Introduction to Pharmacokinetics and Pharmacodynamics

The Quantitative Basis of Drug Therapy

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Lippincott Williams & Wilkins
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Compositor: Circle Graphics
Printer: Courier-Kendallville

351 West Camden Street
Baltimore, MD 21201

530 Walnut St.
Philadelphia, PA 19106

Printed in the United States of America

Library of Congress Cataloging-in-Publication Data

Tozer, Thomas N.
Introduction to pharmacokinetics and pharmacodynamics : the quantitative basis of drug therapy / Thomas N. Tozer, Malcolm Rowland.
p. ; cm.
Includes index.
ISBN 0-7817-5149-7
1.Pharmacokinetics. 2. Drugs—Physiological effect. I. Rowland, Malcolm. II. Title.
[DNLM: 1. Pharmacokinetics. 2. Dose-Response Relationship, Drug. 3. Drug Therapy—methods. 4. Pharmaceutical Preparations—administration & dosage. QV 38 T757i 2006]
RM301.5.T93 2006
615'.7—dc22
2005044560

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CHAPTER 6

Extravascular Dose and Systemic Absorption

OBJECTIVES

The reader will be able to:

- Describe the characteristics of, and the differences between, first-order and zero-order absorption processes.
- Estimate the bioavailability of a drug, given plasma concentration-time profiles following both extravascular and intravascular administration.
- Define the following drug products: immediate-release, modified-release, extended-release, and delayed-release.
- Estimate the relative bioavailability of a drug in different dosage forms given by the same route of administration or the same dosage form given by different routes of administration, when provided with appropriate plasma concentration-time data.
- Determine whether absorption or disposition rate limits drug elimination, given plasma concentration-time data following different dosage forms by the same route of administration or the same dosage form by different routes of administration.
- Anticipate the effect of altering the kinetics of absorption, extent of absorption, clearance, or volume of distribution on the systemic exposure-time following extravascular administration.
- Describe the steps involved in the systemic absorption of a drug after oral administration.
- Distinguish between dissolution and permeability limitations in systemic absorption after oral administration.
- Anticipate the role of gastric emptying and intestinal transit in the systemic absorption of a drug given orally with particular reference to the physicochemical properties of the drug and its dosage form.
- Define bioequivalence and briefly describe how it is assessed.
- Anticipate the influence of food on the systemic absorption of a drug given orally.

Drugs are more frequently administered extravascularly (common routes are listed in Table 6–1) than intravascularly, and the majority are intended to act systemically rather than locally. For these drugs, systemic absorption, the focus of this chapter, is a prerequisite for activity. Delays or losses of drug during systemic input may contribute to variability in drug response and occasionally may result in failure of drug therapy. It is primarily in this context, as a source of variability in systemic response and as a means of controlling the plasma concentration-time profile, that systemic absorption is considered here and through the remainder of the book. Keep in mind, however, that even for those drugs that are used locally (e.g., mydriatics, local anesthetics, nasal decongestants, topical agents, and aerosol bronchodilators), systemic absorption may influence time of onset, intensity, and duration of adverse effects.

This chapter deals primarily with the general principles governing rate and extent of systemic drug absorption from the gastrointestinal tract. Although absorption from other extravascular sites is discussed, emphasis is placed on systemic absorption following oral administration. This is not only because the oral mode of administration is the most prevalent for systemically acting drugs, but also because it illustrates many sources of variability encountered with extravascular administration in general.

A number of oral dosage forms are available. Some are liquids (syrups, elixirs, tinctures, suspensions, and emulsions), whereas the more common ones are solids (tablets and capsules). Tablets and capsules are generally formulated to release drug immediately after their administration to hasten systemic absorption. These are called **immediate-release products.** Other products, **modified-release dosage forms,** have been developed to release drug at a controlled rate. The purpose here is generally either to avoid contact with gastric fluids (acidic environment) or to prolong drug input into the systemic circulation.

Modified-release products fall into two categories. One is **extended-release,** a dosage form that allows a reduction in dosing frequency or diminishes the fluctuation of drug levels on repeated administration compared with that observed with immediate-release dosage forms. Controlled-release and sustained-release products fall into this category. The second category is that of **delayed-release.** This kind of dosage form releases drug, in part or in total, at a time other than promptly after administration. Enteric-coated dosage forms are the most common delayed-release products; they are designed to prevent release of drug in the stomach, where the drug may decompose in the acidic environment or cause gastric irritation, and then to release drug for immediate absorption once in the intestine. Modified-release products are also administered by nonoral extravascular routes. For example, repository (depot) dosage forms are given intramuscularly and subcutaneously in the form of emulsions, solutions in oil, suspensions, and tablet implants.

TABLE 6–1 Extravascular Routes of Administration for Systemic Drug Delivery[a]

Via alimentary canal	
Buccal	Rectal
Oral	Sublingual
Other routes	
Inhalation	Subcutaneous
Intramuscular	Transdermal
Intranasal	

[a]Routes such as dermal, intra-articular, intrathecal, intravaginal, ocular, subdural, and so on, are usually used for local effect.

KINETICS OF ABSORPTION

The oral absorption of drugs often approximates first-order kinetics, especially when given in solution. The same holds true for the systemic absorption of drugs from many other extravascular sites, including subcutaneous tissue and muscle. Under these circumstances, absorption is characterized by an absorption rate constant, *ka*. The corresponding absorption half-life, $t_{1/2,a}$, is related to the absorption rate constant in the same way that elimination half-life is related to elimination rate constant, that is,

$$t_{1/2,a} = \frac{0.693}{ka} \qquad \text{Eq. 6-1}$$

The half-lives for the absorption of drugs administered orally in solution or in a rapidly dissolving (immediate-release) dosage form usually range from 20 minutes to 3 hours. Occasionally, they are longer, especially if dissolution or release from the dosage form is slow.

When absorption occurs by a **first-order** process,

$$\underset{Absorption}{Rate\ of} = \underset{\substack{\text{Absorption}\\ \text{rate constant}}}{ka} \cdot \underset{\substack{\text{Amount}\\ \text{remaining}\\ \text{to be absorbed}}}{Aa} \qquad \text{Eq. 6-2}$$

The rate is proportional to the **amount remaining to be absorbed, *Aa*.** First-order absorption is schematically depicted in Fig. 6–1 by the emptying of water from a cylindrical bucket. The rate of emptying depends on the amount of water in the bucket and the size of the hole at the bottom. With time, the level of water decreases, reducing the rate at which water leaves the bucket. Indeed, the rate of emptying is directly proportional to the level or amount of water in the bucket.

Sometimes, a drug is absorbed at essentially a constant rate. The absorption kinetics is then called **zero order.** Differences between first-order and zero-order kinetics are illustrated in Fig. 6–2. For zero-order absorption, a plot of amount remaining to be absorbed against time yields a straight line, the slope of which is the rate of absorption

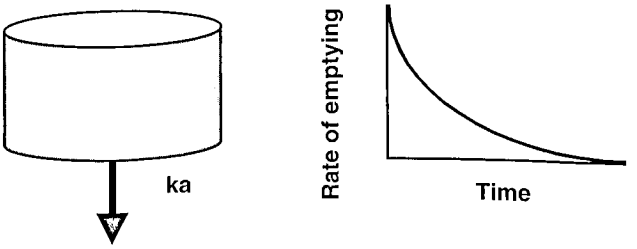

FIGURE 6–1 First-order systemic absorption is analogous to the emptying of water from a hole in the bottom of a cylindrical bucket. The level of water in the bucket decreases with time, as does the rate at which it does so also decreases with time. The slowing of the decline of the water level and the rate of emptying are due to the decrease in water pressure, which depends on the water level (or amount of water) in the bucket. The rate of emptying (g/min), which declines exponentially with time, is proportional to the amount (g) of water in the bucket and the size of the hole. The rate of emptying relative to the amount in the bucket is the fractional rate of emptying, which does not vary with time. In absorption terms, this constant is called the **absorption rate constant, *ka*.**

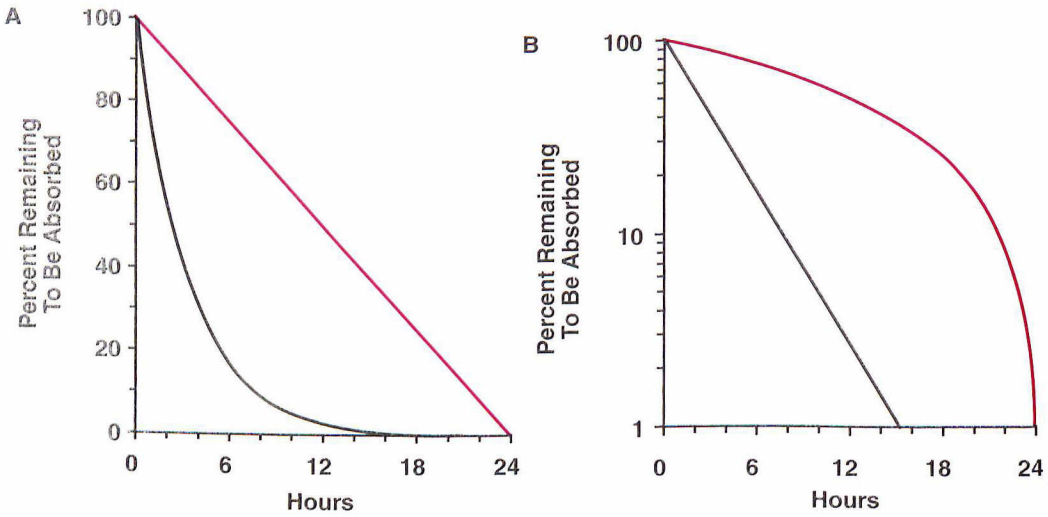

FIGURE 6–2 A comparison of zero-order (colored lines) and first-order (black lines) absorption processes. Depicted are regular (A) and semilogarithmic (B) plots of the percent remaining to be absorbed against time. Note the curvatures of the two processes on the two plots.

(Fig. 6–2A). Recall from Chapter 5 that the fractional rate of decline is constant for a first-order process; the amount declines linearly with time when plotted semilogarithmically. In contrast, for a zero-order absorption process, the fractional rate increases with time, because the rate is constant whereas the amount remaining to be absorbed decreases. This is reflected in an ever-increasingly negative gradient with time in a semilogarithmic plot of the amount remaining to be absorbed (Fig. 6–2B).

For the remainder of this chapter, and for much of the book, systemic absorption is modeled as a first-order process. When it is zero order, the equations subsequently developed in Chapter 9 apply.

EXPOSURE-TIME AND EXPOSURE–DOSE RELATIONSHIPS

The systemic exposure to a drug after a single extravascular dose depends on both systemic absorption and disposition. Consider first how exposure with time after an extravascular dose compares with that seen after an intravenous dose.

Extravascular versus Intravenous Administration

Absorption delays and reduces the magnitude of **peak plasma concentration** compared with that seen after an equal intravenous bolus dose. These effects are portrayed for aspirin in Fig. 6–3.

The rise and fall of the drug concentration in plasma after extravascular administration are best understood by realizing that at any time,

$$\begin{array}{c}\textit{Rate of}\\ \textit{change of}\\ \textit{drug in body}\end{array} = \underbrace{Ka \cdot Aa}_{\substack{\text{Rate of}\\ \text{absorption}}} - \underbrace{k \cdot A}_{\substack{\text{Rate of}\\ \text{elimination}}} \qquad \text{Eq. 6-3}$$

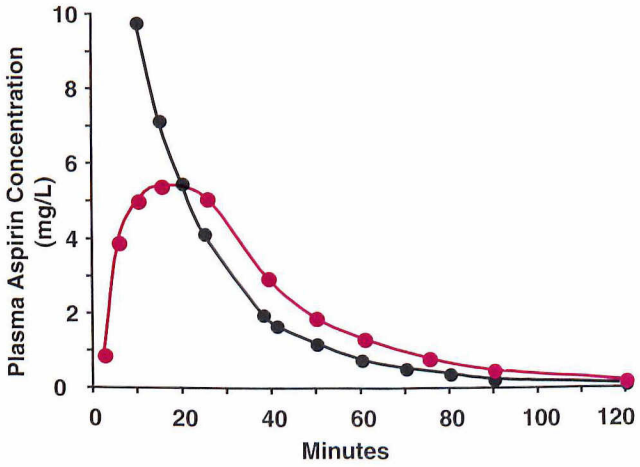

FIGURE 6–3 Aspirin (650 mg) was administered as an intravenous bolus (black) and as an oral solution (color) on separate occasions to the same individual. Absorption causes a delay and a lowering of the peak concentration (1 mg/L = 5.5 μM). *(Modified from the data of Rowland M, Riegelman S, Harris PA, et al. Absorption kinetics of aspirin in man following oral administration of an aqueous solution. J Pharm Sci 1972;67:379–385. Adapted with permission of the copyright owner.)*

The scheme in Fig. 6–4 illustrates the expectation. Drug is input into the reservoir by a first-order process and is eliminated in the same manner as that following an intravenous dose (see Fig. 5–3).

