Modern Pharmaceutics

Third Edition, Revised and Expanded

DIFFUSION LAYER

DRUG PARTICLE SURFACE
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DIFFUSING MOLECULES

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DRUG PARTICLE SURFACE
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DIFFUSING MOLECULES

GI MEMBRANE

edited by
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Third Edition, Revised and Expanded

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Contents

Principles of Drug Absorption

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I. INTRODUCTION

Drugs are most often introduced into the body by the oral route of administration. In fact, the vast majority of drug dosage forms are designed for oral ingestion, primarily for ease of administration. It should be recognized, however, that this route may result in inefficient and erratic drug therapy. Whenever a drug is ingested orally (or by any nonvascular route), one would like to have rapid and complete absorption into the bloodstream for the following reasons:

1. If we assume that there is some relationship between drug concentration in the body and the magnitude of the therapeutic response (which is often the case), the greater the concentration achieved, the greater the response.
2. In addition to desiring therapeutic concentrations, one would like to obtain these concentrations rapidly. The more rapidly the drug is absorbed, the sooner the pharmacological response is achieved.
3. In general, one finds that the more rapid and complete the absorption, the more uniform and reproducible the pharmacological response becomes.
4. The more rapidly the drug is absorbed, the less chance there is of drug degradation or interactions with other materials present in the gastrointestinal tract.

In a broad sense, one can divide the primary factors that influence oral drug absorption and, thereby, govern the efficacy of drug therapy into the following categories: (a) physicochemical variables, (b) physiological variables, and (c) dosage form variables. For the most part, these variables will determine the clinical response to any drug administered by an extravascular route. Although often the total response to a drug given orally is a complex function of the aforementioned variables interacting together, the present discussion is limited to primarily the first two categories involving physicochemical and physiological factors. Dosage form variables influencing the response to a drug and the effect of route of administration are discussed in Chapters 4 and 5.

Almost all drugs in current use and those under development are relatively simple organic molecules obtained from either natural sources or by synthetic methods. This statement is especially true of those drugs administered orally, the route emphasized in this chapter. However, I would be derelict in not noting the virtual revolution in development of new therapeutic entities; those based on the incredible advances being made in the application of molecular biology and biotechnology. These new drugs, especially peptides and proteins, are not the small organic molecules stressed in this chapter. Indeed, those compounds have unique physicochemical properties that are quite different from those of small organic molecules, and they offer remarkable challenges for drug delivery. As a result, new and more complex physical delivery systems are being designed in conjunction with an examination of other, less traditional, routes of administration (e.g., nasal, pulmonary, transdermal, or other). Because of issues of instability in the gastrointestinal tract and poor intrinsic membrane permeability, it now appears unlikely that these new biotechnology-derived drugs will employ the oral route for administration to any appreciable extent. Numerous strategies, however, are being explored, and there is evidence that some measure of gastrointestinal absorption can be achieved for some peptides [1].

II. ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS OF THE GASTROINTESTINAL TRACT

The gastrointestinal tract (GIT) is a highly specialized region of the body, the primary functions of which involve the processes of secretion, digestion, and absorption. Since all nutrients needed by the body, with the exception of oxygen, must first be ingested orally, processed by the GIT, and then made available for absorption into the bloodstream, the GIT represents an important barrier and interface with the environment. The primary defense mechanisms employed by the gut to rid it of noxious or irritating materials are vomiting and diarrhea. In fact, emesis is often a first approach to the treatment of oral poisoning. Diarrheal conditions, initiated by either a pathological state or a physiological mechanism, will result in the flushing away of toxins or bacteria or will represent the response to a stressful condition. Indeed, the GIT is often the first site of the body's response to stress, a fact readily appreciated by students taking a final examination. The nearly instinctive gut response to stress may be particularly pertinent to patients needing oral drug therapy. Since stress is a fact of our daily lives, and since any illness requiring drug therapy may, in some degree, be considered stressful, the implications of the body's response to stress and the resulting influence on drug absorption from the gut may be extremely important.

Figure 1 illustrates the gross functional regions of the GIT. The liver, gallbladder, and pancreas, although not part of the gut, have been included, since these organs secrete materials vital to the digestive and certain absorptive functions of the gut. The lengths of various regions of the GIT are presented in Table 1. The small intestine, comprising the duodenum, jejunum, and ileum, represents greater than 60% of the length of the GIT, which is consistent with its primary digestive and absorptive functions. In addition to daily food and fluid intake (about 1–2 liters), the GIT and associated organs secrete about 8 liters of fluid per day. Of this total, between 100 and 200 ml of stool water is lost per day, indicating efficient absorption of water throughout the tract.

A. Stomach

After oral ingestion, materials are presented to the stomach, the primary functions of which are storage, mixing, and reducing all components to a slurry with the aid of gastric secretions;
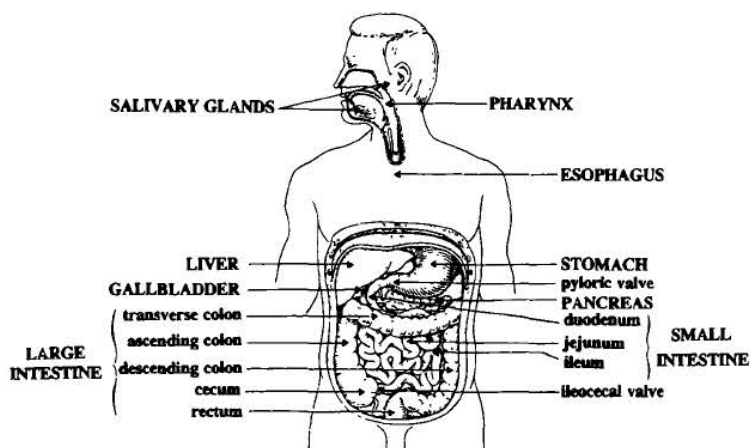
Fig. 1 Diagrammatic sketch of the gastrointestinal tract (and subdivisions of the small and large intestines) along with associated organs. (Modified from Ref. 2.)

and then emptying these contents in a controlled manner into the upper small intestine (duodenum). All of these functions are accomplished by complex neural, muscular, and hormonal processes. Anatomically, the stomach has classically been divided into three parts: fundus, body, and antrum (or pyloric part), as illustrated in Fig. 2. Although there are no sharp distinctions among these regions, the proximal stomach, made up of the fundus and body, serves as a reservoir for ingested material, and the distal region (antrum) is the major site of mixing motions and acts as a pump to accomplish gastric emptying. The fundus and body regions of the stomach have relatively little tone in their muscular wall, as a result these regions can distend outward to accommodate a meal of up to 1 liter.

A common anatomical feature of the entire GIT is its four concentric layers. Beginning with the luminal surface, these are the mucosa, submucosa, muscularis mucosa, and serosa. The three outer layers are similar throughout most of the tract; however, the mucosa has distinctive structural and functional characteristics. The mucosal surface of the stomach is lined by an epithelial layer of columnar cells, the surface mucous cells. Along this surface are many tubular invaginations, referred to as gastric pits, at the bottom of which are found specialized secretory cells. These secretory cells form part of an extensive network of gastric glands that produce and secrete about 2 liters of gastric fluid daily. The epithelial cells of the gastric mucosa represent one of the most rapidly proliferating epithelial tissues, being shed by the normal stomach at the rate of about a half million cells per minute. As a result, the surface epithelial

Table 1 Approximate Lengths of Various Regions of the Human Gastrointestinal Tract

Region	Length (m)
Duodenum	0.3
Jejunum	2.4
Ileum	3.6
Large Intestine	0.9–1.5
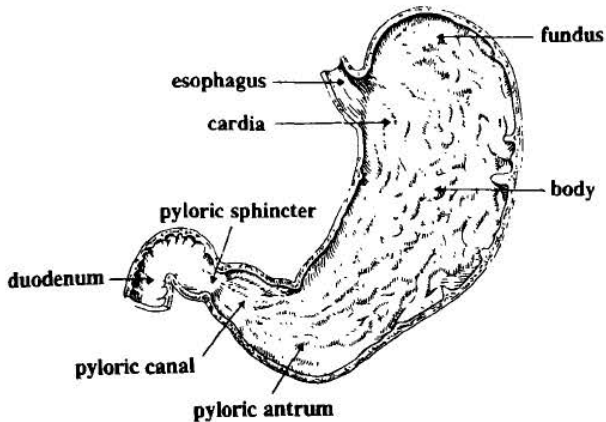
Fig. 2 Diagrammatic sketch of the stomach and anatomical regions. (Modified from Ref. 3.)

layer is renewed every 1–3 days. Covering the epithelial cell surface is a layer of mucus 1.0–1.5 mm thick. This material, made up primarily of mucopolysaccharides, provides a protective lubricating coat for the cell lining.

The next region, the muscularis mucosa, consists of an inner circular and an outer longitudinal layer of smooth muscle. This area is responsible for the muscular contractions of the stomach wall, which are needed to accommodate a meal by stretching, and for the mixing and propulsive movements of gastric contents. An area known as the lamina propria lies below the muscularis mucosa and contains a variety of tissue types, including connective and smooth muscles, nerve fibers, and the blood and lymph vessels. It is the blood flow to this region and to the muscularis mucosa that delivers nutrients to the gastric mucosa. The major vessels providing a vascular supply to the GIT are the celiac and the inferior and superior mesenteric arteries. Venous return from the GIT is through the splenic and the inferior and superior mesenteric veins. The outermost region of the stomach wall provides structural support for the organ.

B. Small Intestine

The small intestine has the shape of a convoluted tube and represents the major length of the GIT. The small intestine, comprising the duodenum, jejunum, and ileum, has a unique surface structure, making it ideally suited for its primary role of digestion and absorption. The most important structural aspect of the small intestine is the means by which it greatly increases its effective luminal surface area. The initial increase in surface area, compared with the area of a smooth cylinder, is due to the projection within the lumen of folds of mucosa, referred to as the folds of Kerckring. Lining the entire epithelial surface are fingerlike projections, the villi, extending into the lumen. These villi range in length from 0.5 to 1.5 mm, and it has been estimated that there are about 10–40 villi per square millimeter of mucosal surface. Projecting from the villi surface are fine structures, the microvilli (average length, 1 mm), which represent the final large increase in the surface area of the small intestine. There are approximately 600 microvilli protruding from each absorptive cell lining the villi. Relative to the surface of a smooth cylinder, the folds, villi, and microvilli increase the effective surface area by factors

(A)   (B)   (C)
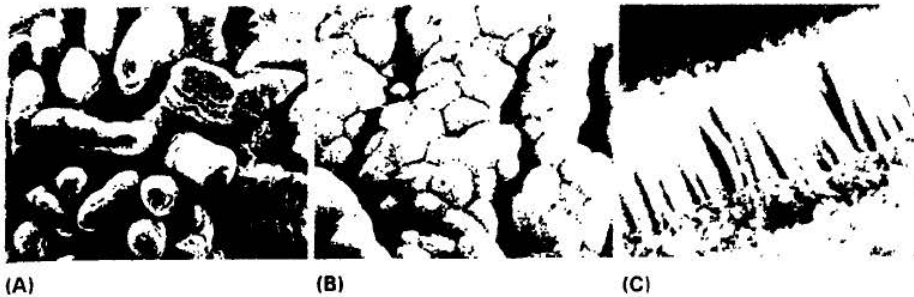
Fig. 3 (A) Photomicrograph of the human duodenal surface illustrating the projection of villi into the lumen (magnification ×75). The goblet cells appear as white dots on the villus surface. (B) Photomicrograph of a single human duodenal villus illustrating surface coverage by microvilli and the presence of goblet cells (white areas; magnification ×2400). (C) Photomicrograph illustrating the microvilli of the small intestine of the dog (magnification ×33,000). (From Ref. 4.)

of 3, 30, and 600, respectively. These structural features are clearly indicated in the photomicrographs shown in Fig. 3. A diagrammatic sketch of the villus is shown in Fig. 4.

The mucosa of the small intestine can be divided into three distinct layers. The muscularis mucosa, the deepest layer, consists of a thin sheet of smooth muscle three to ten cells thick and separates the mucosa from the submucosa. The lamina propria, the section between the muscularis mucosa and the intestinal epithelia, represents the subepithelial connective tissue space and, together with the surface epithelium, forms the villi structure. The lamina propria
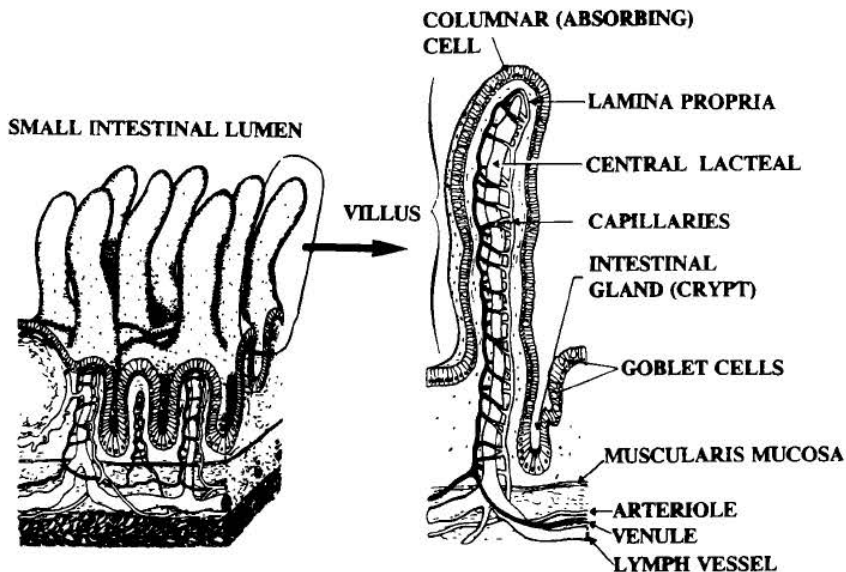
Fig. 4 Diagrammatic sketch of the small intestine illustrating the projection of the villi into the lumen (left) and anatomic features of a single villus (right). (Modified from Ref. 5.)

contains a variety of cell types, including blood and lymph vessels and nerve fibers. Molecules to be absorbed must penetrate this region to gain access to the bloodstream.

The third mucosal layer is that lining the entire length of the small intestine and represents a continuous sheet of epithelial cells. These epithelial cells are columnar, and the luminal cell membrane, upon which the microvilli reside, is called the apical cell membrane. Opposite this membrane is the basal plasma membrane, which is separated from the lamina propria by a basement membrane. A sketch of this cell is shown in Fig. 5. The primary function of the villi is absorption.

The microvilli region has also been referred to as the striated border. It is in this region that the process of absorption is initiated. In close contact with the microvilli is a coating of fine filaments composed of weakly acidic, sulfated mucopolysaccharides. It has been suggested that this region may serve as a relatively impermeable barrier to substances within the gut, such as bacteria and other foreign materials. In addition to increasing the effective luminal surface area, the microvilli region appears to be an area of important biochemical activity.

The surface epithelial cells of the small intestine are renewed rapidly and regularly. It takes about 2 days for the cells of the duodenum to be renewed completely. As a result of its rapid renewal rate, the intestinal epithelium is susceptible to various factors that may influence pro-liferation. Exposure of the intestine to ionizing radiation and cytotoxic drugs (such as folic acid antagonists and colchicine) reduce the cell renewal rate.

C. Large Intestine

The large intestine, often referred to as the colon, has two primary functions: the absorption of water and electrolytes, and the storage and elimination of fecal material. The large intestine, which has a greater diameter than the small intestine (ca., 6 cm), is connected to the latter at the ileocecal junction. The wall of the ileum at this point has a thickened muscular coat, called the ileocecal sphincter, which forms the ileocecal valve, the principal function of which is to prevent backflow of fecal material from the colon into the small intestine. From a functional point of view the large intestine may be divided into two parts. The proximal half, concerned
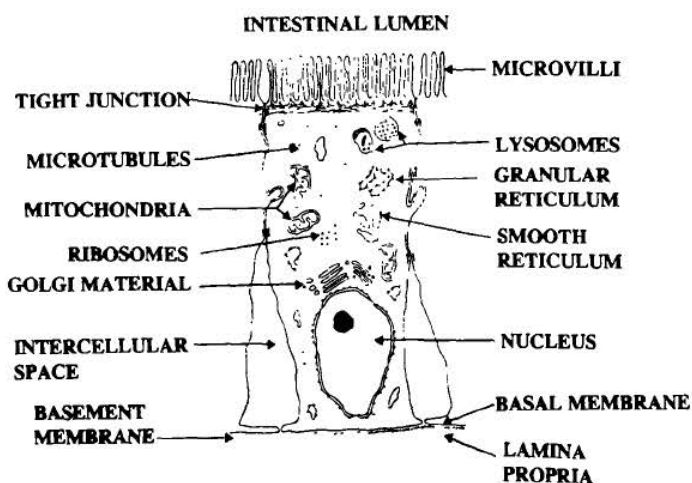
Fig. 5 Diagrammatic sketch of the intestinal absorptive cell. (Modified from Ref. 6.)

primarily with absorption, includes the cecum, ascending colon, and portions of the transverse colon. The distal half, concerned with storage and mass movement of fecal matter, includes part of the transverse and descending colon, the rectum, and anal regions, terminating at the internal anal sphincter (see Fig. 1).

In humans, the large intestine usually receives about 500 ml of fluidlike food material (chyme) per day. As this material moves distally through the large intestine, water is absorbed, producing a viscous and, finally, a solid mass of matter. Of the 500 ml normally reaching the large intestine, approximately 80 ml are eliminated from the gut as fecal material, indicating efficient water absorption.

Structurally, the large intestine is similar to the small intestine, although the luminal surface epithelium of the former lacks villi. The muscularis mucosa, as in the small intestine, consists of inner circular and outer longitudinal layers. Figure 6 illustrates a photomicrograph and diagrammatic sketches of this region.

(A)

(B)　　　　　　(C)
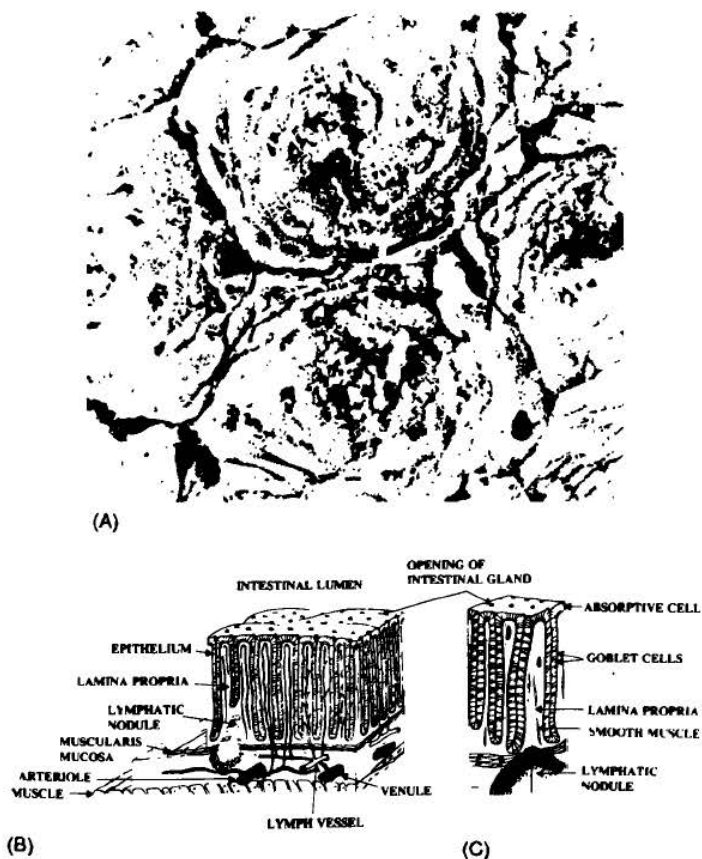
Fig. 6 (A) Scanning electron micrograph of the luminal surface of the large intestine (transverse colon; magnification ×60). (From Ref. 7.) (B) Schematic diagram showing a longitudinal cross section of the large intestine. (C) Enlargement of cross section shown in (B). (B and C modified from Ref. 8.)

D. Pathways of Drug Absorption

Once a drug molecule is in solution, it has the potential to be absorbed. Whether or not it is in a form available for absorption depends on the physicochemical characteristics of the drug (i.e., its inherent absorbability) and the characteristics of its immediate environment (e.g., pH, the presence of interacting materials, and the local properties of the absorbing membrane). If there are no interfering substances present to impede absorption, the drug molecule must come in contact with the absorbing membrane. To accomplish this, the drug molecule must diffuse from the gastrointestinal fluids to the membrane surface. The most appropriate definition of *drug absorption* is the penetration of the drug across the intestinal ''membrane'' and its appearance, unchanged in the blood draining the GIT. There are two important points to this definition: (a) It is often assumed that drug disappearance from the GI fluids represents absorption. This is true only if disappearance from the gut represents appearance in the bloodstream. This is often not the situation; for example, if the drug degrades in GI fluids or if it is metabolized within the intestinal cells. (b) The term *intestinal membrane* is rather misleading, since this membrane is not a unicellular structure, but really a number of unicellular membranes parallel to one another. In fact, relative to the molecular size of most drug molecules, the compound must diffuse a considerable distance. Thus, for a drug molecule to reach the blood, it must penetrate the mucous layer and brush border covering the GI lumen, the apical cell surface, the fluids within this cell, the basal membrane, the basement membrane, the tissue region of the lamina propria, the external capillary membrane, the cytoplasma of the capillary cell, and finally, the inner capillary membrane. Therefore, when the expression intestinal membrane is used, we are discussing a barrier to absorption consisting of several distinct unicellular membranes and fluid regions bounded by these membranes. Throughout this chapter, intestinal membrane will be used in that sense.

For a drug molecule to be absorbed from the GIT and gain access to the body (i.e., the systemic circulation) it must effectively penetrate all the regions of the intestine just cited. There are primarily three factors governing this absorption process once a drug is in solution: the physicochemical characteristics of the molecule, the properties and components of the GI fluids, and the nature of the absorbing membrane. Although penetration of the intestinal membrane is obviously the first part of absorption, we discuss the factors controlling penetration extensively in the following section. At this point, assume that the drug molecule has penetrated most of the barriers in the intestine and has reached the lamina propria region. Once in this region, the drug may either diffuse through the blood capillary membrane and be carried away in the bloodstream, or penetrate the central lacteal and reach the lymph. These functional units of the villi are illustrated in Fig. 4. Most drugs, if not all, reach the systemic circulation by the bloodstream of the capillary network in the villi. The primary reason for this route being dominant over lymphatic penetration is that the villi are highly and rapidly perfused by the bloodstream. Blood flow rate to the GIT in humans is approximately 500–1000 times greater than lymph flow. Thus, although the lymphatic system is a potential route for drug absorption from the intestine, under normal circumstances, it will account for only a small fraction of the total amount absorbed. The major exception to this rule will be drugs (and environmental toxicants, such as insecticides) that have extremely large oil/water partition coefficients (on the order of 10,000). By increasing lymph flow or, alternatively, by reducing blood flow, drug absorption by the lymphatic system may become more important. The capillary and lymphatic vessels are rather permeable to most low-molecular-weight and lipid-soluble compounds. The capillary membrane represents a more substantial barrier than the central lacteal to the penetration of very large molecules or combinations of molecules, as a result of frequent separations of cells along the lacteal surface. This route of movement is

important for the absorption of triglycerides, in the form of chylomicrons, which are rather large (about 0.5 μm in the diameter).

III. PHYSICOCHEMICAL FACTORS GOVERNING DRUG ABSORPTION

A. Oil/Water Partition Coefficient and Chemical Structure

As a result of extensive experimentation, it has been found that the primary physicochemical properties of a drug influencing its passive absorption into and across biological membranes are its oil/water partition coefficient ($K_{o/w}$), extent of ionization in biological fluids, determined by its pK_a value and pH of the fluid in which it is dissolved, and its molecular weight or volume. That these variables govern drug absorption is a direct reflection of the nature of biological membranes. The cell surface of biological membranes (including those lining the entire GIT) is lipid; as a result, one may view penetration into the intestine as a competition for drug molecules between the aqueous environment on one hand, and the lipidlike materials of the membrane, on the other. To a large extent, then, the principles of solution chemistry and the molecular attractive forces to which the drug molecules are exposed will govern movement from an aqueous phase to the lipidlike phase of the membrane.

At the turn of this century, Overton examined the osmotic behavior of frog sartorius muscle soaked in a buffer solution containing various dissolved organic compounds. He reasoned that, if the solute entered the tissue, the weight of the muscle would remain essentially unchanged; whereas, loss of weight would indicate an osmotic withdrawal of fluid and, hence, impermeability to the solute. He noted that, in general, the tissue was most readily penetrated by lipid-soluble compounds and poorly penetrated by lipid-insoluble substances. Overton was one of the first investigators to illustrate that compounds penetrate cells in the same relative order as their oil/water partition coefficients, suggesting the lipid nature of cell membranes. With animal or plant cells, other workers provided data in support of Overton's observations. The only exception to this general rule was the observation that very small molecules penetrate cell membranes faster than would be expected based on their $K_{o/w}$ values. To explain the rapid penetration of these small molecules (e.g., urea, methanol, formamide), it was suggested that cell membranes, although lipid, were not continuous, but were interrupted by small water-filled channels or "pores"; such membranes are best described as being lipid-sieve membranes. As a result, one could imagine lipid-soluble molecules readily penetrating the lipid regions of the membrane while small water-soluble molecules pass through the aqueous pores. Fordtran et al. [9] estimated the effective pore radius to be 7–8.5 and 3–3.8 Å in human jejunum and ileum, respectively. There may be a continuous distribution of pore sizes; a smaller fraction of larger ones and a greater fraction of smaller pores.

Our knowledge of biological membrane ultrastructure has increased considerably over the years as a result of rapid advances in instrumentation. Although there is still controversy over the most correct biological membrane model, the concept of membrane structure presented by Davson and Danielli, as a lipid bilayer is perhaps the one best accepted [10,11]. The most current version of that basic model is illustrated in Fig. 7 and is referred to as the *fluid mosaic* model of membrane structure. That model is consistent with what we have learned about the existence of specific ion channels and receptors within and along surface membranes.

Table 2 summarizes some literature data supporting the general dependence of the rate of intestinal absorption on $K_{o/w}$, as measured in the rat [13,14]. As with other examples that are available, as $K_{o/w}$ increases, the rate of absorption increases. One very extensive study [15–
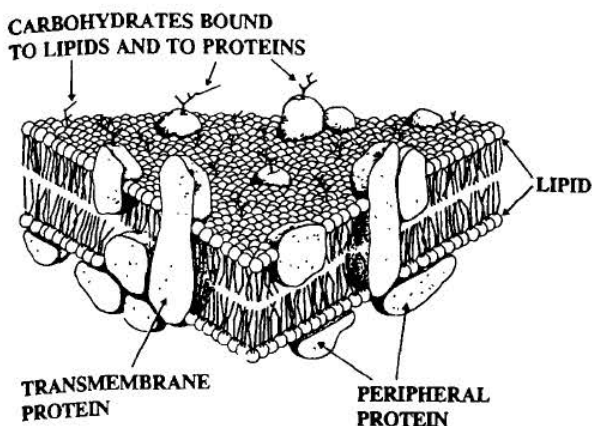
Fig. 7 Diagrammatic representation of the fluid mosaic model of the cell membrane. The basic structure of the membrane is that of a lipid bilayer in which the lipid portion (long tails) points inward and the polar portion (round head) points outward. The membrane is penetrated by transmembrane (or integral) proteins. Attached to the surface of the membrane are peripheral proteins (inner surface) and carbohydrates that bind to lipid and protein molecules (outer surface). (Modified from Ref. 12.)

17] has examined in depth the physicochemical factors governing nonelectrolyte permeability for several hundred compounds. This study employed an in vitro rabbit gallbladder preparation, the mucosal surface of which is lined by epithelial cells. The method used to assess solute permeability is based on measurement of differences in electrical potential (streaming potentials) across the membrane. The more permeable the compound, the smaller the osmotic pres-

Table 2 Influence of Oil/Water Partition Coefficient ($K_{o/w}$) on Absorption from the Rat Intestine

Compound	$K_{o/w}$	Percentage absorbed
Olive oil/water		
Valeramide	0.023	85
Lactamide	0.00058	67
Malonamide	0.00008	27
Chloroform/water		
Hexethal	> 100	44
Secobarbital	50.7	40
Pentobarbital	28.0	30
Cyclobarbital	13.9	24
Butethal	11.7	24
Allybarbituric Acid	10.5	23
Phenobarbital	4.8	20
Aprobarbital	4.9	17
Barbital	0.7	12

sure it exerts, and the smaller the osmotic fluid flow it produces in the opposite direction; this results in a small potential difference. If the compound is impermeable, it produces a large osmotic pressure and osmotic fluid flow, resulting in a large potential difference. Experimentally, one exposes the mucosal membrane surface to a buffer solution containing a reference compound to which the membrane is completely impermeable and measures the resulting potential difference. This is followed by exposing the same membrane to a solution of a test compound and again measuring the resulting potential difference. The ratio of the potential difference of the test compound to that of the reference compound is referred to as the *reflection coefficient* (σ). The reflection coefficient is a measure of the permeability of the test compound relative to a reference solute with the particular membrane being used. The less permeable the test compound, the closer the reflection coefficient approaches 1; the more permeable the test compound, the closer the coefficient approaches zero.

