 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

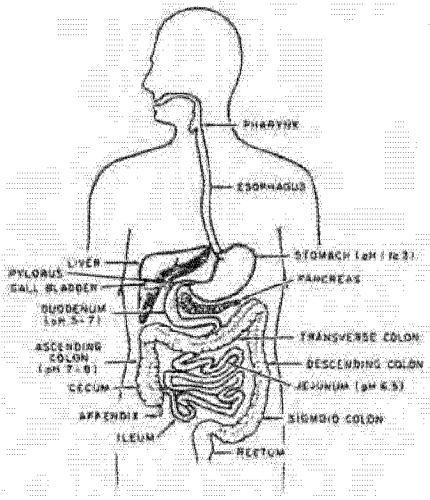


Fig. 4.3 *Anatomical diagram showing the digestive system including the locations involved in drug absorption and their respective pH values.*

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 suface 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 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 affected 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. However, drugs in which absorption depends on passive processes are not affected by these factors as much as those that depend on active transport mechanisms, e.g., calcium, iron, thiamine, and 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 that affect drug dissolution briefly are discussed in the following paragraphs, whereas others will be discussed in succeeding chapters in which they are relevant.

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. This is explained in the Physical Pharmacy Capsule, "Particle Size, Surface Area and Dissolution Rate."

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. A slight variation on this is accomplished by blending and melting the poorly water-soluble powders with a water-soluble polymer, such as polyethylene glycol (PEG). In the molten state and if the drug dissolves in this carrier (PEG), a molecular dispersion of the drug in the carrier results. Upon solidification, a solid-dispersion is formed which can be pulverized and tableted or encapsulated. When this powder is placed in water, the water-soluble carrier rapidly dissolves leaving the poorly soluble drug enveloped in water, thus forming a solution.

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, 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.

Physical Pharmacy Capsule 4.1

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 1/4 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.

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 Physical Pharmacy Capsules in Chapters 3 and 6.

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 chloramphenicol 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 on 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 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." 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 crystal 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 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). 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 on 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. 4.4). 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 with patient response, and 4) the relationship between drug blood levels and clinical efficacy and toxicity.

During the product development stages of a proposed drug product, pharmaceutical manufacturers employ bioavailability studies to compare different formulations of the drug substance to ascertain the one which allows the most desirable absorption pattern. Later, bioavailability studies may be used to compare the availability of the drug substance from different production batches of the product. They may also be used to compare the availability of the drug substance from different dosage forms (as tablets, capsules, elixirs, etc.), or from the same dosage form produced by different (competing) manufacturers.

FDA Bioavailability Submission Requirements

The FDA requires bioavailability data submissions in the following instances (5).

1. *New Drug Applications* (*NDAs*). A section of each NDA is required to describe the human pharmacokinetic data and human bioavailability data, or information supporting a waiver of the bioavailability data requirement (see waiver provisions following).
2. *Abbreviated New Drug Applications* (*ANDAs*). In vivo bioavailability data are required unless information is provided and accepted supporting a waiver of this requirement (see waiver provisions following).

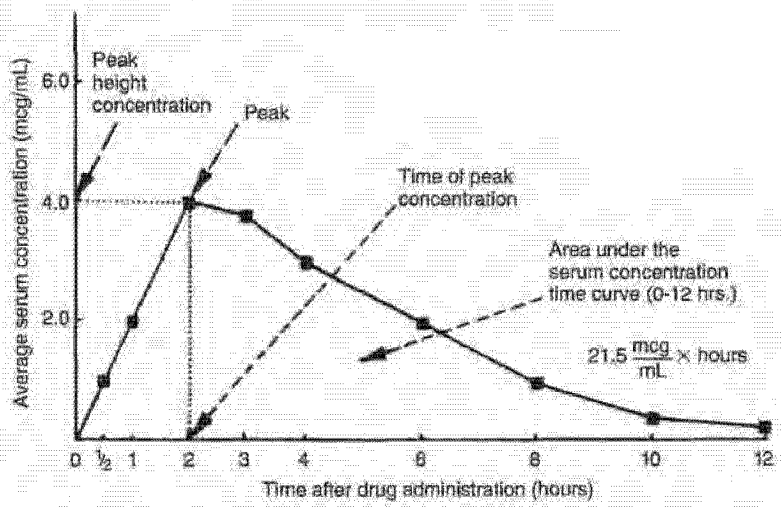


Fig. 4.4 *Serum concentration-time curve showing peak height concentration, time of peak concentration, and area under the curve. (Courtesy of D.J. Chodos and A.R. DiSanto, The Upjohn Company.)*

3. *Supplemental Applications.* In vivo bioavailability data are required if there is a change in the:
   a. Manufacturing process, product formulation or dosage strength, beyond the variations provided for in the approved NDA.
   b. Labeling, to provide for a new indication for use of the drug product and, if clinical studies are required, to support the new indication.
   c. Labeling, to provide for a new or additional dosage regimen for a special patient population (e.g., infants) if clinical studies are required to support the new or additional dosage regimen.

Conditions under which the FDA *may* waive the in-vivo bioavailability requirement include:

1. The product is a solution intended solely for intravenous administration, and contains the same active agent, in the same concentration and solvent, as a product previously approved through a full NDA.
2. The drug product is administered by inhalation as a gas or vapor, and contains the same active agent, in the same dosage form, as a product previously approved through a full NDA.
3. The drug product is an oral solution, elixir, syrup, tincture or similar other solubilized form and contains the same active agent in the same concentration as a previously approved drug product through a full NDA, and contains no inactive ingredient known to significantly affect absorption of the active drug ingredient.
4. The drug product is a topically applied preparation (e.g., ointment) intended for local therapeutic effect.
5. The drug product is an oral dosage form that is not intended to be absorbed (e.g., antacid or radiopaque medium).
6. The drug product is a solid oral dosage form that has been demonstrated to be identical, or sufficiently similar, to a drug product that has met the in-vivo bioavailability requirement.

Most of the bioavailability studies have been applied to drugs contained in solid dosage forms intended to be administered orally for systemic effects. The emphasis in this direction has been primarily due to the proliferation of competing products on the market in recent years, particularly the nonproprietary (generic) capsules and tablets, and the knowledge that certain drug entities when formulated and manufactured differently into solid dosage forms are particularly prone to variations in biologic availability. Thus, the present discussions will be centered around solid dosage forms. However, this is not to imply that systemic drug absorption is not intended from other routes of administration or other dosage forms, or that bioavailability problems may not exist from these products as well. Indeed, drug absorption from other routes is affected by the physicochemical properties of the

drug and the formulative and manufacturing aspects of the dosage form design.

Blood (or Serum or Plasma) Concentration-Time Curve

Following the oral administration of a medication, if blood samples are drawn from the patient at specific time intervals and analyzed for drug content, the resulting data may be plotted on ordinary graph paper to yield the type of drug blood level curve presented in Figure 4.4. The vertical axis of this type of plot characteristically presents the concentration of drug present in the blood (or serum or plasma) and the horizontal axis presents the time the samples were obtained following the administration of the drug. When the drug is first administered (time zero), the blood concentration of the drug should also be zero. As the drug passes into the stomach and/or intestine, it is released from the dosage form, eventually dissolves, and is absorbed. As the sampling and analysis continue, the blood samples reveal increasing concentrations of drug until the maximum (peak) concentration (C_{max}) is reached. Then, the blood level of the drug progressively decreases and, if no additional dose is given, eventually falls to zero. The diminished blood level of drug after the peak height is reached indicates that the rate of drug elimination from the blood stream is greater than the rate of drug absorption into the circulatory system. Drug absorption does not terminate after the peak blood level is reached, but may continue for some time. Similarly the process of drug elimination is a continuous one. It begins as soon as the drug first appears in the blood stream and continues until all of the drug has been eliminated. When the drug leaves the blood it may be found in various body tissues and cells for which it has an affinity until ultimately it is excreted as such or as drug metabolites in the urine or via some other route (Fig. 4.5). A urinalysis for the drug or its metabolites may be used to indicate the extent of drug absorption and/or the rate of drug elimination from the body.

Parameters for Assessment and Comparison of Bioavailability

In discussing the important parameters to be considered in the comparative evaluation of the blood

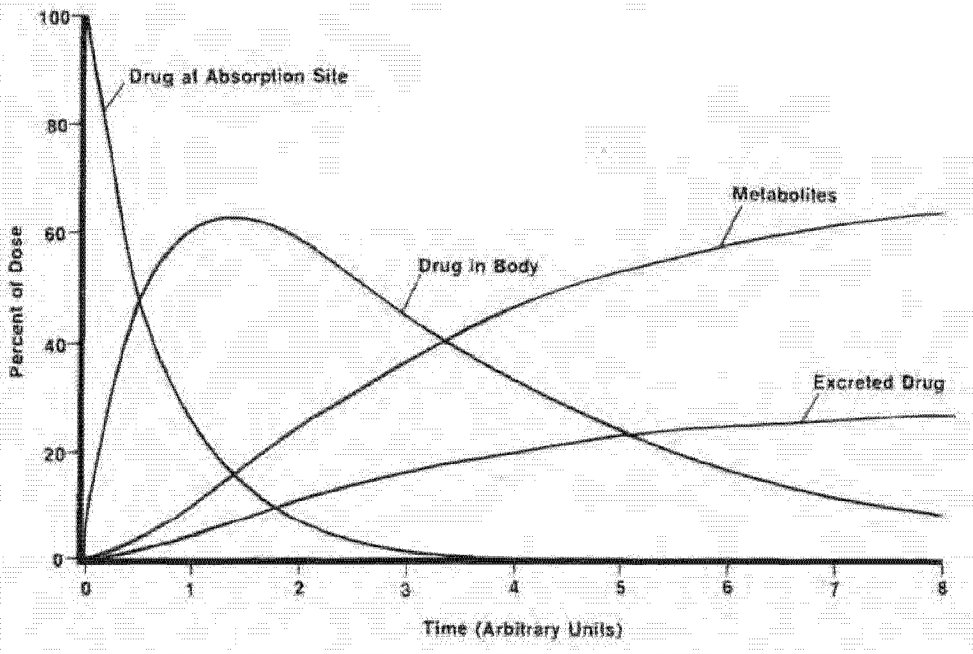


Fig. 4.5 *Time course of drug in the body. (Reprinted with permission from Rowland M, Tozer TN. Clinical Pharmacokinetics 2nd Ed., Philadelphia: Lea & Febiger, 1989.)*

level curves following the oral administration of single doses of two formulations of the same drug entity, Chodos and DiSanto (6) list the following:

1. The Peak Height Concentration (C_{max})
2. The Time of the Peak Concentration (T_{max})
3. The Area Under the Blood (or serum or plasma) Concentration-Time Curve (AUC)

Using Figure 4.4 as an example, the height of the peak concentration is equivalent to 4.0 μg/mL of drug in the serum; the time of the peak concentration is 2 hours after administration; and the area under the curve from 0 to 12 hours is calculated as 21.5 μg/mL × hours. The meaning and use of these parameters are further explained as follows.

Peak Height

Peak height concentration is the maximum drug concentration (C_{max}) observed in the blood plasma or serum following a dose of the drug. For conventional dosage forms, as tablets and capsules, the C_{max} will usually occur at only a single time point, referred to as T_{max}. The amount of drug is usually expressed in terms of its concentration in relation to a specific volume of blood, serum, or plasma. For example, the concentration may be expressed as g/100 mL, μg/mL or mg% (mg/100 mL). Figure 4.6 depicts concentration-time curves showing different peak height concentrations for *equal* amounts of drug from two different formulations following oral administration. The horizontal line drawn across the figure indicates that the minimum effective concentration (MEC) for the drug substance is 4.0 μg/mL. This means that in order for the patient to exhibit an adequate response to the drug, this concentration in the blood must be achieved. Comparing the blood levels of drug achieved after the oral administration of equal doses of formulations "A" and "B" in Figure 4.6, formulation "A" will achieve the required blood levels of drug to produce the desired pharmacologic effect whereas the administration of formulation "B" will not. On the other hand, if the minimum effective concentration for the drug was 2.0 μg/mL and the minimum toxic concentration (MTC) was 4.0 μg/mL as depicted in Figure 4.7, equal doses of the two formulations would result in toxic effects produced by formulation "A" but only desired effects by formulation "B." The objective in the individual dosing of a patient is to achieve the MEC but not the MTC.

