Pharmaceutical Dosage Forms and Drug Delivery Systems

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Loyd V. Allen, Jr.

I am a Pharmacist

- *I am a specialist in medications*

  I supply medicines and pharmaceuticals to those who need them.

  I prepare and compound special dosage forms.

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

- *I am a custodian of medical information*

  My library is a ready source of drug knowledge.

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

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

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

- *I am a companion of the physician*

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

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

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

- *I am a counselor to the patient*

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

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

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

- *I am a guardian of the public health*

  My pharmacy is a center for health-care information.

  I encourage and promote sound personal health practices.

  My services are available to all at all times.

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

Pharmaceutical Dosage Forms and Drug Delivery Systems

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

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Dosage Form Design: Biopharmaceutic Considerations

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

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

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

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

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

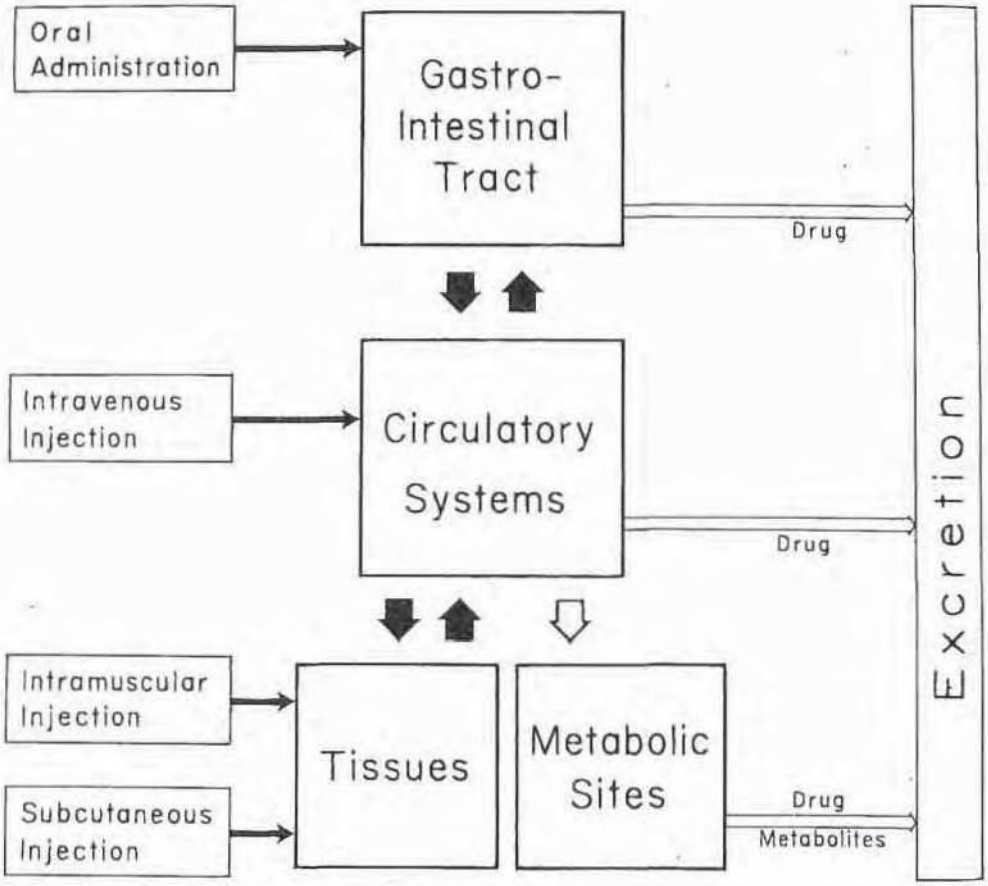

Fig. 3–1. *Schematic representation of events of absorption, metabolism, and excretion of drugs after their administration by various routes.*

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

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

dipivefrin HCl is converted by enzymatic hydrolysis to epinephrine.

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

General Principles of Drug Absorption

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

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

Passive Diffusion

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

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

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

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

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

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

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

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

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

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

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

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

For an acid:

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

For a base:

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

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

By rearranging the equation for an acid:

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

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

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

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

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

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

Table 3–2. pK
Drugs

Acids:

Bases:

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

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

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

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

Specialized Transport Mechanisms

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

Dissociation Constants

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

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

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

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

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

where K_a is the acid dissociation constant.