By using this method, Wright and Diamond were able to reach a number of important conclusions concerning patterns of nonelectrolyte permeability. In general, membrane permeability of a solute increases with $K_{O/w}$, supporting previous findings mentioned earlier. The two classes of exceptions to this pattern are (a) highly branched compounds, which penetrate the membrane more slowly than would be expected based on their $K_{O/w}$; and (b) smaller polar molecules, which penetrate the membrane more readily than would be expected based on their $K_{O/w}$. The latter observation has been noted by other workers and, as mentioned earlier, it has resulted in the development of the lipid-sieve membrane concept, whereby one envisions aqueous pores in the membrane surface. The authors postulate that these small, polar, relatively lipid-insoluble compounds penetrate the membrane by following a route lined by the polar groupings of membrane constituents (i.e., localized polar regions). This concept is an attractive structural explanation of what have been referred to as pores. The accessibility of this route would be limited primarily by the molecular size of the compound as a result of steric hindrance. In fact, it is the first one or two members of a homologous series of compounds that are readily permeable, but beyond these members, it is primarily $K_{O/w}$ that dictates permeability. Table 3 illustrates this effect for several members of various homologous series. Recall that

Table 3 Influence of Chain Length on Membrane Permeability Within Several Homologous Series[a]

Compound	Reflection coefficient, σ	
Urea	0.29	↑
Methyl urea	0.54	│
Ethyl urea	0.92	│
Propyl urea	0.93	—
Butyl urea	0.70	↓
Malononitrile	0.09	↑
Succinonitrile	0.30	—
Glutaronitrile	0.21	↓
Methylformamide	0.28	↑
Methylacetamide	0.51	—
Methylproprionamide	0.22	↓

[a]The reflection coefficient σ is defined in the text The direction of the arrows indicates an increase in permeability from the least permeable member of the series.

the smaller the σ, the more permeable the compound. In each instance, permeability decreases after the first member, reaches a minimum, and then increases again.

The other anomalous behavior was the smaller-than-expected permeability of highly branched compounds. This deviation has been explained on the basis that membrane lipids are subject to a more highly constrained orientation (probably a parallel configuration of hydrocarbon chains of fatty acids) than are those in a bulk lipid solvent. As a result, branched compounds must disrupt this local lipid structure of the membrane and will encounter greater steric hindrance than will a straight-chain molecule. This effect with branched compounds is not adequately reflected in simple aqueous–lipid partitioning studies (i.e., in the $K_{O \cdot w}$ value).

With the exception of rather small polar molecules, most compounds, including drugs, appear to penetrate biological membranes by a lipid route. As a result, the membrane permeability of most compounds is dependent on $K_{O/w}$. The physicochemical interpretation of this general relationship is based on the atomic and molecular forces to which the solute molecules are exposed in the aqueous and lipid phases. Thus, the ability of a compound to partition from an aqueous to a lipid phase of a membrane involves the balance between solute–water and solute–membrane intermolecular forces. If the attractive forces of the solute–water interaction are greater than those of the solute–membrane interaction, membrane permeability will be relatively poor and vice versa. In examining the permeability of a homologous series of compounds and, therefore, the influence of substitution or chain length on permeability, one must recognize the influence of the substituted group on the intermolecular forces in aqueous and membrane phases (e.g., dipole–dipole, dipole-induced dipole, or van der Waals forces). The membrane permeabilities of the nonelectrolytes studied appear to be largely determined by the number and strength of the hydrogen bonds the solute can form with water. Thus, nonelectrolyte permeation is largely a question of physical organic chemistry in aqueous solution. Table 4 summarizes some of the interesting findings of Diamond and Wright relative to the influence of substituent groups on membrane permeation. These data have been interpreted based on the solutes' ability to form hydrogen bonds with water.

Within a homologous series of compounds, the first few small members are readily permeable, owing to the polar route of membrane penetration. Permeability decreases for the next several members (i.e., σ increases), and then increases as the carbon chain length increases. The regular influence of chain length on permeability is a result not of increased solubility in the lipid phase of the membrane, but of the unique interaction of hydrocarbon chains with water. The nonpolar hydrocarbon molecules are surrounded by a local region of water that has a more highly ordered structure than bulk water. This "iceberg" structure of water results in increased $K_{O \cdot w}$ and membrane permeability as the carbon chain length is increased owing to the compound being "pushed out" of the aqueous phase by the resulting gain in entropy.

There have been several, albeit limited, attempts to develop quantitative, structure–activity relationship in drug absorption [18,19]. Such relationships could prove extremely useful to produce optimum absorption characteristics in the early stages of drug design.

B. The pK_a and pH

Most drug molecules are either weak acids or bases that will be ionized to an extent determined by the compound's pK_a and the pH of the biological fluid in which it is dissolved. The importance of ionization in drug absorption is based on the observation that the nonionized form of the drug has a greater $K_{O/w}$ than the ionized form, and since $K_{O/w}$ is a prime determinant of membrane penetration, ionization would be expected to influence absorption. The observation that pH influences the membrane penetration of ionizable drugs is not a recent finding. At the turn of the century, Overton was able to relate pH to the rate of penetration of various alkaloids

Table 4 Influence of Chemical Substitution on the Membrane Permeability of Several Series of Nonelectrolytes

Substituent group	Influence on membrane permeability	Compound	Example	σ^a
Alcoholic hydroxyl group (—OH)	a. At any given chain length, permeability decreases as the number of —OH groups increases	n-Propanol	$CH_3CH_2CH_2OH$	0.02
		1,2-Propanediol	$CH_3CHOHCH_2OH$	0.84
		Glycerol	$CH_2OHCHOHCH_2OH$	0.95
	b. Intramolecular H-bonds formed between adjacent —OH groups result in greater permeability, compared with the same compound with nonadjacent —OH groups owing to decreased H-bond formation with water	2,3-Butanediol	$CH_3CHOHCHOHCH_3$	0.74
		1,3-Butanediol	$CH_3CHOHCH_2CH_2OH$	0.77
		1,4-Butanediol	$CH_2OHCH_2CH_2CH_2OH$	0.86
Ether group (—O—)	Has less of an influence than an —OH group in decreasing permeability	n-Propanol	$CH_3CH_2CH_2OH$	0.02
		Ethyleneglycol-methyl ether	$CH_3—O—CH_2CH_2OH$	0.15
		1,2-Propanediol	$CH_3CHOHCH_2OH$	0.84
Carbonyl group Ketone (—C=O) Aldehyde (—HC=O)	Has less of an influence than an —OH group in decreasing permeability; difficulty in measuring permeability of these compounds per se, as many are unstable in solution forming diols and enolic tautomers	Acetone	$CH_3\overset{O}{\overset{\|}{C}}CH_3$	0.01
		2-Propanol	$CH_3CHOHCH_3$	0.10
		2,5-Hexanedione	$CH_3\overset{O}{\overset{\|}{C}}CH_2 CH_2 \overset{O}{\overset{\|}{C}}CH_3$	0.00
		2,5-Hexanediol	$CH_3CHOHCH_2CH_2CHOHCH_3$	0.59
Ester group $\overset{O}{\overset{\|}{(—C—O—)}}$	Has less of an influence than an —OH group in decreasing permeability	1,2-Propanediol-1-acetate	$CH_3\overset{O}{\overset{\|}{C}}—O—CH_2CHOHCH_3$	0.31
		1,5-Pentanediol	$CH_2OH(CH_2)_3CH_2OH$	0.71
Amide group $\overset{O}{\overset{\|}{—C—NH_2}}$	Causes a greater decrease in permeability than any of the above groups	n-Propanol	$CH_3CH_2CH_2OH$	0.02
		Acetone	$CH_3\overset{O}{\overset{\|}{C}}CH_3$	0.08
		Ethyleneglycol-methyl ether	$CH_3—O—CH_2CH_2OH$	0.15
		Proprionamide	$CH_3CH_2\overset{O}{\overset{\|}{C}}NH_2$	0.66
Urea derivatives $\overset{O}{\overset{\|}{R—NH—C—NH_2}}$	Have lower permeability than amides with the same number of carbons and are about as impermeable as the corresponding dihydroxyl alcohols	n-Butanol	$CH_3CH_2CH_2CH_2OH$	0.01
		n-Butryamide	$CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}—NH_2$	0.42
		1,4-Butanediol	$CH_2OHCH_2CH_2CH_2OH$	0.86
		n-propyl urea	$CH_3CH_2CH_2NH \overset{O}{\overset{\|}{C}}NH_2$	0.89

Table 4 Continued

Substituent group	Influence on membrane permeability	Compound	Example	σ^a
α-Amino acids R–CHCOOH | NH$_2$	Have the lowest $K_{o/w}$ values of all organic molecules and are essentially impermeable owing to large dipole–dipole interactions with water	Proprionamide	$\overset{O}{\overset{\|}{CH_3CH_2CNH_2}}$	0.66 ▲
		1-Amino-2-propanol	$CH_3CHOHCH_2NH_2$	0.89
		1,3-Propanediol	$CH_2OHCH_2CH_2OH$	0.92
		Alanine	$\overset{H_2N\ O}{\overset{\|\ \ \|}{CH_3CHC–OH}}$	1.06
Sulfur Functional Groups				
Sulfur replacement of oxygen	a. Have greater $K_{o/w}$ values and permeate membranes more readily than the corresponding oxygen compound; a result of poor H-bond formation between sulfur and water compared with the oxygen analog	1-Thioglycerol	$CH_2OHCHOHCH_2SH$	0.69 ▲
		Glycerol	$CH_2OHCHOHCH_2OH$	0.95
		Thiodiglycol	$(OHCH_2CH_2)_2S$	0.71
		Diethylene glycol	$(OHCH_2CH_2)_2O$	0.92
	b. Sulfoxides (R$_2$S=O) are less permeable than the corresponding ketone (R$_2$C=O), owing to stronger H-bond formation with water	Acetone	$\overset{O}{\overset{\|}{CH_3CCH_3}}$	0.01 ▲
		Dimethyl sulfoxide	$\overset{O}{\overset{\|}{CH_3SCH_3}}$	0.92

Source. Ref. 15–17

^{a}The reflection coefficient σ is defined in the text. The direction of the arrows indicates an increase in permeability.

into cells, and he noted the resulting influence on toxicity. Other investigators have made similar observations relative to the influence of pH on the penetration of alkaloids through the conjunctival and mammalian skin [20,21]. The rate of penetration of these weak bases is enhanced by alkalinization owing to a greater fraction of the nonionized species being present. Travell [22] examined the influence of pH on the absorption of several alkaloids from the stomach and intestine of the cat. After ligation of the proximal and distal ends of the stomach of an anesthetized cat, a 5.0-mg/kg solution of strychnine at pH 8.5 produced death within 24 min; however, the same dose at pH 1.2 produced no toxic response. Identical results were found with nicotine, atropine, and cocaine. The same trend was also seen when the drug solution was instilled into ligated intestinal segments and after oral administration (by stomach tube) to ambulatory animals. These results indicate that alkaloids, which are weak bases, will be more rapidly absorbed in the nonionized form (high pH) compared with the ionized form (low pH). This fundamental observation is sometimes overlooked in oral acute drug toxicity studies.

In 1940, Jacobs [23] made use of the Henderson–Hasselbalch equation to relate pH and pK_a to membrane transport of ionizable compounds. Extensive experimentation by a group of

investigators in the early 1950s [14,23–28] quantitated many of the aforementioned observations concerning the influence of pH and pK_a on drug absorption from the GIT. These studies have resulted in the so-called pH-partition hypothesis. In essence, this hypothesis states that ionizable compounds penetrate biological membranes primarily in the nonionized form (i.e., nonionic diffusion). As a result, acidic drugs should best be absorbed from acidic solutions for which pH < pK_a, whereas basic compounds would best be absorbed from alkaline solutions for which pH > pK_a. The data in Table 5 illustrate this principle.

These investigators noted some inconsistencies in their data, however, as some compounds (e.g., salicylic acid) that were essentially completely ionized in the buffer solution, nevertheless, were rapidly absorbed. To explain these exceptions, it was suggested that there was a ''virtual membrane pH'' (about pH 5.3), different from the bulk pH of the buffer solution, which was the actual pH determining the fraction of drug nonionized and, hence, dictating the absorption pattern. Although there may indeed be an effective pH at the immediate surface of the intestinal membrane, different from the pH of solutions bathing the lumen, there is overwhelming experimental evidence indicating that many drugs in the ionic form may be well absorbed. Over the years, there has been an unqualified acceptance of the pH–partition hypothesis and, as a result, many texts and considerable literature on drug absorption indicate that acidic drugs are best absorbed from the acidic gastric fluids of the stomach, and basic drugs best absorbed from the relatively more alkaline intestinal fluids. If all other conditions were the same, the nonionized form of the solution would be more rapidly absorbed than the ionized form. However, conditions along the GIT are not uniform and, hence, most drugs, whether ionized or nonionized (i.e., regardless of pH), are best absorbed from the small intestine as a result of the large absorbing surface area of this region. A good example to illustrate this point is presented in Table 6. There are three important comparisons that should be made in examining these data:

1. By comparing gastric absorption at pH 3 and pH 6 when surface area and factors other than pH are constant, one sees that the general principle is supported; acid drugs are more rapidly absorbed from acidic solution, whereas basic drugs are more rapidly absorbed from relatively alkaline solution.
2. At the same pH (i.e., pH 6) acidic and basic drugs are more rapidly absorbed from the intestine compared with the stomach, by virtue of the larger intestinal surface area.

Table 5 Influence of pH on Drug Absorption from the Small Intestine of the Rat*

		Percentage absorbed			
Drug	pK_a	pH 4	pH 5	pH 7	pH 8
Acids					
5-Nitrosalicylic acid	2.3	40	27	<2	<2
Salicylic acid	3.0	64	35	30	10
Acetylsalicylic acid	3.5	41	27	—	—
Benzoic acid	4.2	62	36	35	5
Bases					
Aniline	4.6	40	48	58	61
Aminopyrine	5.0	21	35	48	52
p-Toluidine	5.3	30	42	65	64
Quinine	8.4	9	11	41	54

*Drug buffer solutions were perfused through the in situ rat intestine for 30 min and percentage of drug absorbed was determined from four subsequent 10-min samples of the buffer solution.

Table 6 Influence of pH on Drug Absorption from the Stomach and Intestine of the Rat[a]

| | Apparent first-order absorption rate constant (min^{-1}) | | |
| | Stomach | | Intestine |
Drug	pH 3	pH 6	pH 6
Acids			
Salicylic acid	0.015	0.0053	0.085
Barbital	0.0029	0.0026	0.037
Sulfaethidole	0.004	0.0023	0.022
Bases			
Prochlorperazine	<0.002	0.0062	0.030
Haloperidol	0.0028	0.0041	0.028
Aminopyrine	<0.002	0.0046	0.022

[a]Drug buffer solutions were placed into the GIT of an in situ rat preparation. The apparent first-order absorption rate constants are based on drug disappearance from the buffer solution.

3. Acidic drugs are more rapidly absorbed from the intestine (pH 6), although there is substantial ionization, compared with the rate of gastric absorption, even at a pH at which the drug is in a far more acidic solution (pH 3). Again, this is primarily a result of surface area differences.

Interestingly, in an analysis of the original data used in developing the pH–partition hypothesis, Benet [30] has shown that these data support the findings in point 3. The pH–partition hypothesis provides a useful guide in predicting general trends in drug absorption, and it remains an extremely useful concept. There are numerous examples illustrating the general relation among pH, pK_a, and drug absorption developed in that hypothesis [31–33]. The primary limitation of this concept is the assumption that only nonionized drug is absorbed, when, in fact, the ionized species of some compounds can be absorbed, albeit at a slower rate. There is also the presence of unstirred water layers at the epithelial membrane surface that can alter the rate of drug diffusion [34–37]. Furthermore, the hypothesis is based on data obtained from drug in solution. In a practical sense, there are other considerations that are more likely to govern the pattern of drug absorption, and these include dissolution rate from solid dosage forms, the large intestinal surface area, and the relative residence times of the drug in different parts of the GIT. These factors are discussed in the following section. Numerous authors have reviewed the inconsistencies in the pH–partition hypothesis, and they place the issue in its proper perspective [30,38,39]. In general, then, drug absorption in humans takes place primarily from the small intestine, regardless of whether the drug is a weak acid or a base.

C. Mechanisms of Drug Absorption

A thorough discussion of the mechanisms of absorption is provided in Chapter 4. Water-soluble vitamins (B_2, B_{12}, and C) and other nutrients (e.g., monosaccharides and amino acids) are absorbed by specialized mechanisms. With the exception of various antimetabolites used in cancer chemotherapy, L-dopa, and certain antibiotics (e.g., aminopenicillins, aminocephalosporins), virtually all drugs are absorbed in humans by a passive diffusion mechanism. Passive diffusion indicates that the transfer of a compound from an aqueous phase through a membrane may be described by physicochemical laws and by the properties of the membrane. The

membrane itself is passive, in that it does not partake in the transfer process, but acts as a simple barrier to diffusion. The driving force for diffusion across the membrane is the concentration gradient (more correctly, the activity gradient) of the compound across that membrane. This mechanism of membrane penetration may be described mathematically by Fick's first law of diffusion, which has been simplified by Riggs [40] and discussed by Benet [30].

$$\left(\frac{dQ_b}{dt}\right)_{g \to b} = D_m A_m R_{m/aq} \left[\frac{C_g - C_b}{\Delta X_m}\right] \tag{1}$$

The derivative on the left side of the equation represents the rate of appearance of drug in the blood (amount/time) when the drug diffuses from the gut fluids g to the blood b. The expression reads, the rate of change of the quantity Q entering the bloodstream. The other symbols have the following meanings (and units): D_m, the diffusion coefficient of the drug through the membrane (area/time); A_m, the surface area of the absorbing membrane available for drug diffusion (area); $R_{m/aq}$, the partition coefficient of the drug between the membrane and aqueous gut fluids (unitless); $C_g - C_b$, the concentration gradient across the membrane, representing the difference in the effective drug concentration (i.e., activity) in the gut fluids C_g at the site of absorption and the drug concentration in the blood C_b at the site of absorption (amount/volume); and ΔX_m, the thickness of the membrane (length). This equation nicely explains several of the observations discussed previously. Thus, rate of drug absorption is directly dependent on the membrane area available for diffusion, indicating that one would expect more rapid absorption from the small intestine, compared with the stomach. Furthermore, the greater the membrane aqueous fluid partition coefficient ($R_{m/aq}$), the more rapid the rate of absorption, supporting the previous discussion indicating the dependence of absorption rate on $K_{O/W}$. We know that pH will produce a net effect on absorption rate by altering several of the parameters in Eq. (1). As the pH for a given drug will determine the fraction nonionized, the value of $R_{m/aq}$ will change with pH, generally increasing as the nonionized fraction increases. Depending on the relative ability of the membrane to permit the diffusion of the nonionized and ionized forms, C_g will be altered appropriately. Finally, the value of D_m may be different for the ionized and nonionized forms of the compound. For a given drug and membrane and under specified conditions, Eq. (1) is made up of several constants that may be incorporated into a large constant (K) referred to as the permeability coefficient:

$$\left(\frac{dQ_b}{dt}\right)_{g \to b} = K(C_g - C_b) \tag{2}$$

where K incorporates D_m, A_m, $R_{m/aq}$, and ΔX_m and has units of volume/time, which is analogous to a flow or clearance term. Since the blood volume is rather large compared with the gut fluid volume, and since the rapid circulation of blood through the GIT continually moves absorbed drug away from the site of absorption, C_g is much greater than C_b. This is often referred to as a *sink condition* for drug absorption, indicating a relatively small drug concentration in the bloodstream at the absorption site. As a result, Eq. (2) may be simplified:

$$\left(\frac{dQ_b}{dt}\right)_{g \to b} = KC_g \tag{3}$$

Equation (3) is in the form of a differential equation describing a first-order kinetic process and, as a result, drug absorption generally adheres to first-order kinetics. The rate of absorption should increase directly with an increase in drug concentration in the GI fluids.

Figure 8 illustrates the linear dependence of absorption rate on concentration for several compounds placed into the *in situ* rat intestine. The slopes of these lines represent the rate constant K for absorption in Eq. (3). Alternatively, one may express these data as the percentage absorbed per unit of time as a function of concentration or amount. Several examples illustrating such a treatment are listed in Table 7. As can be seen, for the compounds investigated, the percentage absorbed in any given period is independent of concentration, indicating that these compounds are absorbed by a passive diffusion, or first-order kinetic, process over the concentration ranges studied. Similar studies by other investigators employing an *in situ* rat intestine preparation indicate that several other drugs (see those listed in Table 6) are absorbed in a first-order kinetic fashion.

It is far more difficult to establish the mechanism(s) of drug absorption in humans. Most investigators analyze drug absorption data in humans (from blood or urine data) by assuming first-order absorption kinetics. For the most part, this assumption seems quite valid, and the results of such analyses are consistent with that assumption. As discussed in Chapter 3, one method used to assess the mechanism of drug absorption in humans is based on a pharmacokinetic treatment of blood or urine data and the preparation of log percentage unabsorbed *versus* time plots as developed by Wagner and Nelson [41]. If a straight-line relationship is found, this is indicative of an apparent first-order absorption process, for which the slope of that line represents the apparent first-order absorption rate constant. Some cautions must be taken in the application of this method, as pointed out by several investigators [42,43]. Although the overall absorption process in humans, for many drugs, appears consistent with the characteristics of a first-order kinetic process, there are some questions about which of the sequential steps in the absorption process is rate-limiting. As discussed in a thorough review of mass transport phe-

Concentration, M

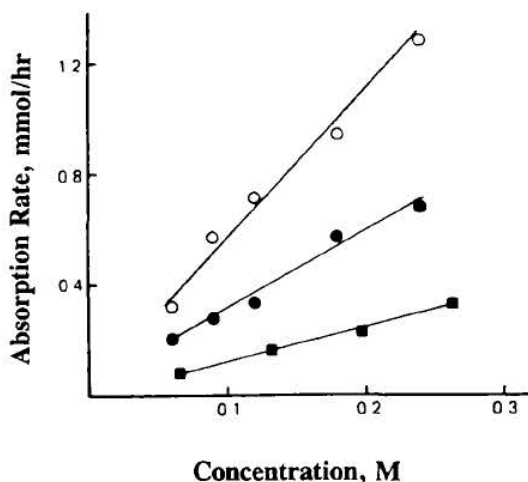**Fig. 8** Influence of concentration on the rate of absorption from the in situ rat intestine. The linear dependence of absorption rate on concentration suggests an apparent first-order absorption process over the range studied. Absorption rates have been calculated from the data in Ref. 13 and the straight lines are from linear regression of the data: (open circle) erythritol; (solid circle) urea; (solid square) malonamide.

Table 7 Influence of Concentration on the Absorption of Various Solutes from the In Situ Rat Intestine

Compound	Concentration (mM)	Percentage absorbed	Compound	Concentration (mM)	Percentage absorbed
Urea[a]	60	20.9	Salicylic Acid[b]	1	12
	90	19.0		2	12
	120	17.0		10	13
	180	20.0			
	240	17.8	Aniline[b]	1	44
Erythritol[a]	60	54.1			
	90	65.0	Benzoic acid[b]	1	12
	120	62.2		2	12
	180	54.4		10	13
	240	55.5			
			Quinine[b]	1	20
Malonamide[a]	66	16.9		10	20
	132	16.8		0.1	58
	198	16.5	Aniline[c]		
	264	18.4		1	54
				10	59
				20	54

Source: [a]Ref. 13, [b]Ref. 14; [c]Ref. 27.

nomena [44], the oil/water partition coefficient of a solute ($K_{o/w}$) will govern its movement across a lipidlike membrane as long as the membrane is the predominant barrier to diffusion. However, for such membranes, when the $K_{o/w}$ becomes very large, the barrier controlling diffusion may no longer be the membrane, but rather, an aqueous diffusion layer surrounding the membrane. Thus, for some molecules, depending on their physicochemical characteristics, the rate-limiting step in membrane transport will be movement through or out of the membrane, whereas for other compounds the rate-limiting step will be diffusion through an aqueous layer. Several investigators have discussed such behavior for a variety of compounds [45–48]. Wagner and Sedman [38] have provided an extensive analysis of much of the previous literature on drug absorption, and based on their mathematical models, they suggest that absorption may be rate-limiting by drug transfer out of the membrane. Other investigators have formulated different models to help conceptualize the transport process [49,50]. Our incomplete understanding of drug transport across biological membranes is not that surprising, given the complexity of the system and the experimental requirements needed to make unequivocal statements about this process on a molecular level. More definitive data are needed to completely characterize and better understand the complex process of drug absorption.

The analysis of absorption data in humans in recent years has moved away from the more traditional modeling and data-fitting techniques [51]. Absorption processes are now more often characterized by a mean absorption (or input) time (i.e., the average amount of time that the drug molecules spend at the absorption site) or by a process called deconvolution. The former analysis results in a single value (similar to absorption half-life), and the latter results in a profile of the absorption process as a function of time (e.g., absorption rate vs. time). These approaches offer additional ways of interpreting the absorption process.

Equation (1) suggests that diluting the GI fluids will decrease drug concentration in these fluids (C_g), lower the concentration gradient ($C_g - C_b$), and thus reduce the rate of absorption.

In fact, oral dilution is often suggested as an emergency first aid approach in treating cases of oral overdose. There are data from experiments in rats that question the usefulness of this procedure. Henderson et al. [52] found that pentobarbital and quinine were absorbed more rapidly and to a greater extent from larger than from smaller volumes of water, whereas volume had no influence on aspirin absorption. These authors suggest that reduction in the concentration gradient is offset by a greater interfacial area between solution and membrane, as a result of the larger fluid volume. This effectively increases the surface area term (A_m) in Eq. (1). Although other factors may be involved, one has to question oral dilution procedures in treating oral overdose.

Most drugs appear to be absorbed in humans by passive diffusion. Since many essential nutrients (e.g., monosaccharides, amino acids, and vitamins) are water-soluble, they have low oil/water partition coefficients, which would suggest poor absorption from the GIT. However, to ensure adequate uptake of these materials from food, the intestine has developed specialized absorption mechanisms that depend on membrane participation and require that the compound have a specific chemical structure. Since these processes are discussed in Chapter 4, we will not dwell on them here. Absorption by a specialized mechanism (from the rat intestine) has been shown for several agents used in cancer chemotherapy (5-fluorouracil and 5-bromouracil) [53,54], which may be considered ''false'' nutrients, in that their chemical structures are very similar to essential nutrients for which the intestine has a specialized transport mechanism. It would be instructive to examine some studies concerned with riboflavin and ascorbic acid absorption in humans, as these illustrate how one may treat urine data to explore the mechanism of absorption. If a compound is absorbed by a passive mechanism, a plot of amount absorbed (or amount recovered in the urine) versus dose ingested will provide a straight-line relationship. In contrast, a plot of percentage of dose absorbed (or percentage of dose recovered in the urine) versus dose ingested will provide a line of slope zero (i.e., a constant fraction of the dose is absorbed at all doses). If the absorption process requires membrane involvement, the absorption process may be saturated as the oral dose increases, making the process less efficient at larger doses. As a result, a plot of amount absorbed versus dose ingested will be linear at low doses, curvilinear at larger doses, and approach an asymptotic value at even larger doses. One sees this type of relationship for riboflavin and ascorbic acid in Figs. 9A and C, suggesting non-passive absorption mechanisms in humans [55,56]. This nonlinear relationship is reminiscent of Michaelis–Menten saturable enzyme kinetics from which one may estimate the kinetic parameters (K_m and V_{max}) associated with the absorption of these vitamins. Figures 9B and D illustrate an alternative plot; percentage absorbed versus dose ingested. For a nonpassive absorption process, the percentage dose absorbed will decrease as the dose increases, as a result of saturation of the transport mechanism and of there being a reduction in absorption efficiency. It has been suggested [56] that one means of overcoming the decrease in absorption efficiency is to administer small divided doses, rather than large single doses, as illustrated later for ascorbic acid.

Several investigators suggest that L-dopa (L-dihydroxyphenylalanine) absorption may be impaired if the drug is ingested with meals containing proteins [57,58]. Amino acids formed from the digestion of protein meals, which are absorbed by a specialized mechanism, may competitively inhibit L-dopa absorption if the drug is also transported by the same mechanism. There is evidence (in animals) indicating a specialized absorption mechanism for phenylalanine and L-dopa, and there are data illustrating L-dopa inhibition of phenylalanine and tyrosine absorption in humans [59–61]. L-Dopa appears to be absorbed by the same specialized transport mechanism responsible for the absorption of other amino acids [62]. In a later section, we discuss several of the complicating factors in L-dopa absorption that influence therapy with this drug.
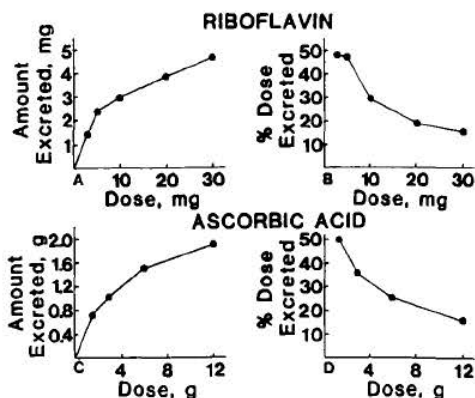
Fig. 9 Urinary excretion of riboflavin (A, B) and ascorbic acid (C, D) in humans as a function of oral dose. A and C illustrate the nonlinear dependence of absorption on dose, which is suggestive of a saturable specialized absorption process. B and D represent an alternative graph of the same data and illustrate the reduced absorption efficiency as the dose increases. (A and B based on the data in Ref. 55 and C and D based on the data in Ref. 56.)