Initially, with the entire dose at the absorption site (bucket) and none in the body (reservoir), rate of absorption is maximal and rate of elimination is zero. Therefore, as drug is absorbed, its rate of absorption decreases, whereas as concentration in the reservoir rises, its rate of elimination increases. Consequently, the difference between the two rates diminishes. As long as the rate of absorption exceeds that of elimination the concentration in the reservoir continues to rise. Eventually, a time, t_{max}, is reached when the rate of elimination matches the rate of absorption; the concentration is then at a maximum, C_{max}. Subsequently, the rate of elimination exceeds the rate of absorption and the concentration declines, as shown in Fig. 6–3 for the plasma concentration of aspirin after a single oral dose.

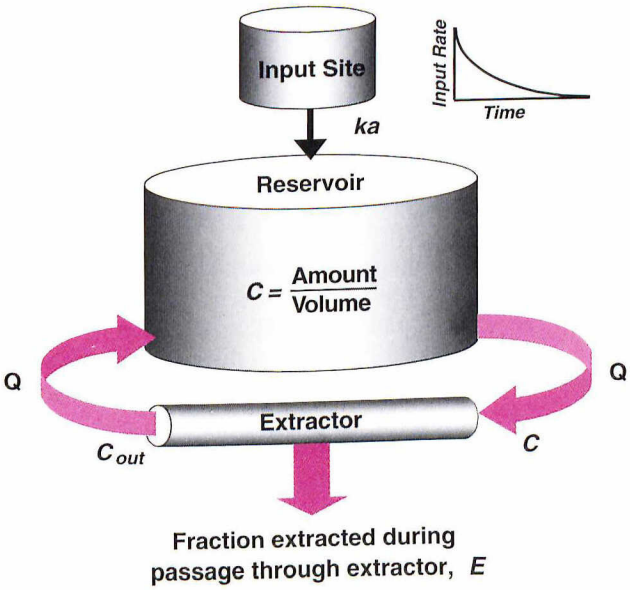

FIGURE 6–4 Scheme for the first-order systemic absorption and elimination of a drug after a single extravascular dose. The systemic absorption is simulated by the emptying of a water bucket (see Fig. 6–1). The rate constant for absorption *ka* is the fractional rate of absorption, that is, the rate of absorption relative to the amount in the bucket. The elimination of the drug from the body (see Fig. 5–3) depends on the extent of its tissue distribution (volume of reservoir, *V*), and how well the drug is extracted from the fluid going to the eliminating organ (*s*) (as measured by *CL*). In this integrated model, the amount of water added to the reservoir is negligible, as is the amount of drug in the extractor and in the fluid going to the extractor, relative to the amount in the reservoir.

The peak plasma concentration following extravascular administration is lower than the initial value following an equal intravenous bolus dose. In the former case, at the peak time some drug remains at the absorption site and some has already been eliminated, while the entire dose is in the body immediately following the intravenous dose. Beyond the peak time, the plasma concentration exceeds that following intravenous administration of the same dose when absorption is complete (total areas are the same) because of continued entry of drug into the body.

Frequently, the rising portion of the plasma concentration-time curve is called the **absorption phase** and the declining portion, the **elimination phase.** As will subsequently be seen, this description may be misleading. Also, if the entire dose does not reach the systemic circulation, the drug concentration may remain lower than that observed after intravenous administration at all times.

Absorption influences the time course of drug in the body; but what of the total area under the exposure-time profile, *AUC*? Recall from Chapter 5 that the rate of elimination is:

$$\text{Rate of elimination} = CL \cdot C \qquad \text{Eq. 6-4}$$

Integrating over all time,

$$\text{Total amount eliminated} = CL \cdot AUC \qquad \text{Eq. 6-5}$$

The total amount eliminated after an oral dose equals the total amount absorbed, $F \cdot Dose$, where the parameter F, **bioavailability**, takes into account that only this fraction of the oral dose reaches the systemic circulation. That is,

$$\underset{\text{Total amount absorbed}}{F \cdot Dose} = \underset{\text{Total amount eliminated}}{CL \cdot AUC} \qquad \text{Eq. 6-6}$$

Bioavailability

Systemic absorption is often incomplete when given extravascularly, for reasons to be discussed subsequently. Knowing the extent of absorption (bioavailability) helps to ensure that the correct dose is given extravascularly to achieve a therapeutic systemic exposure. Although dose is known and area can be determined following an extravascular dose, from Eq. 6-6 it is apparent that clearance is needed to estimate bioavailability. Recall, from Chapter 5 (Eq. 5-21), that to determine clearance, a drug must be given intravascularly, as only then is the amount entering the systemic circulation known (the dose, F = 1). Therefore,

$$Dose_{iv} = Clearance \cdot AUC_{iv} \qquad \text{Eq. 6-7}$$

After an extravascular (ev) dose,

$$F_{ev} \cdot Dose_{ev} = Clearance \cdot AUC_{ev} \qquad \text{Eq. 6-8}$$

Which, upon division of Equation 6-8 by Equation 6-7 and given that clearance is unchanged, yields

$$F_{ev} = \left(\frac{AUC_{ev}}{AUC_{iv}}\right)\left(\frac{Dose_{iv}}{Dose_{ev}}\right) \qquad \text{Eq. 6-9}$$

For example, if the area ratio for the same dose administered orally and intravenously is 0.5, only 50% of the oral dose must have been absorbed systematically.

Relative Bioavailability

Relative bioavailability is determined when there are no intravenous data. Cost to develop, instability, poor solubility, potential adverse events, and lack of regulatory approval are major reasons for the lack of an intravenous preparation. Relative bioavailability is determined by comparing the fractions absorbed for different dosage forms, different routes of administration, or different conditions (e.g., diet or presence of another drug).

Thus, taking the general case of two dosage forms:

Dosage Form A

$$\underset{\text{Total amount absorbed}}{F_A \cdot Dose_A} = \underset{\text{Total amount eliminated}}{Clearance \cdot AUC_A} \qquad \text{Eq. 6-10}$$

Dosage Form B

$$\underset{\text{Total amount absorbed}}{F_B \cdot Dose_B} = \underset{\text{Total amount eliminated}}{Clearance \cdot AUC_B} \qquad \text{Eq. 6-11}$$

So that,

$$Relative\ bioavailability = \left(\frac{AUC_A}{AUC_B}\right) \cdot \left(\frac{Dose_B}{Dose_A}\right) \qquad \text{Eq. 6-12}$$

This relationship holds, regardless of the extravascular route of administration, rate of absorption, or shape of the curve. Constancy of clearance is the only requirement.

CHANGES IN DOSE OR ABSORPTION KINETICS

The concentration-time profile following a change in dose or in the absorption characteristics of a dosage form can be anticipated.

Changing Dose

If all other factors remain constant, as anticipated intuitively, increasing the dose or the fraction of a dose absorbed produces a proportional increase in plasma concentration at all times. The value of t_{max} remains unchanged, but C_{max} and AUC increase proportionally with dose.

Changing Absorption Kinetics

Alterations in absorption kinetics, for example, by changing dosage form or giving the product with food, produce changes in the time profiles of the plasma concentration. This point is illustrated by the three situations depicted in the semilogarithmic plots of Fig. 6–5 involving only a change in the absorption half-life. All other factors (extent of

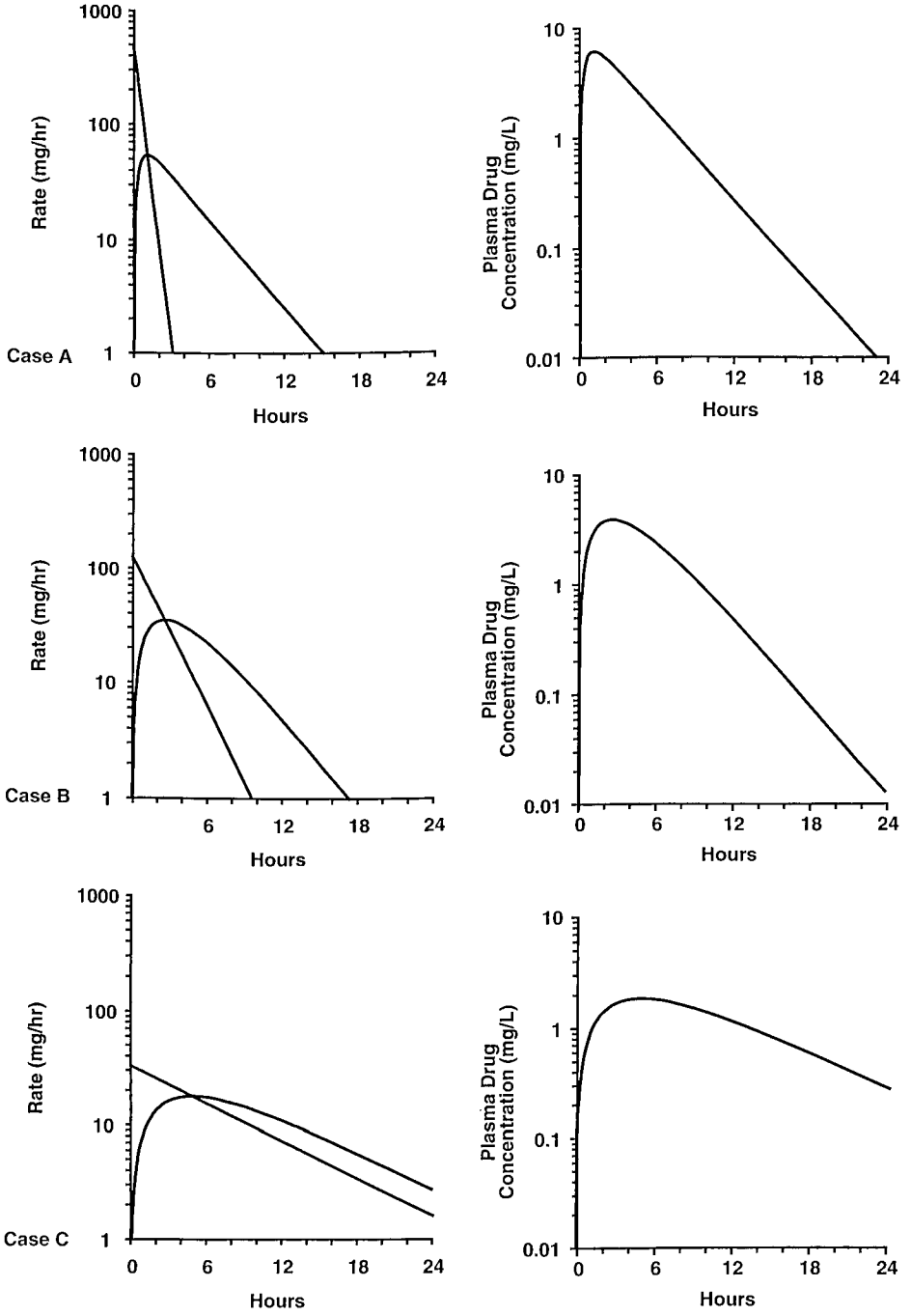

FIGURE 16–5 Rates of absorption (*colored line*) and elimination (*black line*) with time (*graphs on left*) and corresponding plasma concentration-time profiles (*graphs on right*) following a single oral dose of drug under different input conditions. A slowing (from *top to bottom*) of drug absorption delays the attainment (t_{max}) and decreases the magnitude (C_{max}) of the peak plasma drug concentration. In Cases A and B (*top two sets of graphs*), the absorption process is faster than that of elimination and elimination rate limits the decline of the concentration. In Case C (*bottom set of graphs*), absorption rate limits elimination so that the decline of drug in plasma reflects absorption rather than elimination. Because there is a net elimination of drug during the decline phase, the rate of elimination is slightly greater than the rate of absorption. In all three cases, bioavailability is 1.0 and clearance is unchanged. Consequently, the areas under the plasma concentration-time curves (corresponding linear plots of the top three graphs) are identical. The *AUC*s of the linear plots of the rate data are also equal because the integral of the rate of absorption, amount absorbed, equals the integral of the rate of elimination, amount eliminated.

absorption, clearance, and volume of distribution and hence elimination half-life) remain unchanged.