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

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

The dissociation constant is described by:

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

The dissociation of a hydroxyl-containing weak base,

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

The dissociation constant is described by:

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

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

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

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

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

Some practical applications of these equations are as follows.

EXAMPLE 1

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

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

EXAMPLE 2

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

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

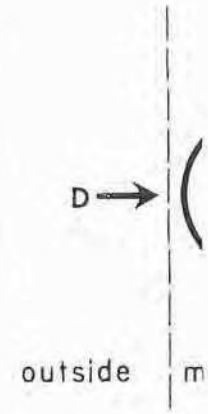

Fig. 3–2. *Active tra drug molecule; C repr (After O'Reilly, W.J.:*

tive transport, as a s transport, denotes feature of the solut the membrane aga that is, from a solu one of a higher co an ion, against an dient. In contrast *diffusion* is a spec having all of the ab the solute is not tr tion gradient and n tion inside the cell

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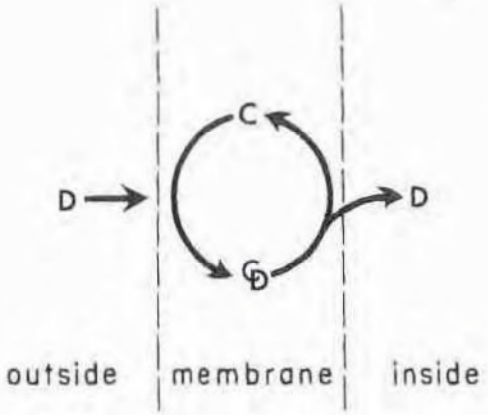

Fig. 3–2. *Active transport mechanism. D represents a drug molecule; C represents the carrier in the membrane. (After O'Reilly, W.J.: Aust. J. Pharm., 47:568, 1966.)*

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

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

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

Dissolution and Drug Absorption

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

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

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

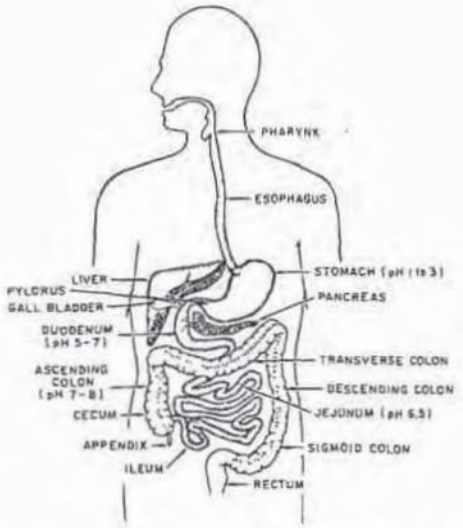

Fig. 3–3. *Anatomical diagram showing the digestive system including the locations involved in drug absorption and their respective pHs.*

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

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

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

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

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

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

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

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

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

Surface Area

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

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

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

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

Crystal or Amorphous Drug Form

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

Particle Size, Surface Area and Dissolution Rate

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

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

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

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

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

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

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

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

Particle Size and Solubility

In addition to dissolution rate, surface area can affect actual solubility, within reason. For example, in the following relationship:

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

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

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

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

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

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

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

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

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

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

Salt Forms

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

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

Other Factors

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

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

Bioavailability and Bioequivalence

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

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

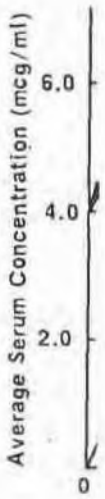

Fig. 3–4. *Serum conc*
the curve. (Courtesy of

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FDA Bioavailabilit Requirements[5]