In addition to some anticancer agents being absorbed by a specialized process in humans (e.g., methotrexate) [63], there is recent evidence to suggest that a similar mechanism exists for the absorption of aminopenicillins (e.g., amoxicillin) [64] and aminocephalosporins (e.g., cefixime) [65]. Absorption of these compounds appears to be linked to cellular amino acid or peptide transporters. Other compounds that have the requisite structural properties may also benefit from those transporting systems (e.g., gabapentin) [66]. This behavior may be an important observation for the new generation of drugs being developed through the application of biotechnology (e.g., peptides), assuming such compounds are sufficiently stable in the GIT. Calcium channel blockers, such as nifedipine, increase the absorption of amoxicillin and cefixime [64,65]. This may result from the role of calcium in the transport process, the inhibition of which (i.e., calcium channel blockers) enhances absorption. Another pertinent observation that may explain why some compounds are poorly absorbed is the discovery of a P-glycoprotein-mediated efflux system that resides near the surface of the intestinal epithelium [67]. The latter has been associated with multidrug resistance in tumor cells. Interestingly, this system, which "pumps" drug out of the cell, may be inhibited by the same calcium channel blockers just noted.

IV. PHYSIOLOGICAL FACTORS GOVERNING DRUG ABSORPTION

A. Components and Properties of Gastrointestinal Fluids

The characteristics of aqueous GI fluids to which a drug product is exposed will exert an important influence on what happens to that dosage form in the tract and on the pattern of drug absorption. To appreciate clearly how physiological factors influence drug absorption, one must consider the influence of these variables on the dosage form *per se*; that is, how these variables influence drug dissolution in the aqueous GI fluids, and finally, what influence these variables exert on absorption once the drug is in solution.

One important property of GI fluids is pH, which varies considerably along the length of the tract. The gastric fluids are highly acidic, usually ranging from pH 1 to 3.5. There appears to be a diurnal cycle of gastric acidity, the fluids being more acidic at night and fluctuating during the day, primarily in response to food ingestion. Gastric fluid pH generally increases when food is ingested and, then, slowly decreases over the next several hours, fluctuating from pH 1 to about 5 [68]. There is, however, considerable intersubject variation in GI fluid pH, depending on the general health of the subject, the presence of local disease conditions along the tract, types of food ingested, and drug therapy. Upper GI pH appears to be independent of gender.

An abrupt change in pH is encountered when moving from the stomach to the small intestine. Pancreatic secretions (200–800 ml/day) have a high concentration of bicarbonate, which neutralizes gastric fluid entering the duodenum and, thus, helps regulate the pH of fluids in the upper intestinal region. Neutralization of acidic gastric fluids in the duodenum is important to avoid damage to the intestinal epithelium, prevent inactivation of pancreatic enzymes, and prevent precipitation of bile acids, which are poorly soluble at acidic pH. The pH of intestinal fluids gradually increases when moving in the distal direction, ranging from approximately 5.7 in the pylorus to 7.7 in the proximal jejunum. The fluids in the large intestine are generally considered to have a pH of between 7 and 8.

Gastrointestinal fluid pH may influence drug absorption in a variety of ways. Because most drugs are weak acids or bases, and because the aqueous solubility of such compounds is influenced by pH, the rate of dissolution from a dosage form, particularly tablets and capsules, is dependent on pH. This is a result of the direct dependence of dissolution rate on solubility, as discussed in Chapter 6. Acidic drugs dissolve most readily in alkaline media and, therefore, will have a greater rate of dissolution in intestinal fluids than in gastric fluids. Basic drugs will dissolve most readily in acidic solutions and, thus, the dissolution rate will be greater in gastric fluids than in intestinal fluids. Since dissolution is a prerequisite step to absorption and is often the slowest process, especially for poorly water-soluble drugs, pH will exert a major influence on the overall absorption process. Furthermore, since the major site of drug absorption is the small intestine, it would seem that poorly soluble basic drugs must first dissolve in the acidic gastric fluids to be well-absorbed from the intestine, as the dissolution rate in intestinal fluids will be low (e.g., dipyridamole, ketaconazole, and diazepam). In addition, the disintegration of some dosage forms, depending on their formulation, will be influenced by pH if they contain certain components (e.g, binding agents or disintegrants) the solubility of which is pH-sensitive. Several studies [e.g., 69–71] have indicated that if the specific products being examined were not first exposed to an acidic solution, the dosage form would not disintegrate and, consequently, dissolution could not proceed.

A complication here, however, is noted with those drugs that exhibit a limited chemical stability in either acidic or alkaline fluids. Since the rate and extent of degradation is directly dependent on the concentration of drug in solution, an attempt is often made to retard dissolution in the fluid in which degradation is seen. There are preparations of various salts or esters of drugs (e.g., erythromycin) that do not dissolve in gastric fluid and, thus, are not degraded there, but that dissolve in intestinal fluid before absorption. A wide variety of chemical derivatives are used for such purposes.

As mentioned previously, pH will also influence the absorption of an ionizable drug once it is in solution, as outlined in the pH–partition hypothesis. Most drugs, however, are best absorbed from the small intestine, regardless of pK_a and pH. In some instances, especially lower down the GIT, there is the possibility of insoluble hydroxide formation of a drug or insoluble film formation with components of a dosage form, which reduces the extent of absorption of, for example, the pamoate salt of benzphetamine [72], aluminum aspirin (in

chewable tablets) [73,74], and iron [75]. The coadministration of acidic or alkaline fluids with certain drugs may exert an effect on the overall drug absorption process for any of the foregoing reasons.

Moreover, in addition to pH considerations, the GI fluids contain various materials that influence absorption, particularly bile salts, enzymes, and mucin. Bile salts, which are highly surface-active, may enhance the rate or extent of absorption of poorly water-soluble drugs by increasing the rate of dissolution in the GI fluids. This effect has been noted in *in vitro* experiments and has also been seen with other natural surface-active agents (e.g, lysolecithin). Increased absorption of the poorly water-soluble drug griseofulvin after a fatty meal [76,77] may reflect bile secretion into the gut in response to the presence of fats, and the bile salts that are secreted increase the dissolution rate and absorption of the drug. The contrast agent, iopanoic acid, used in visualizing the gallbladder, dissolves more rapidly and is better absorbed from the dog intestine in the presence of bile salts. Studies in rats have indicated enhanced intestinal drug absorption from bile salt solutions; however, the implications of these findings for humans are uncertain. Bile salts may also reduce drug absorption (e.g., neomycin and kanamycin) through the formation of water-insoluble, nonabsorbable complexes.

Since intestinal fluids contain large concentrations of various enzymes needed for digestion of food, it is reasonable to expect certain of these enzymes to act on a number of drugs. Pancreatic enzymes hydrolyze chloramphenicol palmitate. Pancreatin and trypsin are able to deacetylate *N*-acetylated drugs, and mucosal esterases appear to attack various esters of penicillin. It has been suggested that the preparation of various fatty acid esters of a drug that can be hydrolyzed by the GI enzymes may provide a method for controlled drug release and absorption from the GIT. Some caution must be applied in the use of such a dosage form, the performance of which depends on specific physiological conditions, as there is likely to be considerable variation within the population relative to enzyme concentration and activity.

Mucin, a viscous mucopolysaccharide that lines and protects the intestinal epithelium, has been thought to bind certain drugs nonspecifically (e.g., quarternary ammonium compounds) and, thereby, prevent or reduce absorption. This behavior may partially account for the erratic and incomplete absorption of such charged compounds. Mucin may also represent a barrier to drug diffusion before reaching the intestinal membrane.

B. Gastric Emptying

For many years, physiologists have been interested in factors that influence gastric emptying and the regulatory mechanisms controlling this process. Our interest in gastric emptying is because most drugs are best absorbed from the small intestine, any factor that delays movement of drug from the stomach to the small intestine will influence the rate (and possibly the extent) of absorption and, therefore, the time needed to achieve maximal plasma concentrations and pharmacological response. As a result, and in addition to rate of dissolution or inherent absorbability, gastric emptying may represent a limiting factor in drug absorption. Only in those rare instances when a drug is absorbed by a specialized process in the intestine will the amount of drug leaving the stomach exceed the capacity of the gut to absorb it.

Gastric emptying has been quantitated with a variety of techniques that use liquid or solid meals or other markers. Gastric emptying is quantitated by one of several measurements, including emptying time, emptying half-time ($t_{1/2}$), and emptying rate. Emptying time is the time needed for the stomach to empty the total initial stomach contents. Emptying half-time is the time it takes for the stomach to empty one-half of its initial contents. Emptying rate is a measure of the speed of emptying. Note that the last two measures are inversely related (i.e., the greater the rate, the smaller the value for emptying half-time).

Gastric emptying and factors that affect that process need to be understood because of the implications for drug absorption and in relation to optimal dosage form design [78]. Gastric-emptying patterns are distinctly different, depending on the absence or presence of food. In the absence of food, the empty stomach and the intestinal tract undergo a sequence of repetitious events referred to as the interdigestive migrating motor (or myoelectric) complex [79]. This complex results in the generation of contractions, beginning with the proximal stomach and ending with the ileum. The first of four stages is one of minimal activity, which lasts for about 1 hr. Stage 2, which lasts 30–45 min, is characterized by irregular contractions that gradually increase in strength, leading to the next phase. The third phase, although lasting only 5–15 min, consists of intense peristaltic waves that result in the emptying of gastric contents into the pylorus. The latter is sometimes referred to as the "housekeeper" wave. The fourth stage represents a transition of decreasing activity, leading to the beginning of the next cycle (i.e., phase 1). The entire cycle lasts for about 2 hr. Thus, a solid dosage form ingested on an empty stomach will remain in the stomach for a time period that depends on the time of dosing relative to the occurrence of the housekeeper. The gastric residence time of a solid dosage form will vary from perhaps 5 to 15 min (if ingested at the beginning of the housekeeper) to about 2 hr or longer (if ingested at the end of the housekeeper). It would not be surprising, however, for gastric residence time to range up to 8–10 hr among some subjects. The latter points undoubtedly explain some of the intersubject variation in rate of absorption, and it raises some question concerning the term, "ingested on an empty stomach." Although it is quite common in clinical research studies for a panel of subjects to ingest a solid test dosage form following an overnight fast and, therefore, on an "empty stomach," it is unlikely that all subjects will be in the same phase of the migrating motor complex. It appears to be the latter point, rather than an empty stomach *per se*, that will determine when emptying occurs and, consequently, when drug absorption is initiated. The foregoing considerations will not apply to liquid dosage forms, however, which are generally able to empty during all phases of the migrating motor complex.

Various techniques have been used to visualize the gastric emptying of dosage forms. Radiopaque tablets undergo relatively mild agitation in the stomach; a point that needs to be considered in the design and interpretation of disintegration and dissolution tests [80]. Although single, large, solid dosage forms (e.g., tablets and capsules) rely on the housekeeper wave for entry into the small intestine, some controversy remains about the influence of particle (or pellet) size (diameter and volume), shape, and density on gastric emptying. There has been a great deal of recent interest in this issue, which has been investigated primarily with use of gamma scintigraphy (a gamma-emitting material is ingested and externally monitored with a gamma camera). These studies are generally performed with the use of nondisintegrating pellets, so that movement throughout the tract may be estimated. It is generally claimed that particles must be smaller than about 1–2 mm to empty from the stomach; larger particles requiring additional digestion. This no longer appears to be correct, as particles as large as 5–7 mm may leave the stomach. Therefore, it is likely that there is a range of particle sizes that will empty from the stomach, rather than there being an abrupt cutoff value. The range of values among individuals will be affected by the size of the pylorus diameter and the relative force of propulsive contractions generated by the stomach. The interest in this issue stems from the desire to develop sustained-release dosage forms that would have sufficient residence time in the GIT to provide constant drug release over a long time. Experimental dosage forms that have been investigated include floating tablets, bioadhesives (to attach to the gastric mucosa), dense pellets, and large dimension forms.

Eating interrupts the interdigestive migrating motor complex. Gastric emptying in the presence of solid or liquid food is controlled by a complex variety of mechanical, hormonal, and

neural mechanisms. Receptors lining the stomach, duodenum, and jejunum that assist in controlling gastric emptying include mechanical receptors in the stomach that respond to distension; acid receptors in the stomach and duodenum; osmotic receptors in the duodenum that respond to electrolytes, carbohydrates, and amino acids; fat receptors in the jejunum; and L-tryptophan receptors. Neural control appears to be through the inhibitory vagal system (the exact neurotransmitter is unknown, but may be dopamine and enkephalin). Hormones involved in controlling emptying include cholecystokinin and gastrin, among others.

As food enters the stomach, the fundus and body regions relax to accommodate the meal. After reaching the stomach, food tends to form layers that are stratified in the order in which the food was swallowed, and this material is mixed with gastric secretions in the antrum. Nonviscous fluid moves into the antrum, passing around any solid mass. Gastric emptying will begin once a considerable portion of the gastric contents become liquid enough to pass the pylorus. Peristaltic waves begin in the fundus region, travel to the prepyloric area, and become more intense in the pylorus. The antrum and pyloric sphincter contract, and the proximal duodenum relaxes. A moment later the antrum relaxes, and the duodenum regains its tone. The pyloric sphincter will remain contracted momentarily to prevent regurgitation, and the contents in the duodenum are then propelled forward. Emptying is accomplished by the antral and pyloric waves, and the rate of emptying is regulated by factors controlling the strength of antral contraction. Gastric emptying is influenced primarily by meal volume, the presence of acids, certain nutrients, and osmotic pressure. Distension of the stomach is the only natural stimulus known to increase the emptying rate. Fat in any form, in the presence of bile and pancreatic juice, produces the greatest inhibition of gastric emptying. This strong inhibitory influence of fats permits time for their digestion, as they are the slowest of all foods to be digested. Meals containing substantial amounts of fat can delay gastric emptying for 3–6 hr or more. These various factors appear to alter gastric emptying by interacting with the receptors noted earlier.

Other than meal volume *per se*, all of the other factors noted in the foregoing result in a slowing of gastric emptying (e.g., nutrients, osmotic pressure, and acidity). It is important to recognize that there are a host of other factors that are known to influence emptying rate. Thus, a variety of drugs can alter absorption of other drugs by their effect on emptying. For example, anticholinergics and narcotic analgesics reduce gastric emptying rate; whereas, metoclopramide increases that rate. A reduced rate of drug absorption is expected in the former instance and an increased rate in the latter. Among other factors that should be recognized: body position (reduced rate lying on left side); viscosity (rate decreases with increased viscosity); emotional state (reduced rate during depression, increased rate during stress). As an illustration, one recent report indicates that absorption rate (and potentially completeness of absorption) may be altered when comparing posture; lying on the left or right side [81]. Acetaminophen and nifedipine absorption rates were faster when the subjects were lying on the right, compared with the left side, suggesting more rapid gastric emptying. For nifedipine, the extent of absorption was greater when the subjects were lying on the right side, which may be due to transient saturation of a presystemic metabolic process (this is discussed in a later section). Miscellaneous factors, for which the exact effect on emptying may vary, include gut disease, exercise, obesity, gastric surgery, and bulimia. Emptying appears not to be influenced by gender, but there are age-related differences (discussed later).

Many investigators have suggested that gastric emptying takes place by an exponential (i.e., first-order kinetic) process. As a result, plots of log volume remaining in the stomach versus time will provide a straight-line relationship. The slope of this line will represent a rate constant associated with emptying. This relationship is not strictly linear, however, especially at early and later times, but the approximation is useful in that one can express a half-time for emptying ($t_{1/2}$). Hopkins [82] has suggested a linear relationship between the square root of the volume

remaining in the stomach versus time. There may be a physical basis for this relationship, since the radius of a cylinder varies with the square root of the volume, and the circumferential tension is proportional to the radius. Methods for analyzing gastric-emptying data have been reviewed [83].

Gastric-emptying rate is influenced by a large number of factors, as noted earlier. Many of these factors account for the large variation in emptying among different individuals and variation within an individual on different occasions. Undoubtedly, much of this variation in emptying is reflected in variable drug absorption. Although gastric emptying probably has little major influence on drug absorption from solution, emptying of solid dosage forms does exert an important influence on drug dissolution and absorption. A prime example are enteric-coated tablets, which are designed to prevent drug release in the stomach. Any delay in the gastric emptying of these forms will delay dissolution, absorption, and the onset time for producing a response. Since these dosage forms must empty as discrete units, the drug is either in the stomach or the intestine. The performance of this dosage form can be seriously hampered if it is taken with or after a meal, as emptying is considerably delayed. Furthermore, if the drug is to be taken in a multiple-dosing fashion, there is a possibility that the first dose will not leave the stomach until the next dose is taken, resulting in twice the desired dose getting into the intestine at one time. Blythe et al. [84] administered several enteric-coated aspirin tablets containing $BaSO_4$ and radiologically examined emptying of these tablets. The tablets emptied in these subjects anywhere from 0.5 to 7 hr after ingestion. Tablets will empty more rapidly when given before a meal compared with administration after a meal. One potential way of improving the emptying and release pattern of enteric-coated products is to use capsules containing enteric-coated microgranules. The median time for 50 and 90% emptying of such a dosage form has been shown to be 1 and 3–3.5 hr, respectively [85].

Several publications have reviewed the effects of food on drug absorption in humans [86–89]. Although not a thorough compilation, the influence of food and several drugs that affect gastric emptying on drug absorption is summarized in Table 8. Food will exert an influence on drug absorption by its effect on gastric emptying and residence time in the GIT, but there are also interactions with various food components. One must also consider the type of food ingested (e.g., carbohydrate, protein, fat, fiber, and so on) and the time of food ingestion relative to drug administration, as these may have different effects on absorption. There is, in addition, the observation that food ingestion may alter hepatic drug extraction subsequent to absorption (i.e., the hepatic first-pass effect) [141]; this point will be discussed later. Foods include liquid nutrients as well as solids, and apple juice has been found to slow gastric emptying [142]. As a general rule, drugs should be ingested on an empty stomach with a glass of water to provide optimal conditions for dissolution and absorption. This rule is particularly important for those compounds unstable in gastric fluids (e.g., penicillin and erythromycin), enteric-coated dosage forms, and those compounds best absorbed in the lower portion of the intestine (e.g., vitamin B_{12}).

As with all general rules and as exemplified in Table 8, there are exceptions. These exceptions include compounds that are irritating to the tract (e.g., phenylbutazone or nitrofurantoin), those compounds absorbed high in the tract by a specialized mechanism (e.g., riboflavin), and those compounds for which the presence of certain food constituents are known to enhance absorption (e.g., griseofluvin). For those compounds that irritate the tract, perhaps the best recommendation is to ingest the drug with or after a light meal that does not contain fatty foods or constituents known to interact with the drug. Nitrofurantoin absorption is improved in the presence of food [121,122]. Riboflavin and ascorbic acid, which are absorbed by a specialized process high in the small intestine, are best absorbed when gastric emptying is delayed by the presence of food [55,93]. As the residence time of the vitamins in the upper

Table 8 Influence of Food and Drugs Affecting Gastric Emptying on Drug Absorption in Humans

Drug	Influence on drug absorption	Ref.
Food		
Acetaminophen	Reduced rate, but not extent	90,91
	Rapid emptying produces greater maximum plasma concentrations and shortens time to achieve maximum concentration; amount absorbed is greater with rapid emptying	92
Ascorbic acid	Increased extent	93
Aspirin	Reduced rate, but not extent	94,95
Bretylium tosylate	Reduced rate and extent	96
Captopril	Reduced rate and extent	97,98
Capuride	Reduced rate, but not extent	99
Cefurozime	Increased extent	100
Cephradine	Reduced rate, but not extent	101,102
Chlorophenoxylisobutyric acid	Increased extent	103
Clindamycin	Reduced rate, but not extent	104
Clobazam	Reduced rate, but not extent	105
Digoxin	Reduced rate, but not extent	106–108
L-Dopa	Any factor reducing emptying rate will reduce rate and extent of absorption	57,109
Ethanol	Reduced rate and extent	110
Fenoprofen	Reduced rate	111
Fenretinide	Increased extent, but not rate	112
Indomethacin	Reduced rate	113
Isoniazid	Reduced rate and extent	114
Isotretinoin	Increased extent	115
Ketoconazole	Reduced extent, but not rate	116,117
Lincomycin	Reduced rate and extent	118
β-Methyl digoxin	Reduced rate, but not extent	119
Methyldopa	No effect	120
Nitrofurantoin	Reduced rate, but increased extent	121,122
Phenylbutazone	No effect	123
Propylthiouracil	No effect	124
Pravastatin	Reduced extent and rate	125
Riboflavin	Increased extent	55
Rifampicin	Reduced rate and extent	126,127
Sulfaisodimidine	No effect	128
Zidovudine (AZT)	Reduced rate and extent	129,130
Drug		
Acetaminophen	Reduced rate, but not extent (propantheline)	131
	Increased rate, but not extent (metoclopramide)	131,132
Digoxin	Increased rate and extent for a slowly dissolving tablet; no effect for a rapidly dissolving tablet (propantheline)	133–135
	Reduced rate and extent (metoclopramide)	134
L-Dopa	Increased rate and extent (metoclopramide)	136
Pivampicillin	Increased rate (metoclopramide)	137
	Reduced rate (atropine)	137
Ranitidine	Increased extent (propantheline)	138
Riboflavin	Reduced rate but increased extent (propantheline)	139
Sulfamethoxazole	Reduced rate (propantheline)	140
Tetracycline	Increased rate (metoclopramide)	137
	Reduced rate (atropine)	137

portion of the intestine is prolonged, contact with absorption sites is increased and absorption becomes more efficient. The influence of food on the absorption of those vitamins is illustrated in Fig. 10, along with improved efficacy of ascorbic acid absorption achieved by administering divided doses. The absorption of griseofulvin, which is a very poorly water-soluble drug, is enhanced when it is coadministered with a fatty meal, as discussed previously [76,77]. The importance of gastric emptying can probably be most readily appreciated by those investigators who have examined drug absorption in patients after a partial or total gastrectomy. Muehlberger [143] notes that, following a near-total gastrectomy, patients often complain of a "sensitivity" to alcohol. This is probably best explained by ethanol moving rapidly from the poorly absorbing surface of the stomach to the small intestine, where absorption will be rapid. Gastric emptying is important in oral L-dopa therapy, and it has been noted [144] that patients with a partial gastrectomy or gastrojejunostomy exhibit a prompt response with less than average doses of the drug. This observation is consistent with rapid absorption from the small intestine in such patients and is essentially equivalent to introduction of the drug into the duodenum. Similar conclusions have been reached for aspirin and warfarin absorption [145,146].

For many drugs, as has been shown for acetaminophen, there will be a direct relation between gastric-emptying rate and maximal plasma concentration, and an inverse relation between gastric-emptying rate and the time required to attain maximal plasma concentrations. Those relations are illustrated in Fig. 11A and B. Also shown in that figure is the influence of a narcotic (heroin) on the gastric emptying and absorption of acetaminophen (see Fig. 11C and D). In attempting to predict such relations, however, it is essential that one consider the physico-chemical characteristics of the drug. Whereas an increased gastric-emptying rate will probably increase the rate (and possibly the extent) of absorption for drugs best absorbed from the small intestine from rapidly dissolving dosage forms, the converse may be true in other circumstances. For example, if the dosage form must first be exposed to the acidic gastric fluids to initiate disintegration or dissolution, rapid emptying may reduce the rate and extent of absorp-
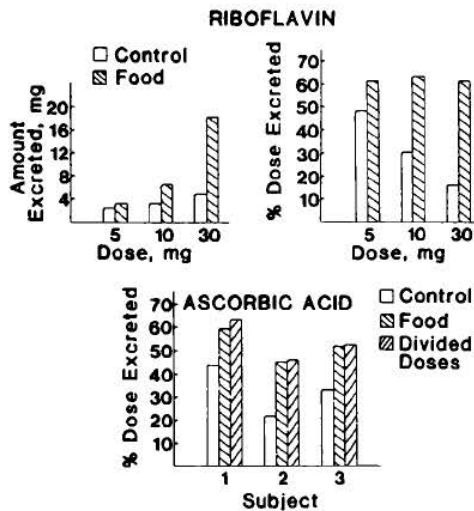

Fig. 10 (Top) Influence of food on the absorption of different doses of riboflavin; (Bottom) influence of food and divided doses on ascorbic acid absorption in three subjects. (Data from Refs. 55 and 93.)
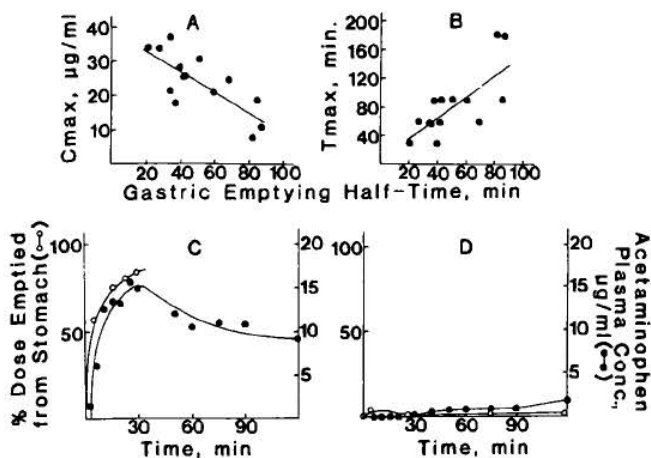
Fig. 11 (A, B) Maximum acetaminophen plasma concentration (C_{max}) and time to achieve that concentration (T_{max}) as a function of gastric emptying half-time. (C) Percentage of an acetaminophen dose emptied from the stomach (open circles) and acetaminophen plasma concentrations (solid circles) as a function of time in one subject. (D) The same plot and for the same subject as in (C) after a 10-mg intramuscular dose of heroin. (A, from Ref. 92; C and D from Ref. 147.)

tion. Similarly, if the drug dissolves slowly from the dosage form, a shortened residence time in the gut may reduce the extent of dissolution and absorption. Obviously, one needs a good deal of fundamental understanding of the chemistry of the drug, its dosage form, and the absorption mechanism before being able to anticipate or rationalize the influence of these various factors on the efficacy of absorption.

The gastric-emptying process can sometimes be observed in plots of log percentage of dose unabsorbed versus time, in which at early times a smaller slope is seen than at later times. The lag time for absorption can also reflect disintegration or dissolution processes, as well as slower absorption in the stomach before emptying.

A final point that should be mentioned here, although it has received relatively little attention, is that of esophageal transit. Delay in movement down the esophagus will delay absorption and, in addition, for certain drugs, may also cause local mucosal damage. Capsule disintegration has been observed to occur in the esophagus within 3–5 min. Esophageal transit is delayed when solid dosage forms are swallowed with little fluid, or when the subject is supine [148,149]. Antipyrine absorption from capsules [150] and acetaminophen absorption from tablets [151] was delayed when esophageal transit was prolonged. To avoid this delay, the dosage form should be swallowed with water or other fluids, and the subject should be in a standing or sitting position.

C. Intestinal Transit

Once a dosage form empties from the stomach and enters the small intestine, it will be exposed to an environment totally different from that in the stomach, as discussed previously. Since the small intestine is the primary site of drug absorption, the longer the residence time in this region, the greater the potential for complete absorption, assuming that the drug is stable in the intestinal fluids and will not form water-insoluble derivatives.

There are primarily two types of intestinal movements: propulsive and mixing. Propulsive movements, generally synonymous with peristalsis, will determine intestinal transit rate and, therefore, the residence time of a drug in the intestine. This time of residence is important, since it will dictate the amount of time the dosage form has in which to release the drug, permit dissolution, and allow for absorption. Obviously, the greater the intestinal motility, the shorter the residence time, and the less time there is for those processes to proceed. Intestinal motility will be most important for those dosage forms that release drug slowly (e.g., sustained-release products) or require time to initiate release (e.g., enteric-coated products), as well as those drugs that dissolve slowly or for which absorption is maximal only in certain regions of the intestine. Peristaltic waves propel intestinal contents down the tract at about 1–2 cm/sec. Peristaltic activity in increased after a meal as a result of the gastroenteric reflex initiated by distension of the stomach and results in increased motility and secretion.

Mixing movements of the small intestine are a result of contractions dividing a given region of the intestine into segments, producing an appearance similar to a chain of sausages. These contractions result in mixing of the intestinal contents with secretions several times a minute. This mixing brings the gut contents into optimal contact with the surface epithelium and, thereby, provides a larger effective area for absorption. In addition, the muscularis mucosa produces folds in the surface epithelium, resulting in an increased surface area and rate of absorption. The villi contract during this process, which results in a "milking" action, so that lymph flows from the central lacteal into the lymphatic system.

These mixing motions will tend to improve drug absorption for two reasons: (a) Any factor that increases rate of dissolution will generally increase the rate (and possibly the extent) of absorption, especially for poorly water-soluble drugs. Since rate of dissolution depends on agitation intensity, mixing movements will tend to increase dissolution rate and, thereby, influence absorption. (b) As rate of absorption depends directly on membrane surface area, and since mixing increases the contact area between drug and membrane, these motions will tend to increase rate of absorption.

As with gastric emptying, there are a variety of factors that will influence intestinal motility and, thereby, may influence drug absorption. Food, although it may be a bulk stimulant for intestinal transit, results in active mixing movements in the intestine. Although these movements may increase the rate of drug dissolution, the general recommendation made in the preceding section still applies; it is best to ingest a drug as much time before a meal as possible. Not only will this avoid problems associated with gastric emptying, but it will reduce potential drug interactions with food components in the small intestine, where these materials are in intimate and prolonged contact. In addition, the presence of food, which tends to provide a viscous environment in the gut, will reduce drug diffusion to the absorbing membrane. Exceptions to this rule were noted earlier. Sustained-release products may represent a general exception, since these dosage forms depend on longer residence time in the tract to completely release the drug. Since the performance of these products may be influenced by the presence of food, the Food and Drug Administration requires that such products be examined in fed and fasted subjects. This requirement was deemed necessary following the observation of "dose-dumping." The latter occurred when the entire dose was released as a result of failure of the release mechanism in response to food.