The size of the dose administered influences the blood level concentration and C_{max} for that drug substance. Figure 4.8 depicts the influence of dose on the blood level time curve for a hypothetical drug administered by the same route and in the same dosage form. In this example, it is assumed that all doses are completely absorbed and eliminated at the same rates. As the dose increases, the C_{max} is proportionately higher and the area-under the-curve (AUC) proportionately greater. The peak time, T_{max} is the same for each dose.

Time of Peak

The second parameter of importance in assessing the comparative bioavailability of two formulations is the time required to achieve the maximum level of drug in the blood (T_{max}). In Figure 4.6, the

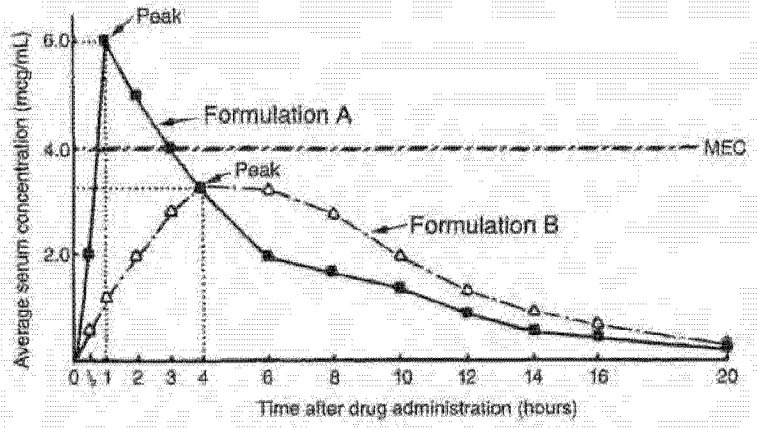


Fig. 4.6 *Serum concentration-time curve showing different peak height concentrations for equal amounts of drug from two different formulations following oral administration. (Courtesy of D.J. Chodos and A.R. DiSanto, The Upjohn Company.)*

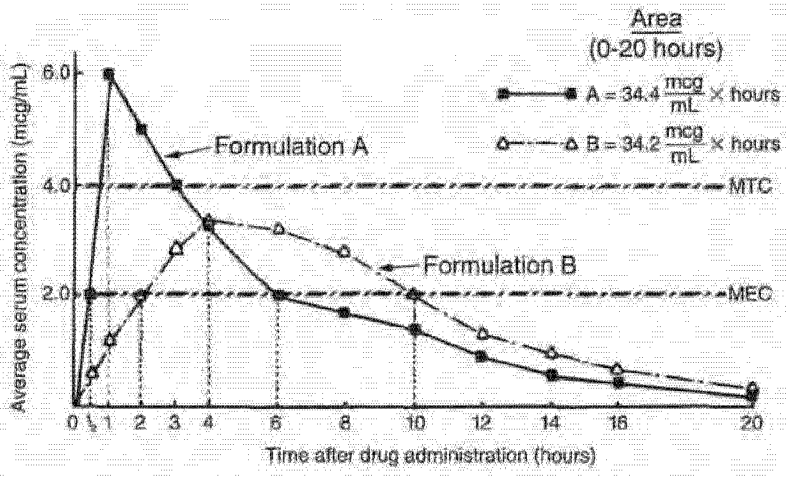


Fig. 4.7 *Serum concentration-time curve showing peak height concentrations, peak height times, times to reach minimum effective concentration (MEC) and areas under the curves for equal amounts of drug from two different formulations following oral administration. (Courtesy of D.I. Chodos and A.R. DiSanto, The Upjohn Company.)*

time required to achieve the peak serum concentration of drug is 1 hour for formulation "A" and 4 hours for formulation "B." This parameter reflects the *rate* of drug absorption from a formulation. It is the rate of drug absorption that determines the time needed for the minimum effective concentration to be reached and thus for the initiation of the desired pharmacologic effect. The rate of drug absorption also influences the period over which the drug enters the blood stream and therefore affects the duration of time that the drug is maintained in the blood. Looking at Figure 4.7, formulation "A" allows the drug to reach the MEC within 30 minutes following administration and a peak concentration in 1 hour. Formulation "B" has a slower rate of drug release. Drug from this formulation reached the MEC 2 hours after administration and its peak concentration 4 hours after administration. Thus formulation "A" permits the greater rate of drug absorption; it allows drug to reach both the MEC and its peak height sooner than drug formulation "B." On the other hand, formulation "B" provides the greater duration of time for drug concentrations maintained above the MEC, 8 hours (from 2 to 10 hours following administration) to 5 1/2 hours (from 30 minutes to 6 hours following administration) for formulation "A." Thus, if a rapid onset of action is desired, a formulation similar to "A" would be preferred, but, if a longer duration of action is desired rather than a rapid onset of action, a formulation similar to "B" would be preferred.

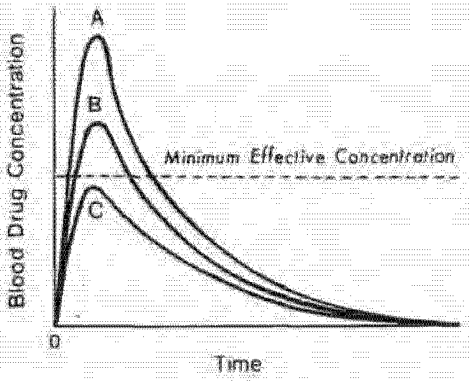


Fig. 4.8 *The influence of dose size on the resultant blood drug concentration-time curves when three different doses of the same drug are administered and the rates of drug absorption and elimination are equal after the three doses. A = 100 mg, B = 80 mg, C = 50 mg. (Reprinted with permission from Ueda CT. Concepts in Clinical Pharmacology. Essentials of Bioavailability and Bioequivalence. The Upjohn Company, 1979).*

In sum, changes in the *rate* of drug absorption will result in changes in the values of both C_{max} and T_{max}. Each product has its own characteristic rate of absorption. When the *rate* of absorption is decreased, the C_{max} is lowered and T_{max} occurs at a later time. If the doses of the drugs are the same and presumed completely absorbed, as in Figure 4.7, the AUC for each is essentially the same.

Area Under the Serum Concentration Time Curve

The area under the curve (AUC) of a concentration-time plot (see Fig. 4.4) is considered representative of the total amount of drug absorbed into the circulation following the administration of a single dose of that drug. Equivalent doses of a drug, when fully absorbed, would produce the same AUC. Thus, two curves dissimilar in terms of peak height and time of peak, as those in Figure 4.7, may be similar in terms of area under the curve, and thus in the amount of drug absorbed. As indicated in Figure 4.7, the area under the curve for formulation "A" is 34.4 μg/mL × hours and for formulation "B" is 34.2 μg/mL × hours, essentially the same. If equivalent doses of drug in different formulation produce *different* AUC values, differences exist in the *extent* of absorption between the formulations. Figure 4.9 depicts concentration-time curves for three different formulations of equal amounts of drug with greatly different areas under the curve. In this example, formulation "A" delivers a much greater amount of drug to the circulatory system than do the other two formulations. In general, the smaller the AUC, the less drug absorbed.

The area under the curve may be measured mathematically, using a technique known as the trapezoidal rule, and is reported in amount of drug/volume of fluid × time (e.g., μg/mL × hours; g/100 × hours; etc.).

According to the trapezoidal rule, the area beneath a drug concentration-time curve can be estimated through the assumption that the AUC can be represented by a series of trapezoids (quadrilateral planes having two parallel and two nonparallel sides). The total AUC would be the sum of the areas of the individual trapezoids. The area of each trapezoid is calculated taking $1/2(C_{n+1} + C_n)(t_n - t_{n-1})$, where C_n and t_n are drug concentrations in the blood plasma, or serum, and time, respectively. The use of the trapezoid is demonstrated by the data reproduced in Table 4.3 and plotted into a plasma drug concentration-time curve as shown in Figure 4.10.

The fraction (F) (or bioavailability) of an orally administered drug may be calculated by comparison of the AUC after oral administration with that obtained after intravenous administration:

$$F = (AUC)_{oral}/(AUC)_{intravenous}$$

In practice, it would be rare for a drug to be completely absorbed into the circulation following oral administration. As noted earlier, many drugs undergo the first-pass effect resulting in some degree of metabolic degradation before entering the general circulation. In addition, factors of drug product formulation, drug dissolution, chemical and physical interactions with the gastrointestinal contents, gastric emptying time, intestinal motility, and others contribute to the incomplete absorption of an administered dose of a drug. The oral dosage strengths of many commerical products are based on considerations of the proportion of the dose administered that is expected to be absorbed and available to its site of action in order to produce the

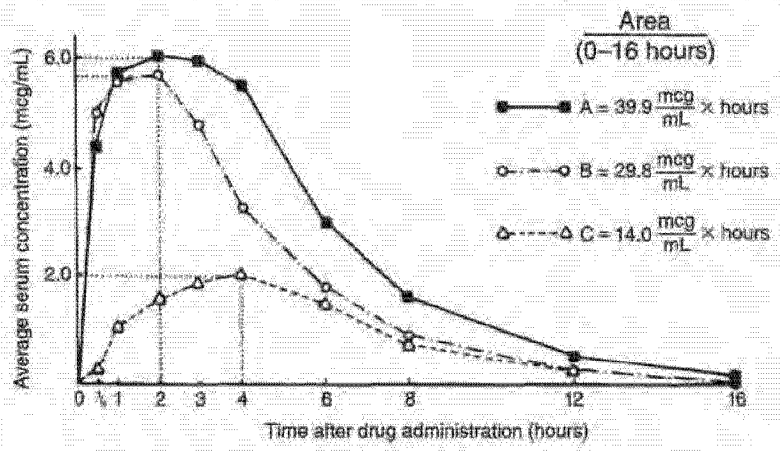


Fig. 4.9 *Serum concentration-time curve showing peak height concentrations, peak height times, and areas under the curves for equal amounts of drugs from three different formulations following oral administration. (Courtesy of Chodos DJ, DiSanto AR, The Upjohn Company.)*

Table 4.3. Determination of AUC Using the Trapezoidal Rule for the Following Plasma Drug Concentration-Time Data*

Sample (n)	*Time (hr)*	*Plasma Concentration (μg/mL)*	*AUC/$t_n t_{n-1}$ (μg/mL × hr)*
1	0	0	½ (0 + 1)(0.5 − 0) = 0.25
2	0.5	1	½ (1 + 11)(1 − 0.5) = 3.00
3	1.0	11	½ (11 + 28)(1.5 − 1) = 9.75
4	1.5	28	½ (28 + 30)(2 − 1.5) = 14.50
5	2	30	½ (30 + 21)(3 − 2) = 25.50
6	3	21	½ (21 + 17)(4 − 3) = 19.00
7	4	17	½ (17 + 9)(6 − 4) = 26.00
8	6	9	½ (9 + 4)(8 − 6) = 13.00
9	8	4	½ (4 + 2)(10 − 8) = 6.00
10	10	2	½ (2 + 1)(12 − 10) = 3.00
11	12	1	½ (1 + 0)(18 − 12) = 3.00
12	18	0	AUC = 123.00

*Reprinted with permission from Ueda CT. Concepts in Clinical Pharmacology. Essentials of Bioavailability and Bioequivalence. The Upjohn Company, 1979.

desired drug blood level and/or therapeutic response. The absolute bioavailability following oral dosing is generally compared to intravenous dosing. As examples, the mean oral absorption of a dose of verapamil (Calan) is reported to be 90%; enalapril (Vasotec) 60%; diltiazem (Cardizem) about 40%, and lisinopril (Zestril) about 25%. However, there is large intersubject variability, and the absorbed doses may vary patient-to-patient.