The FDA requires
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2. *Abbreviated New*
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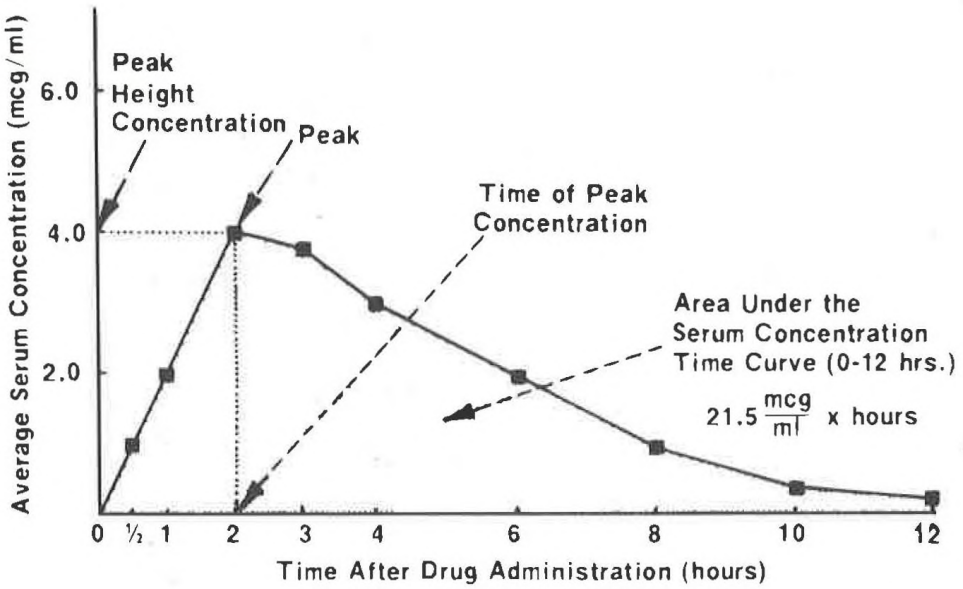

Fig. 3–4. *Serum concentration-time curve showing peak height concentration, time of peak concentration, and area under the curve. (Courtesy of D.J. Chodos and A.R. DiSanto, The Upjohn Company.)*

with patient response, (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[5]

The FDA requires bioavailability data submissions in the following instances.

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).
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 3–4. The verical 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. It should be understood that 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 (see Fig. 3–5). A urinalysis for the drug or its metabolities 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 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 3–4 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 following 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.

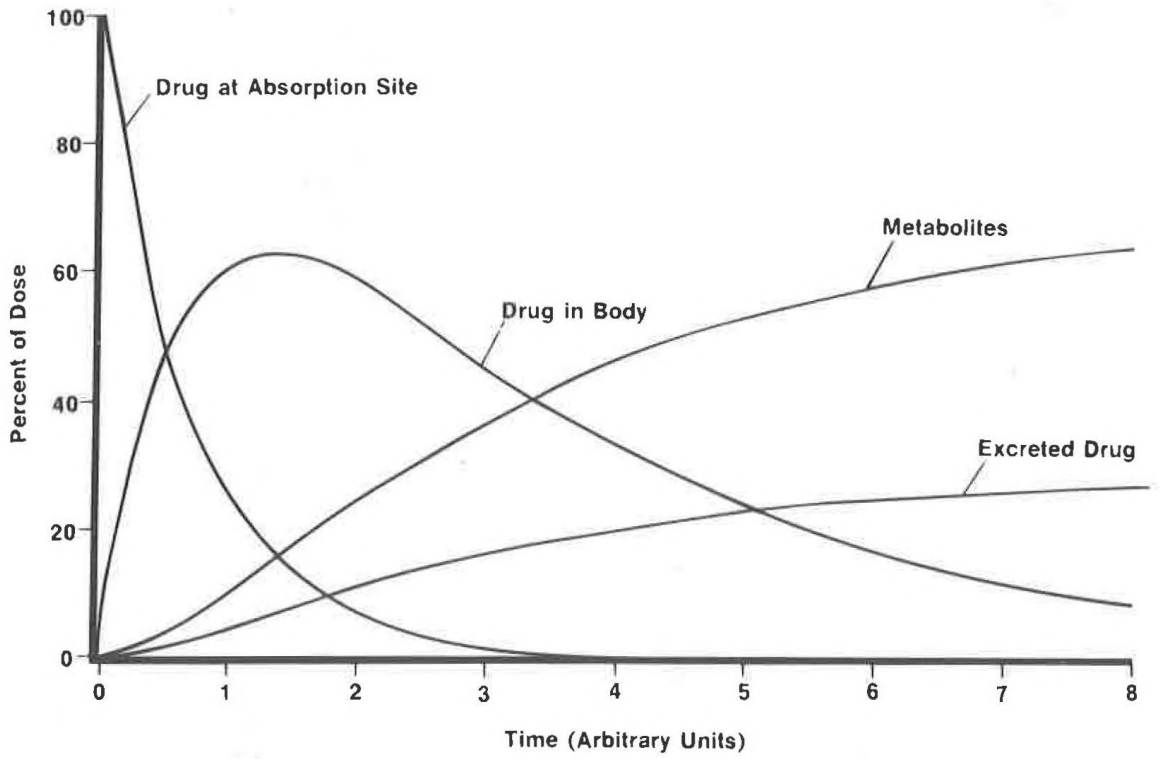

Fig. 3–5. *Time course of drug in the body. (From Rowland, M., and Tozer, T.N.:* Clinical Pharmacokinetics. *2nd Ed., Philadelphia, Lea & Febiger, 1989.)*