As noted in Table 8 metoclopramide will increase the rate of gastric emptying, which often, but not always, will increase the rate of drug absorption. However, metoclopramide will also increase the rate of intestinal transit and thus reduce the residence time in the intestine. These two effects may have an opposing influence on absorption. The net effect on absorption depends on the characteristics of the drug and its dosage form as well as the mechanism of absorption. Metoclopramide or similar-acting drugs will probably have little if any effect on absorption of

a drug given orally in solution, unless the drug (e.g., riboflavin) is absorbed by a specialized process high in the small intestine, in which circumstance there is likely to be a reduction in the amount absorbed. Metoclopramide will probably increase the rate of absorption of a drug from a solid dosage form because of its effect on gastric emptying if the drug is rapidly released and readily dissolved. On the other hand, if the drug dissolves slowly from the dosage form, the extent of absorption may be reduced as a result of shortened residence time in the intestine, even though gastric emptying rate is increased. Similar reasoning may be applied to the influence on drug absorption of various anticholinergics (e.g., atropine and propantheline) and narcotic analgesics that reduce gastric-emptying and intestinal transit rates. Although there will be a reduction in gastric-emptying rate and thus a delay in absorption, these compounds will increase intestinal transit time and possibly increase the extent of absorption, particularly for , slowly dissolving drugs or dosage forms that release drug slowly.

Transit through the small intestine appears to be quite different in a variety of ways from movement through the stomach. Once emptied from the stomach, material (such as pellets and tablets) will move along the small intestine and reach the ileocecal valve in about 3 hr. Although this value may range from about 1 to 6 hr, intestinal residence time appears to be relatively consistent among normal subjects [152]. Values similar to this have been found for food and water movement along the small intestine. Transit appears to be less dependent on the physical nature of the material (liquid vs. solid and size of solids) than with the response of the stomach. Furthermore, food appears not to influence intestinal transit, as it does gastric emptying.

Three to four hours in the small intestine is a relatively short time for a dosage form to completely dissolve or release drug and then be absorbed. This time would be even more critical to the performance of poorly water-soluble drugs, slowly dissolving, coated dosage forms (enteric or polymer coated), and sustained-release forms. If one assumes minimal absorption from the colon (discussed later), gastric residence time may prove a critical issue to the performance of certain drugs and drug dosage forms (especially those in the latter categories) as a result of the relatively short intestinal residence time.

There is less information available concerning the factors that may influence intestinal transit time compared with what we know about gastric residence time. Although based on small populations, there appear to be no gender-related differences in intestinal transit time [153], and vegetarians appear to have longer intestinal transit times than nonvegetarians [154]. The latter point may have implications for drug therapy in the third world where the diet is primarily vegetarian. Other factors that result in an increased transit time include reduced digestive fluid secretion, reduced thyroxine secretion, and pregnancy [155–157].

The distal portion of the GIT, the colon (see Fig. 1), has as its primary function water and electrolyte absorption and the storage of fecal matter before it is expelled. The proximal half of the colon is concerned with absorption and the distal half with storage. Although there are mixing and propulsive movements in the colon, they tend to be rather sluggish. Large circular constrictions occur in the colon that are similar to the segmenting contractions seen in the small intestine. The longitudinal muscles lining the colon also contract, producing a bulging, similar in appearance to sacs, and referred to as haustrations. These movements increase the surface area of the colon and result in efficient water absorption.

Contents within the colon are propelled down the tract, not by peristaltic waves, but by a "mass movement" that occurs only several times a day, being most abundant the first hour after breakfast as a result of a duodenocolonic reflex. The greatest proportion of time moving down the GIT is spent by a meal moving through the colon. In the presence of a diarrheal condition, fluid absorption is incomplete, which results in a watery stool.

Colonic residence time is considerably longer than in other parts of the GIT, and it is also more variable. The transit time can be as short as several hours to as long as 50–60 hr. Transit

along the colon is characterized by abrupt movement and long periods of stasis. In one study of 49 healthy subjects, the average colonic residence time was 35 hr, with the following times associated with different regions: 11 hr in the right (ascending) colon; 11 hr in the left (descending) colon; and 12 hr in the rectosigmoid colon [158]. The latter values do not appear to be influenced by particle size (i.e., pellets vs. tablet), but these times are highly variable and are shortened in response to ingestion of a laxative (average time for a 5-mm tablet in the ascending colon of 8.7 vs. 13.7 hr) [159,160]. Furthermore, the ingestion of food, which is known to increase colonic activity, does not appear to have a dramatic effect on the movement of dosage forms from the ileum into the colon, nor on the movement within the colon [161]. Any differences in colonic transit times as a function of age and gender are not clear at this time, owing to conflicting reports and investigation in small populations of subjects.

The colonic mucosal pH varies along the length of the colon: right colon, pH 7.1; transverse colon, pH 7.4; left colon, pH 7.5; sigmoid colon, pH, 7.4; rectum, pH 7.2. These values were determined in a group of 21 subjects (mean age 54 years), and they are somewhat higher than previous estimates (ca., pH 6.7 in the right colon) [162]. Those values contrast with the proximal small intestine with a pH of about 6.6 and the terminal ileum with a pH of about 7.4. This near-neutral pH in conjunction with low enzymatic activity has made the colon an interesting potential site for drug absorption. Indeed, there is active interest in delivery of drug dosage forms to the colon for site-specific absorption, especially for peptides [e.g., 78,163]. Characteristics of the colon that are thought to provide a good environment for drug absorption include a mild pH, little enzymatic activity, and long residence time. The disadvantage of the colon, however, include several considerations that substantially limit this area for providing good absorption: small surface area, relatively viscous fluidlike environment (which varies along the length of the colon), and the large colonies of bacteria. The latter factors would limit dissolution and contact with the absorbing surface membrane and may result in presystemic drug metabolism.

The intention of colon-specific drug delivery is to prevent the drug from being released from the dosage form (by coating or other release-controlling mechanism) until it reaches the distal end of the large intestine (i.e., the ileocecal valve). Drug release needs to be delayed for about 5 hr, but clearly this delay time will vary from patient to patient and will depend on a host of factors that may affect gastric emptying and intestinal transit (e.g., food or drugs). The dosage form should then release drug over the next 10–15 hr while in the colon. The results of studies that have examined colonic absorption are not that encouraging, although they do indicate that absorption does occur, but to a variable extent (depending on the drug). The hormone, calcitonin, provided an absolute bioavailability from the colon of less than 1%; however, no comparison to oral dosing was made [164]. The relative bioavailability of ranitidine solution from the cecum was about 15% of that following gastric or jejunal administration [165]. Benazepril's relative bioavailability following a colonic infusion was about 23% that of an oral solution [166]. Figure 12 illustrates the plasma concentration–time profiles for those two drugs. The long-lasting analog of vasopressin, (desmopressin; desamino-8-D-arginine vasopressin; dDAVP), a nonapeptide, had a relative bioavailability of about 17 and 21%, compared with duodenal and gastric (and jejunal) solution administration, respectively. Rectal administration provided absorption comparable with that from the colon [167]. Sumatriptan solution was absorbed from the cecum to an extent of about 23%, compared with an oral (and jejunal) dose [168]. In all cases, the rate of absorption is substantially slower than from the upper regions of the GIT. Furthermore, in some instances, the metabolite/parent drug concentration ratios change depending on the site of administration, which may reflect a number of causes (e.g., different extent of presystemic metabolism, differences in metabolite absorption). The latter needs to be a consideration for those compounds for which the metabolites are either pharmacologically active or toxic.
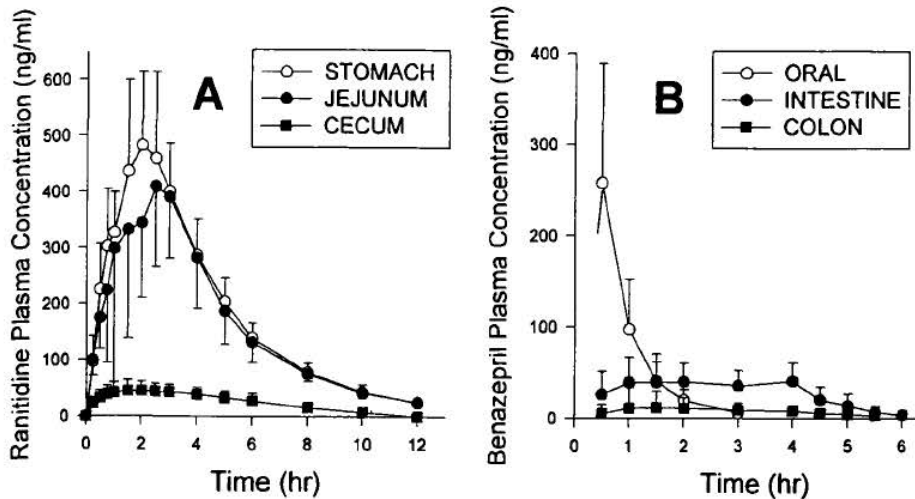
Fig. 12 (A) Ranitidine plasma concentrations as a function of time following administration of a solution into the stomach, jejunum, or cecum. Each value is the mean of eight subjects (the cross-hatched vertical bars are standard deviations). (B) Benazepril plasma concentrations as a function of time following a solution dose taken orally or administered as a 4-hr intestinal or 4-hr colonic infusion. Each value is the mean of 7–13 subjects. (Data from: A, Ref. 165; B, Ref. 166.)

A relevant consideration of absorption from the colonic area is rectal drug administration. Although this is not a frequently used route, it is employed to some extent, especially in infants, children, and those unable to swallow medication. Absorption from the rectum is generally considered to be relatively poor, at least in comparison with absorption from regions of the upper GIT. The reasons for this are essentially those outlined earlier for the colon; small absorbing surface area, little fluid content, and poor mixing movements. There are, in addition, two other considerations. First, the presence of fecal material may provide a site for adsorption that can effectively compete for absorption. Second, the extent of absorption will be dependent on the retention time of the dosage form in the rectum. This may be a critical issue for infants, who often have irregular bowel movements. The readers are referred to a review of this topic [169].

D. Blood Flow

The entire GIT is highly vascularized and, therefore, well perfused by the bloodstream. The splanchnic circulation that perfuses the GIT receives about 28% of cardiac output, and this flow drains into the portal vein, and then, goes to the liver before reaching the systemic circulation. An absorbed drug will first go to the liver, which is the primary site of drug metabolism in the body; the drug may be metabolized extensively before systemic distribution. This has been referred to as the *first-pass* effect or presystemic elimination, and it has important implications in bioavailability and drug therapy.

The fact that the GIT is so well perfused by the bloodstream permits efficient delivery of absorbed materials to the body. As a result of this rapid blood perfusion, the blood at the site of absorption represents a virtual "sink" for absorbed material. Under normal conditions, then, there is never a buildup in drug concentration in the blood at the site of absorption. Therefore, the concentration gradient will favor further unidirectional transfer of drug from the gut to the

blood. Usually, then, blood flow is not an important consideration in drug absorption. Generally, the properties of the dosage form (especially dissolution rate) or the compound's inherent absorbability will be the limiting factors in absorption.

There are circumstances, however, when blood flow to the GIT may influence drug absorption. Those compounds absorbed by active or specialized mechanisms require membrane participation in transport which, in turn, depends on the expenditure of metabolic energy by intestinal cells. If blood flow and, therefore, oxygen delivery is reduced, there may be a reduction in absorption of those compounds. This is the case in rats for the active absorption of phenylalanine [170].

The rate-limiting step in the absorption of those compounds that readily penetrate the intestinal membrane (i.e., have a large permeability coefficient) may be the rate at which blood perfuses the intestine. However, absorption will be independent of blood flow for those compounds that are poorly permeable. Extensive studies have illustrated this concept in rats [171,172]. The absorption rate of tritiated water, which is rapidly absorbed from the intestine, is dependent on intestinal blood flow; but a poorly absorbed compound, such as ribitol, penetrates the intestine at a rate independent of blood flow. In between these two extremes are a variety of intermediate compounds the absorption rate of which is dependent on blood flow at low-flow rates, but is independent of blood flow at higher flow rates. By altering blood flow to the intestine of the dog, as blood flow decreased, the rate of sulfaethidole absorption also decreased [173]. These relationships are illustrated in Fig. 13.

An interesting clinical example of the influence of blood flow on drug absorption is that provided by Rowland et al. [174]. After oral ingestion of aspirin, one subject fainted while a blood sample was being taken. Absorption ceased at that time, but continued when the subject recovered. Interestingly, there was no reduction in the total amount of aspirin absorbed, compared with another occasion when the subject did not faint. Another investigator observed a 3-hr delay in the absorption of sulfamethoxypyridazine in a patient who fainted [175]. The most reasonable explanation of these observations is that in a fainting episode blood is preferentially shunted away from the extremities and other body organs, including the GIT, thereby reducing blood perfusion of the tract and resulting in a decreased rate of absorption. It is
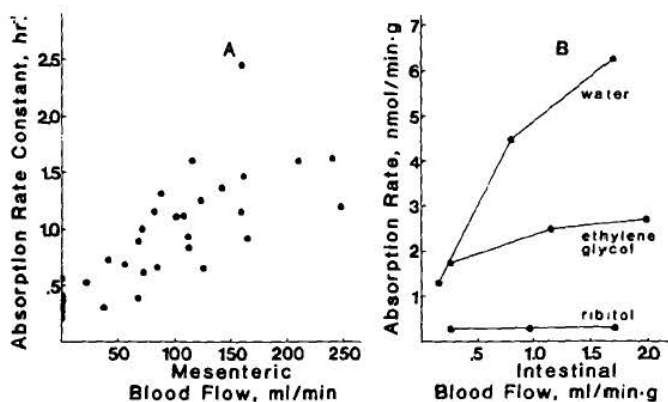

Fig. 13 (A) Absorption rate constant of sulfaethidole in dogs as a function of mesenteric blood flow. (B) Absorption rate of several compounds in rats as a function of intestinal blood flow. (Data from: A, Ref. 173; B, Ref. 172.)

possible that generalized hypotensive conditions may be associated with altered drug absorption. Therefore, consideration needs to be given to the influence of congestive heart failure and other disease conditions that will alter gut blood flow as well as the presence of other drugs that may alter flow. For example, it has been suggested that digoxin absorption is impaired in congestive heart failure, but improves after compensation [176]. The influence of such conditions on absorption has been reviewed elsewhere [177], but there is relatively little information available.

Blood flow to the GIT increases shortly after a meal and may last for several hours. Digestive processes, in general, seem to enhance blood flow to the tract. For the reasons discussed previously, however, coadministration of a drug with a meal would normally not be expected to improve drug absorption. Strenuous physical exercise appears to reduce blood flow to the tract and may reduce absorption.

V. COMPLICATING FACTORS IN DRUG ABSORPTION

A. Drug–Food and Drug–Drug Interactions

There are a variety of factors that may affect the rate or extent of absorption. Interactions in absorption are mediated by physicochemical or physiological factors. Physicochemical considerations include the characteristics of the dosage form and altered solubility, dissolution, and chemical stability within the GIT. Physiological factors include residence time in the tract (i.e., gastric emptying and intestinal transit rates) and blood flow to and the characteristics of the absorbing membrane. Drug–food and drug–drug interactions will alter absorption by one or more of the foregoing mechanisms.

As discussed previously, drug absorption is generally less efficient when food is present in the GIT, although there are several exceptions (see Table 8). Food will reduce the rate or extent of absorption by virtue of reduced gastric-emptying rate, which is particularly important for compounds unstable in gastric fluids and for dosage forms designed to release drug slowly. In addition, food provides a rather viscous environment that will reduce the rate of drug dissolution and drug diffusion to the absorbing membrane. Drugs may also bind to food particles or react with gastrointestinal fluids secreted in response to the presence of food. An interesting example of the influence of food and gastric emptying on the fate of a drug in the body is that of *p*-aminobenzoic acid. This compound is metabolized in the body (acetylation) by a saturable process. The rate of presentation (i.e., the rate of absorption) of the drug to its site of metabolism will influence the extent of acetylation. The more rapid the absorption, the less the extent of acetylation, since the capacity to metabolize is exceeded by the rate of presentation to the enzymatic system. When absorption rate is reduced by slowing gastric emptying (e.g., with fat or glucose), a greater fraction of the dose is metabolized [178]. Similar observations have been made for salicylamide's absorption rate and metabolism [179].

There are problems as well in the absorption of certain drugs in the presence of specific food components. L-Dopa absorption may be inhibited in the presence of amino acids formed from the digestion of proteins [61]. The absorption of tetracycline is reduced by calcium salts present in dairy foods and by several other cations, including magnesium and aluminum [180–182], which are often present in antacid preparations. In addition, iron and zinc reduce tetracycline absorption [183]. Figure 14 illustrates several of these interactions. It is thought that these materials react with tetracycline to form a water-insoluble and nonabsorbable complex. Obviously, these offending materials should not be coadministered with tetracycline antibiotics.
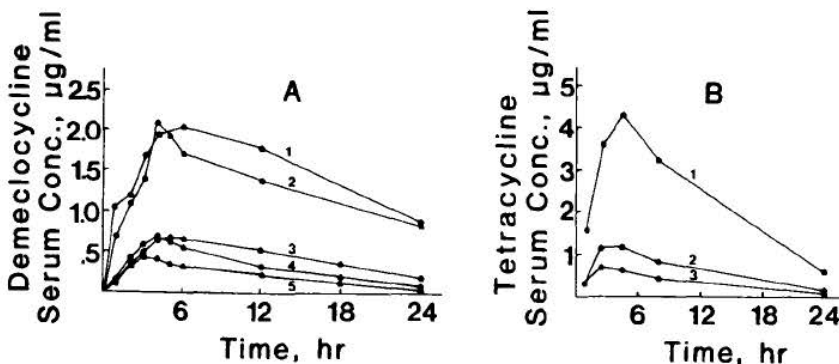
Fig. 14 (A) Demeclocycline serum concentrations as a function of time in four to six subjects after oral ingestion of demeclocycline in the absence or presence of dairy meals. Key: 1, meal (no dairy products); 2, water; 3, 110 g cottage cheese; 4, 240-ml buttermilk; 5, 240-ml whole milk. (B) Tetracycline serum concentrations as a function of time in six subjects after oral ingestion of tetracycline in the absence or presence of iron salts (equivalent to 40-mg elemental iron). Key: 1, control; 2, ferrous gluconate; 3, ferrous sulfate. (Data from: A, Ref. 182; B, Ref. 183.)

The tetracycline example just cited is one type of physicochemical interaction that may alter absorption. The relative influence of complexation on drug absorption will depend on the water-solubility of the drug, the water-solubility of the complex, and the magnitude of the interaction (i.e., the complexation stability constant). If the drug itself is poorly water-soluble, the absorption pattern will be governed by rate of dissolution. Often, such compounds are incompletely and erratically absorbed. As a result, complexation will probably exert more of an influence on the absorption of such a compound than on one that is normally well-absorbed, although this will depend on the nature of the complex. If the complex is water-insoluble, as with tetracycline interactions with various metal cations, the fraction complexed will be unavailable for absorption. Although most complexation interactions are reversible, the greater the stability constant of the complex, the greater the relative influence on absorption. Generally, however, because the interaction is reversible, complexation is more likely to influence the rate than the extent of absorption.

Drug complexation is sometimes used in preparing pharmaceutical dosage forms to improve stability or solubility, or to prolong drug release. There are several examples, however, for which a drug complex results in reduced absorption. Amphetamine interacts with sodium carboxymethyl cellulose to form a poorly water-soluble derivative and a decrease in absorption is seen [184]. Phenobarbital absorption is reduced as a result of interaction with polyethylene glycol 4000 [185]. These large macromolecules have the potential to bind many drugs.

Surface-active agents, because they are able to form micelles above the critical micelle concentration (CMC), may bind drugs either by inclusion within the micelle (solubilization) or by attachment to its surface. Below the critical micelle concentration, surfactant monomers have a membrane-disrupting effect that can enhance drug penetration across a membrane. The latter influence has been seen in drug absorption studies in animals. The influence of surface-active agents on drug absorption will depend on the surfactant concentration and the physicochemical characteristics of the drug. If the drug is capable of partitioning from the aqueous to the micellar phase, and if the micelle is not absorbed, the usual situation, there may be a reduction in rate of absorption. Micellar concentrations of sodium lauryl sulfate or polysorbate

80 (Tween 80) increase the rectal absorption rate of potassium iodide in the rat, but reduce the absorption rate of iodoform and triiodophenol [186,187]. Since potassium iodide is not solubilized by the micelle, the enhanced rate of absorption is attributed to the influence of the surfactant on the mucosal membrane. The other compounds, which partition into the micelle, exhibit a reduced rate of absorption, since there is a decrease in their effective concentration. Similar observations, from pharmacological response data in goldfish, have been made for several barbiturates in the presence of varying surfactant concentrations.

In addition to the aforementioned effects of surfactants, one must consider their influence on drug dissolution from pharmaceutical dosage forms. If the drug is poorly water-soluble, enhanced dissolution rate in the presence of a surface-active agent, even if part of the drug is solubilized, will result in increased drug absorption. The absorption rate of sulfisoxazole suspensions given rectally to rats increased with increasing polysorbate 80 concentration. At surfactant concentrations in excess of that needed to solubilize the drug completely, there was a reduced rate of absorption; however, the rate was greater than that from the control suspension (i.e., without surfactant) [188].

Another important type of physicochemical interaction that may alter absorption is that of drug binding or adsorption onto the surface of another material. As with complexation and micellarization, adsorption will reduce the effective concentration gradient between gut fluids and the bloodstream, which is the driving force for passive absorption. Although absorption frequently reduces the rate of absorption, the interaction is often readily reversible and will not affect the extent of absorption. A major exception is adsorption onto charcoal, which in many cases appears to be irreversible, at least during the time of residence within the GIT. As a result, charcoal often reduces the extent of drug absorption. Indeed, this, along with the innocuous nature of charcoal, is what makes it an ideal antidote for oral drug overdose. The effectiveness of that form of therapy will depend on the amount of charcoal administered and the time delay between overdose and charcoal dosing. Another interesting aspect of charcoal dosing is its influence on shortening the elimination half-life of several drugs. This is a particularly attractive noninvasive means of enhancing drug elimination from the body.

In addition to charcoal, adsorption is often seen with pharmaceutical preparations that contain large quantities of relatively water-insoluble components. A good example is antidiarrheal products and perhaps antacids. The importance of the strength of binding as it influences absorption has been illustrated by Sorby [189], who showed that both attapulgite and charcoal reduce the rate of drug absorption, but only charcoal reduced the extent of absorption. Lincomycin is an example of a drug for which absorption is impaired by an antidiarrheal preparation [190]. Another type of compound that has altered drug absorption by binding is the anion-exchange resins, cholestyramine and colestipol. The foregoing physicochemical interactions that may alter drug therapy may be minimized by not coadministering the interacting compounds at the same time, but separating their ingestion by several hours.

There are other drug–drug interactions in absorption that are mediated by alterations of gut physiology. The mechanism that has received the greatest attention is that associated with changes in gastric emptying and intestinal transit, as discussed previously and illustrated in Table 8. A review of interactions in absorption is available [191].

We noted previously, when discussing mechanisms of drug absorption, that certain calcium channel blockers enhance the gastrointestinal absorption of several aminopenicillin and aminocephalosporin derivatives [64,65]. This type of interaction, although perhaps not of practical clinical importance, is very intriguing in terms of promoting absorption efficiency, and it illustrates the useful (rather than deleterious) aspect of a drug–drug interaction. Another interesting and recently observed drug–food interaction is that between grapefruit juice and certain drugs, especially those with a high hepatic clearance that undergo substantial first-pass hepatic

metabolism (discussed later). Grapefruit juice coadministration with felodipine results in a large increase in the bioavailability of the latter (ca., threefold) [192,193]. This effect is believed to be the result of the inhibition of the hepatic metabolism of the drug by components of the grapefruit juice (e.g., bioflavonoids). One such bioflavonoid, naringin, was directly tested by coadministration with felodipine, but it produced an effect smaller than that with grapefruit juice, suggesting that other factors contribute to the interaction [193]. Grapefruit juice also increases the absorption of similar compounds; nifedipine and nitrendipine [194,195]. Clearly, we need to be more aware of potential food interactions with drugs.

B. Metabolism

Drug metabolism may occur at various sites along the GIT, including within gut fluids, within the gut wall, and by microorganisms present in the low end of the tract. Several examples of enzymatic alteration of certain drugs in gut fluids have been noted previously. Gut fluids contain appreciable quantities of a variety of enzymes that are needed to accomplish digestion of food. An additional consideration, although not involving enzymatic action, is that of acid- or base-mediated drug breakdown. Numerous drugs are unstable in acidic media (e.g., erythromycin and penicillin) and, therefore, will degrade and provide lower effective doses, depending on the pH of the gastric fluid, solubility of the drug, and the residence time of the dosage form in the stomach. Chemical modification of the drug by, for example, salt or ester formation may provide a more stable derivative, the absorption of which will be influenced to a smaller degree by the aforenoted factors. Clorazepate is an interesting example of a prodrug that must first be acid-hydrolyzed to produce the active chemical form; hydrolysis in the gut fluids produces the active form, N-desmethyldiazepam. In this instance, unlike the examples cited earlier, acid hydrolysis is a prerequisite for absorption of the pharmacologically active form. As a result, pH of gastric fluids and gastric emptying time and variables that influence those factors are expected to affect the absorption profile of clorazapate. Greater concentrations of N-desmethyldiazepam are achieved at the lower gastric pH, which is consistent with the more rapid acid hydrolysis at acidic pH [196].

The mucosal cells lining the gut wall represent a major potential site of drug metabolism. The metabolic activity of this region has been studied by a variety of techniques, ranging from subcellular fractions, to tissue homogenates, to methods involving the whole living animal. Metabolic reactions include both phase I and II processes. It appears that the small intestine (duodenum and jejunum) has the greatest enzymatic activity, although most regions of the GIT can partake in metabolism. It is not a simple matter, especially in the whole animal, to distinguish between the sites of metabolism responsible for so-called presystemic elimination (or the first-pass effect). The latter refers to all processes of metabolism before the drug reaches the systemic circulation, which take place primarily in the gut and liver. It is this presystemic elimination that contributes to differences in drug effects as a function of route of administration and that may seriously compromise the clinical efficiency of certain drugs given orally. A thorough discussion of this topic is beyond the scope of this chapter and readers are referred to a review of gut wall metabolism of drugs [197]. Drugs that undergo, or that are suspected to undergo, metabolism in the gut wall include aspirin, acetaminophen, salicylamide, p-aminobenzoic acid, morphine, pentazocine, isoproterenol, L-dopa, lidocaine, and certain steroids. L-Dopa appears to be metabolized by decarboxylase enzymes present in the gastric mucosa, which, as discussed previously, suggests the importance of rapid gastric emptying to achieve maximal absorption of the unchanged compound [198]. Salicylamide and p-aminobenzoic acid are interesting examples because they illustrate another aspect of gut metabolism, that of saturation. In addition, factors affecting absorption rate will influence the fraction of

the dose that reaches the systemic circulation in the form of intact drug. Figure 15 illustrates the relationship between the salicylamide plasma concentration–time curve (AUC) as a function of the oral dose of sodium salicylamide. Normally, that relationship is expected to be linear, and the line should go through the origin. The curvilinearity, especially at low doses, suggests some form of presystemic elimination that becomes saturated above a certain dose. Evidence in animals suggests that the drug is metabolized in the gut wall to sulfate and glucuronide conjugates, although metabolism in the liver also occurs on the first pass. Extrapolation of the straight-line segment to the x-axis in Fig. 15 gives an intercept that has been referred to as the *break-through* dose, which approximates the dose needed to saturate the enzyme system (about 1–1.5 g for salicylamide). Doses less than that value produce only small plasma concentrations of the unchanged drug. Another interesting aspect of this phenomenon is that the rate of drug presentation to the enzymatic system will influence the fraction of the dose reaching the systemic circulation unchanged and will alter the metabolic pattern. The latter factors, therefore, will be influenced by the dosage form characteristics and the rate of gastric emptying. The more rapid the rate of absorption, the more likely the enzymatic system will become saturated. This will result in greater plasma concentrations of unchanged drug and a metabolic pattern with a lower percentage of the drug recovered as the saturable metabolite. At any given dose, the more rapidly soluble sodium salicylamide produces greater plasma concentrations of unchanged drug than salicylamide. The more rapidly soluble dosage forms of salicylamide (solution and suspension) produce smaller fractions of the dose in the form of the saturable metabolite (sulfate conjugate) compared with a slowly dissolving tablet [200]. Observations similar to the latter point have been made for p-aminobenzoic acid. In that instance, however, a delay in gastric emptying produced a greater percentage of the dose in the form of the saturable metabolite (acetyl derivative), which is consistent with a reduced rate of absorption [201].

An interesting example of gut metabolism and gender-dependent differences is that of ethanol. Females appear to have higher blood ethanol concentrations following an oral dose than do males given the same dose. The latter is true even if the data are corrected for weight and lean body mass differences. Ethanol is metabolized by alcohol dehydrogenase present in the
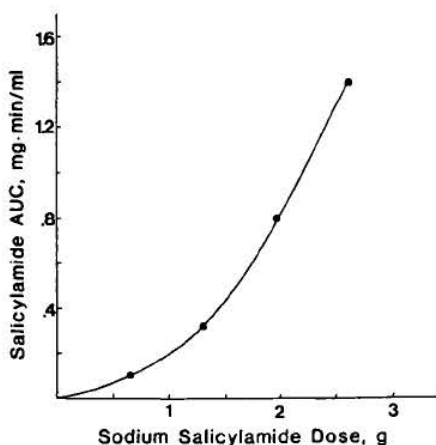

Fig. 15 Area under the salicylamide plasma concentration–time curve (AUC) as a function of the oral dose of sodium salicylamide. Each point is the average of five subjects. (Data from Ref. 199.)

treatment of the morbidly obese. A number of studies have been conducted to examine absorption before and after surgery. As noted in the introduction to this section, care must be exercised in study design and evaluation of data, as large weight loss may alter drug elimination from the body compared with the presurgery condition. Further complications include the time that the study is conducted relative to the time of surgery, and the length and sections of the intestine removed.