Bioequivalence of Drug Products

A great deal of discussion and scientific investigation has been devoted recently to the problem of determining the equivalence between drug products of competing manufacturers.

The rate and extent to which a drug in a dosage form becomes available for biologic absorption or utilization depends in great measure upon the materials utilized in the formulation and also on the method of manufacture. Thus, the same drug when formulated in *different* dosage forms may be found to possess different bioavailability characteristics and hence exhibit different clinical effectiveness. Further, two seemingly "identical" or "equivalent" products, of the same drug, in the same dosage strength and in the *same* dosage form type, but differing in formulative materials or method of manufacture, may vary widely in bioavailability and thus in clinical effectiveness.

Dissolution requirements for capsules and tablets are included in the USP and are integral to bioavailability. Experience has shown that where bioinequivalence has been found between two supposedly equivalent products, dissolution testing can help to define the product differences. According to the USP, significant bioavailability and bioinequivalence problems may be revealed through dissolution testing and are generally the result of one or more of the following causal factors: the drug's particle size; excessive amounts of the lubricant magnesium stearate in the formulation; coating materials, especially shellac; and inadequate amounts of tablet or capsule disintegrants.

The following terms are used by the Food and Drug Administration to define the type or level of "equivalency" between drug products (5).

Pharmaceutical equivalents are drug products that contain identical amounts of the identical active

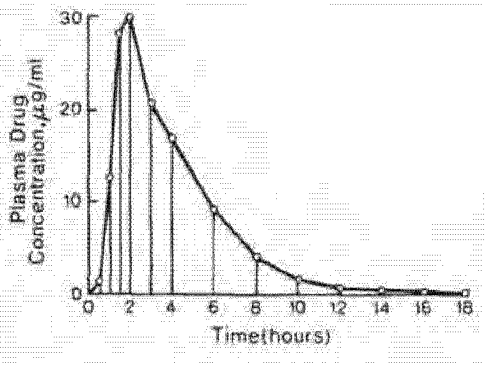


Fig. 4.10 *Estimation of area under the drug concentration-time curve using the trapezoidal rule (see Table 4.3 for raw data). (Reprinted with permission from Ueda CT. Concepts in Clinical Pharmacology. Essentials of Bioavailability and Bioequivalence. The Upjohn Company, 1979).*

drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, in identical dosage forms, but not necessarily containing the same inactive ingredients, and that meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

Bioequivalent drug products are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions, either single dose or multiple dose. Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption, and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, or are considered medically insignificant for the particular drug product studied.

In addition, the term *therapeutic equivalents* has been used to indicate pharmaceutical equivalents which, when administered to the same individuals in the same dosage regimens, will provide essentially the same therapeutic effect.

Differences in bioavailability have been demonstrated for a number of products involving the following and other drugs: tetracycline, chloramphenicol, digoxin, phenylbutazone, warfarin, diazepam, levodopa, and oxytetracycline. Not only has bio*in*equivalence been shown to exist in products of different manufacturers but there have also been variations in the bioavailability of different batches of drug products from the same manufacturer. Variations in the bioavailability of certain drug products have resulted in some therapeutic failures in patients who have taken two inequivalent drug products in the course of their therapy.

The most common experimental plan to compare the bioavailability of two drug products is the simple *crossover design study*. In this method, each of the 12 to 24 individuals in the group of carefully matched subjects (usually healthy adult males between 18 and 40 years of age of similar height and weight) is administered both products under fasting conditions and essentially serves as his own control. To avoid bias of the test results, each test subject is randomly assigned one of the two products for the first phase of the study. Once the first assigned product is administered, samples of blood or plasma are drawn from the subjects at predetermined times and analyzed for the active drug moiety and its metabolites as a function of time. The same procedure is then repeated (*crossover*) with the second product after an appropriate interval of time, i.e., a washout period to ensure that there is no residual amount of drug from the first administered product that would artificially inflate the test results of the second administered product. Afterward, the patient population data are tabulated and the parameters used to assess and compare bioavailability, i.e., C_{max}, T_{max}, AUC, are then analyzed with statistical procedures. Statistical differences in bioavailability parameters may not always be clinically significant in therapeutic outcome.

Inherent differences in individuals result in different patterns of drug absorption, metabolism and excretion. These differences must be statistically analyzed to separate them from the factors of bioavailability related to the products themselves. The value in the crossover-designed experiment is that each individual serves as his own control by taking each of the products. Thus, inherent differences as mentioned between individuals is minimized.

Absolute bioequivalency between drug products rarely, if ever, occurs. Such absolute equivalency would yield serum concentration-time curves for the products involved that would be exactly superimposable. This simply is not expected of products which are made at different times, in different batches, or indeed by different manufacturers. However, some expectations of bioequivalency are expected of products which are considered to be of equivalent merit for therapy.

In most studies of bioavailability, the originally marketed product (frequently referred to as the "prototype," "pioneer," or "innovator" drug product) is recognized as the established product of the drug and is utilized as the standard for the bioavailability comparative studies.

As a result of the implementation of the Drug Price Competition and Patent Term Restoration Act of 1984, many additional drugs became available in generic form. Prior to the 1984 act, only those drugs

marketed before 1962 could be processed by an Abbreviated New Drug Application (ANDA). The ANDA process does not require the sponsor to repeat costly clinical research on active ingredients already found to be safe and effective. The 1984 Act extended the eligibility for ANDA processing to drugs first marketed after 1962, making generic versions immediately possible for many additional off-patent drugs previously available only as brand name (pioneer) products.

According to the FDA, a generic drug is considered bioequivalent if the rate and extent of absorption do not show a significant difference from that of the pioneer drug when administered at the same molar dose of the therapeutic ingredient under the same experimental conditions (7). Because, in the case of a systemically absorbed drug, blood levels even if from an identical product may vary in different subjects, in bioequivalence studies each subject receives both the pioneer and the test drug and thus serves as his own control.

Under the 1984 act, to gain FDA approval a generic drug product must:

- Contain the same active ingredients as the pioneer drug (inert ingredients may vary)
- Be identical in strength, dosage form, and route of administration
- Have the same indications and precautions for use and other labeling instructions
- Be bioequivalent
- Meet the same batch-to-batch requirements for identity, strength, purity, and quality
- Be manufactured under the same strict standards of FDA's Current Good Manufacturing Practice regulations as required for pioneer products

In the design and evaluation of bioequivalence, the FDA employs the "80/20 rule." This rule requires that a study be large enough to provide an 80% probability to detect a 20% difference in average bioavailability. The allowance of a statistical variability of ±20% in bioequivalence applies to both reformulated pioneer drugs and generics. If a pioneer manufacturer reformulates an FDA-approved product, the subsequent formulation must meet the same bioequivalency standards that are required of generic manufacturers of that product (i.e., the approved bioavailability standard for that product).

The FDA recommends generic substitution only among products that it has evaluated to be therapeutically equivalent. Since 1980, the Agency has prepared an annual *Approved Drug Products with Therapeutic Equivalence Evaluations* (known as the "Orange Book") which is published in the USP-DI, Volume III "Approved Drug Products and Legal Requirements." This publication is regularly updated and contains information on about 10,000 approved prescription drug products. About 7,500 of these are available from more than a single manufacturer, with only about 10% considered therapeutically *in*equivalent to the pioneer products. For example, the FDA rates all conjugated estrogens and esterified estrogen products as "not therapeutically equivalent," because no manufacturer to date has submitted an acceptable in vivo bioequivalence study. Therefore, the FDA does not recommend that these products be substituted for each other.

The variables that can contribute to the differences between products are many (Table 4.4). For instance in the manufacture of a tablet, different

Table 4.4. Some Factors Which Can Influence the Bioavailability of Orally Administered Drugs

Drug Substance Physiochemical Properties
Particle Size
Crystalline or Amorphous Form
Salt Form
Hydration
Lipid/Water Solubility
pH and pK_a
Pharmaceutic Ingredients and Dosage Form Characteristics
Pharmaceutic Ingredients
Fillers
Binders
Coatings
Disintegrating Agents
Lubricants
Suspending Agents
Surface Active Agents
Flavoring Agents
Coloring Agents
Preservative Agents
Stabilizing Agents
Disintegration Rate (Tablets)
Dissolution Time of Drug in Dosage Form
Product Age and Storage Conditions
Physiologic Factors and Patient Characteristics
Gastric Emptying Time
Intestinal Transit Time
Gastrointestinal Abnormality or Pathologic Condition
Gastric Contents
Other drugs
Food
Fluids
Gastrointestinal pH
Drug Metabolism (Gut and during first passage through liver).

materials or amounts of such formulative components as fillers, disintegrating agents, binders, lubricants, colorants, flavorants and coatings may be used. The particle size or crystalline form of a therapeutic or pharmaceutic component may vary between formulations. The tablet may vary in shape, size, and hardness depending upon the punches and dies selected for use by the manufacturer and the compression forces utilized in the process. During packaging, shipping and storage the integrity of the tablets may be altered by physical impact, or changes in conditions of humidity, temperature, or through interactions with the components of the container. Each of the factors noted may have an effect on the rates of tablet disintegration, drug dissolution, and consequently on the rate and extent of drug absorption. Although the bioequivalency problems are perhaps greater among tablets than for other dosage forms because of the multiplicity of variables, the same types of problems exist for the other dosage forms and must be considered in bioequivalency evaluations.

There are situations in which even therapeutically equivalent drugs may not be equally suitable for a particular patient. For example, a patient may be hypersensitive to an inert ingredient in one product (brand name or generic) that another product does not contain. Or a patient may 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 4.5 and 4.6. 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.

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 4.11 and Table 4.7, 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.

Table 4.5. Routes of Drug Administration

Term	*Site*
Oral	Mouth
Peroral (per os*)	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

*The abbreviation "po" is commonly used on prescriptions to indicate to be swallowed.

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

Table 4.6. 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
	Gels
	Tablets
	Inserts, suppositories, sponge
Urethral	Solutions
	Suppositories

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 4.8 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 with oral administration.

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 non-first-pass effect route.

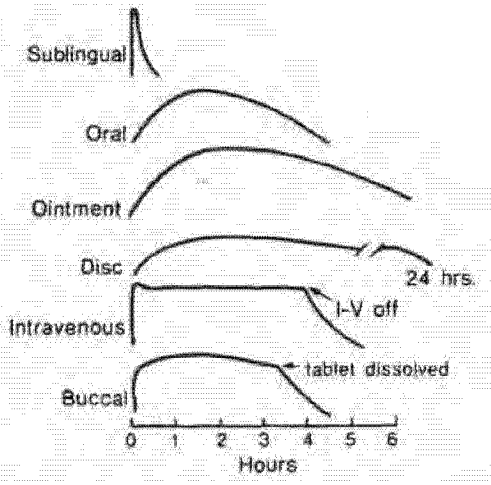


Fig. 4.11 *Blood-level curves of nitroglycerin following administration of dosage forms by various routes. (Reprinted with permission from Abrams J. Nitroglycerin and Long-Acting Nitrates in Clinical Practice. The American Journal of Medicine, Proceedings of a Symposium: First North American Conference on Nitroglycerin Therapy, June 27, 1983).*

Table 4.7. Dosage and Kinetics of Nitroglycerin in Various Dosage Forms

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

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

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

Reprinted with permission from Abrams J. Nitroglycerin and Long-Acting Nitrates in Clinical Practice. Am J Med. Proceedings of a Symposium: First North American Conference of Nitroglycerin Therapy, June 27, 1983, p. 88.

