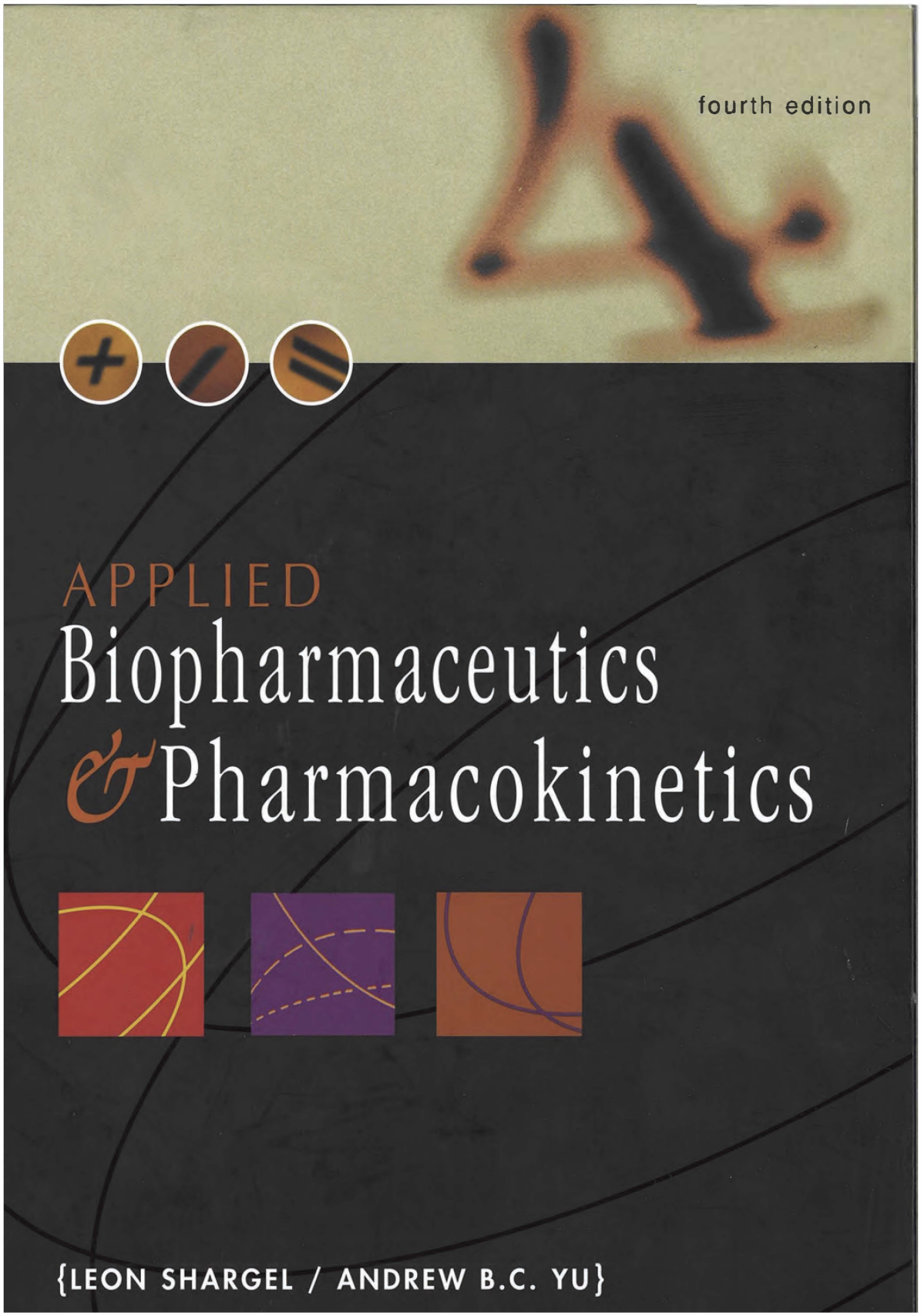


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2

INTRODUCTION TO BIOPHARMACEUTICS AND PHARMACOKINETICS

BIOPHARMACEUTICS

Biopharmaceutics considers the interrelationship of the physicochemical properties of the drug, the dosage form in which the drug is given, and the route of administration on the rate and extent of systemic drug absorption. Thus, biopharmaceutics involves factors that influence the (1) protection of the activity of the drug within the drug product, (2) the release of the drug from a drug product, (3) the rate of dissolution of the drug at the absorption site, and (4) the systemic absorption of the drug. Figure 2-1 is a general scheme describing this dynamic relationship.