Disposition is Rate Limiting

In Case A, the most common situation, absorption half-life is much shorter than elimination half-life. In this case, most of the drug has been absorbed and little has been eliminated by the time the peak is reached. Thereafter, decline of drug is determined primarily by the disposition of the drug, that is, disposition is the rate-limiting step. The half-life estimated from the decline phase is therefore the elimination half-life.

In Case B, absorption half-life is longer than in Case A but still shorter than elimination half-life. The peak occurs later (t_{max} increased) because it takes longer for the concentration to reach the value at which rate of elimination matches rate of absorption; the C_{max} is lower because less drug has been absorbed by that time. Even so, absorption is still essentially complete before the majority of drug has been eliminated. Consequently, disposition remains the rate-limiting step, and the terminal decline still reflects the elimination half-life.

Absorption is Rate Limiting

Occasionally, absorption half-life is longer than elimination half-life, and Case C prevails (Fig. 6–5). The peak concentration occurs later yet and is lower than in the two previous cases, reflecting the slower absorption process. Again, during the rise to the peak, the rate of elimination increases and eventually, at the peak equals the rate of absorption. However, in contrast to the previous situations, absorption is now so slow that considerable drug remains to be absorbed well beyond the peak time. Furthermore, at all times most of the drug is either at the absorption site or has been eliminated; little is ever in the body. In fact, during the decline phase, drug is eliminated virtually as fast as it is absorbed. Absorption is now the rate-limiting step. Under these circumstances, since the rate of elimination essentially matches the rate of absorption, the following approximation ($\approx$) can be written:

$$\underset{\text{Rate of elimination}}{k \cdot A} \approx \underset{\text{Rate of absorption}}{ka \cdot Aa} \qquad \text{Eq. 6-13}$$

That is,

$$\underset{\text{Amount in body}}{A} \approx \left(\frac{ka}{k}\right) \cdot \underset{\text{Amount remaining to be absorbed}}{Aa} \qquad \text{Eq. 6-14}$$

Accordingly, the plasma concentration ($C = A/V$) during the decline phase is directly proportional to the amount remaining to be absorbed. For example, when the amount remaining to be absorbed falls by one-half so does the plasma concentration. The time required for this to occur is the absorption half-life. That is, the half-life of decline of drug in the body now corresponds to the absorption half-life. **Flip-flop** is a common descriptor for this kinetic situation. When it occurs, the terms **absorption**

phase and **elimination phase** for the regions where the plasma concentration-time curve rises and falls, respectively, are clearly misleading.

Distinguishing Between Absorption and Disposition Rate Limitations

Although disposition generally is rate-limiting, the preceding discussion suggests that caution should be exercised in interpreting the meaning of half-life determined from the decline phase following extravascular administration. Confusion is avoided if the drug is also given intravenously. In practice, however, intravenous dosage forms of many drugs do not exist for clinical use. Absorption and disposition rate limitations may be distinguished by altering the absorption kinetics of the drug. This is most readily accomplished by giving the drug either in another dosage form such as a solution or by a different route.

ABSORPTION FROM SOLUTION

Systemic absorption is favored after extravascular administration because the body acts as a sink, producing a concentration difference between the diffusible unbound concentrations at the absorption site and in systemic blood. The concentration gradient across the gastrointestinal absorptive membranes is maintained by distribution to tissues and elimination of absorbed drug. Physiologic and physical factors that determine movement of drug through membranes in general are discussed in Chapter 4. Included among them were the physicochemical properties of the drug, the nature of the membrane, presence of transporters, perfusion, and pH. These factors and others are now considered with respect to drug passage through the gastrointestinal membranes. In this context, absorption is the term that is subsequently used for this process.

However, before a drug can pass through the membranes dividing the absorption site from the blood, it must be in solution. Most drugs are administered as solid preparations. Common examples are tablets and capsules. Before addressing the issues involving drug release from a solid dosage form, let us first consider the events that result in systemic absorption after oral administration of a drug in solution.

Gastrointestinal Absorption

In accordance with the prediction of the pH partition hypothesis, weak acids are absorbed more rapidly from the stomach at pH 1.0 than at pH 8.0, and the converse holds for weak bases. Absorption of acids, however, is much faster from the less acidic small intestine (pH 6.6 to 7.5) than from the stomach. These apparently conflicting observations can be reconciled. Surface area, permeability and, when perfusion rate limits absorption, blood flow are important determinants of the rapidity of absorption. The intestine, especially the small intestine, is favored on all accounts. The total absorptive area of the small intestine, produced largely by microvilli, has been calculated to be about 200 M^2, and an estimated 1 L of blood passes through the intestinal capillaries each minute. The corresponding estimates for the stomach are only 1 M^2 and 150 mL/min. The permeability of the intestinal membranes to drugs is also greater than that of the stomach. These increases in surface area, permeability, and blood flow more than compensate for the decreased fraction of un-ionized acid in the intestine. Indeed, the absorption of *all* compounds—acids, bases, and neutral compounds—is faster from the (small) intestine than from the stomach. Because absorption is greater in the small intestine, the rate of gastric emptying is a controlling step in the speed of drug absorption.

Gastric Emptying

Food, especially fat, slows gastric emptying, which explains why drugs are frequently recommended to be taken on an empty stomach when a rapid onset of action is desired. Drugs that influence gastric emptying also affect the rate of absorption of other drugs, as shown in Fig. 6–6 for acetaminophen, a common analgesic/antipyretic.

Retention of acetaminophen in the stomach increases the percentage of a dose absorbed through the gastric mucosa, but the majority of the dose is still absorbed through the intestinal epithelium. In this regard, the stomach may be viewed as a repository organ from which pulses of drug are ejected by peristalsis onto the absorption sites in the small intestine.

Intestinal Absorption

Throughout its length, the intestine varies in its multifaceted properties and luminal composition. The intestine may be broadly divided into the small and large intestines separated by the ileocecal valve. Surface area per unit length decreases from the duodenum to the rectum. Electrical resistance, a measure of the degree of tightness of the junctions between the epithelial cells, is much higher in the colon than in the small intestine. Proteolytic and metabolic enzymes, as well as active and facilitated transport systems, are distributed variably along the intestine, often in restrictive regions. The colon abounds with anaerobic microflora. The mean pH, 6.6, in the proximal small intestine rises to 7.5 in the terminal ileum, and then falls sharply to 6.4 at the start of the cecum before finally rising again to 7.0 in the descending colon. Transit time of materials is around 3 to 4 hours in the small intestine and from 10 to 36 hours or even longer in the large bowel. Although these and other complexities make precise quantitative prediction of intestinal drug absorption difficult, several general features emerge.

The permeability-surface area product (P · SA) tends to decrease progressively from duodenum to colon. This applies to all drug molecules traversing the intestine epithelium by non–carrier-mediated processes, whether via the transcellular (through cell) or paracellular (around cells) routes, when drugs are placed in different parts of the intestine, as illustrated in Fig. 6–7 for ranitidine. The extent of absorption is decreased when ranitidine is administered into the cecum as reflected by the reduced AUC (Fig. 6–7A).

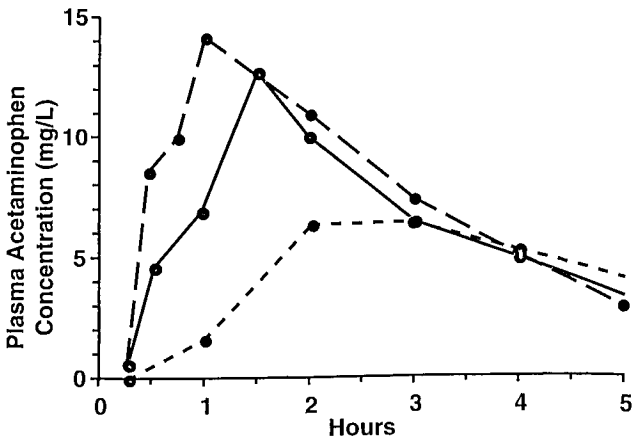

FIGURE 6–6 Slowing gastric emptying by propantheline (30 mg intravenous) slows the rate of absorption of acetaminophen (1500-mg dose) ingested orally by a 22-year-old man, as seen by a decrease in the maximum plasma concentration and a longer time to reach this concentration (·····) compared with values when acetaminophen is given alone (———). Metoclopramide (10 mg intravenous), which shortens the time for gastric emptying, hastens the absorption of acetaminophen (- - -). *(Redrawn from Nimmo J, Heading RC, Tothill P, et al. Pharmacological modification of gastric emptying: effects of propantheline and metoclopramide on paracetamol (acetaminophen) absorption. Br Med J 1973;1:587–588.)*

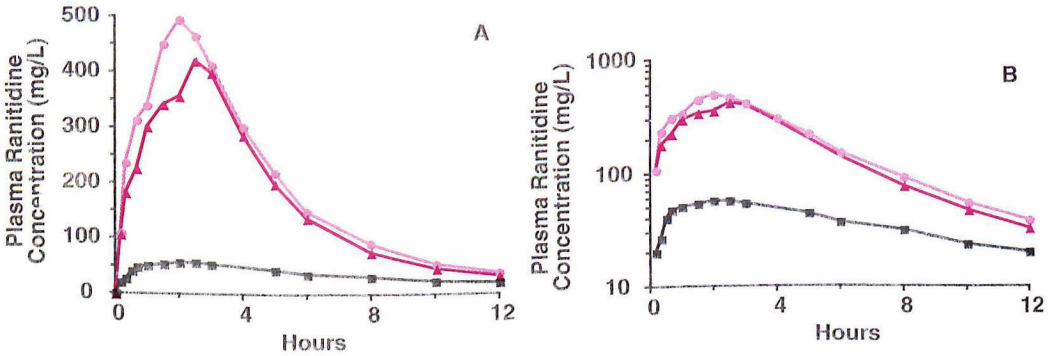

FIGURE 6–7 The gastrointestinal absorption of ranitidine varies with site of application. The variation is shown in linear (A) and semilogarithmic (B) plots of the mean plasma concentration-time profiles of ranitidine observed after placing an aqueous solution (6 mL) containing 150 mg of ranitidine hydrochloride into the stomach (●), jejunum (▲), and colon (■) of eight volunteers via a nasoenteric tube. The much less extensive absorption of this small (MW = 313 g/mol) polar molecule from the colon is consistent with the idea that the permeability-surface area ($P \cdot SA$) product is much lower in the colon than in the small intestine. Notice that absorption of ranitidine effectively ceases (in terminal decline phase) by 3 hours when placed in the stomach or jejunum, even though the drug is incompletely bioavailable (F = 0.6; data not shown). This suggests that the small intestine is the major site of absorption when ranitidine is taken orally. Also, notice in B that the terminal half-life of the decline in the plasma concentration is longer when the drug is administered into the cecum. Absorption from the colon thus appears to be slow and rate limiting. *(Adapted from Williams MF, Dukes GE, Heizer W, et al. Influence of gastrointestinal site of drug delivery on the absorption characteristics of ranitidine. Pharm Res 1992;9:1190–1194.)*

The rate (absorption half-life) is also affected as reflected by an increased terminal half-life (Fig. 6–7B).