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 4.12. Tablet coatings are of several types and for several different purposes. Some called *enteric coatings* are employed to permit safe passage 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 protect the drug substance from the destructive influences of mois-

Table 4.8. 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

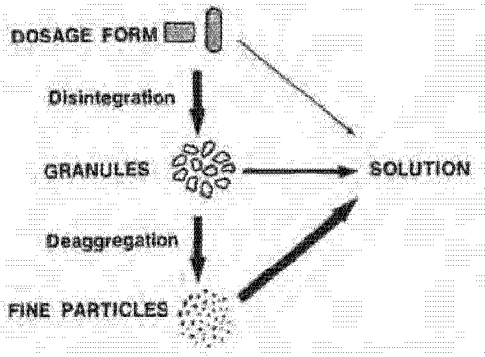


Fig. 4.12 *Schematic drawing showing disintegration of a tablet dosage form and direct availability of the contents in a capsule dosage form for dissolution and drug absorption after oral administration. (Reprinted with permission from Rowland M, Rozer TN. Clinical Pharmacokinetics. 2nd Ed. Philadelphia: Lea & Febiger, 1989).*

ture, 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 on the amount of drug to be administered, and are of distinctive shapes and colors when produced commercially. 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 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 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 cav-

ity 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 used 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 μg) 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 through 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. 4.3) 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 can absorb 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. Approximately 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 (IM), and intravenous (IV) 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 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. 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 oil likely would be much more slowly absorbed than an aqueous solution of the same drug. Slow absorption means prolonged drug action, and when this is achieved through pharmaceutical means, the resulting preparation is referred to as a *depot* or *repository* injection, because it represents a storage reservoir of the drug substance within the body from which it is slowly removed into the systemic circulation. In this regard, even more sustained drug action may be achieved through the use of subcutaneous implantation of compressed tablets, termed pellets that are only slowly dissolved from their site of implantation, releasing their medication at a rather constant rate over a period of several weeks to many months. The repository type of injection is mainly limited to the subcutaneous or intramscular route. It is obvious that drugs injected intraveously do not encounter absorption barriers and thus produce only rapid drug effects. Preparations for intravenous injection must not interfere with the blood components or with circulation and therefore, with few exceptions, are aqueous solutions.

Subcutaneous Injections

The subcutaneous (hypodermic) administration of drugs involves their injection through the layers of skin into the loose subcutaneous tissue. Subcutaneous injections are prepared as aqueous solutions or as suspensions and are administered in relatively small volumes of 2 mL or less. Insulin is an example of a drug administered by the subcutaneous route. Subcutaneous injections are generally given in the forearm, upper arm, thigh, or buttocks. If the patient is to receive frequent injections, it is best to alterate injection sites to reduce tissue irritation. After injection, the drug comes into the immediate vicinity of blood capillaries and permeates them by diffusion or filtration. The capillary wall is an example of a membrane that behaves as a lipid pore barrier, with lipid-soluble substances penetrating the membrane at rates varying with their oil/water partition coefficients. Lipid-insoluble (generally more water-soluble) drugs penetrate the capillary membrane at rates which appear to be inversely related to their molecular size, with smaller molecules penetrating much more rapidly than larger ones. All substances, whether lipid-soluble or not, cross the capillary membrane at rates that are much more rapid than the rates of their transfer across other body membranes. The blood supply to the site of injection is an important factor in considering the rate of drug absorption, consequently the more proximal capillaries are to the site of injection, the more prompt will be the drug's entrance into the circulation. Also, the more capillaries, the more surface area for absorption, and the faster the rate of absorption. Some substances have the capability of modifying the rate of drug absorption from a subcutaneous site of injection. The addition of a vasconstrictor to the injection formulation (or its prior injection) will generally diminish the rate of drug absorption by causing constriction of the blood vessels in the area of injection and thereby reducing blood flow and the capacity for absorption. This principle is used in the administration of local anesthetics by employing the vasoconstrictor epinephrine. Conversely, vasodilators may be used to enhance subcutaneous absorption by increasing blood flow to the area. Physical exercise can also influence the absorption of drug from an injection site. Diabetic patients who rotate subcutaneous injection sites and then do physical exercise, e.g., jogging, must realize the onset of insulin activity might be influenced by the selected site of administration. Because of the movement of the leg and blood circulation to it during running, the absorption of insulin from a thigh injection site would be expected to be faster than that from an abdominal injection site.

Intramuscular Injections

Intramuscular injections are performed deep into the skeletal muscles, generally the gluteal or lumbar muscles. The site is selected where the danger of hitting a nerve or blood vessel is minimal. Aqueous or oleaginous solutions or suspensions may be used intramuscularly. Certain drugs, because of their inherent low solubilities, provide sustained drug action after an intramuscular injection. For instance, one deep intramuscular injection of a suspension of penicillin G benzathine results in effective blood levels of the drug for seven to ten days.

Drugs that are irritating to subcutaneous tissue are often administered intramuscularly. Also, greater volumes (2 to 5 mL) may be administered intramuscularly than subcutaneously. When a volume greater than 5 mL is to be injected, it is frequently administered in divided doses using two injection sites. Injection sites are best rotated when a patient is receiving repeated injections over a period of time.

Intravenous Injections

In the intravenous administration of drugs, an aqueous solution is injected directly into the vein at a rate commensurate with efficiency, safety, comfort to the patient, and the desired duration of drug

response. Drugs may be administered intravenously as a single, small-volume injection or as a large volume, slow intravenous drip infusion (as is common following surgery). Intravenous injection allows the desired blood level of drug to be achieved in an optimal and quantitative manner. Intravenous injections are usually made into the veins of the forearm and are especially useful in emergency situations where immediate drug response is desired. It is essential that the drug be maintained in solution after injection and not be precipitated within the circulatory system, an event that might produce emboli. Because of a fear of the development of pulmonary embolism, oleaginous bases are not usually intravenously administered. However, an intravenous fat emulsion is used therapeutically as a caloric source for patients receiving parenteral nutrition whose caloric requirements cannot be met by glucose. It may be administered either through a peripheral vein or a central venous catheter at a distinct rate to help prevent the occurrence of untoward reactions.

Intradermal Injections

These injections are administered into the corium of the skin, usually in volumes of about a tenth of a milliliter. Common sites for the injection are the arm and the back. The injections are frequently performed as diagnostic measures, as in tuberculin and allergy testing.

Epicutaneous Route

Drugs are administered topically, or applied to the skin, for their action at the site of application or for systemic drug effects.

Drug absorption via the skin is enhanced if the drug substance is in solution, if it has a favorable lipid/water partition coefficient, and if it is a nonelectrolyte. Drugs that are absorbed enter the skin by way of the pores, sweat glands, hair follicles, sebaceous glands, and other anatomic structures of the skin's surface. Because blood capillaries are present just below the epidermal cells, a drug that penetrates the skin and is able to traverse the capillary wall finds ready access to the general circulation.

Among the few drugs currently employed topically to the skin surface for percutaneous absorption and systemic action are nitroglycerin (antianginal), nicotine (smoking cessation), estradiol (estrogenic hormone), clonidine (antihypertensive), and scopolamine (antinausea/antimotion sickness). Each of these drugs is available for use in the form of transdermal delivery systems fabricated as an adhesive disc or patch which slowly releases the medication for percutaneous absorption. Additionally, nitroglycerin is available in an ointment form for application to the skin's surface for systemic absorption. Nitroglycerin is used therapeutically for ischemic heart diease, with the transermal dosage forms becoming increasingly popular because of the benefit in patient compliance through their long-acting (24 hours) characteristics. The nitroglycerin patch is generally applied to the arm or chest, preferably in a hair-free or shaven area. The transdermal scopolamine sytem is also in the form of a patch to be applied to the skin; in this case, behind the ear. The drug system is indicated for the prevention of nausea and vomiting associated with motion sickness. The commercially available product is applied to the postauricular area several hours before need (as prior to an air or sea trip) where it releases its medication over a period of 3 days. The concepts of transdermal therapeutic systems are discussed further in Chapter 10.

For the most part, pharmaceutical preparations applied to the skin are intended to serve some local action and as such are formulated to provide prolonged local contact with minimal absorption. Drugs applied to the skin for their local action include antiseptics, antifungal agents, anti-inflammatory agents, local anesthetic agents, skin emollients, and protectants, against environmental conditions, as the effects of the sun, wind, pests, and chemical irritants. For these purposes, drugs are most commonly administered in the form of ointments and related semisolid preparations such as creams and pastes, as solid dry powders, aerosol sprays or as liquid preparations such as solutions and lotions.

Pharmaceutically, ointments, creams, and pastes are semisolid preparations in which the drug is contained in a suitable base (ointment base), which is itself semisolid and either hydrophilic or hydrophobic in character. These bases play an important role in the proper formulation of semisolid preparations, and there is no single base universally suitable as a carrier of all drug substances or for all therapeutic indications. The proper base for a drug must be determined individually to provide the desired drug release rate, staying qualities after application, and texture. Briefly, *ointments* are simple mixtures of drug substances in an ointment base, whereas *creams* are semisolid emulsions and are less viscid and lighter than ointments. Creams are considered to have greater esthetic appeal due to their nongreasy character and their ability to "vanish" into the skin upon rubbing. *Pastes* contain more solid materials than do ointments and are

therefore stiffer and less penetrating. Pastes are usually employed for their protective action and for their ability to absorb serous discharges from skin lesions. Thus when protective rather than therapeutic action is desired, the formulation pharmacist will favor a paste, but when therapeutic action is required, he will prefer ointments and creams. Commerically, many therapeutic agents are prepared in both ointment and cream form and are dispensed and used according to the particular preference of the patient and the prescribing practitioner.

Medicinal powders are intimate mixtures of medicinal substances usually in an inert base as talcum powder. Depending upon the particle size of the resulting blend, the powder will have varying dusting and covering capabilities. In any case, the particle size should be small enough to ensure against grittiness and consequent skin irritation. Powders are most frequently applied topically to relieve such conditions as diaper rash, chafing, and athlete's foot.

When topical application is desired in liquid form other than solution, lotions are most frequently employed. *Lotions* are suspensions of solid materials in an aqueous vehicle, although certain emulsions and even some true solutions have been designated as lotions because of either their appearance or application. Lotions may be preferred over semisolid preparations because of their nongreasy character and their increased spreadability over large areas of skin.

Ocular, Oral, and Nasal Routes

Drugs are frequently applied topically to the eye, ear, and the mucous membranes of the nose. In these instances, ointments, suspensions, and solutions are generally employed. Ophthalmic solutions and suspensions are sterile aqueous preparations with other quantities essential to the safety and comfort of the patient. Ophthalmic ointments must be sterile, and also free of grittiness. Innovative new delivery systems for ophthalmic drugs continue to be investigated. One dosage form, the Ocusert, is an elliptically shaped unit designed for continuous release of pilocarpine following its placement into the cul-de-sac of the eye. Further, case reports of the ability of soft contact lenses to absorb drug from the eye have spawned research in the development of soft contact lenses impregnated with drug for therapeutic application in the eye. Nasal preparations are usually solutions or suspensions administered by drops or as a fine mist from a nasal spray container. Current research is directed toward the feasibility of the nasal administration of insulin for diabetes mellitus. Otic, or ear preparations are usually viscid so that they have prolonged contact with the affected area. They may be employed simply to soften ear wax, to relieve an earache, or to combat an ear infection. Eye, ear, and nose preparations usually are not used for systemic effects, and although ophthalmic and otic preparations are not usually absorbed to any great extent, nasal preparations *may* be absorbed, and systemic effects after the intranasal application of solution are not unusual.

Other Routes

The lungs provide an excellent absorbing surface for the administration of gases and for aerosol mists of very minute particles of liquids or solids. The gases employed are mainly oxygen and the common general anesthetic drugs administered to patients entering surgery. The rich capillary area of the alveoli of the lungs, which in man covers nearly a thousand square feet, provides rapid absorption and drug effects comparable in speed to those following an intravenous injection. In the case of drug particles, their size largely determines the depth to which they penetrate the alveolar regions, their solubility, the extent to which they are absorbed. After contact with the inner surface of the lungs, an insoluble drug particle is caught in the mucus and is moved up the pulmonary tree by ciliary action. Soluble drug particles that are approximately 0.5 to 1.0 μ in size reach the minute alveolar sacs and are most prompt and efficient in providing systemic effects. Particles that are smaller than 0.5 μ are expired to some extent, and thus their absorption is not total but variable. Particles from 1 to 10 μ in size effectively reach the terminal bronchioles and to some extent the alveolar ducts and are favored for local therapy. Therefore, in the pharmaceutical manufacture of aerosol sprays for inhalation therapy, the manufacturers not only must attain the proper drug particle size but also must ensure their uniformity for consistent penetration of the pulmonary tree and uniform effects.