The study of biopharmaceutics is based on fundamental scientific principles and experimental methodology. These methods must be able to assess the impact of the physical and chemical properties of the drug, drug stability and large scale production of the drug and drug product on the biological performance of the drug. Moreover, biopharmaceutics considers the requirements of the drug and dosage form in a physiological environment and the drug's intended therapeutic use and route of administration.

Studies in biopharmaceutics use both *in-vitro* and *in-vivo* methods. *In-vitro* methods are procedures employing test apparatus and equipment without involving laboratory animals or humans. *In-vivo* methods are more complex studies involving human subjects or laboratory animals. Some of these methods will be discussed in Chapter 5. Historically, pharmacologists evaluated the relative systemic drug availability *in vivo* after giving a drug product to an animal or human and then comparing specific pharmacologic, clinical, or possible toxic responses. For example, a drug such as isoproterenol causes an increase in heart rate when given intravenously but has no observable effect on the heart when given orally at the same dose level. Therefore, systemic drug availability may differ according to the route

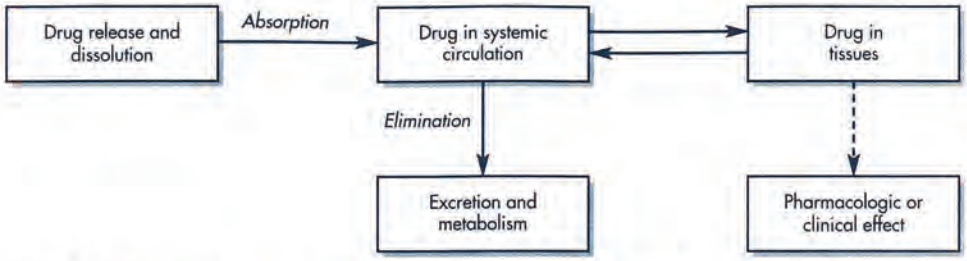


Figure 2-1. Scheme demonstrating the dynamic relationship between the drug, the drug product, and the pharmacologic effect.

of administration. In addition, the bioavailability (a measure of systemic availability of a drug) may differ from one drug product to another containing the same drug. This difference in drug bioavailability may be manifested by observing the difference in the therapeutic effectiveness of the drug products.

PHARMACOKINETICS

Pharmacokinetics involves the kinetics of drug absorption, distribution, and elimination (ie, excretion and metabolism). The description of drug distribution and elimination is often termed *drug disposition*. The study of pharmacokinetics involves both experimental and theoretical approaches. The experimental aspect of pharmacokinetics involves the development of biological sampling techniques, analytical methods for the measurement of drugs and metabolites, and procedures that facilitate data collection and manipulation. The theoretical aspect of pharmacokinetics involves the development of pharmacokinetic models that predict drug disposition after drug administration. The application of statistics is an integral part of pharmacokinetic studies. Statistical methods are used for pharmacokinetic parameter estimation and data interpretation. Statistical methods are applied to pharmacokinetic models to determine data error and structural model deviations. Mathematics and computer techniques form the theoretical basis of many pharmacokinetic methods. Classical pharmacokinetics is a study of theoretical models focusing mostly on model development and parameterization.