Permeability is a limiting factor for many drugs as discussed in Chapter 4. For polar drugs, molecular size is particularly important. Small polar substances move paracellularly across the epithelium. Permeability appears to drop off sharply with molecular weights above 350 g/mole. Thus, large polypeptides, proteins, and other polar macromolecular drugs pass through the intestinal wall slowly even if they are metabolically stable, unless they are absorbed by one of the specialized influx transporters. Molecular size has less of an effect on permeability for lipophilic drugs, which traverse the membranes transcellularly. The ultimate limit to permeability of both polar and nonpolar substances is size, however.

Recall from Chapter 4 that systemic absorption can be reduced by the presence of efflux transporters, such as P-glycoprotein. Low apparent permeability results, not so much from inability to cross intestinal membranes, but from the action of the active reverse pump.

Causes of Changes in Oral Bioavailability

The oral bioavailability (F) of drugs is commonly less than 1. There are many reasons for the reduced systemic absorption.

First-Pass Loss

A drug must pass sequentially from the gastrointestinal lumen, through the gut wall, and through the liver before entering the general circulation (Fig. 6–8). This sequence is an anatomic requirement because blood perfusing virtually all gastrointestinal tissues

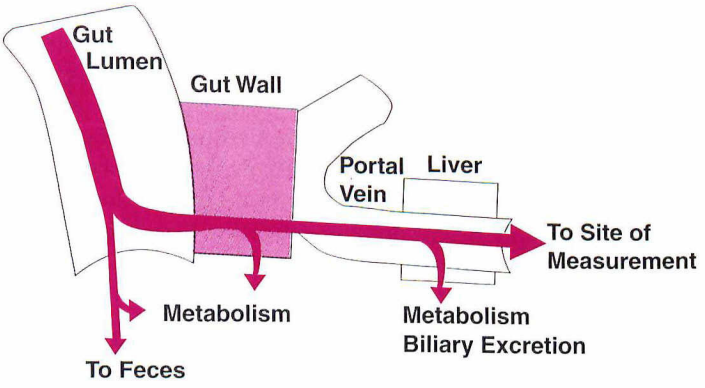

FIGURE 6–8 A drug, given as a solid or a solution, encounters several barriers and sites of loss in its sequential movement from the gastrointestinal tract to the systemic circulation. Dissolution, a prerequisite to movement across the gut wall, is the first step. Incomplete dissolution, slow penetration of the gastrointestinal membranes, and decomposition in the gut lumen are causes of poor bioavailability. Removal of drug as it first passes through gut wall and the liver further reduce the systemic bioavailability.

drains into the liver via the hepatic portal vein. If the only cause of loss is incomplete time for absorption, then the bioavailability is less than 1 and the complement—the fraction appearing in feces unchanged—is a measure of luminal retention. Drug may also be lost by decomposition in the lumen; the fraction entering the intestinal tissues, F_I, is then the fraction neither lost in the feces nor decomposed in the lumen. Of this permeating drug, only a fraction may escape destruction within the walls of the gastrointestinal tract, F_G, thereby reducing the fraction of dose reaching the portal vein further to $F_F \cdot F_G$. If drug is also eliminated in the liver, an additional fraction, F_H, of that reaching the liver escapes extraction there, another site of first-pass loss. Accordingly, the measured overall systemic bioavailability, F, is then

$$F = F_F \cdot F_G \cdot F_H \qquad \text{Eq. 6-15}$$

For example, if 50% of the drug is lost at each step, the bioavailability of the drug, measured systematically, would be $0.5 \times 0.5 \times 0.5 = 0.125$, or 12.5%. Note that the drug can be rendered totally unavailable systemically at any one of these steps.

Aspirin (acetylsalicylic acid) is one of the first synthetic prodrugs. It was marketed at the turn of the 20th century to overcome the unpleasant taste and gastrointestinal irritation associated with salicylic acid. Aspirin was originally thought to be inactive, being designed to be rapidly hydrolyzed within the body to salicylic acid. Only subsequently was aspirin shown to have some pharmacologic effects of its own. Yet, the original design worked; upon ingestion, aspirin, a labile ester, is rapidly hydrolyzed, particularly by esterases in the gut wall and liver. Indeed, intestinal and hepatic hydrolysis is so rapid that a sizeable fraction of aspirin is converted to salicylic acid in a single passage through these organs, resulting in a substantial **first-pass loss** or **first-pass metabolism.**

Another example of a drug showing first-pass loss is orlistat. Apart from having a first-pass loss, one in the gastrointestinal wall (orlistat) and the other primarily in the liver (aspirin), orlistat and aspirin have little in common. They have different chemical structures and possess different pharmacologic activities. Aspirin (M.W. = 190 g/mol) is a simple acetyl ester of salicylic acid, whereas orlistat (Xenical) is a large (M.W. = 496 g/mol) more complex molecule. Aspirin is an anti-inflammatory agent and a prostaglandin

synthesis inhibitor that acts systemically, whereas orlistat acts locally as a lipase inhibitor within the gastrointestinal tract to help control obesity. The almost complete first-pass metabolism of the small fraction of orlistat that permeates the intestine therefore has little impact on its efficacy.

When metabolite(s) formed during the first pass through intestinal wall and the liver are inactive or less potent than the parent drug, the oral dose may need to be larger than the equivalent intravenous or intramuscular dose if the same therapeutic effect is to be achieved. For some drugs, hepatic extraction is so high as to essentially preclude the oral route. The fraction of drug entering the liver that escapes metabolism there is $1 - E_H$, where E_H is the hepatic extraction ratio. Here, no amount of pharmaceutical formulation helps. Either the drug must be given by a parenteral route, or it must be discarded in favor of another drug candidate. Flumazenil, a benzodiazepine receptor antagonist, and naloxone, an opioid antagonist, are examples. These drugs are so highly extracted by the liver that they must be given parenterally to be efficacious.

Extensive hepatic extraction can be advantageously used in therapy. Talwin, a combination product of pentazocine, a potent narcotic analgesic with abuse potential, and naloxone, an analgesic antagonist, is effective as an analgesic when administered orally because naloxone, but not pentazocine, is very extensively metabolized during the first pass through the liver. However, when administered parenterally, the mixture is inactive because of the antagonistic effect of naloxone. The advantage of the combination in the oral product is to prevent its intravenous injection by drug abusers.

Another example is budesonide, a synthetic corticosteroid used in treating Crohn's disease of the ileum and ascending colon. The drug is given in a modified-release dosage form, which releases drug in the region where the disease is common. Drug easily permeates the intestinal wall but, owing to extensive CYP3A4-catalyzed first-pass metabolism in gut wall and liver, systemic availability is low, thereby reducing the adverse systemic effects of the corticosteroid. Co-administration of drugs that inhibit CYP3A4, however, reduces the first-pass loss and increases systemic exposure and therefore adverse events. Co-administration of ketoconazole, a potent inhibitor of CYP3A4 at conventional doses, for example, has been reported to increase by eight-fold the AUC of budesonide.

Some drugs are substrates for both luminal efflux transporters and metabolic enzymes, particularly CYP3A4, within the intestinal cells, as shown in Fig. 6–9. Together, they reduce the oral bioavailability to a greater extent than if only one of the two processes was involved. Drug examples in this category include: HIV-1 protease inhibitors, indinavir (Crixivan), nelfinavir (Viracept), saquinavir (Invernase), and ritonavir

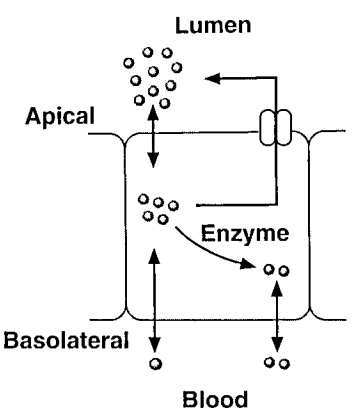

FIGURE 6–9 For some drugs, systemic absorption after oral administration depends on both enzymatic metabolism and efflux transporters (*depicted in color*) in the intestinal epithelium. The presence of efflux transporters on the apical side in concert with the intracellular metabolism may diminish the movement of drug from the intestinal lumen to blood. Inhibition of either the metabolic activity or the efflux transport leads to an increase in the net movement of unchanged drug into the systemic circulation. Symbols: •, drug; •, metabolite.

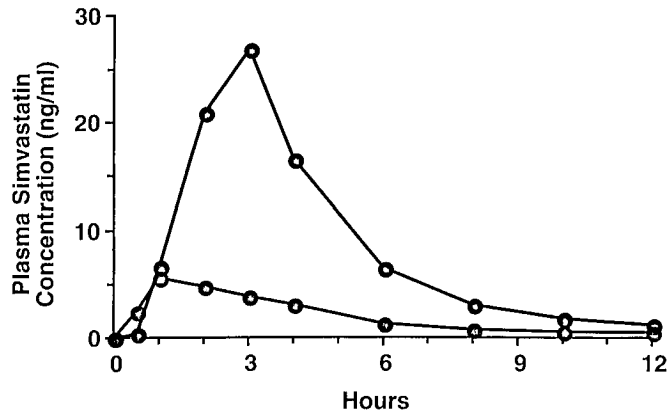

FIGURE 6–10 The mean plasma simvastatin concentration with time after administration of a single 40-mg dose of simvastatin with 200 mL of either water (*black*) or grapefruit juice (*color*) daily for 3 days. Note the large (3.6-fold) increase in area when grapefruit juice is concurrently given. *(Figure adapted from Fig. 1 in Lilja JJ, Neuvonen M, Neuvonen PJ. Effects of regular consumption of grapefruit juice on the pharmacokinetics of simvastatin. Br J Clin Pharmacol 1994;58:56–60.)*

(Norvir); the chemotherapeutic agent, paclitaxel; the cholesterol-lowering drug, simvastatin (Zocor), and the immunosuppressive agent, cyclosporine. The extent to which inhibitors of the enzyme activity and/or the transport system increase systemic availability depends on the contribution of metabolism and transport to first-pass intestinal loss.

The concurrent administration of grapefruit juice and simvastatin is an example of altered first-pass metabolism (Fig. 6–10). The oral bioavailability of the drug is normally about 0.05, but when one glass of grapefruit juice is taken once daily for 3 days and concurrently with 40-mg of simvastatin on day 3, its systemic exposure (as reflected by AUC) is increased 3.6 times. This effect is caused by inhibitors of CYP3A4 within grapefruit juice.

The degree of inhibition of simvastatin first-pass intestinal metabolism is a function of how much, as well as when, grapefruit juice is ingested, as illustrated by the data shown in Table 6–2, when "high dose" grapefruit juice (200 mL of double strength) is given

TABLE 6–2 Mean (± SD) Peak Concentrations (C_{max}) and Total Area Under the Curve *(AUC)* After a Single 40-mg Dose of Simvastatin with and without Grapefruit Juice (GFJ)[a]

Measure	Control (Water Only)	Concurrent Administration of GFJ	Time After Discontinuing GFJ		
			24 hours	3 days	7 days
Cmax (ng/mL)	9.3 ± 4.5 (100)[b]	112 ± 44.8 (1200)[b]	22.0 ± 9.7 (237)[b]	14.2 ± 4.6 (153)[b]	12.4 ± 7.2 (133)[b]
AUC (ng-hr/mL)	28.9 ± 14.5 (100)[b]	390 ± 126 (1350)[b]	59.4 ± 27.6 (206)[b]	39.6 ± 11.9 (137)[b]	30.6 ± 15.8 (106)[b]

[a]The drug was administered with 200 mL water alone (part 1 of study) or following administration of double-strength grapefruit juice (GFJ) 3 × daily at 7:00 AM, noon, and 8:00 PM for 3 days and at 0.5 and 1.5 hours after simvastatin intake (part 2 of study). In part 3, subjects received the GFJ as above, but the dose of simvastatin was withheld for 24 hours, 3 days, or 7 days after discontinuing GFJ.