In certain instances and for local effects, drugs are inserted into the vagina and the urethra. Drugs are usually presented to the vagina in tablet form, as suppositories, ointments, emulsion foams, gels or solutions, and to the urethra as suppositories or solutions. Systemic drug effects may result after the vaginal or urethral application of drugs due to absorption of the drug from the mucous membranes of these sites.

Fate of Drug after Absorption

After absorption into the general circulation from any route of administration, a drug may become bound to blood proteins and delayed in its passage into the surrounding tissues. Many drug substances may be highly bound to blood protein and others little-bound. For instance, when in the blood stream, naproxen is 99% bound to plasma proteins, penicillin G is 60% bound, amoxicillin only 20% bound, and minoxidil is unbound.

The degree of drug binding to plasma proteins is usually expressed as a percentage or as a fraction (termed *alpha*, or α) of the bound concentration (C_b) to the total concentration (C_t), bound plus unbound (C_u) drug:

$$\alpha = \frac{C_b}{C_u + C_b} = \frac{C_b}{C_t}$$

Thus, if one knows two of the three terms in the equation, the third may be calculated. Drugs having an alpha value of greater than 0.9 are considered highly bound (90%); those drugs with an alpha value of less than 0.2 are considered to be little (20% or less) protein bound. Table 4.9 presents approximate serum protein binding characteristics for representative drugs present in the blood under conditions associated with usual therapy. The drug-protein complex is reversible and involves albumin, although globulins are also involved in the binding of drugs, particularly some of the hormones. The binding of drugs to biologic materials involves the formation of relatively weak bonds (e.g., van der Waals, hydrogen, and ionic bonds). The binding capacity of blood proteins is limited, and once they are saturated, additional drug absorbed into the blood stream remains unbound unless bound drug is released, creating a vacant site for another drug molecule to attach. Any unbound drug is free to leave the blood stream for tissues or cellular sites within the body.

Bound drug is neither exposed to the body's detoxication (metabolism) processes nor is it filtered through the renal glomeruli. Bound drug is therefore referred to as the *inactive* portion in the blood, and unbound drug, with its ability to penetrate cells, is termed the *active* blood portion. The bound portion of drug serves as a drug reservoir or a depot, from which the drug is released as the free form when the level of free drug in the blood no longer is adequate to ensure protein saturation. The free drug may be only slowly released, thereby increasing the duration of the drug's stay in the body. For this reason a drug that is highly protein bound may remain in the body for longer periods of time and require less frequent dosage administration than another drug that may be only slightly protein bound and may remain in the body for only a short period of time. Evidence suggests that the concentration of serum albumin decreases about 20% in the elderly. This may be clinically significant for drugs that bind strongly to albumin, e.g., phenytoin, because if there is less albumin available to bind the drug there will be a corresponding increase of the free drug in the body. Without a downward dosage adjustment in an elderly patient, there could be an increased incidence of adverse effects.

A drug's binding to blood proteins may be affected by the simultaneous presence of a second (or more) drug(s). The additional drug(s) may result in

Table 4.9. Examples of Drug Binding to Plasma Proteins

Drug	*Percent Bound*
Naproxen (Naprosyn)	>99
Chlorambucil (Leukeran)	>99
Etodolac (Lodine)	>99
Warfarin (Coumadin)	>97
Fluoxetine (Prozac)	>95
Cloxacillin (Tegopen)	>95
Ceftriaxone (Rocephin)	85–95
Cefoperazone (Cefobid)	82–93
Cefonicid (Monocid)	>90
Indomethacine (Indocin)	>90
Spironolactone (Aldactone)	>90
Digitoxin (Crystodigin)	>90
Cyclosporine (Sandimmune)	>90
Sulfisoxazole (Gantrisin)	>85
Diltiazem (Cardizem)	70–80
Penicillin V (Veetids)	>75
Nitroglycerin (Nitro-Bid)	>60
Penicillin G Potassium	>60
Methotrexate	>50
Methicillin (Staphcillin)	>40
Ceftizoxime (Cefizox)	>30
Captopril (Capozide)	25–30
Ciprofloxacin (Cipro)	20–40
Digoxin (Lanoxin)	20–25
Ampicillin (Omnipen)	>20
Amoxicillin (Amoxil)	>20
Metronidazole (Flagyl)	<20
Mercaptopurine (Purinethol)	>19
Cephradine (Velosef)	8–17
Ranitidine (Zantac)	>15
Ceftazidime (Tazicef)	<10
Nicotine (Prostep)	<5
Minoxidil (Loniten)	> 0

Average literature values, based on conditions usually associated with drug therapy.

drug effects or durations of drug action quite dissimilar to that found when each is administered alone. Salicylates, for instance, have the effect of decreasing the binding capacity of thyroxin, the thyroid hormone, to proteins. Phenylbutazone is an example of a drug that competitively displaces several other drugs from serum binding sites, including other antiinflammatory drugs, oral anticoagulants, oral antidiabetics, and sulfonamides. Through this action, the displaced drugs become less protein bound and their activity (and toxicity) may be increased. The intensity of a drug's pharmacologic response is related to the ratio of the bound drug *versus* free, active drug, and the therapeutic index of the drug. Warfarin, an anticoagulant is 97% bound to plasma protein leaving 3% in free form to exert its effect. If a second drug, such as naproxen, which is strongly bound to plasma proteins is administered and results in only 90% of the warfarin being bound, this means that 10% of warfarin is now in the free form. Thus, the blood level of the free warfarin (3 to 10%) has tripled and could result in serious toxicity. The displacement of drugs from plasma protein sites is typical in the elderly who normally are maintained on numerous medicines. Coupled with the aforementioned decrease in serum protein through the aging process the addition of a highly protein-bound drug to an elderly patient's existing treatment regimen could pose significant problems if the patient is not monitored carefully for signs of toxicity.

In the same manner as they are bound to blood proteins, drugs may become bound to specific components of certain cells. Thus drugs are not distributed uniformly among all cells of the body, but rather tend to pass from the blood into the fluid bathing the tissues and may accumulate in certain cells according to their permeability capabilities and chemical and physical affinities. This affinity for certain body sites influences their action, for they may be brought into contact with reactive tissues (their *receptor sites*) or deposited in places where they may be inactive. Many drugs, because of their affinity for and solubility in lipids, are found to be deposited in fatty body tissue, thereby creating a storage place or drug reservoir from which they are slowly released to other tissues.

Drug Metabolism (Biotransformation)

Although some drugs are excreted from the body in their original form, many drugs undergo biotransformation prior to excretion. Biotransformation is a term used to indicate the chemical changes that occur with drugs within the body as they are metabolized and altered by various biochemical mechanisms. The biotransformation of a drug results in its conversion to one or more compounds that are more water soluble, more ionized, less capable of binding to proteins of the plasma and tissues, less capable of being stored in fat tissue, and less able to penetrate cell membranes, and thereby less active pharmacologically. Because of its new characteristics, a drug so transformed is rendered less toxic and is more readily excreted. It is for this reason that the process of biotransformation is also commonly referred to as the "detoxification" or "inactivation" process. (However, sometimes the metabolites are more active than the parent compound; see *prodrugs*, following.)

The exact metabolic processes (pathways) by which drugs are transformed represent an active area of biomedical research. Much work has been done with the processes of animal degradation of drugs and in many instances the biotransformation in the animal is thought to parallel that in man. There are four principal chemical reactions involved in the metabolism of drugs: oxidation, reduction, hydrolysis, and conjugation. Most oxidation reactions are catalyzed by enzymes (oxidases) bound to the endoplasmic reticulum, a tubular system within liver cells; only a small fraction of drugs are metabolized by reduction, through the action of reductases, present in the gut and liver; esterases in the liver participate in the hydrolytic breakdown of drugs containing ester groups as well as amides; glucuronide conjugation is the most common pathway for drug metabolism, through combination of the drug with glucuronic acid, forming ionized compounds that are easily eliminated (2). Other metabolic processes, including methylation and acylation conjugation reactions, occur with certain drugs to foster elimination.

In recent years, much interest has been shown in the metabolites of drug biotransformation. Certain metabolites may be as active or even more active pharmacologically than the original compound. Occasionally an active drug may be converted into an active metabolite, which must be excreted as such or undergo further biotransformation to an inactive metabolite, e.g., amitriptyline to nortriptyline. In other instances of drug therapy, an inactive parent compound, referred to as a *prodrug*, may be converted to an active therapeutic agent by chemical transformation in the body. An example is the prodrug enalapril (Vasotec), which after oral administration is hydrolyzed to enalaprilat, an active angiotensin-converting enzyme (ACE) inhibitor used

in the treatment of hypertension. Enalaprilat itself is poorly absorbed when taken orally (and thus the prodrug) but may be administered intravenously in aqueous solution. The use of these active metabolites as "original" drugs represents a new area of drug investigation and a vast reservoir of potential therapeutic agents.

Several examples of biotransformations occurring within the body are as follows:

(1) Acetaminophen (active) $\xrightarrow{\text{conjugation}}$ Acetaminophen glucuronide (inactive)

(2) Amoxapine (active) $\xrightarrow{\text{oxidation}}$ 8-hydroxy-amoxapine (inactive)

(3) Procainamide (active) $\xrightarrow{\text{hydrolysis}}$ p-Aminobenzoic acid (inactive)

(4) Nitroglycerin (active) $\xrightarrow{\text{reduction}}$ 1–2 and 1–3 dinitroglycerol (inactive)

Some parent compounds undergo full, partial, or no biotransformation following administration. Lisinopril (Zestril), for example, does not undergo metabolism and is excreted unchanged in the urine. On the other hand, verapamil (Calan) metabolizes to at least 12 metabolites, the most prevalent of which is norverapamil. Norverapamil has 20% of the cardiovascular activity of the parent compound. Diltiazem (Cardizem) is partially metabolized (about 20%) to desacetyldiltiazem, which has 10–20% the coronary vasodilator activity of the parent compound. Indomethacin (Indocin) is metabolized in part to desmethyl, desbenzoyl, and desmethyldesbenzoyl metabolites. Propoxyphene napsylate (Darvon N) is metabolized to norpropoxyphene, which has less central nervous system depressant action than the parent compound but greater local anesthetic effects. The majority of metabolic transformations takes place in the liver, with some drugs as diltiazem and verapamil undergoing extensive first-pass effects. Other drugs, such as terazosin (Hytrin), undergo minimal first-pass metabolism effects. The excretion of both drug and metabolites takes place primarily, but to varying degrees, via the urine and feces. For example, indomethacin and its metabolites are excreted primarily (60%) in the urine, with the remainder in the feces, whereas terazosin and its metabolites are excreted largely (60%) through the feces, and the remainder in the urine.

It is important to mention that several factors influence drug metabolism. For example, there are marked differences between *species* in pathways of hepatic metabolism of a given drug. Species differences make it extremely difficult to extrapolate from one species to another, e.g., laboratory animals to humans. Furthermore, there are many examples of *interindividual variations* in hepatic metabolism of drugs within one species. Genetic factors are involved in the determination of the basal activity of the drug metabolizing enzyme systems. Thus, there can be marked intersubject variation in the rate at which certain individuals metabolically handle drugs. Because of this variation, a physician must individualize therapy to maximize the chances for a constructive therapeutic outcome with minimal toxicity. Studies in humans have demonstrated that these differences have occurred within the cytochrome P-450 genetic codes for a family of isoenzymes responsible for drug metabolism.