CLINICAL PHARMACOKINETICS

Clinical pharmacokinetics is the application of pharmacokinetic methods in drug therapy. Clinical pharmacokinetics involves a multidisciplinary approach to individually optimized dosing strategies based on the patient's disease state and patient-specific considerations. The study of clinical pharmacokinetics of drugs in disease states requires input from medical and pharmaceutical research. Table 2.1 is a list of 10 age-adjusted rates of death from 10 leading causes of death in the USA, 1993. The influence of many diseases on drug disposition is not adequately studied. Age, gender, genetic, and ethnic differences can also result in pharmacokinetic differences that may affect the outcome of drug therapy. The study of pharmacokinetic differences of drugs in various population groups is termed *population*

TABLE 2.1 Ratio of Age-Adjusted Death Rates, by Male/Female Ratio from the 10 Leading Causes of Death in the USA, 1993

DISEASE	RANK	MALE:FEMALE
Disease of heart	1	1.9
Malignant neoplasms	2	1.5
Cerebrovascular diseases	3	1.2
Chronic obstructive pulmonary diseases	4	1.6
Accidents and others*	5	2.6
Pneumonia and influenza	6	1.6
Diabetes mellitus	7	1.2
HIV infections	8	6.3
Suicide	9	4.4
Homicide and legal intervention	10	3.8

*Death due to adverse effects suffered as defined by CDC.

Source: CDC-MMWR (Morbidity and Mortality Weekly Report), March 1, 45:8, 1996.

pharmacokinetics (Sheiner and Ludden, 1992). Another important aspect of pharmacokinetics is *therapeutic drug monitoring* (TDM). When drugs with narrow therapeutic indices are used in patients, it is necessary to monitor plasma drug concentrations closely by taking periodic blood samples. The pharmacokinetic and drug analysis services necessary for safe drug monitoring are generally provided by the *clinical pharmacokinetic service* (CPKS). Some drugs frequently monitored are the aminoglycosides and anticonvulsants. Other drugs closely monitored are those used in cancer chemotherapy in order to minimize adverse side effects (Rodman and Evans, 1991).

PHARMACODYNAMICS

Pharmacodynamics refers to the relationship between the drug concentration at the site of action (receptor) and pharmacologic response, including biochemical and physiologic effects that influence the interaction of drug with the receptor. The interaction of a drug molecule with a receptor causes the initiation of a sequence of molecular events resulting in a pharmacologic or toxic response. Pharmacokinetic-pharmacodynamic models are constructed to relate plasma drug level to drug concentration in the site of action and establish the intensity and time course of the drug. Pharmacodynamics and pharmacokinetic-pharmacodynamic models are discussed more fully in Chapter 19.

TOXICOKINETICS AND CLINICAL TOXICOLOGY

Toxicokinetics is the application of pharmacokinetic principles to the design, conduct and interpretation of drug safety evaluation studies (Leal et al, 1993) and used in validating dose related exposure in animals. Toxicokinetic data aids in the interpretation of toxicologic findings in animals and extrapolation of the resulting data to humans. Toxicokinetic studies are performed in animals during preclinical drug development and may continue after the drug has been tested in clinical trials.

Clinical toxicology is the study of adverse effects of drugs and toxic substances (poisons) in the body. The pharmacokinetics of a drug in an over-medicated (intoxicated) patient may be very different from the pharmacokinetics of the same drug given in therapeutic doses. At very high doses, the drug concentration in the body may saturate enzymes involved in the absorption, biotransformation, or active renal secretion mechanisms thereby changing the pharmacokinetics from *linear* to *nonlinear* pharmacokinetics. Nonlinear pharmacokinetics is discussed in Chapter 16. Drugs frequently involved in toxicity cases include acetaminophen, salicylates, morphine and the tricylic antidepressants (TCA). Many of these drugs can be assayed conveniently by fluorescence immunoassay (FIA) kits.

MEASUREMENT OF DRUG CONCENTRATIONS

Sensitive, accurate, and precise analytical methods are available for the direct measurement of drugs in biologic samples, such as milk, saliva, plasma, and urine. Measurements of drug concentrations in these biological samples are generally validated so that accurate information is generated for pharmacokinetic and clinical monitoring. In general, chromatographic methods are more discriminating since chromatography separates the drug from other related materials that may cause assay interference.

Sampling of Biologic Specimens

Only a few biologic specimens may be obtained safely from the patient to gain information as to the drug concentration in the body. *Invasive* methods include sampling blood, spinal fluid, synovial fluid, tissue biopsy, or any biologic material that requires parenteral or surgical intervention in the patient. In contrast, *noninvasive* methods include sampling of urine, saliva, feces, expired air, or any biologic material that can be obtained without parenteral or surgical intervention. The measurement of drug concentration in each of these biologic materials yields different information.