[b]Percent of the control value.

three times a day for 3 days. The fall-off in the inhibition of the metabolism after discontinuing grapefruit juice is examined by waiting 1, 3, and 7 days before giving the drug. Notice that the high-dose grapefruit ingestion increases the exposure of simvastatin 13.5 times (compared with 3.6 times when only one standard glass of grapefruit is given daily; Fig. 6–10). Also, note that 24 hours after stopping grapefruit juice intake, the increase in AUC is only about 10% of that observed when currently administered, and that the AUC has essentially returned to the control value 1 week later. The therapeutic impact of this interaction is tempered by the fact that several metabolites of simvastatin are also active, such that the increase in exposure of total active species in plasma is less than simvastatin itself.

Insufficient Time for Absorption

The $P \cdot SA$ term for drugs appears to drop sharply with movement from the small intestine to the colon. How much of this drop is due to a decrease in permeability and how much to a decrease in surface area between small and large intestine is not known for certain. For permeable drugs, absorption is rapid and probably complete within the small intestine. Even if some drug were to enter the large intestine, the permeability there would still be sufficiently high to ensure that all that entered was absorbed. Absorption of less permeable, generally more polar, drugs still primarily occurs within the small intestine but may not be complete within the limited 2- to 4-hour transit period. Evidence supporting this notion is provided with the H_2-antagonist ranitidine. This relatively polar-stable compound is almost totally excreted unchanged when given intravenously. When given orally, 60% is absorbed but all within the first 3 to 4 hours after administration (Fig. 6–7); the rest is recovered unchanged in feces. When given intracolonically, the extent of absorption is greatly reduced, and absorption becomes rate-limiting. Evidently, very little ranitidine is absorbed from the large intestine even though drug can be there for 24 hours or more.

Drugs with low permeability characteristics show reduced oral bioavailability not only because of the low permeability, but because of the lack of time for absorption in the regions of the gastrointestinal tract where the $P \cdot SA$ product is at its highest. The relationship between bioavailability and permeability of many drugs that have minor first-pass loss is shown in Fig. 6–11. Clearly, low-permeability drugs are poorly absorbed.

Competing Reactions

Any reaction that competes with absorption may reduce the oral bioavailability of a drug. Table 6–3 lists various reactions that occur within the gastrointestinal tract. Reactions can be either enzymatic or nonenzymatic in nature. Acid hydrolysis in the stomach is a common nonenzymatic reaction. Enzymatic reactions include those caused by digestive enzymes, metabolic enzymes within the intestinal epithelium, and microfloral enzymes, predominantly in the large bowel. The reaction products are often inactive or less potent than the parent molecule. Complexation reactions with other drugs also occur; the result may be low drug bioavailability. For example, co-administration of charcoal or cholestyramine reduces the absorption of a number of drugs, including leflunomide, cephalexin, and piroxicam. When both an adsorbent and an *adsorbable* drug are concurrently used, their administration must be timed to avoid mixing within the gastrointestinal tract. Otherwise, the bioavailability of the drug may be greatly reduced.

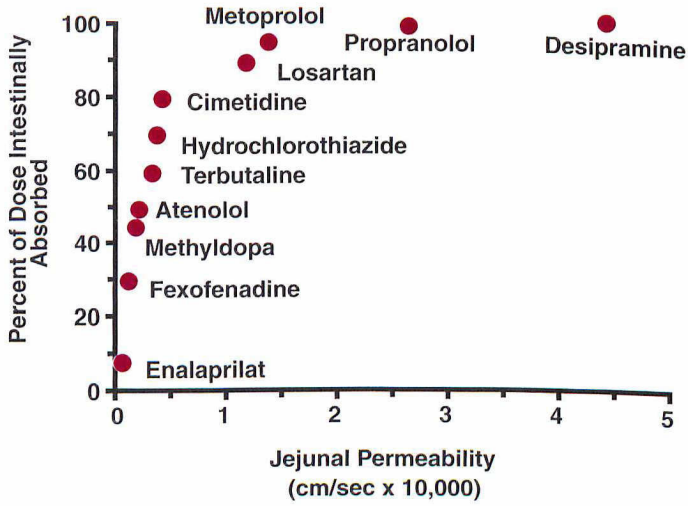

FIGURE 6–11 The fraction of a dose absorbed intestinally after oral administration correlates with human jejunal permeability. Drugs with permeabilities less than 1.0 are likely to be incompletely absorbed. The lower the permeability is below this value, the greater is the likelihood. *(Adapted from Petri N, Lennernäs H. In vivo permeability studies in the gastrointestinal tract. In: van der Waterbeemd H, Lennernäs H, Artusson P, eds. Drug Bioavailability, Estimation of Solubility, Permeability, Absorption and Bioavailability. Berlin: Wiley-VCH, 2003:345–386).*

The complexities that occur in vivo preclude accurate prediction of the contribution of a competing reaction to decreased bioavailability. Sometimes, the problem of incomplete absorption can be circumvented by physically protecting the drug from destruction in the stomach or by synthesizing a more stable derivative, which is converted to the active molecule within the gastrointestinal tract or within the body. Similarly, to enhance absorption, more permeable derivatives are made, which are rapidly converted to the active molecule, often during passage through the intestinal wall. For example, absorption of the polar antibiotic ampicillin is incomplete. Its systemic delivery is improved substantially by administering a more lipophilic and permeable inactive ester prodrug, pivampicillin. Another example is that of valganciclovir (Valcyte), an antiviral agent. The hydrolysis of this compound within the intestine by digestive esterases is so rapid that only ganciclovir is detected in the systemic circulation. Valganciclovir is therefore, by design, also a prodrug.

Sometimes the oral bioavailability of a drug is very low (0.005 to 0.2), but is still used for systemic effects. Pyridostigmine, a cholinesterase inhibiter used in treating myasthenia gravis, is a quaternary ammonium compound. Because it is positively charged at all physiologic pH values, its bioavailability is low despite a relatively small molecular weight (181 g/mol). Alendronate (Fosamax), a bisphosphonate used in treating osteoporosis, is an example of a small (M.W. = 305 g/mol) anionic molecule that is very poorly absorbed (F = 0.005). Although these two agents are given orally for systemic delivery, many drugs with these characteristics are not given orally, not so much because of their low bioavailability but because of their excessively variable oral absorption. They are instead given parenterally, that is, by a route outside the enteric tract for which bioavailability is more reproducible. Occasionally, poorly absorbed drugs have utility in treating diseases of the alimentary canal itself. Some of the polar antibiotics, such as the aminoglycosides, are examples.

TABLE 6–3 Representative Reactions Within the Gastrointestinal Tract that Compete with Drug Absorption from Solution

Reaction	Drug	Comment
Adsorption	Sumatriptan	Adsorption to charcoal; adsorbed material is not absorbed.
Conjugation		
Sulfoconjugation	Ethinyl estradiol	Concurrent administration of inhibitors of sulfoconjugation (e.g., ascorbic acid and acetaminophen) increase bioavailability of this drug.
Glucuronidation	Morphine	Two glucuronides are formed. The 6-glucuronide has analgesic activity; the 3-glucuronide is inactive.
Decarboxylation	Levodopa	*Loss of activity:* Given with a peripheral L-dopa decarboxylase inhibitor to reduce gastrointestinal metabolism.
Efflux transport	Fexofenadine	Efflux transporters reduce absorption of this drug.
Hydrolysis		
Acid	Penicillin G	*Loss of activity:* Product is inactive.
	Erythromycin	*Loss of activity:* Product is inactive.
	Digoxin	Products (digitoxides) have variable activity.
Enzymatic	Aspirin	Salicylic acid, an active anti-inflammatory compound is formed.
	Pivampicillin	*Active ampicillin formed:* Pivampicillin (ester) is inactive.
	Insulin	*Loss of activity:* Product is inactive.
Oxidation	Cyclosporine	*Loss of activity:* Products are less active or inactive.
Reduction (microflora)	Olsalazine	Intended for local (colon) anti-inflammatory action; parent drug not systemically absorbed, but is reduced to two molecules of the active metabolite, 5-aminosalicylic acid.

Absorption From Intramuscular and Subcutaneous Sites

The General Case

In contrast to the gastrointestinal tract, absorption of most drugs in solution from muscle and subcutaneous tissue is perfusion rate limited. For example, consider the data in Table 6–4 for the local anesthetic lidocaine. Shown are the peak plasma concentrations observed when the same dose of lidocaine is administered parenterally at different sites of the body. Recall from Fig. 6–5, for a given dose, when the peak concentration is higher, the drug absorption is faster. Large differences in speed of absorption are clearly evident, the speed increasing from subcutaneous tissue to intercostal muscle, in line with an increasing tissue perfusion.

The dependence of rapidity of absorption on local blood flow is taken advantage of when lidocaine is used as a local anesthetic. The addition of epinephrine, a vasoconstrictive agent, reduces the blood flow and prolongs the local anesthetic effect. When a drug is administered intramuscularly or subcutaneously and systemic action is desired, reduced local perfusion may not be an advantage. In extreme cases, such as hemorrhagic shock, perfusion of muscle tissue is drastically reduced. It is therefore inappropriate to give drugs by this route in this condition if rapid onset of action is needed.

TABLE 6–4 Influence of Site of Injection on the Peak Venous Lidocaine Concentration Following Injection of a 100-mg Dose[a]

Injection Site	Peak Plasma Lidocaine Concentration (mg/L)	Perfusion Rate
Intercostal	1.46	
Paracervical	1.20	
Caudal	1.18	
Lumbar epidural	0.97	
Brachial plexus	0.53	
Subarachnoid	0.44	
Subcutaneous	0.35	

[a]Taken from Covino BG. Pharmacokinetics of local anaesthetic drug. *In:* Prys-Roberts C, Hug, CC, eds. Pharmacokinetics of Anaesthesia. Oxford: Blackwell Scientific Publications, 1984:270–292.

This dependence of absorption on perfusion may be explained by the nature of the barrier (capillary membrane) between the site of injection (interstitial fluid) and blood. This membrane, a much more loosely knit structure than the epithelial lining of the gastrointestinal tract (see Chapter 4), offers little impedance to the movement of drugs into blood, even for polar ionized drugs. For example, gentamicin, a water-soluble, ionized, polar base with a molecular weight of 1486 g/mol, is poorly absorbed when given orally because it has great difficulty penetrating the gastrointestinal mucosa. It also does not pass the blood–brain barrier, nor is it reabsorbed in the renal tubule. However, it is rapidly and completely absorbed systemically from an intramuscular site. This low impedance by the capillary membrane in muscle and subcutaneous tissue applies to all drugs, independent of charge, degree of ionization, and molecular size up to approximately 5000 g/mol.

Macromolecules and Lymphatic Transport

In contrast to small molecules, size, polarity, and charge are important for administration of proteins and large polypeptide drugs; their transport across many membranes is hindered. Furthermore, because of their polarity and decomposition by proteolytic enzymes in the gastrointestinal tract, their oral absorption is often low and erratic. Most of the information on these kinds of drugs has been obtained following nonvascular parenteral administration. For the subcutaneous and intramuscular routes, drug reaches the systemic circulation by two parallel mechanisms: diffusion through the interstitial fluids into blood capillaries and convective flow of the interstitial fluids into and through lymphatic channels. Molecular size is of primary importance for passage across the capillary endothelium. Polypeptides of less than approximately 5000 g/mol primarily reach the systemic circulation by this pathway. Polypeptides of greater than about 20,000 g/mol are less able to traverse the capillary membranes; by default, they primarily reach the blood via the lymphatic system. Some drug, of course, is still moving across the capillary membrane, just at a slower rate. A diagrammatic representation of the lymphatic system is shown in Fig. 6–12.