Age of the patient is another significant factor that influences drug metabolism. Although pharmacokinetic calculations have not been able to develop a specific correlative relationship with age, it is known, for example, that the ability to metabolize drugs decreases at the extremes of the age scale, i.e., elderly, neonate. Liver blood flow is reduced by aging at about 1% per year beginning around age 30.[9] This decreased blood flow to the liver reduces the capacity for hepatic drug metabolism and elimination. For example, the half-life of chlordiazepoxide increases from about 6 hours at age 20 to about 36 hours at age 80. Further, an immature hepatic system disallows the effective metabolism of drugs by the newborn or premature infant. As mentioned earlier, the half-life of theophylline ranges between 14 to 58 hours in the premature infant to 2.5 to 5 hours in young children between the ages of 1 to 4 whose liver enzyme systems are mature.

Diet has also been demonstrated to modify the metabolism of some drugs. For example, the conversion of an asthmatic patient from a high to a low protein diet will increase the half-life of theophylline. It has also been demonstrated that the production of polycyclic hydrocarbons by the charcoal broiling of beef enhances the hepatic metabolism and shortens the plasma half-life of theophylline. It is conceivable that this effect could also occur with drugs that are metabolized in similar fashion to theophylline. Diet type, e.g., starvation, certain vegetables (brussels sprouts, cabbage, broccoli), has been shown to influence the metabolism of certain drugs. Lastly, it is important to mention that exposure to other drugs or chemicals, e.g., pes-

ticides, alcohol, nicotine, and the presence of disease states, e.g., hepatitis, have all demonstrated an influence on the drug metabolism and consequently the pharmacokinetic profile of certain drugs.

Excretion of Drugs

The excretion of drugs and their metabolites terminates their activity and presence in the body. They may be eliminated by various routes, with the kidney playing the dominant role by eliminating drugs via the urine. Drug excretion with the feces is also important, especially for drugs that are poorly absorbed and remain in the gastrointestinal tract after oral administration. Exit through the bile is significant only when the drug's reabsorption from the gastrointestinal tract is minimal. The lungs provide the exit for many volatile drugs through the expired breath. The sweat glands, saliva, and milk play only minor roles in drug elimination. However, it should be recognized that if a drug gains access to the milk of a mother during lactation, it could easily exert its drug effects in the nursing infant. Examples of drugs that do enter breast milk and may be passed on to nursing infants include theophylline, penicillin, reserpine, codeine, meperidine, barbiturates, diltiazem, and thiazide diuretics. It is generally good practice for the mother to abstain from taking medication during the period of time she is nursing her infant. If she must take medication, she should abide by a dosage regimen and nursing schedule that permit her own therapy yet ensure the safety of her child. Not all drugs gain entrance into the milk; nevertheless, caution is advisable. Manufacturers' package inserts contain product-specific information (usually in the "Precautions" section) on drug migration into breast milk.

The unnecessary use of medications during the early stages of pregnancy is likewise restricted by physicians, because certain drugs are known to have the ability to cross the placental barrier and gain entrance to the tissues and blood of the fetus. Among the many drugs known to do so after administration to an expectant mother are all of the anesthetic gases, many barbiturates, sulfonamides, salicylates, and a number of other potent agents like quinine, meperidine, and morphine, the latter two drugs being narcotic analgesics with great addiction liabilities. In fact, it is not unusual for a newborn infant to be born an addict due to the narcotic addiction of its mother and the passage of the narcotic drugs across the placental barrier.

The kidney, as the main organ for the elimination of drugs from the body, must be functioning adequately if drugs are to be efficiently eliminated. For instance, elimination of digoxin occurs largely through the kidney according to first-order kinetics; that is, the quantity of digoxin eliminated at any time is proportional to the total body content. Renal excretion of digoxin is proportional to the glomerular filtration rate which when normal results in a digoxin half-life that may range from 1.5 to 2.0 days. When the glomerular filtration rate becomes impaired or disrupted, however, as in an anuric patient, the elimination rate decreases. Consequently, the half-life of digoxin may be between 4 to 6 days. Because of this prolongation of digoxin's half-life, the dosage of the drug must be decreased or the dosage interval prolonged. Otherwise, the patient will experience digoxin toxicity. The degree of impairment can be estimated by measurements of glomerular filtration rates, most often by creatinine clearance determination. Usually, however, this is not feasible and the patient's serum creatinine value is used within appropriate pharmacokinetic equations to help determine a drug's dosage regimen.

Some drugs may be reabsorbed from the renal tubule even after having been sent there for excretion. Because the rate of reabsorption is proportional to the concentration of drug in unionized form, it is possible to modify this rate by adjusting the pH of the urine. By acidifying the urine, as with the oral administration of ammonium chloride, or by alkalinizing it, as with the administration of sodium bicarbonate, one can increase or decrease the ionization of the drug and thereby alter its prospect of being reabsorbed. Alkalinization of the urine has been shown to enhance the urinary excretion of weak acids such as salicylates, sulfonamides, and phenobarbital. The opposite effect can be achieved by acidifying the urine. Thus, the duration of a drug's stay within the body may be markedly altered by changing the pH of the urine. Some foods, such as cranberry juice, can also serve to acidify the urine and may alter drug excretion rates.

The urinary excretion of drugs may also be retarded by the concurrent administration of agents capable of inhibiting their tubular secretion. A well-known example is the use of probenecid to inhibit the tubular secretion of various types of penicillin, thereby reducing the frequency of dosage administrations usually necessary to maintain adequate therapeutic blood levels of the antibiotic drug. In this particular instance, the elevation of penicillin blood levels, by whatever route the antibiotic is administered, to twofold and even fourfold levels has been demonstrated by adjuvant therapy with probenecid. The effects are completely reversible

upon withdrawal of the probenecid from concomitant therapy.

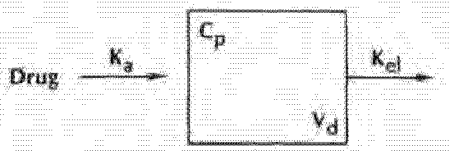
The fecal excretion of drugs appears to lag behind the rate of urinary excretion partly because a day or so elapses before the feces reach the rectum. It should be easily seen that drugs administered orally for local activity within the gastrointestinal tract and not absorbed will be eliminated completely via the feces. Unless a drug is particularly irritating to the gastrointestinal tract, there is generally no urgency in removing unabsorbable drugs from the system by means other than the normal defecation process. Some drugs that are only partially absorbed after oral administration will naturally be partly eliminated through the rectum.

Pharmacokinetic Principles

This section introduces the concept of pharmacokinetics and how it interrelates the various processes that take place when one administers a drug to a patient, i.e., absorption, distribution, metabolism, excretion. It is not intended to be comprehensive, and thus for further information about the subject the reader is referred to other appropriate literature sources.

A problem encountered when one needs to determine a more accurate dosage of a drug or a more meaningful interpretation of a biologic response to a dose is the inability to determine the drug concentration at the active site in the body. Consequently, to solve this dilemma, the concept of compartmental analysis is used within the discipline of pharmacokinetics in an attempt to quantitatively define what has become of the drug as a function of time from the moment it is administered until it is no longer in the body. Pharmacokinetic analysis utilizes mathematical models to simplify or simulate the disposition of the drug in the body. The idea is to begin with a simple model and then modify as necessary. The principal assumption is that the human body may be represented by one or more *compartments* or pools in which a drug resides in a dynamic state for a short period of time. A compartment is a hypothetical space bound by an unspecified membrane across which drugs are transferred (Fig. 4.13). The transfer of drugs into and out of this compartment is indicated by arrows that point in the direction of drug movement into or out of the compartment. The rate at which a drug is transferred throughout the system is designated by a symbol that usually represents an exponential rate constant. Typically, the letter K or k with numerical or alpha-numerical subscripts is utilized.

There are several assumptions associated with



Where:
C_p is the drug concentration in plasma
V_d is the volume of the compartment or volume of distribution

Fig. 4.13 *Schematic of a one-compartment system.*

modeling of drug behavior once in the body. It is assumed that the volume of each compartment remains constant. Thus, an equation that describes the time course of the amount of drug in the compartment can be converted to an equation that depicts the time course of the drug concentration in the compartment by dividing both sides of the equation by the volume of the compartment. Secondly, it is assumed that once a drug enters the compartment it is instantaneously and uniformly distributed throughout the entire compartment. Thus, it is assumed that a sampling of any one portion of the compartment will yield the drug concentration of the entire compartment.

In compartment models it is assumed that drug passes freely into and out of compartments. Thus, these compartmental systems are known as "open" systems. Typically, the process of drug transport between compartments follows first-order kinetics, herein a constant fraction of drug present is eliminated per unit time, and can be described by ordinary differential equations. In these linear systems the time constants that describe the rate at which the plasma or blood concentration curve of a drug decays are independent of the dose of the drug, the volume of distribution of the drug and the route of administration.

The simplest pharmacokinetic model is the single compartment *open-model system* (Figure 4.13). This model depicts the body as one compartment characterized by a certain volume of distribution (V_d) that remains constant. Each drug has its own distinct volume of distribution and this can be influenced by certain patient factors, e.g., age, disease state status. In this scheme a drug can be instantaneously introduced into the compartment, i.e., rapid intravenous administration, or gradually, e.g., oral administration. In the former example it is assumed that the drug distributes immediately to tissues with instantaneous attainment of equilibrium. In

the latter example, the drug is absorbed at a certain rate and is characterized by the rate constant K_a. Lastly, the drug is eliminated from the compartment at a certain rate that is characterized by a rate constant K_{el}.

It is relevant at this point to consider the *volume of distribution*, V_d. The volume of distribution is a proportionality constant and is a term that refers to the volume into which the total amount of drug in the body would have to be uniformly distributed to provide the concentration of drug actually measured, e.g., in plasma, in blood. This term can be misleading because it does not represent a specific body fluid or volume. It is influenced by the plasma-protein binding and tissue binding characteristics of a drug. These then influence the distribution of the drug between plasma water, extracellular fluid, intracellular fluid and total body water. Further, because a drug can partition between fat and water according to its unique partition coefficient, this can also influence the volume of distribution. Because of these phenomena, pharmacokineticists find it convenient to describe a drug distribution in terms of compartment models.

To determine the rate of drug transfer into and out of the compartment, plasma, serum, or blood samples are drawn at predetermined times after the drug is administered and analyzed for drug concentration. Once a sufficient number of experimental data points is determined, these are plotted on semi-logarithmic paper and an attempt is made to fit the experimental points with the smoothest curve to fit these points. Figure 4.14 depicts the plasma concentration *versus* time profile for a hypothetical drug following rapid intravenous injection of a bolus dose of the drug with instantaneous distribution. For drugs whose distribution follows first-order, one-compartment pharmacokinetics, a plot of the logarithm of the concentration of drug in the plasma (or blood) versus time will yield a straight line. The equation that describes the plasma decay curve is:

$$C_p = C^0_p\, e^{-K_{el}t} \qquad \text{(Equation 4.1)}$$

where K_{el} is the first-order rate of elimination of the drug from the body, C_p is the concentration of the drug at a time equal to t, and C^0_p is the concentration of drug at time equal to zero, when all the drug administered has been absorbed but none has been removed from the body through elimination mechanisms, e.g., metabolism, renal excretion. The apparent first-order rate of elimination, K_{el}, is usually the sum of the rate constants of a number of individual processes, e.g., metabolic transformation, renal excretion.

For the purpose of pharmacokinetic calculation it is simpler to convert Equation 4–1 to natural logs:

$$\text{Ln } C_p = \text{Ln } C^0_p - K_{el}\,(t) \qquad \text{(Equation 4.2)}$$

and then to log base_{10}:

$$\text{Log } C_p = \text{Log } C^0_p - K_{el}\,(t)/2.303 \qquad \text{(Equation 4.3)}$$

Equation 4–3 is then thought of in terms of the Y-intercept form:

$$Y = b + m \times$$
$$\text{Log } C_p = \text{Log } C^0_p - K_{el}/2.303\,(t)$$

and interpreted as such in the semi-logarithmic plot illustrated in Figure 4.14. Most drugs administered orally can be adequately described using a one-compartment model, whereas drugs administered by rapid intravenous infusion are usually best described by a two-compartment or three-compartment model system.