One excellent study [219] employed intravenous and oral dosing at each of several times after surgery (1–2 weeks, 6 and 12 months). This design permits valid conclusions about the absorption process. There was a significant reduction after surgery in ampicillin absorption, but no change in propylthiouracil absorption. Other studies suggest reduced absorption of hydrochlorothiazide and phenytoin [220,221], but these findings must be qualified by the aforementioned concerns.

In those instances during which a patient's response to a drug is less than expected and there is reason to believe that this is a result of impaired absorption owing to any of the pathological conditions or disease states cited earlier, a first attempt in seeking to improve drug therapy is to optimize absorption from the GIT. To do this, a practical approach might well be to administer the drug in a form readily available for absorption. Usually, if such a form is marketed or easily prepared, administration of a drug in solution will represent the best way to achieve maximal absorption, as this will eliminate the time for drug dissolution in the gut needed by solid oral dosage forms. When absorption cannot be sufficiently improved by use of a drug solution, alternative routes of administration must be considered (e.g., intramuscular).

D. Age

Most of the information discussed to this point and most of the literature concerned with drug absorption involve studies performed in young, healthy (usually male) adults. In contrast, there is considerably less information concerning absorption in subjects at either end of the age spectrum (i.e., pediatric and geriatric populations). For a variety of reasons, one would expect the absorption process in the latter groups to be different from that in young adults; unfortunately, there is as yet little information to present valid general statements.

The pediatric population (neonates, infants, and children) presents a particularly difficult group in which to conduct clinical experimentation because of ethical considerations. A further complication is the rapid development of organ function, which is likely to influence results, even over a relatively short experimental period (e.g, 2–4 weeks), especially in neonates and infants. An additional consideration in the latter groups is whether the neonate is premature or full-term. Most often, plasma AUC data are obtained after an oral dose for the purpose of estimating elimination half-life or to provide a basis for the development of a multiple-dosing regimen. Such data provide very limited information about rate or extent of absorption. Indeed, most reviews of drug disposition in the pediatric population indicate the lack of rigorous information on this topic.

Gastric fluid is less acidic in the newborn than in adults, since acid secretion is related to the development of the gastric mucosa. This condition appears to last for some time, as pH values similar to the adult are not reached until after about 2 years. The higher gastric fluid pH, along with a smaller gut fluid volume, may influence dissolution rate and the stability of acid-unstable drugs. The gastric-emptying rate appears to be slow, approaching adult values after about 6 months. An interesting example in support of that suggestion is a study that examined riboflavin absorption in a 5-day-old neonate and a 10-month-old infant [222]. The maximum urinary excretion rate was considerably greater in the infant, whereas excretion rate in the neonate was constant and prolonged. This suggests more rapid absorption in the infant,

gastric mucosa, and it appears that this enzyme is present in smaller quantities in females. This results in a greater fraction of the dose not being metabolized compared with males and a subsequent higher blood ethanol concentration. Females absorb about 91% of the dose as ethanol, compared with about 61% in males [202]. More recent evidence suggests that alcohol dehydrogenase activity is lower in young women (younger than about 50 years of age), elderly males, and in alcoholics [203]. A recent review has examined first-pass metabolism in oral absorption and factors that affect that process [204].

The gastrointestinal microflora is another site of drug metabolism within the GIT, and it has received some attention. In normal subjects, the stomach and proximal small intestine contain small numbers of microorganisms. Concentrations of these organisms increase toward the distal end of the intestine. A wide variety of aerobic and anaerobic organisms are present in the gut. The microflora, derived primarily from the environment, tend to adhere to the luminal surface of the intestine. Within an individual, the microflora tend to remain rather stable over long periods. The primary factors governing the numbers and kinds of microorganisms present in the tract include (a) the activity of gastric and bile secretions, which tend to limit the growth of these organisms in the stomach and upper part of the GIT; and (b) the propulsive motility of the intestine, which is responsible for continually cleansing the tract, thereby limiting the proliferation of microorganisms. Gastric atrophy permits increased numbers of microorganisms to pass into the small intestine, and reduced intestinal motility results in overgrowth.

A review of drug metabolism by intestinal microorganisms indicates that most studies have dealt with animals other than humans [205]. These studies indicate a wide range of primarily phase I metabolic pathways. Various drugs that are glucuronidated in the body are secreted into the intestine by the bile, and these are subject to cleavage by bacterial glucuronidase enzymes. The cleavage product may then be in a form available for absorption. Various drug conjugates may be similarly deconjugated by other bacterial enzymes (e.g., the glycine conjugate of isonicotinic acid). Although some drugs may be rendered inactive, bacterial metabolism of other drugs may give rise to more active or toxic products. The formation of the toxic compound cyclohexylamine from cyclamate is an example [206]. Salicylazosulfapyridine (sulfasalazine), which is used in treating ulcerative colitis, provides an interesting example of a drug for which its metabolites represent the active phamacological species. The parent drug is metabolized to 5-aminosalicylate and sulfapyridine. In conventional rats, both metabolites and their conjugates appear in urine and feces. In germ-free rats, however, the metabolites are not excreted. This suggests that the intestinal flora play a role in reducing the parent compound and formation of the two metabolites. If this is true, factors influencing the population and types of intestinal microorganisms may, in turn, influence the absorption and effectiveness of the drug. For example, concomitant antibiotic therapy, by reducing the population of microorganisms, may prevent the parent drug from being metabolized.

C. Disease States

Gastrointestinal disorders and disease states are likely to influence drug absorption. Although this important area has not been explored thoroughly, numerous studies have addressed this issue. One major concern in this area is that many of these studies have not been correctly designed. This has resulted in conflicting reports and in our inability to reach generally valid conclusions. The majority of these studies are conducted after administration of an oral dose, and the area under the plasma concentration–time curve (AUC) is measured. The latter parameter is frequently used in assessing bioavailability. The resulting AUC is compared with that from a control group of different subjects, or within the same subject, during the time the disorder is present, and compared with the value before or after the disorder is resolved. The

problem here is that a value for AUC depends as much on the body's ability to clear or eliminate the drug as it does on absorption. Differences in the former parameter are likely to be present between subjects as well as within a subject from time to time (especially in the presence of a disease). Therefore, AUC values after oral dosing may lead to incorrect conclusions. To use such a value properly, one must be certain that drug clearance is not different between, or within, the subjects. In the ideal situation, an intravenous dose would be given to establish the correctness of that assumption. This is an approach, unfortunately, that is not generally used. A recent review of the influence of gastrointestinal disease on drug absorption has been published [207].

Elevated gastric pH is seen in subjects with achlorhydria as a result of reduced acid secretion. Aspirin appeared to be better absorbed in achlorhydric subjects than in normal subjects [208]. In contrast, the absorption of tetracycline, which is most soluble at acidic pH, appears to be unaffected by achlorhydria or after surgery in which the acid-secreting portion of the stomach was removed [209,210]. The absorption of clorazepate would be expected to be reduced in achlorhydria (for the reasons discussed earlier), but as yet, the data are not conclusive. The clinical significance of altered gut pH for drug absorption is not clearly established. Alterations in drug absorption caused by changes in gut pH will most likely be mediated by its influence on dissolution rate.

Changes in gastric emptying are expected to influence the rate and, possibly, the extent of absorption, for the reasons discussed previously. Emptying may be severely hampered and absorption altered soon after gastric surgery, or as a result of pyloric stenosis, or in the presence of various disease states. Riboflavin absorption is increased in hypothyroidism and reduced in hyperthyroidism, conditions that alter gastric emptying and intestinal transit rates [211]. There is the indication that absorption is impaired during a migraine attack, possibly as a result of reduced gastric-emptying rate, since metoclopramide administration increases the rate of drug absorption [212].

Diarrheal conditions may decrease drug absorption as a result of reduced intestinal residence time. The absorption of several drugs was decreased in response to lactose- and saline-induced diarrhea [213]. Digoxin absorption from tablets was impaired in one subject who developed chronic diarrhea as a result of x-ray treatment [214]. Abdominal radiation or the underlying disease reduces digoxin and clorazepate absorption [215]. A dosage form that provides rapid drug dissolution (e.g., solution) may partially resolve this problem.

There are various malabsorption syndromes known to influence the absorption of certain nutrients. Although not thoroughly investigated, such syndromes may exert an influence on the efficacy of drug absorption. Heizer et al. [216] have noted reduced absorption of digoxin in patients with sprue, with malabsorption syndrome, or with pancreatic insufficiency. The dosage form of digoxin, especially dissolution rate from tablets, will partially determine the influence of malabsorption states on absorption, the problem being compounded by poorly dissolving tablets. Phenoxymethyl penicillin absorption is reduced in patients with steatorrhea [217], and ampicillin and nalidixic acid absorption appears to be impaired in children with shigellosis [218].

There are a variety of other disease states for which influence on drug absorption has been reported, including cystic fibrosis, villous atrophy, celiac disease, diverticulosis, and Crohn's disease. The results of these studies are frequently divergent; therefore, general statements cannot be made. A thorough discussion of these findings is beyond the scope of this chapter, and the interested reader is referred to a recent review [207].

As most drugs are best absorbed from the small intestine, any surgical procedure that removes a substantial portion of the small intestine is likely to influence absorption; however, and as discussed previously, the characteristics of the dosage form may affect the findings. Although the procedure has fallen out of favor, intestinal bypass surgery has been used in

studies indicate an inverse relation between urinary xylose recovery and age after an oral dose
(lines B and C). It is this observation that has suggested reduced absorption with age. However,
the same inverse relation is found after an intravenous dose (line A), an observation that cannot
be explained by impaired absorption, but rather, by reduced renal clearance of xylose. Line D
shows the ratio of urinary recovery (oral to intravenous), which suggests that absorption is not
altered with age. A more recent study in which each subject (age range, 32–85 years) received
both an oral and an intravenous dose indicates no relation between xylose bioavailability and
age [225].

There are substantial changes in a variety of physiological functions in the elderly that may
influence drug absorption [223], including a greater incidence of achlorhydria, altered gastric
emptying, reduced gut blood flow, and smaller intestinal surface area. One recent example
indicates that gastric pH may be an important determinant of drug absorption in the elderly
[226]. Dipyridamole is a poorly water-soluble weak base, the dissolution of which would be
optimal in an acidic environment. Elevated gastric pH caused by achlorhydria (a condition that
is more prevalent in the elderly than in the young) results in impaired absorption of dipyri-
damole. The ingestion of glutamic acid by achlorhydric subjects improves absorption. There
are, in addition, other factors that may influence absorption, such as a greater incidence of GI
disease, altered nutritional intake and eating habits, and ingestion of drugs that may affect the
absorption of other drugs. Although data are still somewhat limited, the general impression is
that the rate of absorption is frequently reduced, whereas there is little if any change in the
extent of absorption [223]. This is a tentative statement that needs to be qualified for the specific
drug and for the health status of the subject. For example, the absorption of drugs that undergo
hepatic first-pass metabolism may be improved in the elderly (e.g., propranolol) as a conse-
quence of reduced hepatic clearance with age.

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whereas absorption in the neonate proceeds for a longer time. For the reasons discussed previously, these data suggest slower emptying or intestinal transit rates in the neonate (recall that riboflavin is absorbed by a specialized process high in the small intestine). Intestinal transit tends to be irregular and may be modified by the type of food ingested and the feeding pattern.

Intestinal surface area and total blood flow to the GIT are smaller than in adults and may influence the efficiency of absorption. Relative to the use of rectal suppositories, one needs to remember that the completeness of absorption will be a function of retention time in the rectum. Since bowel movements in the young are likely to be irregular, the retention time may limit the efficiency of absorption by that route. In light of the little information available about absorption in the young, it would seem reasonable to attempt to optimize absorption by using solution, rather than solid, dosage forms.

Only in recent years has there been any substantial progress made in better understanding drug disposition in the elderly. Active research programs in gerontology have begun to provide more information about rational drug dosing in this population. There are several important and unique characteristics of the elderly that make a compelling argument for the need of such information (e.g., they ingest more drugs per capita, their percentage of the population is increasing, and they suffer from more disease and physical impairments). As noted for the pediatric population, there are a variety of complex issues associated with the conduct of research in the elderly. Careful consideration must be given to experimental design and data analysis. Some considerations include the appropriate definition of age, cross-sectional *versus* longitudinal study design, and health status of the subject [223].

There have been numerous statements in the literature to the effect that GI absorption in the elderly is impaired and less efficient than in young adults. Although there have been few data to support the suggestion, one basis for that statement has been the results obtained from the application of the so-called xylose tolerance test, which is often used in assessing malabsorption. This conclusion of impaired absorption in the elderly presents a good example of the need for careful study design and appropriate pharmacokinetic analysis of data. Figure 16 illustrates the results of several studies that have examined xylose absorption [224]. Most
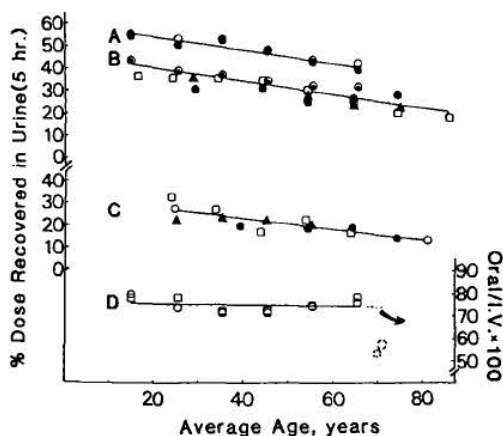

Fig. 16   Percentage xylose dose recovered in urine as a function of age after (A) a 5-g intravenous dose; (B) 5-g oral dose; and (C) 25-g oral dose. Line D is the ratio of urinary recoveries (oral to intravenous) after 5-g doses (*y*-axis on right). Symbols represent data obtained from different studies. (From Ref. 224.)

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Pharmacokinetics

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I. INTRODUCTION

Drug therapy is a dynamic process. When a drug product is administered, absorption usually proceeds over a finite time interval; and distribution, metabolism, and excretion (ADME) of the drug and its metabolites proceed continuously at various rates. The relative rates of these "ADME processes" determine the time course of the drug in the body, most importantly at the receptor sites that are responsible for the pharmacological action of the drug.

The usual aim of drug therapy is to achieve and maintain effective concentrations of drug at the receptor site. However, the body is constantly trying to eliminate the drug and, therefore, it is necessary to balance absorption against elimination to maintain the desired concentration. Often the receptor sites are tucked away in a specific organ or tissue of the body, such as the central nervous system, and it is necessary to depend on the blood supply to distribute the drug from the site of administration, such as the gastrointestinal tract, to the site of action.

Since the body may be viewed as a very complex system of compartments, at first, it might appear to be hopeless to try to describe the time course of the drug at the receptor sites in any mathematically rigorous way. The picture is further complicated because, for many drugs, the locations of the receptor sites are unknown. Fortunately, body compartments are connected by the blood system, and distribution of drugs among the compartments usually occurs much more rapidly than absorption or elimination of the drug. The net result is that the body behaves as a single homogeneous compartment relative to many drugs, and the concentration of the drug in the blood directly reflects or is proportional to the concentration of the drug in all organs and tissues. Thus, it may never be possible to isolate a receptor site and determine the concentration of drug around it, but the concentration at the receptor site usually can be controlled if the blood concentration can be controlled.

The objective of pharmacokinetics is to describe the time course of drug concentrations in blood in mathematical terms so that (a) the performance of pharmaceutical dosage forms can be evaluated in terms of the rate and amount of drug they deliver to the blood, and (b) the

dosage regimen of a drug can be adjusted to produce and maintain therapeutically effective blood concentrations with little or no toxicity. The primary objective of this chapter will be to describe the mathematical tools needed to accomplish these aims when the body behaves as a single homogeneous compartment and when all pharmacokinetic processes obey first-order kinetics

On some occasions, the body does not behave as a single homogenous compartment and multicompartment pharmacokinetics are required to describe the time course of drug concentrations. In other instances, certain pharmacokinetic processes may not obey first-order kinetics and saturable or nonlinear models may be required. Readers interested in such advanced topics are referred to several texts that describe these more complex pharmacokinetic models in detail [1–5].

II. PRINCIPLES OF FIRST-ORDER KINETICS

A. Definition and Characteristics of First-Order Processes

The science of kinetics deals with the mathematical description of the rate of the appearance or disappearance of a substance. One of the most common types of rate processes observed in nature is the first-order process in which the rate is dependent on the concentration or amount of only one component. An example of such a process is radioactive decay, in which the rate of decay (i.e., the number of radioactive decompositions per minute) is directly proportional to the amount of undecayed substance remaining. This may be written mathematically as follows:

$$\text{Rate of radioactivity decay} \propto [\text{undecayed substance}] \tag{1}$$

or

$$\text{Rate of radioactive decay} = k(\text{undecayed substance}) \tag{2}$$

where k is a proportionality constant called the first-order rate constant.

Chemical reactions usually occur through collision of at least two molecules, very often in a solution, and the rate of the chemical reaction is proportional to the concentrations of all reacting molecules. For example, the rate of hydrolysis of an ester in an alkaline-buffered solution depends on the concentration of both the ester and hydroxide ion:

$$\text{Ester} + \text{OH}^- \rightarrow \text{acid}^- + \text{alcohol} \tag{3}$$

The rate of hydrolysis may be expressed as follows:

$$\text{Rate of hydrolysis} \propto [\text{ester}][\text{OH}^-] \tag{4}$$

or

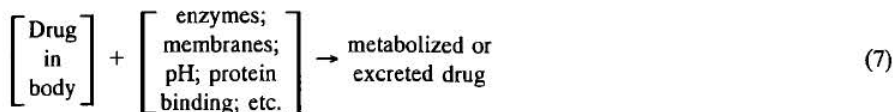$$\text{Rate of hydrolysis} = k[\text{ester}][\text{OH}^-] \tag{5}$$

where k is the proportionality constant called the second-order rate constant.

But, in a buffered system, $[\text{OH}^-]$ is constant. Therefore, at a given pH, the rate of hydrolysis is dependent only on the concentration of the ester and may be written:

$$\text{Rate of hydrolysis}_{(pH)} = k^*[\text{ester}] \tag{6}$$

where k^* is the pseudo-first-order rate constant at the pH in question. (The pseudo-first-order rate constant k^*, is the product of the second-order rate constant and the hydroxide ion concentration: $k^* = k[\text{OH}]^-$).

Fortunately, most ADME processes behave as pseudo-first-order processes—not because they are so simple, but because everything except the drug concentration is constant. For example, the elimination of a drug from the body may be written as follows:

$$\begin{bmatrix} \text{Drug} \\ \text{in} \\ \text{body} \end{bmatrix} + \begin{bmatrix} \text{enzymes;} \\ \text{membranes;} \\ \text{pH; protein} \\ \text{binding; etc.} \end{bmatrix} \rightarrow \begin{matrix} \text{metabolized or} \\ \text{excreted drug} \end{matrix} \tag{7}$$

If everything except the concentration of drug in the body is constant, the elimination of the drug will be a pseudo-first-order process. This may seem to be a drastic oversimplification, but most in vivo drug processes, in fact, behave as pseudo-first-order processes.

B. Differential Rate Expressions

In the previous discussion of radioactive decay it was noted that the rate of decay is directly proportional to the *amount* of undecayed substance remaining. In a solution of a radioactive substance, a similar relationship would hold for the *concentration* of undecayed substance remaining. If a solution of a radioactive substance were allowed to decay and a plot were constructed of the concentration remaining versus time, the plot would be a curve such as that shown in Fig. 1.

In this system, the rate of decay might be expressed as a change in concentration per unit time, $\Delta C/\Delta t$, which corresponds to the slope of the line. But the line in Fig. 1 is curved, which means that the rate is constantly changing and, therefore, cannot be expressed in terms of a finite time interval. By resorting to differential calculus, it is possible to express the rate of
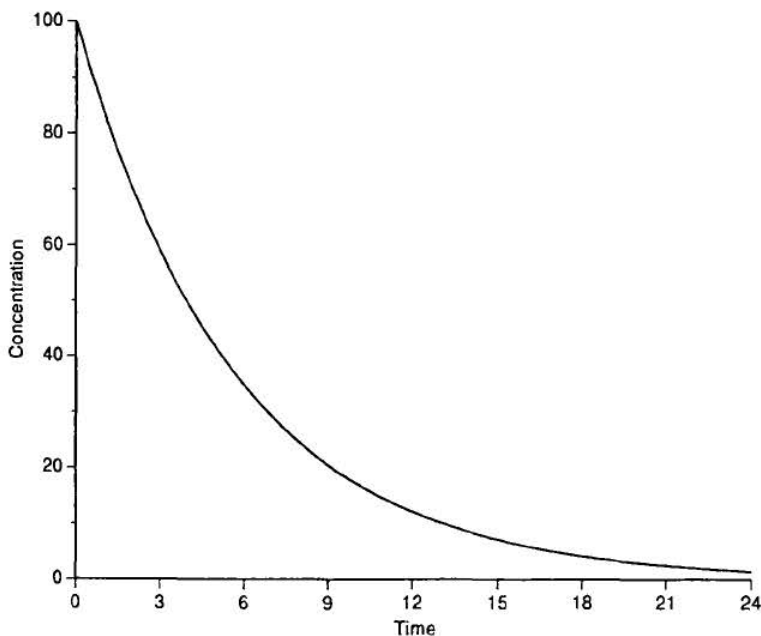

Fig. 1 Plot of concentration remaining versus time for a first-order process (e.g., radioactive decay).

decay in terms of an infinitesimally small change in concentration (dC) over an infinitesimally small time interval (dt). The resulting function, dC/dt, is the slope of the line, and it is this function that is proportional to concentration in a first-order process.

Thus,

$$\text{Rate} = \frac{dC}{dt} = -kC \tag{8}$$

The negative sign is introduced because the concentration is falling as time progresses.

Equation (8) is the differential rate expression for a first-order reaction. The value of the rate constant k could be calculated by determining the slope of the concentration versus time curve at any point and dividing by the concentration at that point. However, the slope of a curved line is difficult to measure accurately, and k can be determined much more easily using integrated rate expressions.

C. Integrated Rate Expressions and Working Equations

Equation (8) can be rearranged and integrated as follows:

$$\frac{dC}{C} = -k\, dt \tag{9}$$

$$\int \frac{dC}{C} = -k \int dt$$

$$\ln C = -kt + \text{constant} \tag{10}$$

where $\ln C$ is the natural logarithm (base e) of the concentration.

The constant in Eq. (10) can be evaluated at zero time when $kt = 0$ and $C = C_0$, the initial concentration. Thus,

$$\ln C_0 = \text{constant}$$

and since $\ln x = 2.30 \log x$, Eq. (10) can be converted to common logarithms (base 10) as follows:

$$2.30 \log C = -kt + 2.30 \log C_0 \tag{11}$$

$$\log C = \frac{-kt}{2.30} + \log C_0$$

Equation (11) is the integrated rate expression for a first-order process and can serve as a working equation for solving problems. It is also in the form of the equation of a straight line:

$$y = mx + b$$

Therefore, if $\log C$ is plotted against t, as shown in Fig. 2, the plot will be a straight line with an intercept (at $t = 0$) of $\log C_0$, and the slope of the line (m) will be $-k/2.30$. Such plots are commonly used to determine the order of a reaction; that is, if a plot of $\log C$ versus time is a straight line, the reaction is assumed to be a first-order or pseudo-first-order process.

The slope of the line and the corresponding value of k for a plot such as that shown in Fig. 2 may be calculated using the following equation:

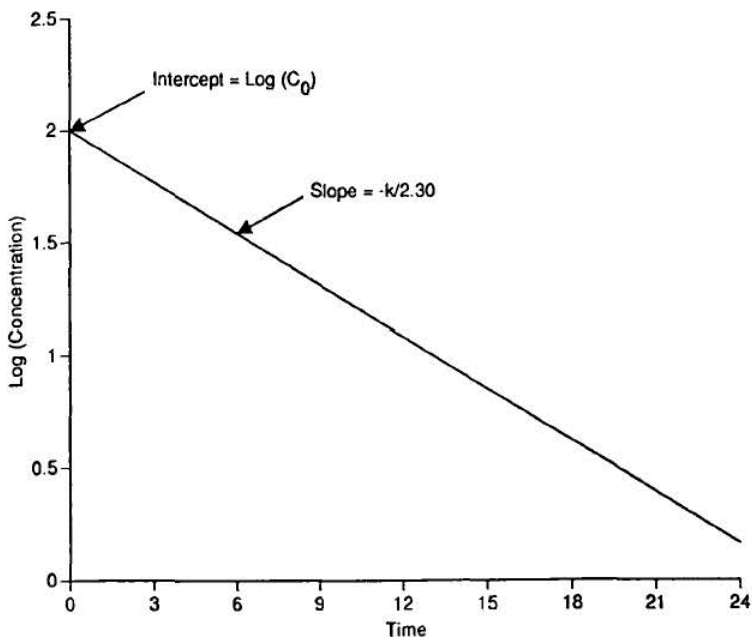$$\text{Slope } (m) = \frac{\log C_1 - \log C_2}{t_1 - t_2} = -\frac{k}{2.30} \tag{12}$$

Fig. 2 Plot of log (concentration remaining) versus time for a first-order process.

EXAMPLE. A solution of ethyl acetate in pH 10.0 buffer (25°C) 1 hr after preparation was found to contain 3 mg/ml. Two hours after preparation, the solution contained 2 mg/ml. Calculate the pseudo-first-order rate constant for hydrolysis of ethyl acetate at pH 10.0 (25°C).

$$\text{Slope } (m) = \frac{\log 3 - \log 2}{(1 - 2) \text{ hr}} = -\frac{k}{2.30}$$

$$= \frac{0.477 - 0.301}{(1 - 2) \text{ hr}}$$

$$= -0.176 \text{ hr}^{-1} = -\frac{k}{2.30}$$

$$k = 0.176 \times 2.30 \text{ hr}^{-1}$$

$$= 0.405 \text{ hr}^{-1}$$

Note that since log C is dimensionless, the rate constant k has the dimensions of reciprocal time (i.e., day^{-1}, hr^{-1}, min^{-1}, sec^{-1}).

Another useful working equation can be obtained by rearranging Eq. (11) as follows:

$$\log C - \log C_0 = -\frac{kt}{2.30}$$

$$\log C_0 - \log C = \frac{kt}{2.30}$$

$$\log \frac{C_0}{C} = \frac{kt}{2.30} \tag{13}$$

Equation (13) shows that since $k/2.30$ is a constant for a given process, the ratio C_0/C is determined solely by the value of t. For example, C_0/C will be equal to 2 after the same length of time, no matter what was the value of the initial concentration (C_0).

EXAMPLE.   For the foregoing ethyl acetate hydrolysis ($k = 0.405$ hr^{-1}), if $C_0 = 3$ mg/ml, when would $C = 1.5$ mg/ml?

$$\log \frac{C_0}{C} = \frac{kt}{2.30}$$

$$\log \frac{3}{1.5} = \frac{0.405 \times t}{2.30}$$

$$\log 2 = \frac{0.405 \times t}{2.30}$$

$$0.301 = 0.176 \times t$$

$$t = 1.71 \text{ hr}$$

If $C_0 = 1.5$ mg/ml, when would $C = 0.75$ mg/ml?

$$\log \frac{C_0}{C} = \frac{kt}{2.30}$$

$$\log \frac{1.5}{0.75} = \frac{0.405 \times t}{2.30}$$

$$\log 2 = 0.176 \times t$$

$$t = 1.71 \text{ hr}$$

The time required for the concentration to fall to $C_0/2$ is called the half-life, and the foregoing example shows that the half-line for a first-order or pseudo-first-order process is a constant throughout the process; it also demonstrates that a first-order process theoretically never reaches completion, since even the lowest concentration would fall to only half its value in one half-life.

For most practical purposes, a first-order process may be deemed ''complete'' if it is 95% or more complete. Table 1 shows that five half-lives must elapse to reach this point. Thus, the elimination of a drug from the body may be considered to be complete after five half-lives have elapsed (i.e., 97% completion). This principle becomes important, for example, in cross-over bioavailability studies in which the subjects must be rested for sufficient time between each drug administration to ensure that ''washout'' is complete.

The half-life of a first-order process is very important. Since it is often desirable to convert a half-life to a rate constant, and vice versa, a simple relationship between the two is very useful. The relationship may be derived as follows:

$$\log \frac{C_0}{C} = \frac{kt}{2.30}$$

When $C_0/C = 2$ and $t = t_{1/2}$. Thus,

$$\log 2 = \frac{kt_{1/2}}{2.30}$$

Table 1 Approach to Completeness with Increasing Half-Lives

Number of half-lives elapsed	Initial concentration remaining (%)	"Completeness" of process (%)
0	100.0	0.0
1	50.0	50.0
2	25.0	75.0
3	12.5	87.5
4	6.25	93.75
5	3.13	96.87
6	1.56	98.44
7	0.78	99.22

$$0.301 = \frac{kt_{1/2}}{2.30}$$

$$kt_{1/2} = 0.693$$

$$k = \frac{0.693}{t_{1/2}} \tag{14}$$

$$t_{1/2} = \frac{0.693}{k} \tag{15}$$

D. Examples of Calculations

Equations (13), (14), and (15) can be used to solve three types of problems involving first-order processes. These types of problems are illustrated in the following examples:

Type 1

Given the rate constant or half-life and the initial concentration, calculate the concentration at some time in the future.