Drug Concentrations in Blood, Plasma, or Serum

Measurement of drug concentration (levels) in the blood, serum, or plasma is the most direct approach to assessing the pharmacokinetics of the drug in the body. *Whole blood* contains the cellular elements including red blood cells, white blood cells, platelets, and various other proteins, such as albumin and globulins. In general, serum or plasma is used for drug measurement. To obtain *serum*, whole blood is allowed to clot and the serum is collected from the supernatant after centrifugation. *Plasma* is obtained from the supernatant of centrifuged whole blood to which an anticoagulant, such as heparin, has been added. Therefore, the protein content of serum and plasma is not the same. Plasma perfuses all the tissues of the body including the cellular elements in the blood. Assuming that a drug in the plasma is in dynamic equilibrium with the tissues, then changes in the drug concentration in plasma will reflect changes in tissue drug concentrations.

Plasma Level–Time Curve

The plasma level–time curve is generated by measuring the drug concentration in plasma samples taken at various time intervals after a drug product is administered.

The concentration of drug in each plasma sample is plotted on rectangular coordinate graph paper against the corresponding time at which the plasma sample was removed. As the drug reaches the general (systemic) circulation, plasma drug concentrations will rise up to a maximum. Usually absorption of a drug is more rapid than elimination. As the drug is being absorbed into the systemic circulation, the drug is distributed to all the tissues in the body and is also simultaneously being eliminated. Elimination of a drug can proceed by excretion or biotransformation or a combination of both.

The relationship of the drug level–time curve and various pharmacologic parameters for the drug is shown in Figure 2-2. MEC and MTC represent the *minimum effective concentration* and *minimum toxic concentration* of drug, respectively. For some drugs, such as those acting on the autonomic nervous system, it is useful to know the concentration of drug that will just barely produce a pharmacologic effect (ie, MEC). Assuming the drug concentration in the plasma is in equilibrium with the tissues, the MEC reflects the minimum concentration of drug needed at the receptors to produce the desired pharmacologic effect. Similarly, the MTC represents the drug concentration needed to just barely produce a toxic effect. The *onset time* corresponds to the time required for the drug to reach the MEC. The *intensity* of the pharmacologic effect is proportional to the number of drug receptors occupied, which is reflected in the observation that higher plasma drug concentrations produce a greater pharmacologic response, up to a maximum. The *duration* of drug action is the difference between the onset time and the time for the drug to decline back to the MEC.

In contrast, the pharmacokineticist can also describe the plasma level–time curve in terms of such pharmacokinetic terms as peak plasma level, time for peak plasma level, and area under the curve, or AUC (Fig. 2-3). The time of peak plasma level is the time of maximum drug concentration in the plasma and is a rough marker of average rate of drug absorption. The peak plasma level or maximum drug con-

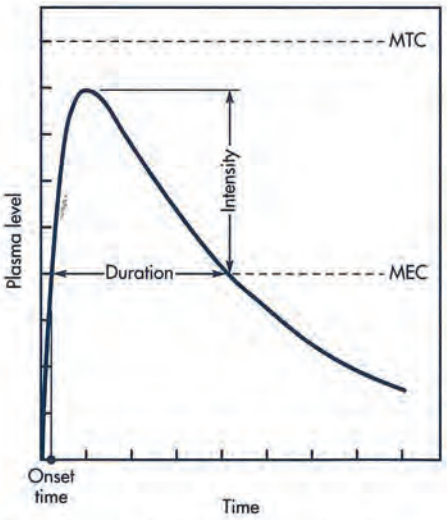


Figure 2-2. Generalized plasma level–time curve after oral administration of a drug.