Assuming that a drug's volume of distribution, V_d, is constant within this system, the total amount of drug in the body (Q_b) can be calculated from the following equation:

$$Q_b = [C^0_p]\,[V_d] \qquad \text{(Equation 4.4)}$$

Usually, C^0_p is determined by extrapolating the drug-concentration time plot back to time zero.

In this simple one-compartment system it is assumed that the administered drug is confined to

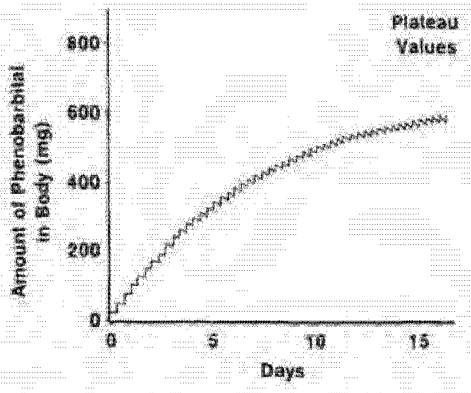
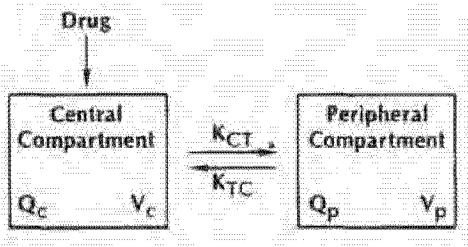


Fig. 4.14 *Plot of the plasma concentration-time data. (Reprinted with permission from Rowland M, Tozer TN. Clinical Pharmacokinetics. 2nd Ed., Philadelphia: Lea & Febiger, 1989).*

the plasma (or blood) and then excreted. Drugs that exhibit this behavior will have small volumes of distribution. For example, a drug such as warfarin which is extensively bound to plasma albumin will have a volume of distribution equivalent to that of plasma water, about 2.8 liters in an average 70 kg adult. Some drugs, however, will initially be distributed at somewhat different rates in various fluids and tissues. Consequently, these drugs' kinetic behavior can best be illustrated by considering an expansion of the one-compartment system to the *two compartment model* (Fig. 4.15).

In the two-compartment system, a drug enters into and is instantaneously distributed throughout the central compartment. Its subsequent distribution into the second or peripheral compartment is slower. For simplicity, on the basis of blood perfusion and tissue-plasma partition coefficients for a given drug, various tissues and organs are considered together and given the designation as central compartment or peripheral compartment. The central compartment is usually considered to include the blood, the extracellular space, and organs with good blood perfusion, e.g., lungs, liver, kidneys, heart. The peripheral compartment is usually constituted by those tissues and organs which are poorly perfused by blood, e.g., skin, bones, fat.

Figure 4.16 depicts the plasma-drug concentration versus time plot for a rapidly administered intravenous dose of a hypothetical drug which exhibits kinetic behavior exemplifying a two-compartment system. Note the initial steep decline of the plasma drug concentration curve. This typifies the distribution of the drug from the central compartment to the peripheral compartment.



Where:
Q_c = Quantity of drug in central compartment
V_c = Volume of the central compartment
Q_p = Quantity of drug in peripheral compartment
V_p = Volume of the peripheral compartment

Fig. 4.15 *Schematic of a two-compartment system.*

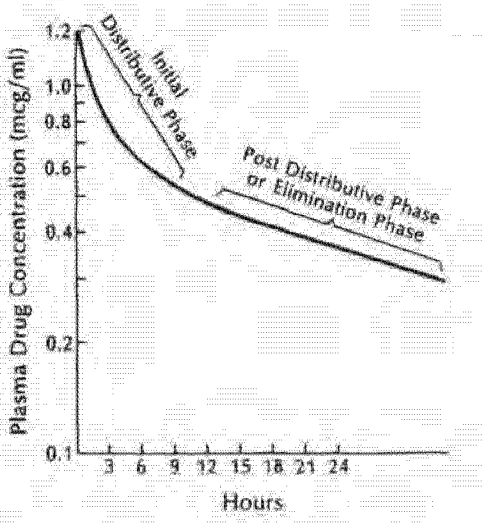


Fig. 4.16 *A semilogarithmic plasma concentration versus time plot of an intravenously administered drug that follows first order, two-compartment pharmacokinetics.*

During this phase the drug concentration in the plasma will decrease more rapidly than in the post-distributive phase, i.e., elimination phase. Whether or not this distributive phase is apparent will depend upon the timing of the plasma samples, particularly in the time immediately following administration. A distributive phase can be very short, a few minutes, or last for hours and even days.

A semi-logarithmic plot of the plasma concentration versus time after rapid intravenous injection of a drug which is best described by a two-compartment model system can often be resolved into two linear components. This procedure can be performed by the method of residuals (or feathering), Figure 4.17. In this procedure, a straight line is fitted through the tail of the original curve and extrapolated back to the Y-axis (the value obtained is B). A plot is then made of the absolute difference values of the original curve and the resultant extrapolated straight line. The slope of the feathered line (−a/2.303) and the extrapolated line (−b/2.303) and the intercepts, A and B, are determined. Then the following equation is constructed that describes a two-compartment system:
(Equation 4–5)

$$C_p = Ae^{-at} + Be^{-bt}$$

This is a bi-exponential equation which describes the two-compartment system.

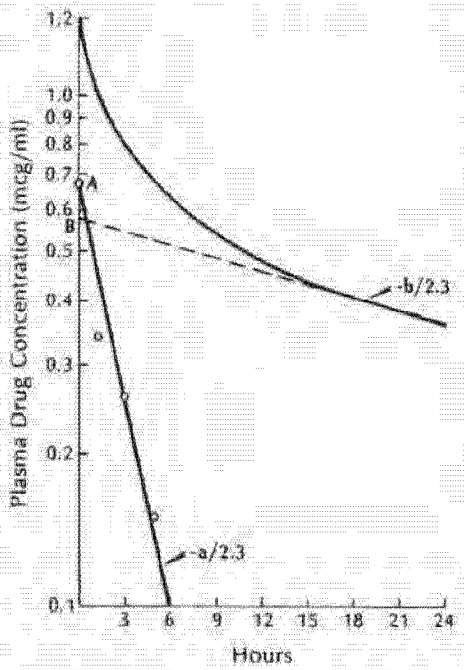


Fig. 4.17 *The logarithm of the drug concentration in plasma plotted versus time (solid line) after intravenous administration of a drug whose disposition can be described by a two-compartment model.*

In this scheme, the slope of the line, i.e., −a/2.303, obtained from feathering yields the distributive rate of the drug. The slope of the terminal linear phase or elimination phase, i.e., −b/2.303, describes the rate of loss of the drug from the body, and usually is considered to be a reflection of the metabolic processes and renal elimination from the body. Appropriate pharmacokinetic formulas allow the clinician to calculate the various volumes of distribution and rates of distribution and elimination for drugs whose pharmacokinetic behavior is exemplified by the two-compartment system.

Half-Life

The half-life ($T_{1/2}$) of a drug describes the time required for a drug's blood or plasma concentration to decrease by one half. This fall in drug concentration is a reflection of metabolic processes and/or excretion, e.g., renal, fecal. The biological half-life of a drug in the blood may be determined graphically off of a pharmacokinetic plot of a drug's blood-concentration time plot, typically after intravenous administration to a sample population. The amount of time required for the concentration of the drug to decrease by one half is considered its half-life. The half-life can also be mathematically determined. Recall Equation 4–3 and rearrange the equation as follows:

$$\frac{K_{el}\, t}{2.303} = \text{Log}\, C_p^0 - \text{Log}\, C_p = \text{Log}\, \frac{C_p^0}{C_p} \qquad \text{(Equation 4.6}$$

Then, if it assumed that C_p is equal to one-half of C^0_p, the equation will become:

$$\frac{K_{el}\, t}{2.303} = \text{Log}\, \frac{C_p^0}{0.5\, C_p^0} = \text{Log}\, 2 \qquad \text{(Equation 4.7}$$

Thus,

$$t_{1/2} = \frac{2.303\ \text{Log}\ 2}{K_{el}} = \frac{0.693}{K_{el}} \qquad \text{(Equation 4.8}$$

If this latter equation is rearranged, the half-life finds utility in the determination of drug elimination from the body, provided of course that the drug follows first-order kinetics. Rearranging the previous equation:

$$K_{el} = \frac{0.693}{t_{1/2}} \qquad \text{(Equation 4.9}$$

Elimination rate constants are reported in time^{-1} e.g., minutes^{-1}, hours^{-1}. Thus, an elimination constant of a drug is 0.3 hr^{-1} indicates that 30% of the drug is eliminated per hour.

The half-life varies widely between drugs; for some drugs it may be a few minutes, whereas for other drugs it may be hours or even days (Table 4.10). Data on a drug's biologic half-life are useful in determining the most appropriate dosage regimen to achieve and maintain the desired blood level of drug. Such determinations usually result in such recommended dosage schedules for a drug, as the drug to be taken every 4 hours, 6 hours, 8 hours etc. Although these types of recommendations generally suit the requirements of most patients, they do not suit all patients. The most exceptional patients are those with reduced or impaired ability to metabolize or excrete drugs. These patients, generally suffering from liver dysfunction or kidney disease, retain the administered drug in the blood or tissues for extended periods of time due to their decreased ability to eliminate the drug. The resulting extended biologic half-life of the drug generally ne

Table 8.10. Some Elimination Half-Life Values

Drug Substance/Product	*Elimination Half-Life* ($t_{1/2}$)*
Acetaminophen (Tylenol)	1–4 hours
Amoxicillin (Amoxil)	1 hour
Butabarbital Sodium (Butisol Sodium)	100 hours
Cimetidine (Tagamet)	2 hours
Digitoxin (Crystodigin)	7–9 days
Digoxin (Lanoxin)	1.5–2 days
Diltiazem (Cardizem)	2.5 hours
Ibuprofen (Motrin)	1.8–2 hours
Indomethacin (Indocin)	4.5 hours
Lithium Carbonate (Eskalith)	24 hours
Nitroglycerin (Tridil)	3 minutes†
Phenytoin Sodium (Dilantin)	7–29 hours
Pentobarbital Sodium (Nembutal Sodium)	15–50 hours
Propoxyphene (Darvon)	6–12 hours
Propranolol HCl (Inderal)	4 hours
Ranitidine HCl (Zantac)	2.5–3 hours
Theophylline (Theo-Dur)	3–15 hours
Tobramycin Sulfate (Nebcin)	2 hours
Tolbutamide (Orinase)	4.5–6.5 hours

*Mean, average, or value ranges, taken from product information found in *Physicians' Desk Reference*, 52nd ed., 1998, Medical Economics Data, Montvale, New Jersey. Half-life values may vary depending upon patient characteristics (age, liver or renal function, smoking habits, etc.), dose levels administered, and routes of administration.

†After intravenous infusion, nitroglycerin is rapidly metabolized to dinitrates and mononitrates.

cessitates an individualized dosage regimen calling for less frequent drug administration than that called for in patients with normal processes of drug elimination, or a maintenance of the usual dosage schedule, but a decrease in the amount of drug administered.