EXAMPLE. A penicillin solution containing 500 units/ml has a half-life of 10 days. What will the concentration be in 7 days?

$$k = \frac{0.693}{t_{1/2}} = \frac{0.693}{10 \text{ day}} = 0.069 \text{ day}^{-1}$$

$$\log \frac{C_0}{C} = \frac{kt}{2.30}$$

$$\log \frac{500 \text{ units/ml}}{C} = \frac{0.069 \text{ day}^{-1} \times 7 \text{ days}}{2.30} = 0.210$$

$$\frac{500 \text{ units/ml}}{C} = \text{antilog } (0.210) = 1.62$$

$$C = 308 \text{ units/ml}$$

Type 2

Given the half-life or rate constant and the initial concentration, calculate the time required to reach a specified lower concentration.

EXAMPLE. A penicillin solution has a half-life of 21 days. How long will it take for the potency to drop to 90% of the initial potency?

$$k = \frac{0.693}{21 \text{ days}} = 0.033 \text{ day}^{-1}$$

$$\log \frac{C_0}{C} = \frac{kt}{2.30}$$

$$\log \frac{100\%}{90\%} = \frac{0.033 \times t}{2.30}$$

$$t = 3.2 \text{ days}$$

Type 3

Given an initial concentration and the concentration after a specified elapsed time, calculate the rate constant or half-life.

EXAMPLE. A penicillin solution has an initial potency of 125 mg/5 ml. After 1 month in a refrigerator, the potency is found to be 100 mg/5 ml. What is the half-life of the penicillin solution under these storage conditions?

$$\log \frac{C_0}{C} = \frac{kt}{2.30}$$

$$\log \frac{125 \text{ mg/5 ml}}{100 \text{ mg/5 ml}} = \frac{k \times 30 \text{ day}}{2.30}$$

$$k = 0.0074 \text{ day}^{-1}$$

$$t_{1/2} = \frac{0.693}{0.0074 \text{ day}^{-1}} = 94 \text{ days}$$

For each type of problem the following assumptions are made: (a) The process follows first-order kinetics, at least over the time interval and concentration range involved in the calculations; and (b) all time and concentration values are accurate.

The latter assumption is particularly critical in solving problems such as type 3, for which a rate constant is being calculated. It would be unwise to rely on only two assay results at two time points to calculate such an important value. Normally, duplicate or triplicate assays would be performed at six or more time points throughout as much of the reaction as possible. The resulting mean assay values and standard deviation values would be plotted on semilogarithmic graph paper, and a straight line would be carefully fitted to the data points. The half-life could then be determined using Eq. (14).

EXAMPLE. A solution of ethyl acetate in pH 9.5 buffer (25°C) was assayed in triplicate several times over a 20-hr period. The data obtained are presented in Table 2. The results were plotted on semilogarithmic graph paper as shown in Fig. 3. Calculate the pseudo-first-order rate constant for the hydrolysis of ethyl acetate at pH 9.5 (25°C).

By fitting a straight line through the data points in Fig. 3 (this can be done by eye using a transparent straight edge) and extrapolating to $t = 0$, the intercept C_0 is found to be 3.13 mg/ml. The half-life is the time at which the concentration equals 1.57 mg/ml, and this is found by interpolation to be 2.4 hr. The value of k is then given by

$$k = \frac{0.693}{t_{1/2}} = \frac{0.693}{2.4 \text{ hr}} = 0.289 \text{ hr}^{-1}$$

Table 2 Assay of Ethyl Acetate

Time (hr)	Concentration (mg/ml) ± SD
2	1.83 ± 0.15
4	1.01 ± 0.09
6	0.58 ± 0.07
8	0.33 ± 0.06
10	0.18 ± 0.04
12	0.10 ± 0.02
16	0.031 ± 0.006
20	0.012 ± 0.002

Semilogarithmic graph paper is readily available from many graph paper manufacturers. It consists of a logarithmic scale on the y axis and a cartesian scale on the x axis (see Fig. 3). On the log scale, the spatial distribution of lines is such that the position of each line is proportional to the log of the value represented by the mark. For example, plotting a concentration of 1.83 mg/ml on semilog paper is equivalent to looking up the log of 1.83 and plotting it on a cartesian scale. This type of graph paper is extremely useful for kinetic calculations because raw concentration data can be plotted directly without converting to logs, and concentration values can be extrapolated and interpolated from the plot without converting logs to numbers.
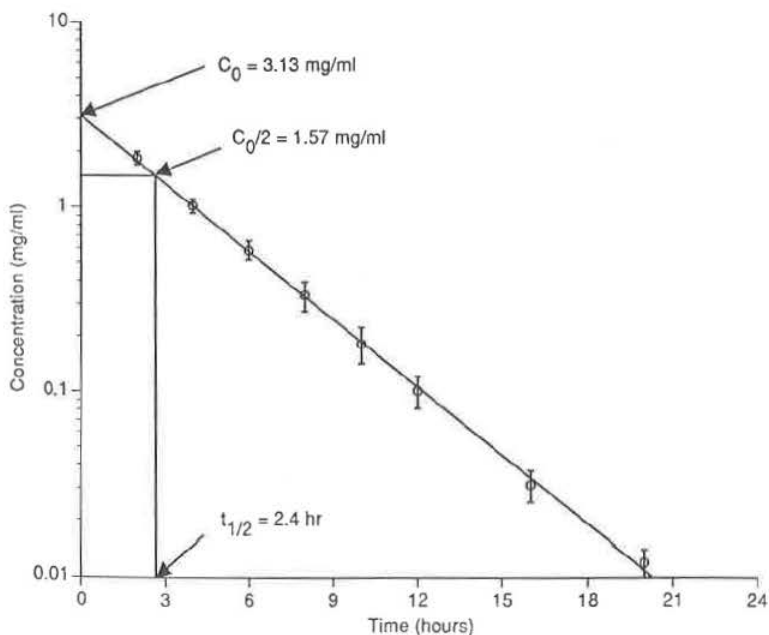

Fig. 3 Semilogarithmic plot of concentration versus time for the hydrolysis of ethyl acetate. (Data shown in Table 2; one standard deviation is indicated by error bars.)

For example, to determine the half-life in the preceding example, the C_0 value and the time at which $C = C_0/2$ were both read directly from the graph. If Fig. 3 had been a plot of log C (on a Cartesian scale) versus time, it would have been necessary to read log C_0 from the graph, convert it to C_0, divide by 2, convert back to log $(C_0/2)$, then read the half-life off the graph. If the rate constant is determined for this example using Eq. (12), the slope must be calculated. To calculate the slope of the line it is necessary first to read C_1 and C_2 from the graph and then take the logarithm of each concentration as described in Eq. (12).

III. FIRST-ORDER PHARMACOKINETICS: DRUG ELIMINATION FOLLOWING RAPID INTRAVENOUS INJECTION

It was mentioned previously that drug elimination from the body most often displays the characteristics of a first-order process. Thus, if a drug is administered by rapid intravenous (IV) injection, after mixing with the body fluids, its rate of elimination from the body is proportional to the amount remaining in the body.

Normally, the plasma concentration is used as a measure of the amount of drug in the body, and a plot of plasma concentration versus time has the same characteristics as the plot in Fig. 1. A semilogarithmic plot of plasma concentration versus time is a straight line, with a slope equal to $k_{el}/2.30$, where k_{el} is the overall elimination rate constant. The intercept at $t = 0$ is C_p^0, the hypothetical plasma concentration after the drug is completely mixed with body fluids, but before any elimination has occurred.

A typical semilog plasma concentration versus time plot is shown in Fig. 4. This figure shows that pharmacokinetic data can also be expressed in terms of a half life, called the *biological half-life*, which bears the same relation to k_{el} as that shown in Eqs. (14) and (15).

Since all the kinetic characteristics of the disappearance of a drug from plasma are the same as those for the pseudo-first-order disappearance of a substance from a solution by hydrolysis, the same working equations [Eqs. (11) and (13)] and the same approach to solving problems can be used.

EXAMPLE. A 250-mg dose of tetracycline was administered to a patient by rapid IV injection. The initial plasma concentration (C_p^0) was 2.50 μg/ml. After 4 hr the plasma concentration was 1.89 μg/ml. What is the biological half-life $(t_{1/2})$ of tetracycline in this patient?

$$\log \frac{C_p^0}{C_p} = \frac{k_{el}t}{2.30}$$

$$\log \frac{2.50}{1.89} = \frac{k_{el} \times 4}{2.30}$$

$$k_{el} = \frac{2.30 \times 0.121}{4}$$

$$= 0.0698 \text{ hr}^{-1}$$

$$t_{1/2} = \frac{0.693}{0.0698 \text{ hr}^-} = 9.93 \text{ hr}$$

Note that this approach involves the following assumptions: (a) the drug was eliminated by a pseudo-first-order process, and (b) the drug was rapidly distributed so that an "initial plasma concentration" could be measured before any drug began to leave the body. The latter assumption implies that the body behaves as a single homogeneous compartment throughout which the drug distributes instantaneously following IV injection. In pharmacokinetic terms,
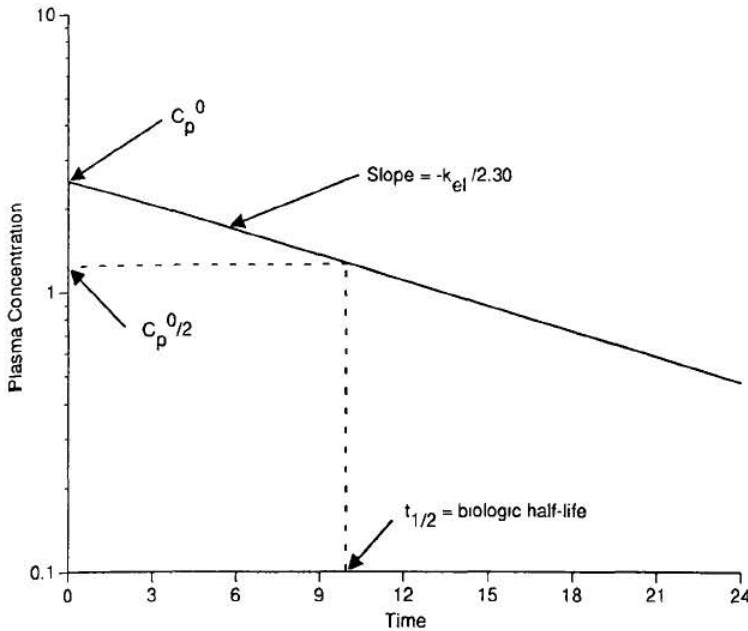
Fig. 4 Semilogarithmic plot of plasma concentration versus time for a drug administered by rapid intravenous injection.

this is referred to as the *one-compartment model*. Although most drugs do not, in fact, distribute instantaneously, they do distribute very rapidly, and the one-compartment model can be used for many clinically important pharmacokinetic calculations.

An important parameter of the one-compartment model is the apparent volume of the body compartment, because it directly determines the relation between the plasma concentration and the amount of drug in the body. This volume is called the *apparent volume of distribution*, V_d, and it may be calculated using the relationship:

$$\text{Volume} = \frac{\text{amount}}{\text{concentration}}$$

The easiest way to calculate V_d is to use C_p^0, the plasma concentration when distribution is complete (assumed to be instantaneous for a one-compartment model) and the entire dose is still in the body. Thus,

$$V_d = \frac{\text{dose}}{C_p^0}$$

EXAMPLE.   Calculate V_d for the patient in the previous example;

$$V_d = \frac{250 \text{ mg}}{2.50 \text{ }\mu\text{g/ml}}$$
$$V_d = 100 \text{ liters}$$

Note: Since 1 μg/ml = 1 mg/liter, dividing the dose in milligrams by the plasma concentration in micrograms per milliliter will give V_d in liters.

The apparent volume of distribution of a drug very rarely corresponds to any physiological volume and, even in cases where it does, it must never be construed as showing that the drug enters or does not enter various body spaces. For example, the 100-liter volume calculated in the foregoing example is much greater than either plasma volume (about 3 liters) or whole blood volume (about 6 liters) in a standard (70-kg) man; it is even greater than the extracellular fluid volume (19 liters) and total body water (42 liters) in the same average man. Based on the calculated value of V it cannot be said that tetracycline is restricted to the plasma, or that it enters or does not enter red blood cells, or that it enters or does not enter any or all extracellular fluids.

A discussion of all the reasons for this phenomenon is beyond the scope of this chapter, but a simple example will illustrate the concept. Highly lipid soluble drugs, such as pentobarbital, are preferentially distributed into adipose tissue. The result is that plasma concentrations are extremely low after distribution is complete. When the apparent volumes of distribution are calculated, they are frequently found to exceed total body volume, occasionally by a factor of two or more. This would be impossible if the concentration in the entire body compartment were equal to the plasma concentration. Thus, V_d is an empirically fabricated number relating the concentration of drug in plasma (or blood) with the amount of drug in the body. For drugs such as pentobarbital, the ratio of the concentration in adipose tissue to the concentration in plasm in much greater than unity, resulting in a large value for V_d. In calculating V_d from Eq. (16), the assumption is made that the drug concentration in the entire body equals that in plasma.

IV. PHARMACOKINETIC ANALYSIS OF URINE DATA

Occasionally, it is inconvenient or impossible to assay the drug in plasma, but it may be possible to follow the appearance of the drug in urine. If the drug is not metabolized to any appreciable degree, the pharmacokinetic model may be written as shown in Scheme 1.

$$D_B \overset{k_{el}}{\to} D_U$$
Scheme 1
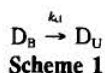
A plot of cumulative amount of drug appearing in urine (D_U) versus time will be the mirror image of a plot of amount of drug remaining in the body (D_B) versus time. This is illustrated in Fig. 5, which shows that the total amount of drug recovered in urine throughout the entire study (D_U^∞) is equal to the dose (D_B^0) and, at any time, the sum of drug in the body (D_B) plus drug in urine (D_U) equals the dose (D_B^0).

A kinetic equation describing urine data can be developed as follows.

If

$$\frac{dD_B}{dt} = -k_{el}D_B \qquad \text{then,} \qquad \frac{dD_U}{dt} = +k_{el}D_B$$

But,

$$D_B + D_U = D_U^\infty$$
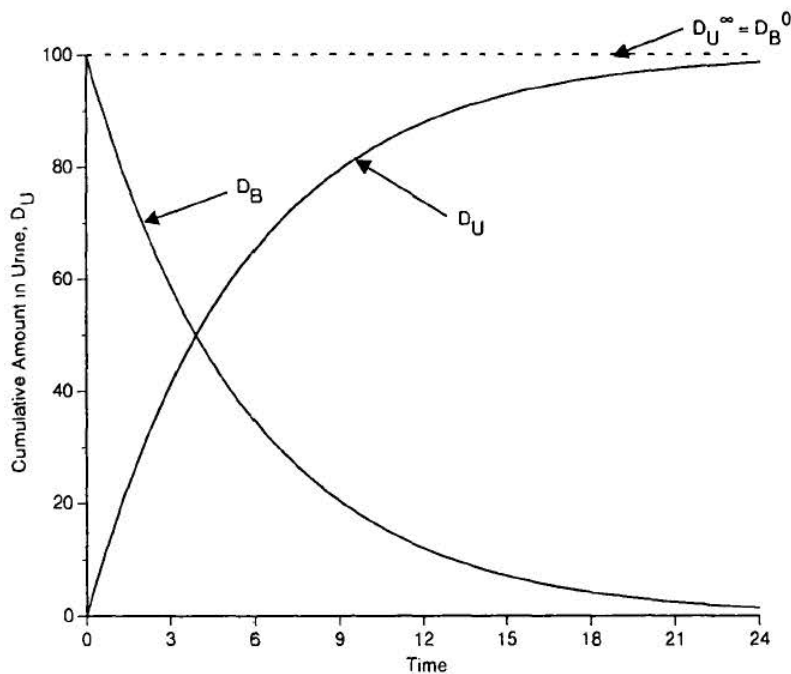
$$= \text{amount recovered in urine}$$

Fig. 5 Plot of cumulative amount of drug in urine, D_U (solid line), and amount of drug in body, D_B (second solid line), versus time according to Scheme 1.

Then,

$$D_B = D_U^\infty - D_U$$

Therefore,

$$\frac{dD_U}{dt} = k_{el}(D_U^\infty - D_U) \quad \text{or} \quad \frac{dD_U}{D_U^\infty - D_U} = k_{el}\,dt$$

Integration gives

$$\int \frac{dD_U}{D_U^\infty - D_U} = k_{el} \int dt$$

$$-\ln(D_U^\infty - D_U) + \ln(D_U^\infty - D_U^0) = k_{el}t$$

Since $\ln(x) = 2.30 \log(x)$ and $D_U^0 = 0$ (there is no drug in urine when $t = 0$),

$$\log(D_U^\infty - D_U) - \log D_U^\infty = -\frac{k_{el}t}{2.30}$$

$$\log(D_U^\infty - D_U) = -\frac{k_{el}t}{2.30} + \log D_U^\infty \tag{17}$$

Equation (17) is in the form of the equation for a straight line ($y = mx + b$), where t is one variable (x), $-k_{el}/2.30$ is the slope (m), $\log D_U^\infty$ is the constant (b), and $\log(D_U^\infty - D_U)$ the

other variable (y). Thus a plot of log ($D_U^\infty - D_U$) versus time is a straight line with a slope equal to $-k_{el}/2.30$ and an intercept of log D_U^∞. Since D_U^∞ is the total amount excreted and D_U is the amount excreted up to time t, $D_U^\infty - D_U$ is the amount remaining to be excreted (ARE). A typical ARE plot is shown in Fig. 6.

EXAMPLE.   The plot in Fig. 6 was constructed using the data shown in Table 3. Note that the concentration of the drug in each urine specimen is not the information analyzed. The total amount excreted over each time interval and throughout the entire study must be determined. As a result, the experimental details of a urinary excretion study must be very carefully chosen, and strict adherence to the protocol is required. Loss of a single urine specimen, or even an unknown part of a urine specimen, makes construction of an ARE plot impossible.

V.   CLEARANCE RATE AS AN EXPRESSION OF DRUG ELIMINATION RATE

A *clearance rate* is defined as the volume of blood or plasma completely cleared of drug per unit time. It is a useful way to describe drug elimination because it is related to blood or plasma perfusion of various organs of elimination, and it can be directly related to the physiological function of these organs. For example, the renal clearance rate (RCR) of a drug can be calculated using the following equation:

$$RCR = \frac{\text{amount excreted in urine per unit time}}{\text{plasma concentration}} \tag{18}$$
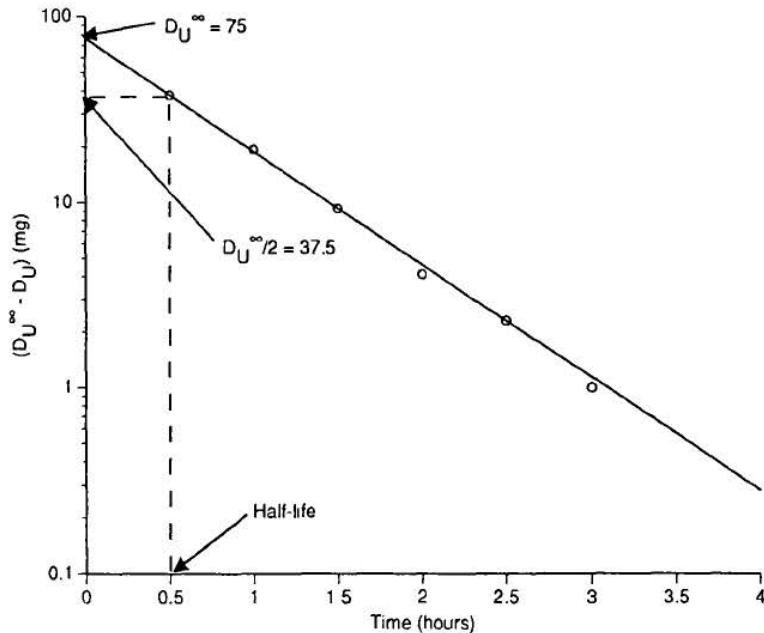

Fig. 6 Semilogarithmic plot of amount of drug remaining to be excreted (ARE) into urine, $D_U^\infty - D_U$, versus time.

Table 3 Drug Excreted into the Urine Versus Time

Time interval (hr)	Amount excreted (mg)	Cumulative amount excreted, D_U (mg)	$D_U^\infty - D_U$ (mg)
0.0–0.5	37.5	37.5	37.8
0.5–1.0	18.5	56.0	19.3
1.0–1.5	10.0	66.0	9.3
1.5–2.0	5.2	71.2	4.1
2.0–2.5	1.8	73.0	2.3
2.5–3.0	1.3	74.3	1.0
3.0–6.0	1.0	75.3	0.0
6.0–12.0	0.0	75.3	0.0

$D_U^\infty = 75.3$ mg.

EXAMPLE. In the example plotted in Fig. 6, the amount of drug excreted over the 0- to 0.5-hr interval was 37.5 mg. If the plasma concentration at 0.25 hr (the middle of the interval) was 10 μg/ml, what was the renal clearance rate? From Eq. (18),

$$RCR = \frac{37.5 \text{ mg/0.5 hr}}{10 \text{ μg/ml}}$$

$$= 7.5 \text{ liters/hr}$$

$$= 125 \text{ ml/min}$$

The glomerular filtration rate (GFR) in normal males is estimated to be 125 ml/min, and the results of the example calculation suggest that the drug is cleared by GFR. If the RCR had been less than 125 ml/min, tubular reabsorption of the drug would have been suspected. If it had been greater than 125 ml/min, tubular secretion would have been involved in the drug elimination.

Drugs can be cleared from the body by metabolism as well as renal excretion, and when this occurs, it is not possible to measure directly the amount cleared by metabolism. However, the total clearance rate (TCR), or total body clearance, of the drug can be calculated from its pharmacokinetic parameters using the following equation:

$$TCR = k_{el}V_d \tag{19}$$

EXAMPLE. The biological half-life of procaine in a patient was 35 min, and its volume of distribution was estimated to be 58 liters. Calculate the TCR of procaine.

$$k_{el} = \frac{0.693}{35 \text{ min}} = 0.0198 \text{ min}^{-1}$$

$$TCR = k_{el}V_d$$

$$= 0.0198 \text{ min}^{-1} \times 58 \text{ liters}$$

$$= 1.15 \text{ liters/min}$$

When a drug is eliminated by both metabolism and urinary excretion, it is possible to calculate the metabolic clearance rate (MCR) by the difference between TCR and RCR:

$$MCR = TCR - RCR \qquad (20)$$

The RCR can be determined from urine and plasma data using Eq. (18), and the TCR can be determined from the pharmacokinetic parameters using Eq. (19). Alternatively, the RCR can be calculated by multiplying the TCR by the fraction of the dose excreted unchanged into urine, f_e:

$$RCR = f_e\,TCR \qquad (21)$$

If it is assumed that the fraction of the dose not appearing as unchanged drug in urine has been metabolized, the MCR can be calculated as follows:

$$MCR = (1 - f_e)\,TCR \qquad (22)$$

EXAMPLE. Sulfadiazine in a normal volunteer had a biological half-life of 16 hr and a volume of distribution of 20 liters. Sixty percent of the dose was recovered as unchanged drug in urine. Calculate TCR, RCR, and MCR for sulfadiazine in this person.

$$k_{el} = \frac{0.693}{16\ hr} = 0.0433\ hr^{-1}$$

$$
\begin{aligned}
TCR &= k_{el}V_d\\
&= 0.0433\ min^{-1} \times 20\ liters\\
&= 0.866\ liter/hr\\
&= 14.4\ ml/min
\end{aligned}
$$

$$
\begin{aligned}
RCR &= f_e\,TCR\\
&= 0.6 \times 14.4\ ml/min\\
&= 8.64\ ml/min
\end{aligned}
$$

$$
\begin{aligned}
MCR &= (1 - f_e)\,TCR\\
&= (1 - 0.6) \times 14.4\ ml/min\\
&= 5.76\ ml/min
\end{aligned}
$$

It should be emphasized that the assumption that any drug not appearing as unchanged drug in urine has been metabolized may introduce a great amount of error into the values of the clearance rates estimated using Eqs. (21) and (22). By this assumption, unchanged drug eliminated in the feces would be included with metabolized drug, as would any orally administered drug that was unabsorbed.

VI. PHARMACOKINETICS OF DRUG ELIMINATED BY SIMULTANEOUS METABOLISM AND EXCRETION

Although some drugs are excreted unchanged in urine, most are partially eliminated by metabolism. Usually both the urinary excretion of unchanged drug and the metabolism are first-order processes, with the rate of excretion and metabolism dependent on the amount of unchanged drug in the body. This results in a "branch" in the kinetic chain representing exit of

drug in the body as depicted in the accompanying pharmacokinetic model (Scheme 2).

$$\text{Drug in body} \xrightarrow{\;k_e\;} \text{unchanged drug in urine} \; (D_U)$$

$$\downarrow k_m$$

$$\text{metabolite} \; (D_M)$$
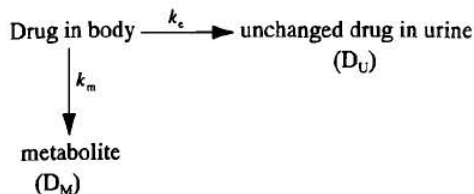
Scheme 2

In Scheme 2, the rate of loss of drug from the body is determined by both k_e and k_m, and this can be written in differential form as follows:

$$\frac{dD_B}{dt} = -k_e D_B - k_m D_B \tag{23}$$
$$= -(k_e + k_m)D_B$$

Thus, the overall elimination rate constant (k_{el}) here is the sum of the urinary excretion rate constant (k_e) and the metabolism rate constant (k_m):

$$k_{el} = k_e + k_m \tag{24}$$

For drugs that are both metabolized and excreted unchanged, semilogarithmic plots of plasma concentrations versus time have slopes equal to $-k_{el}/2.3$.

Urine data are required to determine the individual values of k_e and k_m. The required equations are derived next.

Derivation

From Scheme 2, the differential equation describing overall rate of disappearance of drug from the body may be written:

$$\frac{dD_B}{dt} = -k_{el} D_B$$

and the following integrated equation can be written [see also Eq. (10)]:

$$\ln D_B = \ln D_B^0 - k_{el}t$$

Taking antilogs yields

$$D_B = D_B^0 \exp(-k_{el}t) \tag{25}$$

It should be noted that Eq. (25) is another form of an integrated rate equation. This form makes use of an exp $(-x)$ term and may be referred to as an exponential rate expression. These expressions are useful for visualizing the characteristics of a first-order process. For example, when $t = 0$, $\exp(-k_{el}t) = 1$, and $D_B = D_B^0$. When $t = t_{1/2}$, $\exp(-k_{el}t_{1/2}) = 0.5$, and $D_B = 0.5 \times D_B^0$. When $t = \infty$, $\exp(-k_{el}t) = 0$, and $D_B = 0$. Thus, the value of $\exp(-k_{el}t)$ varies from 1 to 0 as time varies from 0 to ∞. At any time between 0 and ∞, the fraction of the dose remaining in the body is equal to $\exp(-k_{el}t)$.

Exponential rate expressions are also useful in deriving kinetic equations because they can be substituted into differential equations that can then be integrated. For example, from Scheme

2 the differential equation describing the rate of appearance of unchanged drug in urine may be written:

$$\frac{dD_U}{dt} = + k_e D_B \tag{25a}$$

Substituting Eq. (25) into Eq. (25a) gives:

$$\frac{dD_U}{dt} = + k_e[D_B^0 \exp(-k_{el}t)]$$

$$dD_U = + k_e[D_B^0 \exp(-k_{el}t)] \, dt$$

Integration yields:

$$D_U = -\frac{k_e}{k_{el}} D_B^0 \exp(-k_{el}t) + \text{constant}$$

at $t = 0$, $D_U = 0$, and $\exp(-k_{el}t) = 1$; therefore, the constant equals $(k_e/k_{el}) D_B^0$, and

$$D_U = \frac{k_e}{k_{el}} D_B^0[1 - \exp(-k_{el}t)] \tag{26}$$

At $t = \infty$ after elimination is complete, the total amount of drug excreted unchanged in urine (D_U^∞) can be calculated using Eq. (26) as follows:

$$D_U^\infty = \frac{k_e}{k_{el}} D_B^0(1 - 0)$$

$$\frac{D_U^\infty}{D_B^0} = \frac{k_e}{k_{el}} = f_e \tag{27}$$

Equation (27) shows that the function of the dose appearing as unchanged drug in urine (f_e) is equal to the fraction of k_{el} attributable to k_e. [An equation analogous to Eq. (27) for D_M^∞ and k_m could be derived in much the same way.]

Substituting Eq. (27) into Eq. (26) and rearranging gives

$$D_U^\infty - D_U = D_U^\infty \exp(-k_{el}t)$$

Taking logs yields

$$\log(D_U^\infty - D_U) = \frac{-k_{el}t}{2.30} + \log D_U^\infty \tag{28}$$

Equation (28) is identical with Eq. (17), for the case in which all eliminated drug was excreted unchanged in urine. ($D_U^\infty - D_U$) is the amount remaining to be excreted (ARE), and Eq. (28) shows that an ARE plot of unchanged drug in urine versus time will be a straight line, with a slope equal to $-k_{el}/2.30$, even when the drug is partially eliminated by metabolism (see Figs. 6 and 7). With Eq. (27) and the total amount of unchanged drug excreted in urine (D_U^∞), it is possible to calculate k_e. Also, k_m can be calculated from Eq. (24). Thus, all the rate constants in Scheme 2 can be calculated solely on the basis of urinary excretion of unchanged drug.