Lymph flow is very slow (movement of interstitial fluid into lymphatic vessels is 500 times and return of lymph to blood is 5000 times slower than blood flow) and causes

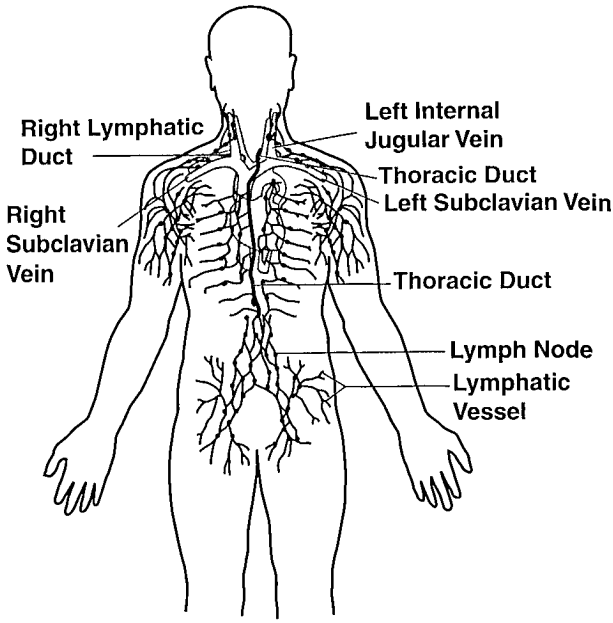

FIGURE 6–12 A sketch of the lymphatic system. Note that drug in the interstitial fluids of subcutaneous or muscular tissue, placed there by injection, moves through the lymphatic vessels and one or several lymph nodes before reaching the systemic circulation. Lymph returns drug to the bloodstream from a portion of the right side of the body via the right lymphatic duct and from the tissues of the rest of the body via the thoracic duct. These ducts empty into the right and left subclavian veins, respectively.

absorption from nonvascular parenteral sites to continue for many hours, as shown in Fig. 6–13 for filgrastim. Filgrastim (Neupogen) is a glycosylated recombinant human granulocyte-macrophage colony-stimulating factor (M.W. = 15,000 to 34,000 g/mol) used to decrease the incidence of infection, as manifested by febrile neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs. This drug has a half-life of 68 minutes after intravenous administration of a single dose, but after subcutaneous administration, the plasma concentration is prolonged for at least 42 hours, with a rate of decline indicating continuing input even at this time. Elimination of this protein drug after subcutaneous administration is clearly absorption rate–limited.

Nonvascular parenteral routes offer the advantage of providing prolonged input for short half-life proteins. This may allow for less frequent administration than is required

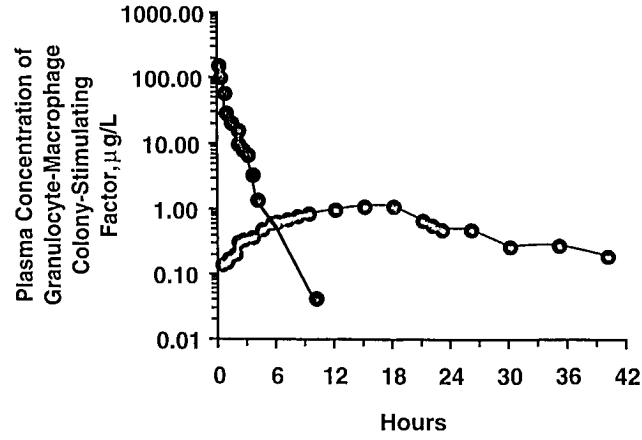

FIGURE 6–13 Plasma concentrations of glycosylated recombinant human granulocyte-macrophage colony-stimulating factor following intravenous (*black*) and subcutaneous (*color*) bolus injections of 8 µg/kg on separate occasions. *(Adapted from Hovgaard D, Mortensen BT, Schifter S, et al. Clinical pharmacokinetic studies of a human haemopoietic growth factor, GM-CSF. Duro J Clin Invest 1992;22:45–49.)*

by the intravenous route. However, one must take into account that nonvascular parenteral administration often results in reduced systemic bioavailability. Proteolytic enzymes are known to be present, particularly in lymph nodes, through which the protein drugs must pass. This is in contrast to small molecular drugs, which are almost always completely available systemically when given by these routes.

The speed of absorption, after both intramuscular and subcutaneous administration and for both small molecules and macromolecules, have been shown to be highly dependent on the site of injection, local temperature, and rubbing at the injection site, which increases movement of drug into both the vasculature and the lymphatic system.

For all routes of administration, consideration should be given to both the particular properties of the site of administration and the drug itself. For example, when given rectally, a drug is often not retained long enough for absorption to be complete. Nonetheless, the factors influencing absorption from this less conventional site are in common with those generally influencing absorption from oral, intramuscular, and subcutaneous sites.

ABSORPTION FROM SOLID DOSAGE FORMS

When a drug is taken orally in a solid dosage form, such as tablets or capsules, a number of processes must occur before it can be systemically available. The dosage form must disintegrate and deaggregate and the drug must dissolve, as shown in Fig. 6–14. Dissolution is a key factor, but not the only one. Table 6–5 summarizes factors that determine the release of a drug from a solid dosage form and the rate and extent of systemic absorption after an oral dose. The factors are classified into four groups, namely, release characteristics of the dosage form, physicochemical properties of drug, physiology of gastrointestinal tract, and presence of gastrointestinal tract abnormalities and diseases.

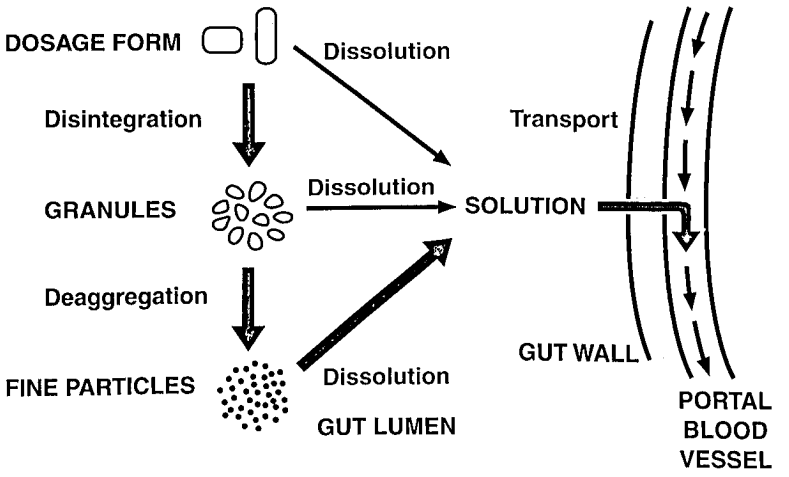

FIGURE 6–14 After oral administration of a typical immediate-release solid dosage form, tablet, or capsule, the product undergoes disintegration to granules. These granules further deaggregate to fine particles. Dissolution of drug occurs at all stages, but usually becomes predominant from the fine particles (see thickness of arrows). The drug, now in solution, must cross the membranes of the gastrointestinal tract to reach the mesenteric blood vessels, which carry the drug via the portal vein and liver to the systemic circulation.

TABLE 6–5 Factors Determining the Release and Absorption Kinetics of a Drug Following Oral Administration of a Solid Dosage Form

Release Characteristics of Dosage Form
Disintegration/deaggregation
Dissolution of drug from granules (also dependent on inactive ingredients and formulation variables)
Physicochemical Properties of Drug
Ionization (acid/base)
Partition coefficient (octanol/water)
Solubility in water
Physiology of Gastrointestinal Tract
Colonic retention
Gastric emptying
Intestinal motility
Perfusion of the gastrointestinal tract
Permeability of gut wall
Gastrointestinal Tract Abnormalities and Diseases
Crohn's disease
Gastric resection (e.g., in obesity)
Diarrhea

Dissolution

The reason why dissolution is so important may be gained by realizing that absorption following a solid requires drug dissolution.

$$\text{Drug in Product} \xrightarrow[\textit{Dissolution}]{} \text{Drug in solution} \xrightarrow[\textit{Absorption}]{} \text{Absorbed drug} \qquad \text{Eq. 6-16}$$

Two situations are now considered. The first, less common, depicted in Fig. 6–15A, is one in which dissolution is a much faster process than is absorption. Consequently, most of the drug is dissolved before an appreciable fraction is absorbed. Here, commonly, permeability rather than dissolution rate-limits absorption. An example is the gastrointestinal absorption of sucralfate, an agent used in treating gastric and intestinal ulcers, when given as a tablet. This polar drug dissolves rapidly from the tablet, but has difficulty penetrating the gastrointestinal epithelium. So, little drug is absorbed. The systemic input is **absorption rate–limited** due to poor permeability. Differences in rates of dissolution of sucralfate from different tablet formations have relatively little or no effect on the speed of systemic absorption of this drug.

In the second, and more common, situation shown in Fig. 6–15B, dissolution proceeds relatively slowly, and any dissolved drug readily traverses the gastrointestinal epithelium. Absorption cannot proceed any faster, however, than the rate at which the drug dissolves. That is, absorption is **dissolution rate–limited.** In this case, changes in dissolution profoundly affect the rate, and sometimes the extent, of drug absorption. Evidence supporting dissolution rate–limited absorption comes from the noticeably slower systemic absorption of most drugs from solid dosage forms than from a simple aqueous solution after oral administration. It also comes from modified-release dosage forms in which release, and therefore dissolution, is intentionally prolonged.

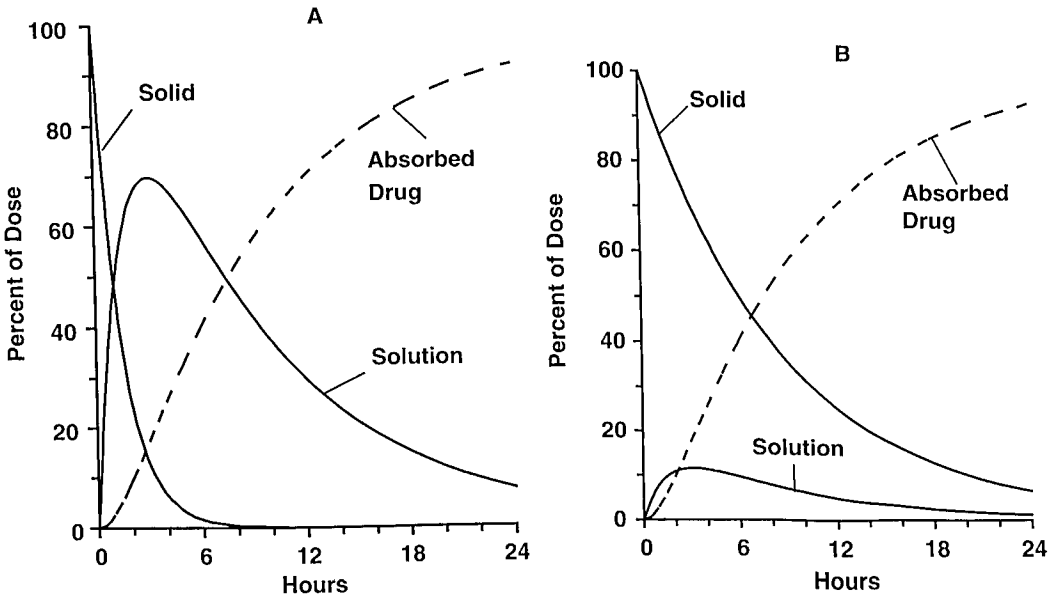

FIGURE 6–15 When absorption is permeability rate-limited (A), most of the drug has dissolved (*colored line*) in the gastrointestinal tract before an appreciable fraction has been absorbed. In contrast, when dissolution rate limits absorption (B), very little drug is in solution (*colored line*) at the absorption site at any time; drug is absorbed almost as soon as it dissolves. Notice that the majority of drug yet to be absorbed is always found at the rate-limiting step: in solution in Case A and as a solid in Case B.

Gastric Emptying and Intestinal Transit

Before discussing the role of gastric emptying on absorption of drugs given as solids, consider the information provided in Fig. 6–16. Shown are the mean transit times in the stomach and small intestine of small nondisintegrating pellets (diameters between 0.3 and 1.8 mm) and of large, single nondisintegrating units (either capsules, 25 mm by 9 mm; or tablets, 8 to 12 mm in diameter).