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, mcg/mL or mg% (mg/100 mL). Figure 3–6 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 mcg/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 3–6, it is apparent that 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 mcg/mL and the mimimum toxic concentration (MTC) was 4.0 mcg/mL as depicted in Figure 3–7, 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 3–8 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. It is evident that as the dose increases, the C_{max} is proportionately higher and the area-under-the-curve (AUC) proportionately greater. The peak time, T_{max}, if 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

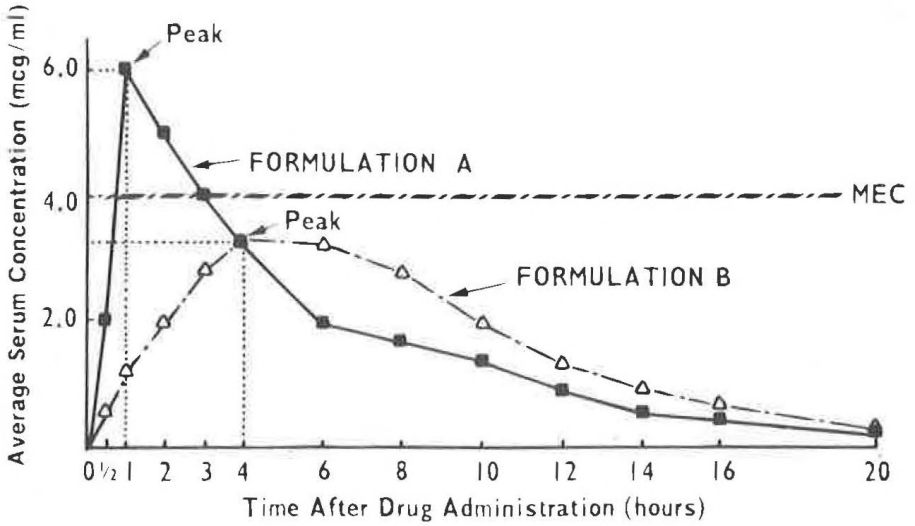

Fig. 3–6. *Serum concentration-time curve showing different peak height concentrations for equal amounts of drug from two different formulations following oral administration. (Courtesy of D.J. Chodos and A.R. DiSanto, The Upjohn Company.)*

(T_{max}). In Figure 3–6, the 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 of time 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 3–7, 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

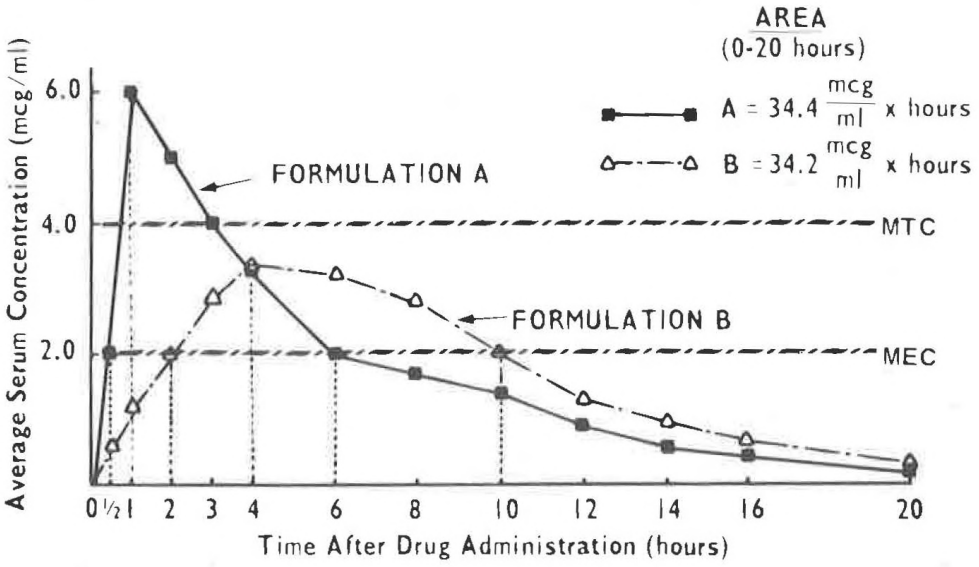

Fig. 3–7. *Serum concentration-time curve showing peak height concentrations, peak height times, times to reach minimum effective concentration (MEC) and areas under the curves for equal amounts of drug from two different formulations following oral administration. (Courtesy of D.I. Chodos and A.R. DiSanto, The Upjohn Company.)*