EXAMPLE. Five hundred milligrams of a drug was administered IV to a normal healthy volunteer, and various amounts of unchanged drug were recovered from the urine over the 24-hr postdrug period (Table 4). Calculate k_{el}, k_e, and k_m for this drug. A plot of ($D_U^\infty - D_U$) on a log
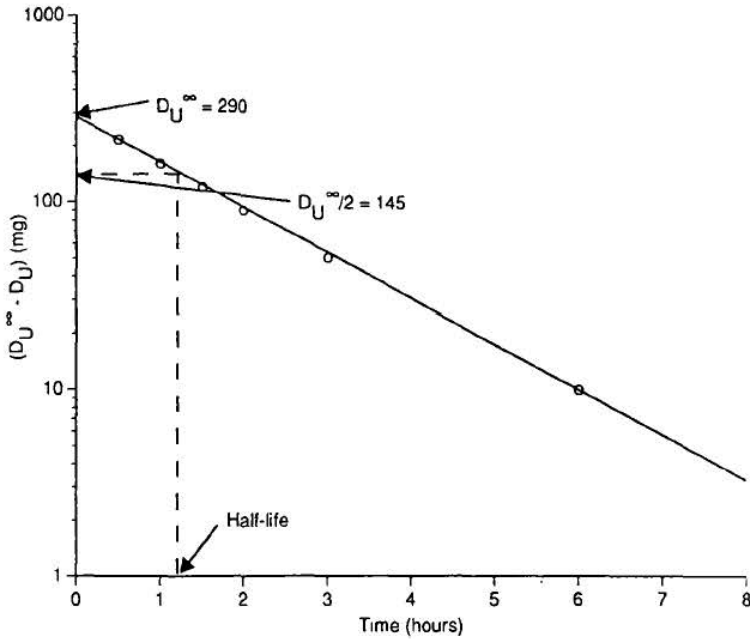
Fig. 7 Semilogarithmic plot of amount of unchanged drug remaining to be excreted into urine, $D_U^\infty - D_U$, versus time according to Scheme 2.

scale versus time is shown in Fig. 7. A half-life of 1.2 hr can be estimated from the line in Fig. 7.

$$k_{el} = \frac{0.693}{1.2 \text{ hr}} = 0.578 \text{ hr}^{-1}$$

Table 4 Drug Recovered in Urine

Time interval (hr)	Amount excreted unchanged (mg)	Cumulative amount excreted unchanged, D_U' (mg)	$D_U^\infty - D_U$ (mg)
0.0–0.5	75	75	215
0.5–1.0	55	130	160
1.0–1.5	40	170	120
1.5–2.0	30	200	90
2.0–3.0	40	240	50
3.0–6.0	40	280	10
6.0–12.0	10	290	0
12.0–24.0	0	290	0

$D_U^\infty = 290$ mg.

From Eq. (27):

$$\frac{D_U^\infty}{D_B^0} = \frac{k_e}{k_{el}}$$

$$\frac{290 \text{ mg}}{500 \text{ mg}} = \frac{k_e}{0.578 \text{ hr}^{-1}}$$

$$k_e = 0.335 \text{ hr}^{-1}$$

From Eq. (24),

$$k_{el} = k_e + k_m$$

$$k_m = 0.578 - 0.335 = 0.243 \text{ hr}^{-1}$$

It is important to reemphasize the following assumptions inherent in this type of calculation:

1. It must be assumed that urine collections were accurately timed and that complete urine specimens were obtained at each collection time. It is also assumed that the assay procedure is accurate and reproducible.
2. It is assumed that all processes of elimination obey first-order kinetics.
3. It is assumed that any drug not appearing unchanged in urine has been metabolized. Furthermore, if the drug is not administered by IV injection, it must also be assumed that the dose is completely absorbed. (The IV route was chosen for the preceding example specifically to avoid the need to introduce this assumption.)

A.   Significance of k_e and k_m in Patients with Kidney or Liver Disease

In the foregoing example, the drug was administered to a healthy subject who had normal kidney and liver function. The estimated biological half-life in this person was 1.2 hr. If the same drug were administered to a person with no kidney function, but with a normal liver, it would be impossible for this individual to excrete unchanged drug. They would, however, be able to metabolize the drug at the same rate as a normal individual. The net result would be that the overall k_{el} would be reduced to the value of k_m, and the biological half-life would increase to

$$\frac{0.693}{k_m} = \frac{0.693}{0.243 \text{ hr}^{-1}} = 2.85 \text{ hr}$$

Similarly, if the patient had no liver function, but normal kidney function, the half-life would increase to

$$\frac{0.693}{k_e} = \frac{0.693}{0.335 \text{ hr}^{-1}} = 2.07 \text{ hr}$$

Thus, the biological half-life of a drug can increase dramatically when the organs of elimination are diseased or nonfunctional; it may increase to varying degrees if these organs are partially impaired.

Currently, no simple relationship exists between clinical measurements of liver function and the value of k_m. Fortunately, kidney function can be measured quantitatively using standard clinical tests, and it is directly related to k_e for a number of drugs. Great success has been achieved in using kidney clearance measurements to predict the biological half-lives of several drugs. This is best illustrated with a drug that is eliminated exclusively by urinary excretion.

EXAMPLE. Kanamycin is a member of the aminoglycoside class of antibiotics, all of which are eliminated exclusively by glomerular filtration. Creatinine is a natural body substance that is cleared almost exclusively by glomerular filtration, and creatinine clearance rate is frequently used as a diagnostic tool to determine glomerular filtration rate. The relation between creatinine clearance rate and kanamycin clearance rate is shown in Fig. 8. Creatinine clearance rate can be determined as a standard clinical procedure, and the corresponding kanamycin clearance rate can be determined by interpolation on the plot in Fig. 8. Since clearance rate = $k_{el}V_d$ [see Eq. (19)], the kanamycin clearance rate can be converted to kanamycin elimination rate constant by dividing by the V_d value for kanamycin, estimated to be about 27% of the patient's body weight.

Although determination of creatinine clearance rate is a standard clinical procedure, it is difficult to carry out, mainly because accurate collection of total urine output over a 24-hr period is required. It is never certain that the patient (or the nurse) has met this requirement. Since creatine is produced continuously in muscle and is cleared by the kidney, renal failure is characterized by elevated serum creatinine levels. The degree of elevation is directly related to the degree of renal failure—if it is assumed that the production of creatinine in the muscle mass is constant and that renal function is stable. When these assumptions are valid, there is a direct relation between serum creatinine level and kanamycin half-life as shown in Fig. 9. The equation of the line in Fig. 9 is

Kanamycin half-life (hr) = 3 × serum creatinine concentration (mg/100 ml)

Thus, kanamycin half-lives (hr) can be predicted in patients with varying degrees of (stable) renal failure by multiplying the serum creatinine level (in mg/100 ml) by 3.
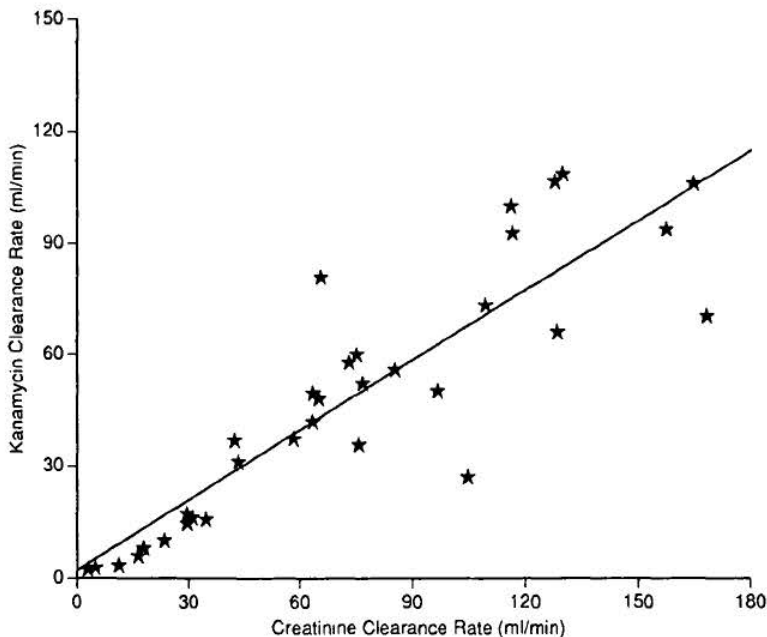

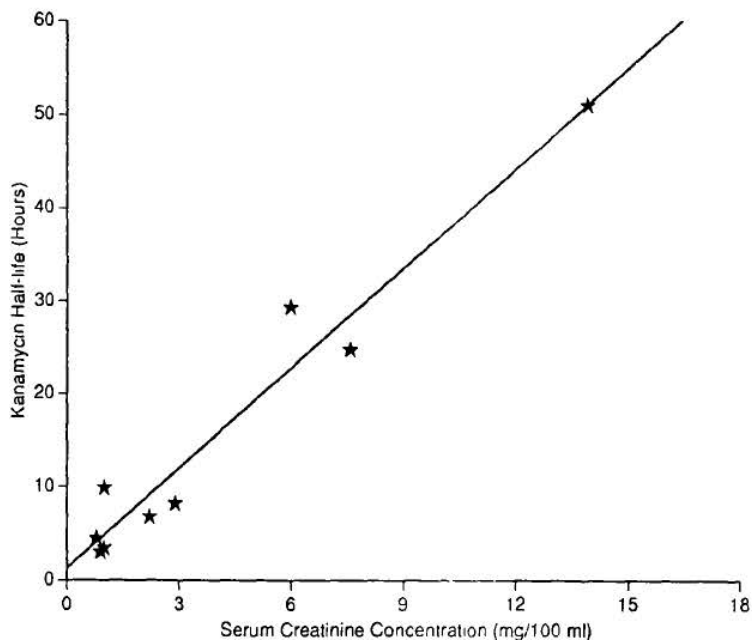**Fig. 8** Plot of kanamycin clearance rate versus creatinine clearance rate.

Fig. 9 Plot of kanamycin elimination half-life versus serum creatinine concentration in patients with varying degrees of (stable) renal failure.


VII. KINETICS OF DRUG ABSORPTION

For all commonly used routes of administration, except intravenous, the drug must dissolve in body fluids and diffuse through one or more membranes to enter the plasma. Thus, all routes except intravenous are classed as extravascular routes, and absorption is defined as appearance of the drug in plasma.

The most common extravascular route is oral. When a solution or a rapidly dissolving solid dosage form is given orally, the absorption process often obeys first-order kinetics. In these cases, absorption can be characterized by evaluating the absorption rate constant k_a, from plasma concentration versus time data.

A. The Method of "Residuals" ("Feathering" the Curve)

When absorption is first-order, the kinetic model may be written as shown in Scheme 3:

$$D_G \xrightarrow{k_a} D_B \xrightarrow{k_{el}} D_E$$
Scheme 3
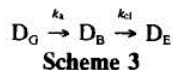
where

D_G = drug at the absorption site (gut)
D_B = drug in the body
D_E = eliminated drug

k_a = first-order absorption rate constant
k_{el} = overall elimination rate constant

The differential equations describing the rates of change of the three components of Scheme 3 are

$$\frac{dD_G}{dt} = -k_a \, D_G \tag{29}$$

$$\frac{dD_B}{dt} = k_a \, D_G - k_{el} \, D_B \tag{30}$$

$$\frac{dD_E}{dt} = + k_{el} \, D_B \tag{31}$$

To determine k_a from plasma concentration versus time data, it is necessary to integrate Eq. (30). This is best achieved through exponential expressions. First, integration of Eq. (29) gives

$$D_G = D_G^0 \, \exp(-k_a t) \tag{32}$$

where D_G^0 is the initial amount of drug presented to the absorbing region of the gut. (D_G^0 = dose, if absorption is complete.)

Substituting Eq. (32) into Eq. (30) gives

$$\frac{dD_B}{dt} = +k_a \, D_G^0 \, \exp(-k_a t) - k_{el} \, D_B \tag{33}$$

Integration of Eq. (33) may be accomplished with Laplace transforms.* The result is

$$D_B = \frac{D_G^0 \, k_a}{k_a - k_{el}} \, [\exp(-k_{el}t) - \exp(-k_a t)] \tag{34}$$

Thus, the amount of drug in the body following administration of an extravascular dose is a constant $[(D_G^0 \, k_a)/(k_a - k_{el})]$ multiplied by the difference between two exponential terms—one representing elimination $[\exp(-k_{el}t)]$ and the other representing absorption $[\exp(-k_a t)]$.

Dividing both sides of Eq. (34) by V_d yields an equation for plasma concentration versus time:

$$C_p = \frac{D_G^0 \, k_a}{V_d(k_a - k_{el})} \, [\exp(-k_{el}t) - \exp(-k_a t)] \tag{35}$$

Equation (35) describes the line in Fig. 10, which is a semilog plot of C_p versus time for an orally administered drug absorbed by a first-order process. The plot begins as a rising curve and becomes a straight line with a negative slope after 6 hr. This behavior is the result of the biexponential nature of Eq. (35). Up to 6 hr, both the absorption process $[\exp(-k_a t)]$ and the elimination process $[\exp(-k_{el}t)]$ influence the plasma concentration. After 6 hr, only the elimination process influences the plasma concentration.

This separation of the processes of absorption and elimination is the result of the difference in the values of k_a and k_{el}. If k_a is much larger than k_{el} (a good rule is that it must be at least five times larger), the second exponential term in Eq. (35) will approach zero much more

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*Full details of this integration may be found in Mayersohn and Gibaldi, Am. J Pharm. Ed., 34, 608 (1970), Eq. (27).
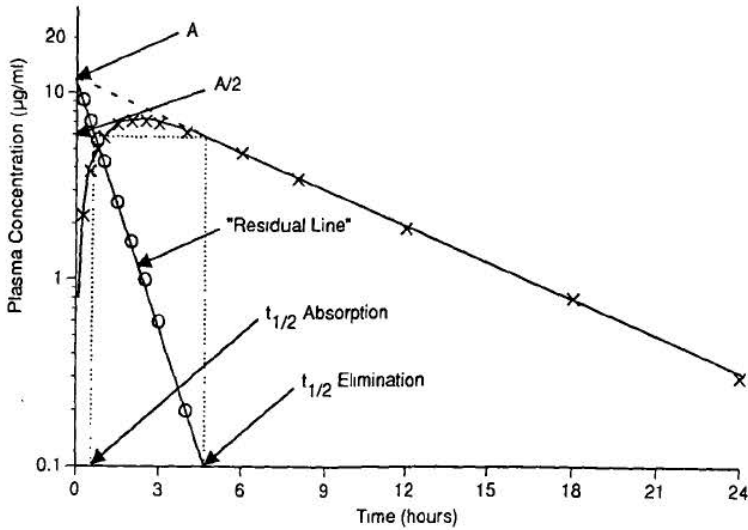
Fig. 10 Semilogarithmic plot of observed plasma concentrations (crosses) and "residuals" (circles), versus time for an orally administered drug absorbed by a first-order process.

rapidly than the first exponential term. And at large values of t, Eq. (35) will reduce to

$$C_p = \frac{D_G^0 \, k_a}{V_d(k_a - k_{el})} \left[\exp(-k_{el}t)\right] \tag{36}$$

or

$$C_p = A \, \exp(-k_{el}t)$$

where A is a constant term.

Converting to common logs we obtain

$$\log C_p = \frac{-k_{el}t}{2.30} + \log A \tag{37}$$

Thus, after 6 hr the semilog plot of C_p versus time shown in Fig. 10 becomes a straight line, with a slope of $-k_{el}/2.30$. Therefore, the overall elimination rate constant for a drug may be accurately determined from the "tail" of a semilog plot of plasma concentration versus time following extravascular administration, if k_a is at least five times larger than k_{el}.

The value of k_a can also be determined from plots like Fig. 10 using the following logic: In Fig. 10 the curved line up to 6 hr is given by

$$C_{p1} = A \, \exp(-k_{el}t) - A \, \exp(-k_a t)$$

The straight line after 6 hr and the extrapolated (dashed) line before 6 hr is given by

$$C_{p2} = A \, \exp(-k_{el}t)$$

The difference ("residual") between the curved line and the extrapolated (dashed) line up to 6 hr is given by

$$\text{Residual} = C_{p2} - C_{p1}$$
$$= A \exp(-k_a t)$$

Converting to common logs:

$$\log (\text{residual}) = \frac{-k_a t}{2.30} + \log A \tag{38}$$

As shown in Fig. 10, a semilog plot of residuals versus time is a straight line, with a slope of $-k_a/2.30$.

The intercepts (A) for both the extrapolated (dashed) line [Eq. (37)] and the residuals line [Eq. (38)] are the same and are equal to the constant in Eq. (35):

$$A = \frac{D_G^0 \, k_a}{V_d(k_a - k_{el})} \tag{39}$$

A is a function of the two rate constants (k_a and k_{el}), the apparent volume of distribution (V_d), and the amount of drug absorbed (D_G^0). After k_a and k_{el} have been evaluated and A has been determined by extrapolation, a value for V_d can be calculated if it is assumed that D_G^0 is equal to the dose administered (i.e., absorption is 100% complete).

EXAMPLE.   Fig. 10 is a plot of the data shown in Table 5. The extrapolated value of A is 11.8 µg/ml.

The $t_{1/2}$ (elimination) is the time at which the elimination line crosses $A/2 = 4.5$ hr:

$$k_{el} = \frac{0.693}{t_{1/2} \text{ (elimination)}} = 0.154 \text{ hr}^{-1}$$

Table 5 Plasma Concentrations and "Residuals" Versus Time

Time (hr)	Observed C_p (µg/ml)	Extrapolated C_p (µg/ml)	Residuals (µg/ml)
0.0	0.0	11.8	11.8
0.25	2.2	11.4	9.2
0.5	3.8	10.9	7.1
0.75	5.0	10.6	5.6
1.0	5.8	10.1	4.3
1.5	6.8	9.4	2.6
2.0	7.1	8.7	1.6
2.5	7.1	8.1	1.0
3.0	6.9	7.5	0.6
4.0	6.2	6.4	0.2
6.0	4.8	4.8	
8.0	3.5	3.5	
12.0	1.9	1.9	
18.0	0.8	0.8	
24.0	0.3	0.3	

The $t_{1/2}$ (absorption) is the time at which the residuals line crosses $A/2 = 0.7$ hr:

$$k_a = \frac{0.693}{t_{1/2} \text{ (absorption)}} = 0.990 \text{ hr}^{-1}$$

Assuming that the 100-mg dose of drug was completely absorbed, the V_d can be calculated from Eq. (39):

$$A = 11.8 \ \mu g/ml = \frac{100 \text{ mg} \times 0.990 \text{ hr}^{-1}}{V_d(0.990 - 0.154) \text{ hr}^{-1}}$$

$V_d = 10.0$ liters

This method of calculation is often referred to as the *method of residuals* or *feathering the curve*. It is important to remember that the following assumptions were made:

1. It is assumed that k_a is at least five times larger than k_{el}; if not, neither constant can be determined accurately.
2. It is assumed that the absorption and elimination processes are both strictly first-order; if not, the residuals line and, perhaps, the elimination line will not be straight.
3. It is assumed that absorption is complete; if not, the estimate of V_d will be erroneously high.

B. The Wagner-Nelson Method*

A major shortcoming of the method of residuals for determining the absorption rate constant from plasma concentration versus time data following administration of oral solid dosage forms is the necessity to assume that the absorption process obeys first-order kinetics. Although this assumption is often valid for solutions and rapidly dissolving dosage forms for which the absorption process itself is rate-determining, if release of drug from the dosage form is rate-determining, the kinetics are often zero-order, mixed zero- and first-order, or even more complex processes.

The Wagner-Nelson method of calculation does not require a model assumption concerning the absorption process. It does require the assumption that (a) the body behaves as a single homogeneous compartment, and (b) drug elimination obeys first-order kinetics. The working equations for this calculation are developed next.

Derivation

For any extravascular drug administration, the mass balance can be written as amount absorbed (A) equals amount in body (W) plus amount eliminated (E), or

$$A = W + E$$

Taking the derivative relative to time yields

$$\frac{dA}{dt} = \frac{dW}{dt} + \frac{dE}{dt}$$

But

$$W = V_d C_p \quad \text{or} \quad \frac{dW}{dt} = V_d \frac{dC_p}{dt}$$

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*See Wagner and Nelson, J. Pharm. Sci. 53, 1392 (1964).

and

$$\frac{dE}{dt} = k_{el}W$$

$$= k_{el}V_dC_p$$

Therefore,

$$\frac{dA}{dt} = V_d\frac{dC_p}{dt} + k_{el}V_dC_p$$

$$dA = V_ddC_p + k_{el}V_dC_p\ dt$$

Integrating from $t = 0$ to $t = t$

$$\int_0^t dA = V_d\int_0^t dC_p + k_{el}V_d\int_0^t C_p\ dt$$

$$A_t = V_dC_p^t + k_{el}V_d\int_0^t C_p\ dt$$

Rearranging we have

$$\frac{A_t}{V_d} = C_p^t + k_{el}\int_0^t C_p\ dt$$

where A_t/V_d is the amount of drug absorbed up to time t divided by the volume of distribution, C_p^t is plasma (serum or blood) concentration at time t, and $\int_0^t C_p\ dt$ is the area under the plasma (serum or blood) concentration versus time curve up to time t (see Sec. VIII.A). An equation similar to Eq. (40) can be derived by integration from $t = 0$ to $t = \infty$. Since $C_p = 0$ at $t = \infty$, the equation becomes

$$\frac{A_{max}}{V_d} = k_{el}\int_0^\infty C_p\ dt \tag{41}$$

where A_{max} is the total amount of drug absorbed from the dosage form divided by the volume of distribution; and $\int_0^\infty C_p\ dt$ is the area under the entire plasma (serum or blood) concentration versus time curve (Sec. VIII.A).

Equation (41) is useful for comparing the bioavailabilities of two dosage forms of the same drug administered to the same group of subjects. If it is assumed that k_{el} and V_d are the same for both administrations, it can be seen that the relative availabilities of the dosage forms is given by the ratio of the areas under the plasma concentration versus time curves:

$$\frac{A_{max_1}}{A_{max_2}} = \frac{\displaystyle\int_0^\infty (C_p\ dt)_1}{\displaystyle\int_0^\infty (C_p\ dt)_2} \tag{42}$$

Other methods of comparing bioavailabilities will be discussed in a later section.

A great deal can be learned about the absorption process by applying Eqs. (40) and (41) to plasma concentration versus time data. Since there is no model assumption relative to the

Table 6 Data Illustrating the Wagner-Nelson Calculation

Time (hr)	C_p (μg/ml)	$\int_0^t C_p\, dt$	$k_{el}\int_0^t C_p\, dt$	$\dfrac{A_t}{V_d}$	$\dfrac{A_{max}}{V_d} - \dfrac{A_t}{V_d}$
0.25	0.6	0.1	0.0	0.6	9.4
0.50	1.2	0.3	0.1	1.3	8.7
0.75	1.8	0.7	0.1	1.9	8.1
1.0	2.3	1.2	0.2	2.5	7.5
1.5	3.4	2.6	0.4	3.8	6.2
2.0	4.3	4.5	0.7	5.0	5.0
3.0	6.0	9.7	1.5	7.5	2.5
6.0	5.6	27.1	4.1	9.7	0.3
12.0	2.3	50.8	7.6	9.9	0.1
18.0	0.9	60.4	9.1	10.0	
24.0	0.4	64.3	9.6	10.0	

Note: $A_{max}/V_d = 10.0$.

absorption process, the calculated values of A_t/V_d can often be manipulated to determine the kinetic mechanism that controls absorption. This is best illustrated by an example.

EXAMPLE.   A tablet containing 100 mg of a drug was administered to a healthy volunteer and the plasma concentration (C_p) versus time data shown in Table 6 were obtained. Figure 11 shows a semilog plot of these C_p versus time data. The half-life for elimination of the drug can be estimated from the straight line "tail" of the plot to be 4.7 hr. The overall elimination
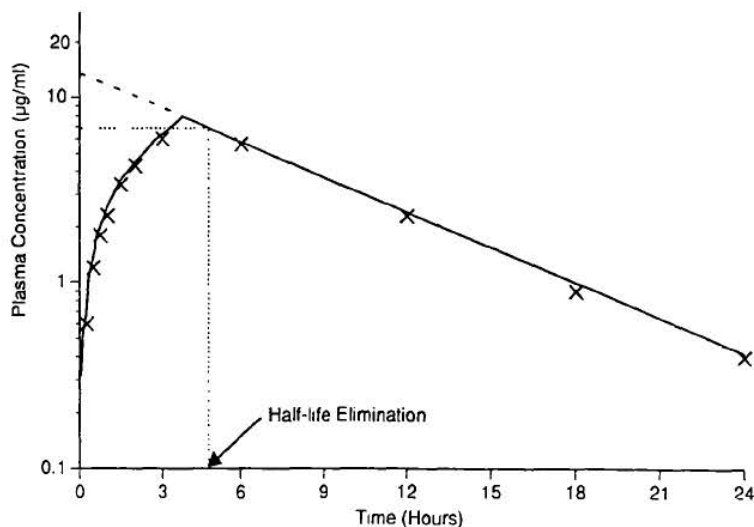

Fig. 11 Semilogarithmic plot of observed plasma concentrations (crosses) versus time for an orally administered drug absorbed by a zero-order process. (Data shown in Table 6).

rate constant is then

$$k_{el} = \frac{0.693}{4.7 \text{ hr}} = 0.147 \text{ hr}^{-1}$$

Table 6 illustrates the steps involved in carrying out the Wagner-Nelson calculation. The third column ($\int_0^t C_p \, dt$) shows the area under the C_p versus time curve calculated sequentially from $t = 0$ to each of the time points using the trapezoidal rule (see Sec. VIII.A). The fourth column ($k_{el} \int_0^t C_p \, dt$) shows each of the preceding areas multiplied by k_{el} (as estimated from the "tail") constituting the second term of the Wagner-Nelson equation [see Eq. (40)]. The fifth column (A_t/V_d) shows the sums of the values indicated in the second and fourth columns according to Eq. (40). A_{max}/V_d is the maximum value in fifth column (i.e., 10.0), and the sixth column shows the residual between A_{max}/V_d and each sequential value of A_t/V_d in the fifth column.

If the absorption process obeyed first-order kinetics, a semilog plot of the residuals in the sixth column would be a straight line with a slope of $-k_a/2.3$. However, the regular cartesian plot of the residuals shown in Fig. 12 is a straight line showing the absorption process obeys zero-order kinetics; that is, the process proceeds at a constant rate (25 mg/hr), stopping abruptly when the dose has been completely absorbed.

This example illustrates the usefulness of the Wagner-Nelson calculation for studying the mechanism of release of drugs from dosage forms in vivo. Whereas the absorption process itself usually obeys first-order kinetics, dissolution of capsules, tablets, and especially, sustained-release dosage forms often must be described by more complex kinetic mechanisms. Although pure zero-order absorption, such as that just illustrated, is almost never observed in
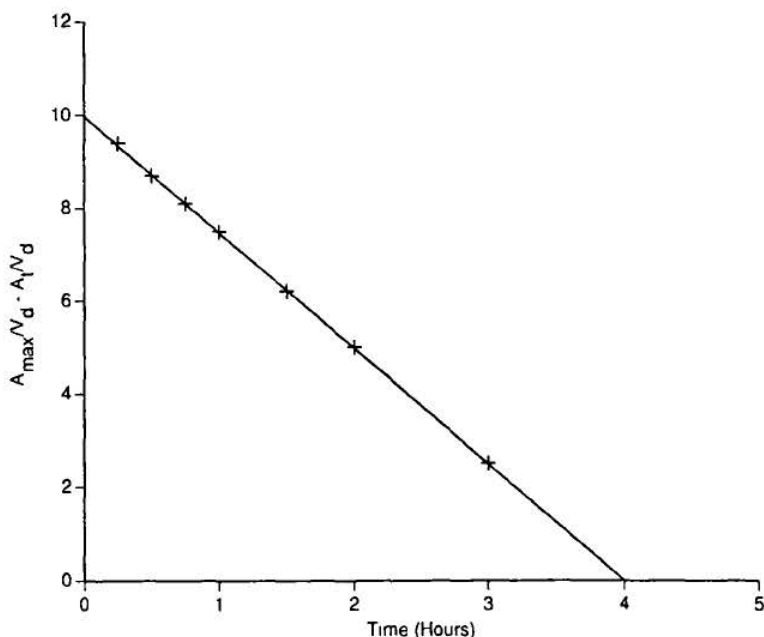

Fig. 12 Plot of the residuals (crosses) between A_{max}/V_d and A_t/V_d versus time (last column of Table 6).

practice, many sustained-release dosage forms are designed to produce as close to zero-order release as possible, since constant absorption produces constant plasma levels.

C. The Method of "Inspection"

Often, it is unnecessary to calculate an exact value for an absorption rate constant. For example, when several oral tablets containing the same drug substance are all completely absorbed, it may be sufficient to merely determine if the absorption rates are similar to conclude that the products would be therapeutically equivalent. In another instance, it would be possible to choose between an elixir and a sustained-release tablet for a specific therapeutic need without assigning accurate numbers to the absorption rate constant for the two dosage forms.

In these instances the *time of the peak* in the plasma concentration versus time curve provides a convenient measure of the absorption rate. For example, if three tablets of the same drug are found to be completely absorbed and all give plasma peaks at 1 hr, it can be safely concluded that all three tablets are absorbed at essentially the same rate. (In fact, if all tablets are completely absorbed and all peak at the same time, it would be expected that all three plasma concentration versus time curves would be identical, within experimental error.)

The time of the peak can also be used to roughly estimate the absorption rate constant. If it is assumed that k_a is at least $5 \times k_{el}$, then it can be assumed that absorption is at least 95% complete at the peak time; that is, the peak time represents approximately five absorption half-lives (see Table 1). The absorption half-life can then be calculated by dividing the time of the peak by 5, and the absorption rate constant can be calculated by dividing the absorption half-life into 0.693.

EXAMPLE. Inspection of Fig. 10 gives a peak time of about 2.5 hr. The absorption half-life can be estimated to be 0.5 hr and the absorption rate constant, to be 1.4 hr^{-1}.