During fasting, gastric emptying of both small and large solids is seen, on average, to be rapid, with a mean time of around 1 hour, although there is considerable interindividual variability. In this state, the stomach displays a complex temporal pattern of motor activity with alternating periods of quiescence and moderate contraction of varying frequency, the "house-keeping wave," which moves material into the small intestine. The exact ejection time of a solid particle therefore depends on its size, when it is ingested during the motor activity cycle and where it is located within the stomach. The likelihood of ejection is greatest when the solid particle is in close proximity to the pyloric sphincter when the house-keeping wave occurs. Thus, even for small solid particles and fasting conditions, gastric emptying can vary from minutes to several hours.

The situation is very different after eating. As shown in Fig. 6–16, when taken on a fed stomach, the gastric transit time of solids is increased. This increase is greater after a heavy meal than after a light one and is much greater for a large single unit than for small pellets. For example, the mean gastric transit time among subjects for large single unit systems is now almost 7 hours, with some pellets still in the stomach in some subjects 11 hours after ingestion. These observations are explained by the sieving action of a fed stomach. Solids with diameters greater than 7 to 10 mm pass into the small

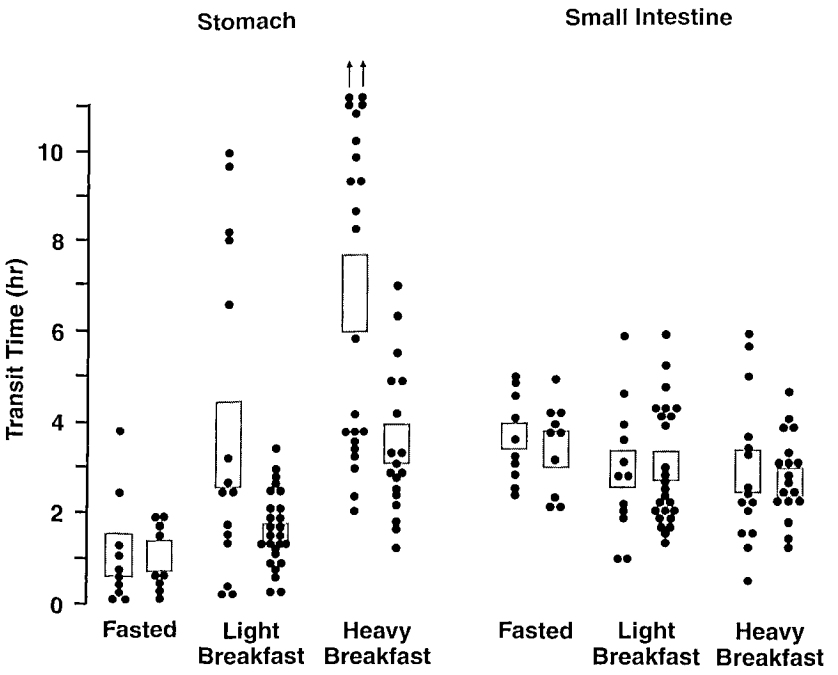

FIGURE 6–16 Food, particularly a heavy meal, increases the gastric transit time of small pellets (*black circles*) and, even more markedly, of large single pellets (*colored circles*). In contrast, neither food nor the physical size of the solid affects the small intestine transit time. The data (*individual points, black* or *colored circles,* and their mean ± S.E., indicated by the *rectangles*) were obtained in healthy young adults using drug-free nondisintegrating materials. The points with an arrow indicate the solid was still in the stomach at the time of the last observation, 16 hours. *(Adapted from Davis SS, Hardy JG, Fara J. Transit of pharmaceutical dosage forms through the small intestine. Gut 1986;27:886–892.)*

intestine more slowly and less predictably than those of small diameter. Some individuals consistently show prolonged gastric emptying of large pellets in the fed state, whereas for others it is much less apparent. These differences have largely been ascribed to interindividual differences in the size of the pyloric sphincter. This retention of large pellets is generally consistent with the physiologic role of the stomach, that is, to retain larger food particles until they are reduced in size to facilitate further digestion. With conventional tablets, rapid disintegration, and deaggregation into fine particles achieves the same objective. As long as the stomach remains in a fed state, the conditions above prevail. For those persons who eat three hearty meals a day with several snacks in between, gastric emptying of large pellets may be slowed most of the waking hours of the day.

In contrast to events in the stomach, the transit time of solids within the small intestine varies little among subjects, appears to be independent of either the size of a solid or the presence of food in the stomach, and is remarkably short, approximately 3 hours (Fig. 6–16), a time similar to that found for the transit of liquids. Both solids and liquids appear to move down the small intestine as a plug with relatively little mixing. As the mouth-to-anus transit time is typically 1 to 3 days, these data on gastric and small intestinal transit times indicate that, for the majority of this time, unabsorbed materials are in either the large bowel or rectum. Provided with the physiologic information above, the possible role of gastric emptying and intestinal transit on the absorption of drugs given in solid dosage forms can be understood. Consider the following situations.

Rapid Dissolution in Stomach

This is the common situation seen with many permeable and soluble drugs, such as ibuprofen and acetaminophen, in conventional immediate-release tablets and capsules. Drug dissolves so rapidly in the stomach that most of it is in solution before much of the drug has entered the intestine. Here, gastric emptying clearly influences the rate of drug absorption, but only to the extent that liquids and deaggregated particles are retained within the stomach. Thus, hastening gastric emptying quickens drug absorption in such circumstances.

Rapid Dissolution in Intestine

Sometimes, drug does not materially dissolve within the stomach, whereas in the intestine it rapidly both dissolves and moves across the intestinal wall. Gastric emptying then also affects the rate of drug absorption. An enteric-coated product is an extreme example of this situation. Erythromycin and penicillin G are rapidly hydrolyzed to inactive products in the acidic environment of the stomach. Salicylic acid is a gastric irritant. A solution to both types of problems has been to coat these drug products with a material resistant to acid but not to the intestinal fluids. If such enteric-coated products are large single tablets, the time taken for an intact tablet to pass from the stomach into the intestine varies unpredictably from 20 minutes to several hours when taken on an empty stomach, and up to 12 hours or even more when taken on a fed stomach (see Fig. 6–16). Accordingly, such enteric-coated products cannot be used when a rapid and reliable absorption is required. A product composed of enteric-coated granules is an improvement because the rate of delivery of the granules to the intestine is expected to be more reliable, being less dependent on a single event, a "house-keeping wave," and on food.

Poor Dissolution

Some drugs, such as the oral antifungal broad-spectrum anthelmintic, albendazole, are sparingly soluble or almost insoluble in both gastric and intestinal fluids. When these drugs are administered as a solid, there may already be insufficient time for complete dissolution and absorption. With a fixed short time within the small intestine, slow release from the stomach increases the time for drug to dissolve before entering the intestine, thereby favoring increased bioavailability. As mentioned, food—fat in particular—delays gastric emptying. This delay may be one of the explanations for the observed five-fold increase in the plasma concentration of albendazole sulfoxide, its primary metabolite, when parent drug is taken with a fatty meal. Subsequently, intestinal fluid and contents move into the large intestine and water is reabsorbed. The resulting compaction of the solid contents may severely limit further dissolution and hence absorption of such drugs.

Absorption From Other Sites

Drugs may be administered at virtually any site on or within the body. In recent years, there has been considerable interest in exploiting some of the less conventional sites, such as the lung, nasal cavity, and buccal cavity, as a means of delivering drugs systemically. Polypeptide and protein drugs have received particular attention, as shown in Table 6–6. Transdermal application has become popular for systemic delivery of small, generally lipophilic, potent molecules that require low input rates to achieve effective

TABLE 6–6 Examples of Unconventional Sites and Methods of Administration of Polypeptide and Protein Drugs

Polypeptide/Protein	Therapeutic Use[a]	Site and Method of Administration
Bacitracin zinc and polymyxin B sulfate (anti-infective agent)	Superficial ocular infections (local effect)	Eye. Application of ointment
Calcitonin-salmon (thyroid hormone that acts primarily on bone)	Postmenopausal osteoporosis (systemic effect)	Nasal spray. The relative bioavailability (compared with IM dose) is 3%
Desmopressin (synthetic form of antidiuretic hormone)	Primary nocturnal enuresis and diabetes insipidus (systemic effect)	Intranasal. Administered through a soft, flexible, plastic rhinal tube; also nasal spray
Dornase alfa (recombinant human deoxyribonuclease)	Cystic fibrosis (local effect)	Oral. Also, inhalation using nebulizer
Gladase (papain, a proteolytic enzyme, plus urea)	Removal of necrotic tissue (local effect)	Topical. Ointment applied directly to wound
Leuprolide acetate (naturally occurring gonadotropin-releasing hormone)	Advanced prostatic cancer (systemic effect)	Implant. Inserted subcutaneously on inner side of upper arm. Product constantly releases 120 μg per day and is replaced once yearly
Pancrelipase powder (lipase, protease, and amylase—digestive enzymes)	Cystic fibrosis (local intestinal effect)	Taken orally with meals.

[a]Therapeutic use and note on whether the effect is obtained locally or systemically.

therapy. Examples of transdermal and other transmembrane delivery systems are listed in Table 6–7.

ASSESSMENT OF PRODUCT PERFORMANCE

Formulation

Equality of drug content does not guarantee equality of response. The presence of different **excipients** (ingredients in addition to active drug) or different manufacturing processes may result in dosage forms containing the same amount of drug behaving differently in vivo. This is why testing for bioavailability of drug products is essential. Generally, the primary concern is with the extent of absorption. Variations in absorption rate with time may also be therapeutically important.

The major cause of differences in systemic absorption of a drug from various solid products is dissolution. There is, therefore, a strong need to control the content and purity of the numerous inactive ingredients used to stabilize the drug; to facilitate manufacture and maintain integrity of the dosage form during handling and storage; and to facilitate, or sometimes control, release of drug following administration of the dos-

TABLE 6–7 Examples of Transdermal Delivery Systems

Drug	Use	Delivery
Clonidine	Treatment of hypertension	Delivery of 0.1, 0.2, or 0.3 mg clonidine per day for 1 week
Estradiol	Estrogen replacement, menopause	Constant rate of delivery applied twice weekly to once weekly with 14–16 days off depending on indication.
Fentanyl	Continuous pain relief	Applied every 3 days
Norelgestromin/ ethinyl estradiol	Prevention of pregnancy	Weekly change of patch for 3 weeks. One week no patch
Oxybutynin	Treatment of overactive bladder	Applied every 3 to 4 days
Progesterone	Progesterone supplementation, secondary amenorrhea	Vaginally, twice daily for progesterone supplement, every other day for treating amenorrhea
Scopolamine	Motion sickness	Effect lasts for 3 days (1.0 mg delivered)
Testosterone Patch Gel Buccal system	Testosterone replacement therapy, male hypogonadism	Once daily application

age form. Intended or otherwise, each ingredient can influence the rate of dissolution of the drug, as can the manufacturing process. The result is a large potential for differences in absorption of drug among products. Indeed, a large variety of dosage forms of drugs are marketed in which release is intentionally delayed (lag in time when input starts) or extended (input over an extended time period). Such differences in release characteristics can be achieved without regard to the physicochemical properties of the drug. Key to the use of such products in vivo, however, is that the extent of absorption not be affected and that release rate limits systemic absorption. To maintain these properties for oral products, the drug must be highly permeable (high $P \cdot SA$ product) in both the small and large intestines.

Many factors influence the release of drug from a solid pharmaceutical formulation and therefore the rate and extent of systemic absorption. **Biopharmaceutics** is a comprehensive term used to denote the study of pharmaceutical formulation variables on the performance of a drug product in vivo.

Assessment of absorption is useful not only to determine the effect of formulation, but also to examine the effects of food, current drug administration, concurrent diseases of alimentary canal, and other conditions that may alter systemic absorption. One unique kind of bioavailability assessment, which is widely used, is that of **bioequivalence** testing.