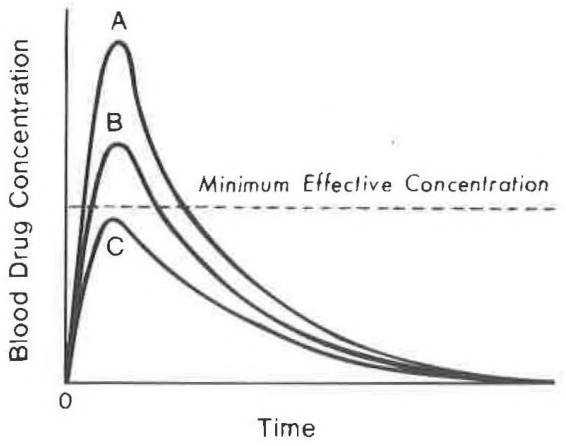

Fig. 3–8. *The influence of dose size on the resultant blood drug concentration-time curves when three different doses of the same drug are administered and the rates of drug absorption and elimination are equal after the three doses. A = 100 mg, B = 80 mg, C = 50 mg. (From C.T. Ueda, "Concepts in Clinical Pharmacology. Essentials of Bioavailability and Bioequivalence," 1979, The Upjohn Company, Reproduced with permission.)*

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 5½ 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.

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 3–7, 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 (Fig. 3–4) 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 much unalike in terms of peak height and time of peak, as those in Figure 3–7, may be much alike in terms of area under the curve, and thus in the amount of drug absorbed. As indicated in Figure 3–7, the area under the curve for formulation "A" is 34.4 mcg/mL × hours and for formulation "B" is 34.2 mcg/mL × hours, essentially the same. If equivalent doses of drug in different formulation produce *different* AUC values, differences exist

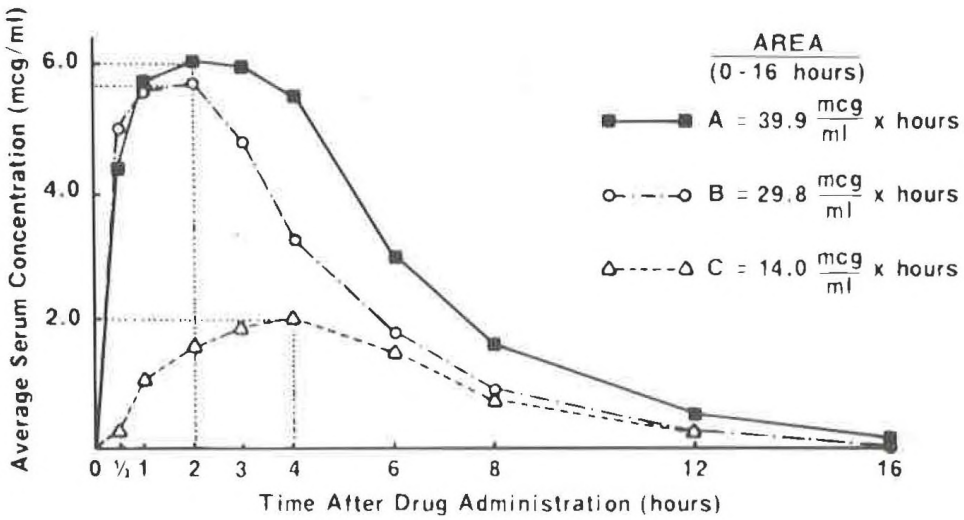

Fig. 3–9. *Serum concentration-time curve showing peak height concentrations, peak height times, and areas under the curves for equal amounts of drugs from three different formulations following oral administration. (Courtesy of D.J. Chodos and A.R. DiSanto, The Upjohn Company.)*

in the *extent* of absorption between the formulations. Figure 3–9 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., mcg/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 $\frac{1}{2}(C_{n+1} + C_n)(t_n - t_{n-1})$, where C_n and t_n are drug concentrations in the blood plasma, or serum, and time, respectively. Ueda demonstrates the use of the trapezoid by the data reproduced in Table 3–3 and plotted into a plasma drug concentration-time curve as shown in Figure 3–10.