The drug digoxin presents a good example of a drug having a half-life which is affected by the patient's pathologic condition. Digoxin is eliminated in the urine. Renal excretion of digoxin is proportional to glomerular filtration rate. In subjects with normal renal function, digoxin has a half-life of 1.5 to 2.0 days. In anuric patients (absence of urine formation), the half-life may be prolonged to 4 to 6 days. Theophylline also demonstrates differing half-lives dependent upon certain patient populations. In premature infants with immature liver enzyme systems in the cytochrome P-450 family, the half-life of theophylline ranges from 14 to 58 hours, whereas in young children between the ages of 1 to 4 whose liver enzyme systems are more mature the theophylline half-life ranges between 2 to 5.5 hours. In adult nonsmokers, the half-life ranges from 6.1 to 12.8 hours, whereas in adult smokers the average half-life of theophylline is 4.3 hours. The increase in theophylline clearance from the body among smokers is believed to be due to an induction of the hepatic metabolism of theophylline. The half-life of theophylline is decreased and total body clearance is enhanced to such a degree in smokers that these individuals may actually require a 50 to 100% increase in theophylline dosage to produce effective therapeutic results. Between 3 months and 2 years may actually be required to normalize the effect of smoking on theophylline metabolism in the body once the patient stops smoking. Because theophylline is metabolized in the liver, the half-life of theophylline will be extended in liver disease. For example, in one study 9 patients with decompensated cirrhosis, the average theophylline half-life was 32 hours.

The half-life of a drug in the blood stream may also be affected by a change in the extent to which it is bound to blood protein or cellular components. Such a change in a drug's binding pattern may be brought about by the administration of a second drug having a greater affinity than the first drug for the same binding sites. The result is the displacement of the first drug from these sites by the second drug and the sudden availability of free (unbound) drug which may pass from the blood stream to other body sites, including those concerned with its elimination. It should be noted that the displacement of one drug from its binding sites by another is generally viewed as an undesired event, since the amount of free drug resulting is greater than the level normally achieved during single drug therapy and may result in untoward drug effects.

Concept of Clearance

The three main mechanisms by which a drug is removed or cleared from the body include (1) the hepatic metabolism, i.e., hepatic clearance, Cl_h, of a drug to either an active or inactive metabolite, (2) the renal excretion, i.e., renal clearance, Cl_r, of a drug unchanged in the urine, and (3) elimination of the drug into the bile and subsequently into the intestines for excretion in feces. An alternate way to express this removal or elimination from the body is to use total body clearance (Cl_B), which is defined as the fraction of the total volume of distribution that can be cleared per unit time. Because most drugs when administered will undergo one or more of these processes, the total body clearance, Cl_B, of a drug is the sum of these clearances, usu-

ally hepatic, Cl_h and renal clearances Cl_r. Clearance via the bile and feces is usually not significant for most drugs.

These processes of elimination within the body work together and consequently a drug that is eliminated by renal excretion and hepatic biotransformation will have an overall rate of elimination, K_{el}, that is the sum of the renal excretion, k_e, and hepatic biotransformation, k_m. In the one compartment model described earlier, total body clearance is the product of the volume of distribution, V_d, and the overall rate of elimination, k_{el}:

$$Cl_B = V_d \times k_{el} \qquad \text{(Equation 4.10)}$$

But, recall that k_{el} equals $0.693/t_{1/2}$. If this is substituted into Equation 4–10, and one solves for the half-life, $t_{1/2}$, the following equation is obtained:

$$t_{1/2} = \frac{0.693 V_d}{Cl_B} \qquad \text{(Equation 4.11)}$$

Recall that total body clearance is a function of one or more processes, thus if a drug were eliminated from the body through hepatic biotransformation and renal clearance, Equation 4–11 becomes:

$$t_{1/2} = \frac{0.693 V_d}{Cl_h + Cl_r} \qquad \text{(Equation 4.12)}$$

Thus, a drug's half-life is directly proportional to the volume of distribution and inversely proportional to the total body clearance which is comprised of hepatic and renal clearances. Illustratively, if one considers infants and children who exhibit larger volumes of distribution and have lower clearance values, drugs will usually have greater half-lives than that exhibited in adults.

A decrease in the hepatic or renal clearances will prolong the half-life of a drug. This typically occurs for example in renal failure, and consequently, if one can estimate the percentage decrease in excretion due to renal failure one can use Equation 4–12 to calculate the new half-life of the drug in the patient. Thus, an adjusted dosage regimen can then be calculated to decrease the chance of drug toxicity.

Dosage Regimen Considerations

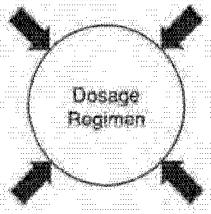
In the previous chapter those factors that can influence the dosage of a drug were mentioned. The question of how much drug and how often to administer it for a desired therapeutic effect is not easily attainable. Basically, there are two approaches to the development of dosage regimens. The first is the *empirical approach*, which involves the administration of a drug in a certain quantity, noting the therapeutic response and then modifying the dosage of drug and the dosing interval accordingly. Unfortunately, experience with the administration of a drug usually starts with the first patient, and eventually a sufficient number of patients receive the drug so that a fairly accurate prediction can be made. Besides the desired therapeutic effect, consideration must also involve the occurrence and severity of side effects. Empirical therapy is usually employed when the drug concentration in serum or plasma does not reflect the concentration of drug at the receptor site in the body, or the pharmacodynamic effect of the drug is not related (or correlated) with the receptor site drug concentration. Empirical therapy, for example, is utilized for many anticancer drugs that demonstrate effects long after they have been excreted from the body. It is difficult to relate the serum level of these drugs with the desired therapeutic effect.

The second approach to the development of a dosage regimen is through the use of pharmacokinetics or the *kinetic approach*. This approach is based on the assumption that the therapeutic and toxic effects of a drug are related to the amount of drug in the body or to the plasma (or serum) concentration of drug at the receptor site. Through careful pharmacokinetic evaluation of a drug's absorption, distribution, metabolism and excretion in the body from a single dose, the levels of drug attained from multiple dosing can be estimated. One can then determine the appropriateness of a dosage regimen to achieve a desired therapeutic concentration of drug in the body and evaluate the regimen based upon therapeutic response.

When one considers the development of a dosage regimen, pharmacokinetics is but one of a number of factors that should be considered. Table 4.11 illustrates a number of these. Certainly an important factor is the inherent activity, i.e., pharmacodynamics, and toxicity, i.e., toxicology of the drug. A second consideration is the pharmacokinetics of the drug, which are influenced by the dosage form in which the drug is administered to the patient, e.g., biopharmaceutical considerations. The third factor focuses upon the patient to whom the drug will be given and encompasses the clinical state of the patient and how the patient will be managed. Lastly, atypical factors may influence the dosage regimen. Collectively, all of these factors influence the dosage regimen.

Table 4.11. Factors That Determine a Dosage Regimen*

Activity-Toxicity	*Pharmacokinetics*
Minimum therapeutic dose	Absorption
Toxic dose	Distribution
Therapeutic index	Metabolism
Side effects	Excretion
Dose-response relationships	



Clinical Factors		*Other Factors*
Clinical State of Patient	*Management of Therapy*	
Age, weight, urine pH	Multiple drug therapy	Tolerance-dependence
Condition being treated	Convenience of regimen	Pharmacogenetics-idiosyncrasy
Existence of other disease states	Compliance of patient	Drug interactions

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The dosage regimen of a drug may simply involve the administration of a drug once for its desired therapeutic effect, e.g., pinworm medication, or encompass the administration of drug for a specific time through multiple doses. In the latter instance, the objective of pharmacokinetic dosing is to design a dosage regimen that will continually maintain a drug's therapeutic serum or plasma concentration within the drug's therapeutic index, i.e., above the minimum effective concentration but below the minimum toxic level.

Frequently drugs are administered between 1 to 4 times per day, most often in a fixed dose, e.g., 75 mg 3 times daily after meals. As mentioned earlier, after a drug is administered its level within the body varies because of the influence of all of the processes, e.g., absorption, distribution, metabolism and excretion. A drug will accumulate in the body when the dosing interval is less than the time needed for the body to eliminate a single dose. For example, Figure 4.18 illustrates the plasma concentration for a drug given by intravenous administration and oral administration. The 50 mg dose of this drug was given at a dosing interval of 8 hours. The drug has an elimination half-life of 12 hours. As one can see with continued dosing the drug concentration reaches a *steady state* or *plateau* concentration. At this limit the amount of drug lost per interval is replenished when the drug is dosed again. Consequently the concentration of drug in the plasma or serum fluctuates between a minimum concentration and a maximum concentration. Thus for certain patient types it is optimal to target dosing so that the plateau concentration resides within the therapeutic index of a drug to maintain a minimum effective concentration of drug. For example, the asthmatic patient maintained on theophylline must have a serum concentration between 10 and 20 μg/mL. Otherwise the patient may be susceptible to an asthma attack. Thus, when dosing the asthmatic patient it is preferable to give theophylline around the clock 4 times daily to sustain levels at least above 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 some 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 exam-

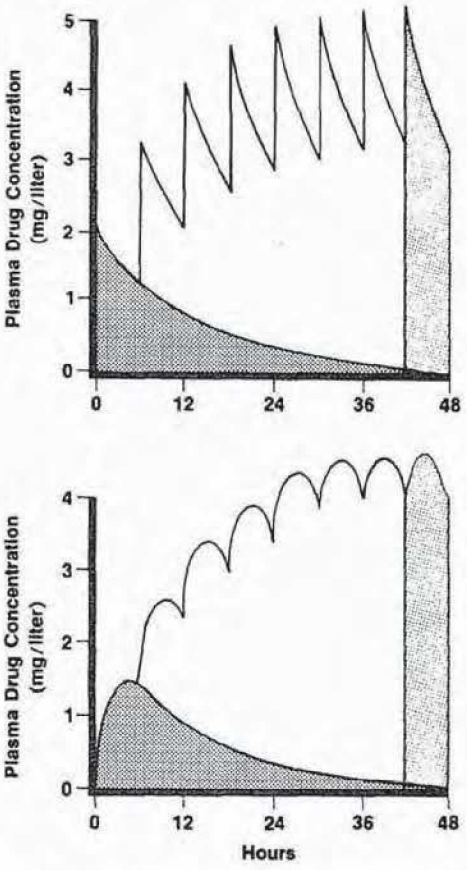

Fig. 4.18 *Plasma concentration of a drug given intravenously (top) and orally (bottom) on a fixed dose of 50 mg and fixed dosing interval of 8 hours. The half-life is 12 hours. Note that the area under the plasma concentration-time curve during a dosing interval at steady state is equal to the total area under the curve for a single dose. The fluctuation of the concentration is diminished when given orally (half-life of absorption is 1.4 hours) but the average steady-state concentration is the same as that after intravenous administration, since F = 1. (Reprinted with permission from Rowland M, Tozer TN. Clinical Pharmacokinetics. Philadelphia: Lea & Febiger, 1989).*

ple, once the physician prescribes a certain amount of drug and monitors the clinical response, it is the 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 pharmacist who interprets the result, and consults with the physician regarding subsequent dosages.

Fig. 4.19 *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.)*

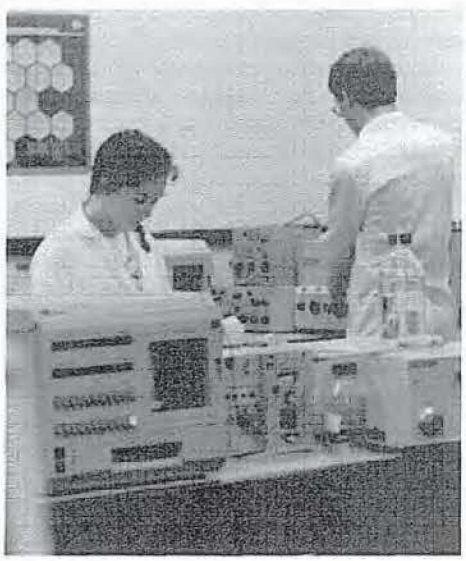

Fig. 4.20 *Assay of biological fluids using Waters HPLC (High Performance Liquid Chromatography) system consisting of (from left to right) Autosampler (Model 712 Wisp), Pump (Model M-45), Shimadzu Fluorescence Detector (Model RF-535). (Courtesy of Elan Corporation, plc.)*

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 4.19 and 4.20.

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