VIII.   BIOAVAILABILITY (EXTENT OF ABSORPTION)

If a drug is administered by an extravascular route and acts systemically, its potency will be directly related to the amount of drug the dosage form delivers to the blood. Also, if the pharmacologic effects of the drug are related directly and instantaneously to its plasma concentration, the rate of absorption will be important because the rate will influence the height of the plasma concentration peak and the time at which the peak occurs. Thus, the *bioavailability of a drug product is defined in terms of the amount of active drug delivered to the blood and the rate at which it is delivered.*

Whenever a drug is administered by an extravascular route, there is a danger that part of the dose may not reach the blood (i.e., absorption may not be complete). When the intravenous route is used, the drug is placed directly in the blood; therefore an IV injection is, by definition, 100% absorbed. The absolute bioavailability of an extravascular dosage form is defined relative to an IV injection. If IV data are not available, the relative bioavailability may be defined relative to a standard dosage form. For example, the bioavailability of a tablet may be defined relative to an oral solution of the drug.

In Sec. VII we dealt with methods of determining the rate (and mechanism) of absorption. In this section we will deal with methods of determining the extent of absorption. In every example, the calculation will involve a comparison between two studies carried out in the same group of volunteers on different occasions. Usually, it will be necessary to assume that the volunteers behaved identically on both occasions, especially relative to their pharmacokinetic parameters.

A. Area Under the Plasma Concentration Versus Time Curve

In the development of equations for the Wagner-Nelson method of calculation, the following equation was derived [see Eq. (42)]:

$$\frac{A_{max_1}}{A_{max_2}} = \frac{\int_0^\infty (C_p \, dt)_1}{\int_0^\infty (C_p \, dt)_2}$$

This equation shows that the amounts of drug absorbed from two drug products (i.e., the relative bioavailability of product 1 compared with product 2) can be calculated as the ratio of the areas under the plasma concentration versus time curves (AUCs), assuming k_{el} and V_d were the same in both studies. This assumption is probably valid when the studies are run with the same group of volunteers and within a few weeks of one another.

If dosage form 2 (Eq. (42)) is an intravenous dosage form, the *absolute bioavailability* of the extravascular dosage form (dosage form 1) is given by:

$$\begin{array}{l} \text{Absolute bioavailability} \\ \text{(extravascular dosage form)} \end{array} = \frac{AUC_{extravascular}}{AUC_{IV}} \qquad (43)$$

The AUC for a plasma concentration versus time curve can be determined by using the trapezoidal rule. For this calculation, the curve is divided into vertical segments, as shown in Fig. 13. The top line of each segment is assumed to be straight, rather than slightly curved, and the area of the segment is calculated as though it were a trapezoid; for example, the area of segment 10 is

$$Area_{10} = \frac{C_{p9} + C_{p10}}{2} \times (t_{10} - t_9) \qquad (44)$$

The total AUC is then obtained by summing the areas of the individual segments. [Equation (44) can be programmed into a microcomputer that will calculate the areas and sum them as rapidly as the C_p values can be entered.]

It should be readily apparent that the trapezoidal rule does not measure AUC exactly. However, it is accurate enough for most bioavailability calculations, and the segments are chosen on the basis of the time intervals at which plasma was collected.

EXAMPLE. The AUC for Fig. 10 can be calculated from the data given in Table 7.

Assuming that the AUC for a 100-mg IV dose given to the same group of volunteers was 86.7 hr · μg/ml, the absolute bioavailability of the extravascular dosage form is

$$\text{Absolute bioavailability} = \frac{AUC_\infty}{AUC_{IV}} \times 100 = \frac{67.2}{86.7} \times 100 = 77.5\%$$

It is not necessary to apply the trapezoidal rule to the entire plasma concentration versus time curve to calculate the total AUC. After the semilog plot becomes a straight line, the remaining area out to $t = \infty$ can be calculated from the following equation:

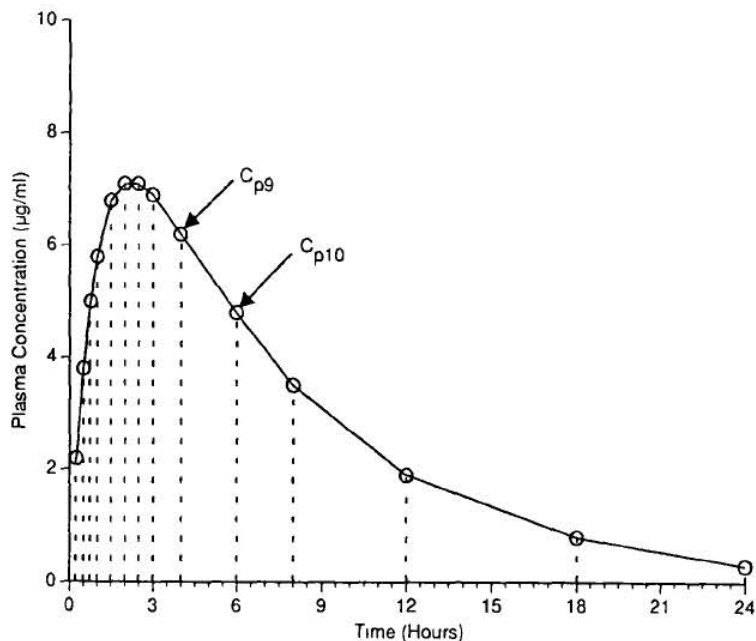$$AUC_{(t \text{ to } \infty)} = \frac{C_p^t}{k_{el}} \qquad (45)$$

Fig. 13 Plot of plasma concentrations (circles) versus time with the curve divided into vertical segments. (Data shown in Table 7).

Table 7 Calculation of Area Under the Plasma Concentration Versus Time Curve (AUC) Using the Trapezoidal Rule

Time (hr)	C_p (µg/ml)	Area of segment (hr µg/ml)	Cumulative area up to time = t (hr µg/ml)
0.0	0.0	0.275	0.275
0.25	2.2	0.75	1.025
0.5	3.8	1.1	2.125
0.75	5.0	1.35	3.475
1.0	5.8	3.15	6.625
1.5	6.8	3.475	10.10
2.0	7.1	3.55	13.65
2.5	7.1	3.50	17.15
3.0	6.9	6.55	23.70
4.0	6.2	11.0	34.70
6.0	4.8	8.3	43.0
8.0	3.5	10.8	53.8
12.0	1.9	8.1	61.9
18.0	0.8	3.3	65.2
24.0	0.3	2.0	67.2*
∞	—	—	

*AUC_∞ = 67.2 hr · µg/ml.

Once a semilog plasma concentration versus time plot begins to follow simple first-order elimination kinetics, the remaining AUC can be calculated in one step from Eq. (45).

EXAMPLE. In the previous problem, the AUC from 24 hr to infinity is given by

$$AUC_{(24\ hr\ to\ \infty)} = \frac{0.3\ \mu g/ml}{0.15\ hr^{-1}} = 2.0\ hr \cdot \mu g/ml$$

It follows that if the entire semilog plot were straight, as it would be for a one-compartment drug following IV administration, the total AUC would be given by

$$AUC_{IV} = \frac{C_p^0}{k_{el}} \tag{45a}$$

EXAMPLE. For IV administration in the foregoing problem, the AUC was calculated as follows:

$$AUC_{IV} = \frac{13.0\ \mu g/ml}{0.15\ hr^{-1}} = 86.7\ hr \cdot \mu g/ml$$

B. Cumulative Urinary Excretion

In the development of equations for calculating urine data when the drug is partially metabolized and partially excreted unchanged in urine, the following equation was derived [see Eq. (27)]:

$$\frac{D_U^\infty}{D_B^0} = f_e$$

where D_U^∞ is the amount of drug recovered from urine, D_B^0 is the amount of drug absorbed, and f_e is the fraction of the absorbed amount recovered as unchanged drug in urine. Equation (27) may be rearranged and written for two dosage forms as follows:

$$D_{U_1}^\infty = D_{B_1}^0 \times f_{e_1} \qquad \text{and} \qquad D_{U_2}^\infty = D_{B_2}^0 \times f_{e_2}$$

Dividing the first equation by the second gives:

$$\frac{D_{U_1}^\infty}{D_{U_2}^\infty} = \frac{D_{B_1}^0 \times f_{e_1}}{D_{B_2}^0 \times f_{e_2}}$$

Assuming that $f_{e_1} = f_{e_2}$, we have

$$\frac{D_{U_1}^\infty}{D_{U_2}^\infty} = \frac{D_{B_1}^0}{D_{B_2}^0} = \text{relative bioavailability} \tag{46}$$

Similarly,

$$\frac{D_{U(extravascular)}^\infty}{D_{U(IV)}^\infty} = \text{absolute bioavailability} \tag{47}$$

Thus, if it is assumed that the same fraction of absorbed drug always reaches the urine unchanged, the bioavailability can be calculated as the ratio of total amounts of unchanged drug recovered in urine.

EXAMPLE. When potassium penicillin G was administered IV to a group of volunteers, 80% of the 500-mg dose was recovered unchanged in urine. When the same drug was administered

orally to the same volunteers, 280 mg was recovered unchanged in urine. What is the absolute bioavailability of potassium penicillin G following oral administration? From Eq. (47),

$$\text{Absolute bioavailability} = \frac{280}{400} \times 100$$

$$= 70\%$$

For the calculation, it is unnecessary to assume that V_d or k_{el} or both, are the same for the two studies. It is necessary that only f_e be the same in both studies. This is usually a valid assumption unless the drug undergoes a significant amount of "first-pass" metabolism in the gut wall or liver following oral administration or a significant amount of decomposition at an intramuscular (IM) injection site. When this occurs, the availability of the extravascular dosage form may appear to be low, but the fault will not lie with the formulation. The bioavailability will be a true reflection of the therapeutic efficacy of the drug product, and reformulation may not increase bioavailability.

C. The Method of "Inspection"

Bioavailability studies are frequently carried out for the sole purpose of comparing one drug product with another, with the full expectation that the two products will have identical bioavailabilities; that is, their rates and extents of absorption will be identical. Such studies are called *bioequivalence studies* and are often employed when a manufacturer wishes to market a "generic equivalent" of a product already on the market. To take advantage of the safety and efficacy data the product's originator has filed with the FDA, the second manufacturer must show that his product gives an *identical plasma concentration versus time curve.*

In these cases, it is not necessary to determine the absolute bioavailability or the absorption rate constant for the product under study. It is necessary only to prove that the plasma concentration versus time curve is not significantly different from the reference product's curve. This is done by comparing the means and standard deviations of the plasma concentrations for the two products at each sampling time using an appropriate statistical test.

A discussion of the statistical methods used in analyzing the data from the bioequivalence studies is beyond the scope of this chapter. For a discussion of these considerations, the reader is referred to a description by Westlake [6].

IX. MULTIPLE-DOSING REGIMENS (REPETITIVE DOSING)

Drugs are infrequently used in single doses to produce an acute effect, the way aspirin is used to relieve a headache. More often, drugs are administered in successive doses to produce a repeated or prolonged effect, the way aspirin is used to relieve the pain and inflammation of arthritis. A properly designed multiple-dosing regimen will maintain therapeutically effective plasma concentrations of the drug while avoiding toxic concentrations. Such regimens are easily designed if the pharmacokinetic parameters of the drug are known.

When drugs are administered on a multiple-dosing regimen, each dose (after the first) is administered before the preceding doses are completely eliminated. This results in a phenomenon known as *accumulation*, during which the amount of drug in the body (represented by plasma concentration) builds up as successive doses are administered. The phenomenon of accumulation for a drug administered IV is shown in Fig. 14.

Figure 14 shows that the plasma concentrations do not continue to build forever, but reach a plateau where the same maximum (C_{max}) and minimum (C_{min}) concentrations are reproduced over and over. The objectives of designing a dosing regimen are to keep C_{min} above the *min-*
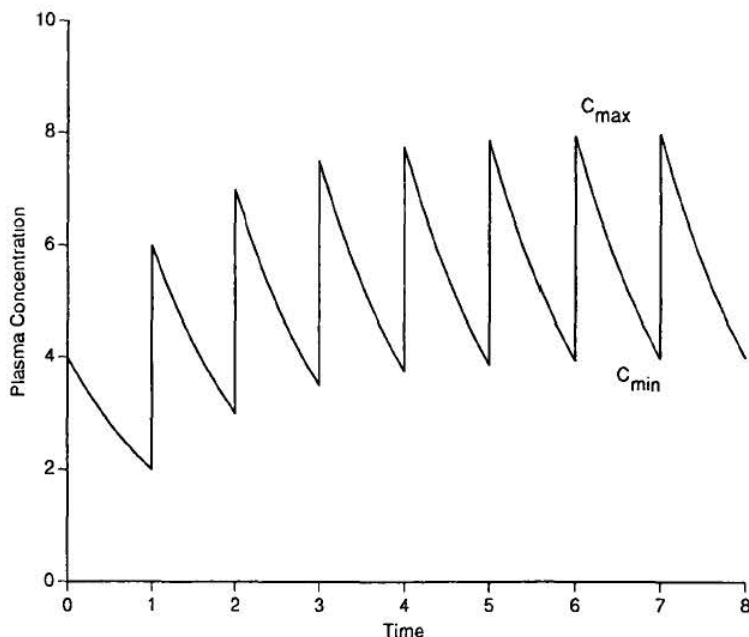
Fig. 14 Plot of plasma concentration versus time showing accumulation following multiple intravenous injections.

imum effective concentration (MEC) and to keep C_{max} below the *minimum toxic concentration* (MTC).

A. Repetitive Intravenous Dosing

The plasma concentrations in Fig. 14 can be calculated as follows: From Eq. (25) the plasma concentration at the *end of the first dosing interval* (T) is given by:

$$C_{p_1}^T = C_{p_1}^0 \exp(-k_{el}T) \tag{48}$$

Immediately after the second dose is given, the plasma concentration will be,

$$C_{p_2}^0 = C_{p_1}^T + C_{p_1}^0 = C_{p_1}^0 \exp(-k_{el}T) + C_{p_1}^0 \tag{49}$$

and so on.

It is now helpful to define the parameter R as the *fraction of the initial plasma concentration that remains at the end of any dosing interval*; R is given by the following equation:

$$R = \exp(-k_{el}T) = 10^{-k_{el}T/2.30} \tag{50}$$

As was pointed out in Sec. VI, when $T = t_{1/2}$, $R = 0.5$. The plot in Fig. 14 was constructed by using these conditions; therefore, the plasma concentration at the end of each dosing interval is half the concentration at the beginning of the dosing interval.

Equations (48) and (49) can be simplified to

$$C_{p_1}^T = C_{p_1}^0 R$$

for the *plasma concentration at the end of the first dosing interval,* and

$$C_{p_2}^0 = C_{p_1}^0 R + C_{p_1}^0$$

for the *plasma concentration at the beginning of the second dosing interval.*
The series can be carried further for more doses:

$$C_{p_2}^T = (C_{p_1}^0 R + C_{p_1}^0)R$$

$$C_{p_3}^0 = (C_{p_1}^0 R + C_{p_1}^0)R + C_{p_1}^0$$

$$C_{p_3}^T = [(C_{p_1}^0 R + C_{p_1}^0)R + C_{p_1}^0]R, \ldots, \text{etc.}$$

The plasma concentrations at the beginning and end of the nth dosing interval are given by the following power series:

$$\text{Beginning} = C_{p_1}^0 + C_{p_1}^0 R + C_{p_1}^0 R^2 + \cdots + C_{p_1}^0 R^{n-1} \tag{51}$$

$$\text{End} = C_{p_1}^0 R + C_{p_1}^0 R^2 + C_{p_1}^0 R^3 + \cdots + C_{p_1}^0 R^n \tag{52}$$

Since R is always smaller than 1, R^n becomes smaller as n increases. For example, if $R = 0.5$, $R^{10} = 0.001$. Therefore, the high power terms in Eq. (51) and (52) become negligible as n increases, and additional doses do not change the value of $C_{p_n}^0$ or $C_{p_n}^T$ significantly. This explains why the plasma concentrations reach a plateau instead of continuing to rise as more doses are given.

Hence, C_{max} and C_{min} (see Fig. 14) are defined as the plasma concentrations at the beginning and end, respectively, of the nth dosing interval after the *plateau* has been reached (i.e., $n = \infty$). When $n = \infty$, Eqs. (51) and (52) become

$$C_{max} = \frac{C_{p_1}^0}{1 - R} \tag{53}$$

$$C_{min} = C_{max}R = \frac{C_{p_1}^0 R}{1 - R} \tag{54}$$

Thus, the maximum and minimum plasma concentrations on the plateau of a repetitive IV dosing regimen can be calculated if the dosing interval (T), the overall elimination rate constant (k_{el}), and the initial plasma concentration (C_p^0) are known.

EXAMPLE. A drug has a biological half-life of 4 hr. Following an IV injection of 100 mg, C_p^0 is found to be 10 µg/ml. Calculate C_{max} and C_{min} if the 100-mg IV dose is repeated very 6 hr until a plasma concentration plateau is reached.

$$k_{el} = \frac{0.693}{4 \text{ hr}} = 0.173 \text{ hr}^{-1}$$

$$R = 10^{-k_{el}T/2.30}$$

$$= 10^{-0.173 \times 6/2.30} = 10^{-0.451}$$

$$= 0.354$$

$$C_{max} = \frac{10 \text{ µg/ml}}{1 - 0.354} = 15.5 \text{ µg/ml}$$

$$C_{min} = 15.5 \text{ µg/ml} \times 0.354 = 5.49 \text{ µg/ml}$$

EXAMPLE.   As indicated earlier, when $T = t_{1/2}$, $R = 0.5$. As a result, on the plateau in Fig. 14,

$$C_{max} = \frac{C_p^0}{1 - 0.5} = 2 \times C_p^0$$

$$C_{min} = \frac{C_p^0 \times 0.5}{1 - 0.5} = C_p^0$$

Thus, when a dose is administered every half-life, C_{max} will be twice C_p^0 and C_{min} will be half C_{max} or equal to C_p^0.

The second example illustrates a very simple and often-used dosage regimen; that is, administration of a *maintenance dose every half-life*. The calculations indicate that on this regimen, C_{min} will be $C_{max}/2$ and C_{max} will be $2 \times C_p^0$. Figure 14 indicates that approximately *five half-lives will be required to reach the plasma concentration plateau*. If the drug has a relatively long half-life, many hours, perhaps days, may be required for the plasma concentrations to reach the ideal range. If the patient's condition is serious, the physician may not want to wait for this to happen. It is under these circumstances that a *loading dose* is indicated. The loading dose immediately puts the plasma concentrations in the plateau range, and the maintenance dose maintains that condition.

For IV administration, the easiest way to determine the loading dose is in terms of C_p^0 and C_{max}. For example, if the desired C_{max} is 20 $\mu g/ml$ and a dose of 100 mg gives a C_p^0 of 10 $\mu g/ml$, a loading dose of 200 mg should give a C_p^0 of 20 $\mu g/ml$, which is the desired C_{max}. If this loading dose is followed by maintenance doses of 100 mg every half-life, the plasma concentrations can be maintained at the plateau from the very beginning and throughout the entire dosing regimen. Thus, *for the maintenance dose every half-life regimen, the ideal loading dose is twice the maintenance dose.*

EXAMPLE.   *Kanamycin* is an aminoglycoside antibiotic that exerts a toxic effect on the hearing. If the plasma concentrations are allowed to remain above 35 $\mu g/ml$ (MTC) for very long, permanent hearing loss may result. The minimum effective concentration (MEC) of kanamycin in plasma is estimated to be about 10 $\mu g/ml$ for most organisms against which it is used. Thus, kanamycin is a classic example of a drug with a *narrow therapeutic index* for which a very precise dosing regimen is an absolute necessity. (In fact, this is true of all aminoglycosides.) When kanamycin is administered IV in a dose of 7.5 mg/kg to adults, it yields a C_p^0 of about 25 $\mu g/ml$ and a half-life of about 3 hr. What would be a good dosing regimen for kanamycin?

Since 25 $\mu g/ml$ is well above the MEC but below the MTC, a loading dose of 7.5 mg/kg might be given initially. After one half-life (3 hr), the plasma concentration should be 12.5 $\mu g/ml$. Since this is just above the MEC and corresponds to half the initial 25 $\mu g/ml$, a maintenance dose of 3.75 mg/kg could be administered. With repeated 3.75 mg/kg maintenance doses every 3 hr, C_{max} should be 25 $\mu g/ml$ and C_{min} should be 12.5 $\mu g/ml$, which would allow some margin for error on either side.

EXAMPLE.   The kanamycin problem could be solved more aggressively as follows: Let C_{max} = 35 $\mu g/ml$ and C_{min} = 10 $\mu g/ml$. From Eqs. (53) and (54), the value of R on the plateau may be calculated as follows:

$$C_{p_1}^0 = C_{max}(1 - R) = (35 \text{ } \mu g/ml)(1 - R)$$

$$C_{p_1}^0 = \frac{C_{min}(1 - R)}{R} = \frac{(10 \text{ } \mu g/ml)(1 - R)}{R}$$

$$35 \ \mu g/ml(1 - R) = \frac{(10 \ \mu g/ml)(1 - R)}{R}$$

$$R = \frac{10}{35} = 0.286$$

$$= 10^{-k_{el}T/2.30} \qquad \left(k_{el} = \frac{0.693}{3 \ hr} = 0.231 \ hr^{-1} \right)$$

$$0.286 = 10^{-0.231T/2.30}$$

$$= 10^{-0.100T}$$

$$-0.544 = 0.100T$$

$$T = 5.44 \ hr \ (dosing \ interval)$$

A loading dose that produces a $C_{p_1}^0$ of 35 $\mu g/ml$ is desired, and this can be calculated as follows [from Eq. (16)]:

$$\frac{Dose_1}{C_{p_1}^0} = \frac{Dose_2}{C_{p_2}^0}$$

$$\frac{7.5 \ mg/kg}{25 \ \mu g/ml} = \frac{x \ mg/kg}{35 \ \mu g/ml}$$

Loading dose = 10.5 mg/kg

The *amount of drug remaining in the body* at the end of the first dosing interval can be calculated in a similar way from the known C_{min}:

$$\frac{7.5 \ mg/kg}{25 \ \mu g/ml} = \frac{x \ mg/kg}{10 \ \mu g/ml}$$

Amount remaining = 3 mg/kg

The maintenance dose needed to replace the amount lost over the dosing interval is the difference between the loading dose and the amount remaining at the end of the interval:

Maintenance dose = (10.5 − 3) mg/kg = 7.5 mg/kg

Thus, the regimen would be a loading dose of 10.5 mg/kg, followed by maintenance doses of 7.5 mg/kg every 5.44 hr. This regimen is not only impractical but, were it carried out, it would produce C_{max} and C_{min} concentrations too close to the limiting values to allow for any errors. A better approach would be to define clinically relevant C_{max} and C_{min} values and use the approach in the previous section to develop a useful dosing regimen.

B. Repetitive Extravascular Dosing

Although the equations become considerably more complex than for the IV example, C_{max} and C_{min} can be calculated when the drug is administered by an extravascular route. The required equations may be developed as follows: The equation describing the plasma concentration versus time curve following one extravascular administration was discussed previously. Equation (35) may be written as follows:

$$C_p = \frac{FD}{V_d} \times \frac{k_a}{k_a - k_{el}} \left[\exp(-k_{el}t) - \exp(-k_a t) \right] \tag{55}$$

where D is the dose administered and F is the fraction of the administered dose absorbed [$FD = D_G^0$ in Eq. (35)].

If n doses of the drug are administered at fixed time intervals (T), the plasma concentrations following the nth dose are given by

$$C_p = \frac{FD}{V_d} \times \frac{k_a}{k_a - k_{el}} \left[\frac{1 - \exp(-nk_{el}T)}{1 - \exp(-k_{el}T)} \exp(-k_{el}t') - \frac{1 - \exp(-nk_aT)}{1 - \exp(-k_aT)} \exp(-k_at') \right] \quad (56)$$

where t' is the time elapsed after the nth dose. When n is large (i.e., when the plasma concentrations reach a plateau), the terms $\exp(-nk_{el}T)$ and $\exp(-nk_aT)$ become negligibly small, and Eq. (56) simplifies to

$$C_p = \frac{FD}{V_d} \times \frac{k_a}{k_a - k_{el}} \left[\frac{\exp(-k_{el}t')}{1 - \exp(-k_{el}T)} - \frac{\exp(-k_at')}{1 - \exp(-k_aT)} \right] \quad (57)$$

Equation (57) can be used to calculate the C_{max} and C_{min} values on the plasma concentration plateau by substituting values for t' that correspond to the "peaks" and "valleys" in the C_p versus t curve. Thus, if $t' = t_{max}$ (the time of the peak), Eq. (57) gives C_{max}:

$$C_{max} = \frac{FD}{V_d} \times \frac{k_a}{k_a - k_{el}} \left[\frac{\exp(-k_{el}t_{max})}{1 - \exp(-k_{el}T)} - \frac{\exp(-k_at_{max})}{1 - \exp(-k_aT)} \right] \quad (58)$$

If $t' = 0$ (the time at which another dose is to be given), Eq. (57) gives C_{min}:

$$C_{min} = \frac{FD}{V_d} \times \frac{k_a}{k_a - k_{el}} \left[\frac{1}{1 - \exp(-k_{el}T)} - \frac{1}{1 - \exp(-k_aT)} \right] \quad (59)$$

EXAMPLE. The results of a single IM dose of kanamycin show that the dose is completely absorbed ($F = 1.0$), $V_d = 20$ liter, $k_{el} = 0.3$ hr^{-1}, and the time of the peak is about 1 hr ($k_a = 3.47$ hr^{-1}). If 800-mg doses of kanamycin are administered IM every 6 hr, what will C_{max} and C_{min} be when the plasma concentration plateau is reached?

$$C_{max} = \frac{1.0 \times 800 \text{ mg}}{20 \text{ liters}} \times \frac{3.47 \text{ hr}^{-1}}{(3.47 - 0.3) \text{ hr}^{-1}} \left[\frac{\exp(-0.3 \times 1)}{1 - \exp(-0.3 \times 6)} \right.$$
$$\left. - \frac{\exp(-3.47 \times 1)}{1 - \exp(-3.47 \times 6)} \right] = 37.5 \text{ } \mu\text{g/ml}$$

From Eq. (59),

$$C_{min} = \frac{1.0 \times 800 \text{ mg}}{20 \text{ liters}} \times \frac{3.47 \text{ hr}^{-1}}{(3.47 - 0.3) \text{ hr}^{-1}} \left[\frac{1}{1 - \exp(-0.3 \times 6)} \right.$$
$$\left. - \frac{1}{1 - \exp(-3.47 \times 6)} \right] = 8.67 \text{ } \mu\text{g/ml}$$

Note: The value of $\exp(-x)$ can be calculated directly with a scientific calculator or as the inverse or antilog(base e).

The foregoing example shows the calculation of the two most important features of a repetitive-dosing regimen, the maximum and minimum plasma concentrations on the plateau. But if Eq. (56) had been used, it would have been possible to calculate the plasma concentration at any time throughout an entire dosing regimen. Although these calculations are complex and laborious when done by hand, relatively inexpensive programmable calculators and now microcomputers can solve Eq. (56) in seconds. As a result, a plasma concentration versus time

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```
480  CP = KA * (E1 - E2) / (VD * (KEL - KA))
490  PRINT TIME,CP: NEXT TIME
500  PRINT : PRINT "*** MENU ***": PRINT
510  PRINT "1) NEW PATIENT"
520  PRINT "2) NEW DOSING REGIMEN"
530  PRINT "3) NEW DOSE INTERVAL"
540  PRINT "4) QUIT PROGRAM"
550  PRINT : INPUT "ENTER CHOICE ";T
560  IF T < 1 OR T > 4 THEN  GOTO 500
570  ON T GOTO 10,200,300,600
600  END
```

Comments: This program has been written to be as flexible as possible for use in clinical situations; therefore, many parameters are entered in a form different from their form in Eq. (56). The following comments should clarify the relationships:

1. The program accepts half-lives for the elimination and absorption processes and converts them into rate constants, but both half-lives must be in the same time units. (If the half-life for absorption is unknown, the time of the peak divided by 5 gives a reasonable estimate; see Sec. VII.C.)
2. The fraction of the dose absorbed must be estimated in a separate study or from past experience.
3. The volume of distribution is expressed as a fraction of the body weight, and the program calculates V_d in liters using the next entry, subject weight, in kilograms.
4. Since loading doses are often used clinically, the program is written to accept both a loading dose and a maintenance dose. If no loading dose is given, these two entries are the same value.
5. The time units for the dosing interval (T) and the step interval (*int*) must be the same as those for the half-lives of elimination and absorption.
6. Once the number of maintenance doses (n) is entered the program calculates C_p for the nth-dosing interval.
7. This program can be used in the following ways:
    a. The entire plasma concentration versus time profile for a repetitive-dosing regimen can be calculated by starting with $n = 0$ and calculating C_p for the first-dosing interval. Then $n = 1$ is entered, and the second interval C_p values calculated. The process can be repeated for as many dosing intervals as desired.
    b. The plasma concentration versus time profile for a dosing interval on the plateau can be calculated by entering $n = 50$. The values of C_{min} and C_{max} can then be determined by noting the maximum and minimum values calculated. [*Note*: When $n = 50$, or some other large number, Eq. (56) becomes Eq. (57). Thus, calculations involving Eqs. (57), (58), and (59) can also be performed with this program if a large number is entered for n.]
    c. The entire plasma concentration versus time profile for a single-dose administration can be calculated if the dose is entered as the loading dose (D_0), 50 (or any large number) is entered for T, and 0 is entered for d_0 and n. [Equation (56) becomes Eq. (55).]