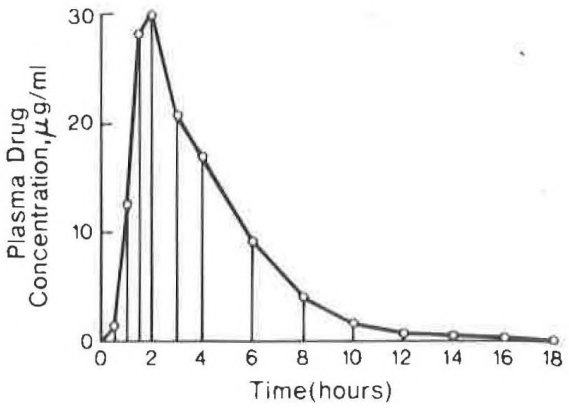

Fig. 3–10. *Estimation of area under the drug concentration-time curve using the trapezoidal rule (see Table 4–3 for raw data). (From C.T. Udea, "Concepts in Clinical Pharmacology. Essentials of Bioavailability and Bioequivalence," 1979, The Upjohn Company, Reproduced with permission.)*

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

Table 3–3. 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	$\frac{1}{2}(0 + 1)(0.5 - 0) = 0.25$
2	0.5	1	$\frac{1}{2}(1 + 11)(1 - 0.5) = 3.00$
3	1.0	11	$\frac{1}{2}(11 + 28)(1.5 - 1) = 9.75$
4	1.5	28	$\frac{1}{2}(28 + 30)(2 - 1.5) = 14.50$
5	2	30	$\frac{1}{2}(30 + 21)(3 - 2) = 25.50$
6	3	21	$\frac{1}{2}(21 + 17)(4 - 3) = 19.00$
7	4	17	$\frac{1}{2}(17 + 9)(6 - 4) = 26.00$
8	6	9	$\frac{1}{2}(9 + 4)(8 - 6) = 13.00$
9	8	4	$\frac{1}{2}(4 + 2)(10 - 8) = 6.00$
10	10	2	$\frac{1}{2}(2 + 1)(12 - 10) = 3.00$
11	12	1	$\frac{1}{2}(1 + 0)(18 - 12) = 3.00$
12	18	0	
			AUC = 123.00

* From C. T. Ueda, "Concepts in Clinical Pharmacology. Essentials of Bioavailability and Bioequivalence," 1979, The Upjohn Company, Reproduced with permission.

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 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.

It has become well established that 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 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.

It should be recognized that there are inherent differences in individuals which 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 published an annual *Approved Drug Products with Therapeutic Equivalence Evaluations* (also known as the "Orange Book"). This publication is updated monthly 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 3–4). For instance in the manufacture of a tablet, different 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 doage 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

Table 3–4. Some Factors Which Can Influence the Bioavailability of Orally Administered Drugs

I. *Drug Substance Physiochemical Properties*
  A. Particle Size
  B. Crystalline or Amorphous Form
  C. Salt Form
  D. Hydration
  E. Lipid/Water Solubility
  F. pH and pK_a
II. *Pharmaceutic Ingredients and Dosage Form Characteristics*
  A. Pharmaceutic Ingredients
    1. Fillers
    2. Binders
    3. Coatings
    4. Disintegrating Agents
    5. Lubricants
    6. Suspending Agents
    7. Surface Active Agents
    8. Flavoring Agents
    9. Coloring Agents
    10. Preservative Agents
    11. Stabilizing Agents
  B. Disintegration Rate (Tablets)
  C. Dissolution Time of Drug in Dosage Form
  D. Product Age and Storage Conditions
III. *Physiologic Factors and Patient Characteristics*
  A. Gastric Emptying Time
  B. Intestinal Transit Time
  C. Gastrointestinal Abnormality or Pathologic Condition
  D. Gastric Contents
    1. Other drugs
    2. Food
    3. Fluids
  E. Gastrointestinal pH
  F. Drug Metabolism (Gut and during first passage through liver).

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

Routes of Drug Administration

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

Table 3–5. Routes of Drug Administration

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

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

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

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