Bioequivalence Testing

The purpose of bioequivalence testing is to be able to predict the clinical (therapeutic) outcome of the use of a new product of a drug, when the clinical trials used for collecting efficacy and safety data were obtained with another product of the same drug. The basic idea is that if the pharmaceutical products are equivalent and the pharmacokinetics in terms of the exposure-time profile (which reflects rate and extent of absorption) are sufficiently similar, then the therapeutic outcome should be the same; that is, the

products would show therapeutic equivalence. Another full clinical trial investigating efficacy and safety is thereby not necessary. In this sense, the bioequivalence trial serves as a surrogate for the full clinical trial. The major concern is prescribability, the ability of products to have the same therapeutic effect when therapy is started. Two products are considered to be bioequivalent if their concentration-time profiles are sufficiently similar so that they are unlikely to produce clinically relevant differences in either therapeutic or adverse effects. The common measures used to assess differences in exposure are *AUC*, C_{max}, and t_{max}.

In practice, C_{max} and t_{max} are estimated from the highest concentration measured and the time of its occurrence. As the plasma concentration-time curve is often flat near the peak and because of assay variability and infrequent sampling times, the value of t_{max} observed may not be a good representation of the actual value. Furthermore, the accuracy of the t_{max} estimate is statistically limited by samples being obtained only at discrete sampling times. Emphasis in bioequivalence testing is therefore placed on *AUC* and C_{max}.

Bioequivalence testing arises when a patent on an innovator's drug expires. Other manufacturers may then wish to market a similar formulation of the drug. Formulations that are pharmaceutically equivalent (contain the same drug, at the same dose, and dosage form, e.g., tablet) and also bioequivalent with that of the innovator's product and bearing the generic name of the drug are called **generic products.** Bioequivalence testing is also performed during the course of development of new drugs, for example, when a marketable tablet is developed but the original full clinical trial was conducted using another preparation, such as a capsule formulation.

A typical bioequivalence trial is conducted with a cross-over design (both treatments given to each subject on separate occasions and in random order). Usually about 24 to 36 healthy adult subjects are used. The test and reference products are given in single doses. The *AUC* and C_{max} are examined statistically. If the 90% confidence interval for the ratio of the measures in the generic or new product (test product) to the innovator's product or product used in full clinical trials (reference product) is within the limits of 0.8 and 1.25 for both *AUC* and C_{max}, the test product is declared to be bioequivalent.

The statistical methods applied in bioequivalence testing are different from those applied in bioavailability assessment. In bioavailability studies, questions often asked are ones such as: "Is the oral bioavailability of Drug X in tablet Formulation 1 different from that in tablet Formulation 2?," "Is the peak exposure following an oral solution greater than that after a capsule dosage form?" "What is the oral bioavailability and how confident are we in its estimate?" In bioequivalence testing, the question asked is: "Are the exposure measures (AUC and C_{max}) of the test product no less than 80% or no more than 125% of the reference product?" The question is not whether or not they are different, but whether or not they are sufficiently similar. The 80% and 125% values are the criteria used most commonly in regulatory guidances to define how similar the measures must be. The distinction between the two kinds of questions is emphasized in Fig 6–17.

We have now covered the critical determinants of the pharmacokinetics of drugs after a single dose administered intravenously and extravascularly. Such information now needs to be placed within the context of the responses produced after such administration, the content of the next chapter, *Response Following a Single Dose.*

SUMMARY

- Systemic absorption after extravascular administration is often modeled as a first-order process.

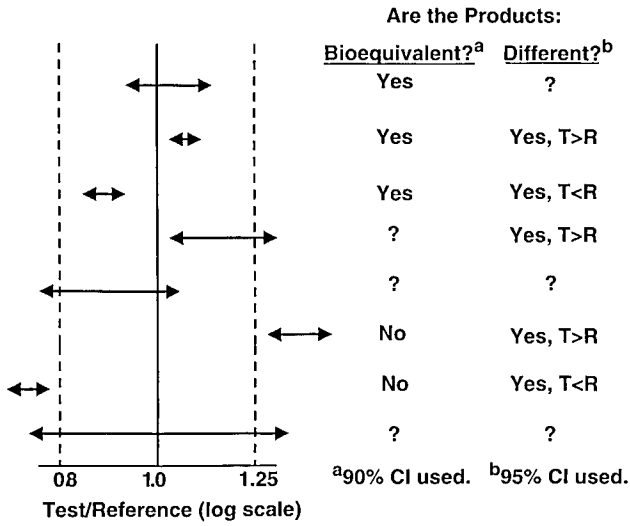

FIGURE 6-17 Declarations possible following the determination of confidence intervals (CI, *colored arrows*). In bioequivalence testing, the question is "Are the two products sufficiently similar to call them the same?" In bioavailability testing, the question is often "Do the products differ in their systemic delivery of the drug?" Note that the 90% CI is used in bioequivalence testing, whereas the 95% CI is typically used in difference testing. From a regulatory perspective, of the products tested only those that are bioequivalent to the innovator's product (reference) are permitted to be marketed.

- The plasma concentration-time profile after a single extravascular dose is characterized by a rise and a subsequent fall. The rise is a result of input being greater than elimination; the fall is the result of the converse.
- The bioavailability of a drug is determined from the areas under the curve after extravascular and intravascular administration, with correction for dose differences, if necessary.
- Systemic absorption after oral administration requires that a drug dissolve in the luminal fluids and traverse gastrointestinal membranes.
- Gastric emptying plays a major role in determining the rate and extent of systemic absorption after oral administration. Surface area, membrane permeability, and intestinal blood flow are additional primary determinants of systemic absorption.
- Low oral bioavailability can result from limited transit time in the gastrointestinal tract. This result applies to both highly polar (permeability rate-limited) and nonpolar (dissolution rate-limited) drugs. Decomposition due to low gastric pH, digestive enzymes, or enzymes of the colonic microflora also reduce systemic absorption. Metabolism within the gut wall and liver during the first-pass through these organs further reduces oral bioavailability.
- Systemic absorption from intramuscular and subcutaneous sites is rapid for small molecules (<5000 g/mol) whether polar or not. Macromolecules (>20,000 g/mol) primarily reach the systemic circulation via the lymphatics. This occurs, by default, because they more slowly cross blood capillary membranes.
- Bioavailability is usually 100% following subcutaneous and intramuscular administration for small molecules, but can be greatly reduced for protein drugs because of proteolytic activity within the lymphatic system.

- Bioequivalence testing is performed to determine whether the systemic exposure-time profiles following two different products of the same drug and dose are sufficiently similar to conclude that therapeutic equivalence is likely.

KEY TERM REVIEW

Absorption phase
Absorption rate–limited elimination
Amount remaining to be absorbed
Area under the curve (AUC)
Bioavailability
Bioequivalence
Biopharmaceutics
Delayed-release product
Disposition rate–limited elimination
Dissolution
Dissolution rate–limited absorption
Dosage forms
Drug product
Elimination phase
Excipients
Extravascular route
Extended-release product
First-order process
First-pass metabolism
Flip-flop
Formulation
Formulation (drug product)
Gastric emptying
Generic products
Hepatic extraction
Immediate-release product
Intramuscular injection
Intravascular route
Lag time
Lymphatic system
Macromolecules
Modified-release product
Paracellular transport
Peak plasma concentration
Permeability
Permeability rate–limited absorption
Permeability–surface area product
pH
Prodrugs
Rate-limiting step
Relative bioavailability
Solubility
Subcutaneous absorption
Systemic absorption
Time of peak plasma concentration
Transcellular transport
Transit time

STUDY PROBLEMS

Answers to study problems are in Appendix D.

1. List at least five reasons why oral bioavailability of drugs is often less than 100%.
2. The concentration-time profile following a single 25-mg oral dose of a drug is shown in Fig. 6-18. Draw on the plot the expected concentration-time profile (rough approximation) when:
   a. The extent of absorption is halved, but there is no change in absorption kinetics, that is, ka is constant. An example of this situation is one in which a drug, which undergoes extensive first-pass metabolism, is administered concurrently with another drug, which is an inducer of the first drug's metabolism.
   b. The absorption process is slowed (ka is 10 × smaller), but the extent of absorption (F) is the same. This situation might occur when the dosage form is changed, such as from a rapid-release to a slow-release product.

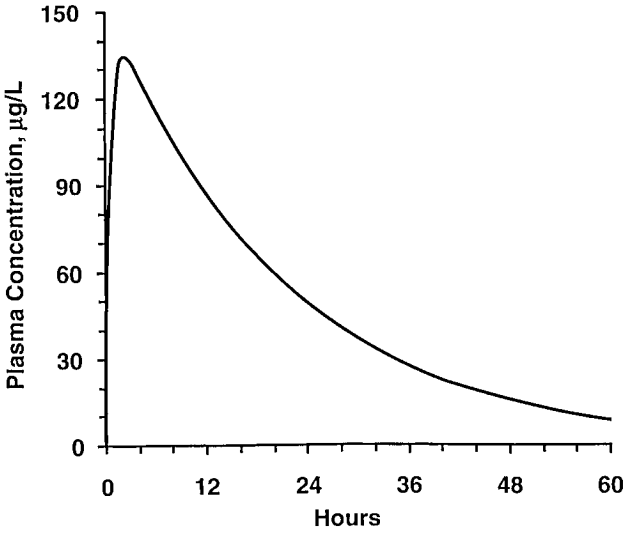

FIGURE 6–18

3. Briefly determine which of the following statements are correct or incorrect. For those that are ambiguous, supply a qualification.
   a. All other parameters remaining unchanged, the slower the absorption process, the higher is the peak plasma concentration after a single oral dose.
   b. For a given drug and subject, AUC is proportional to the amount of drug absorbed systemically.
   c. The absorption rate constant (ka) is smaller than the elimination rate constant (k). Therefore, the terminal decline of the plasma concentration versus time curve reflects absorption, not elimination.
   d. After a single oral dose, an increase in the extent of absorption causes the peak time to shorten.
   e. Zero-order absorption is characterized by a constant rate of drug input until no more drug remains to be absorbed.
4. Comment on the likely influence of a heavy meal, relative to the fasting state, on the rate and extent of oral absorption of a drug in each of the following cases. All of the drugs, except the one in Part c, are chemically stable in the gastrointestinal tract.
   a. A water-soluble highly permeable drug is administered in an immediate-release tablet.
   b. A sparingly soluble lipophilic drug is administered as an intended immediate-release capsule dosage form. Oral bioavailability is typically only 26% due to low solubility.
   c. An acid-labile drug is taken as a single enterically coated (resistant to acidic gastric pH) 0.8 g tablet.
5. The pharmacokinetics of sumatriptan, a serotonin receptor agonist used in treating migraine headaches, has been compared following subcutaneous, oral, rectal, and intranasal administration. Table 6–8 lists key observations following these four routes of administration.
   a. Calculate the bioavailability of sumatriptan following the oral tablet, rectal suppository, and nasal spray relative to that following subcutaneous administration.

TABLE 6–8 Total Systemic Exposure (*AUC*), Peak Exposure (C_{max}), Time of Peak Exposure (t_{max}), and Terminal Half-life of Sumatriptan Following Administration by the Subcutaneous, Oral, Rectal, and Intranasal Routes[a]

	Subcutaneous	Oral	Rectal	Intranasal
Dose administered (mg)	6	25	25	20
AUC (μg•hr/L)	90.3	52.2	71.6	47.8
C_{max} (μg/L)	69.5	16.5	22.9	12.9
t_{max} (hr)	0.17	1.5	1.0	1.5
Terminal $t_{1/2}$ (hr)	1.9	1.7	1.8	1.8

[a]Adapted from Duquesnoy C, Mamet JP, Sumner D, Fuseau E. Comparative clinical pharmacokinetics of single doses of sumatriptan following subcutaneous, oral, rectal, and intranasal administration. Eur J Pharm Sci 1998;6:99–104.

b. By completing the table below, compare the maximum plasma concentrations (C_{max}) and the ratio of the maximum concentration to the area under the curve (C_{max}/AUC) observed following an equivalent 25-mg dose of drug by the four routes of administration.

Observation	Subcutaneous Solution	Oral Tablet	Rectal Suppository	Nasal Spray
C_{max} (μg/L)[a]				
C_{max}/AUC (hr^{-1})[b]				

[a]Per 25 mg of sumatriptan.

[b]C_{max}/AUC has also been used as a measure of rate of drug input.

c. How would you explain the much higher values of C_{max} and C_{max}/AUC following the subcutaneous route without a change in half-life?