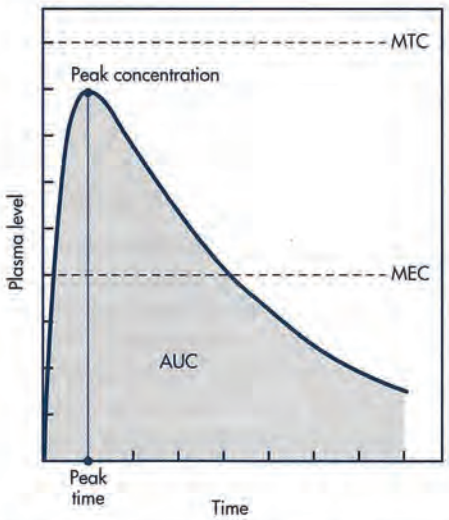


Figure 2-3. Plasma level–time curve showing peak time and concentration. The shaded portion represents the AUC (area under the curve).

centration is related to the dose, the rate constant for absorption, and elimination constant of the drug. The AUC is related to the amount of drug absorbed systemically. These and other pharmacokinetic parameters are discussed in succeeding chapters.

Drug Concentrations in Tissues

Tissue biopsies are occasionally removed for diagnostic purposes such as the verification of a malignancy. Usually, only a small sample of tissue is removed, making drug concentration measurement difficult. Drug concentrations in tissue biopsies may not reflect drug concentration in other tissues nor drug concentration in the tissue from which the biopsy material was removed. For example, if the tissue biopsy was for the diagnosis of a tumor within the tissue, the blood flow to the tumor cells may not be the same as the blood flow to other cells in this tissue. In fact, for many tissues, blood flow to one part of the tissues need not be the same as the blood flow to another part of the same tissue. The measurement of the drug concentration in tissue biopsy material may be used to ascertain if the drug reached the tissues and obtained the proper concentration within the tissue.

Drug Concentrations in Urine and Feces

Measurement of drug in *urine* is an indirect method to ascertain the bioavailability of a drug. The rate and extent of drug excreted in the urine reflects the rate and extent of systemic drug absorption. The use of urinary drug excretion measurements to establish various pharmacokinetic parameters is discussed in Chapter 10.

Measurement of drug in *feces* may reflect drug that has not been absorbed after an oral dose or may reflect drug that has been expelled by biliary secretion after systemic absorption. Fecal drug excretion is often performed in mass balance studies in which the investigator attempts to account for the entire dose given to the patient. For a mass balance study, both urine and feces are collected and their drug content measured. For certain solid oral dosage forms that do not dissolve in the gastrointestinal tract but slowly leach out drug, fecal collection is performed to recover the dosage form. The undissolved dosage form is then assayed for residual drug.

Drug Concentrations in Saliva

Saliva drug concentrations have been reviewed for many drugs for therapeutic drug monitoring (Pippenger and Massoud, 1984). Because only free drug diffuses into the saliva, saliva drug levels tend to approximate free drug rather than total plasma drug concentration. The saliva/plasma drug concentration ratio is less than 1 for many drugs. The saliva/plasma drug concentration ratio is mostly influenced by the pKa of the drug and pH of the saliva. Weak acid drugs and weak base drugs with pKa significantly different than pH 7.4 (plasma pH) generally have better correlation to plasma drug levels. The saliva drug concentrations taken after equilibrium with the plasma drug concentration generally provide more stable indication of drug levels in the body. The use of salivary drug concentrations as a therapeutic indicator should be used with caution and preferably used as a secondary indicator.

Forensic Drug Measurements

Forensic science is the application of science to personal injury, murder, and other legal proceedings. Drug measurements in tissues obtained at autopsy or in other bodily fluids such as saliva, urine, and blood may be useful if the person has taken an overdose of a legal medication, has been poisoned, or has been using drugs of abuse such as opiates (eg, heroin), cocaine or marijuana. The appearance of social drugs in blood, urine, and saliva drug analysis show short-term drug abuse. These drugs may be eliminated rapidly, making it more difficult to prove that the subject has been using drugs of abuse. The analysis for drugs of abuse in hair samples by very sensitive assay methods, such as gas chromatography coupled with mass spectrometry, provides information regarding past drug exposure. A recent study (Cone et al, 1993) showed that the hair samples from subjects who were known drug abusers contained cocaine and 6-acetylmorphine, a metabolite of heroine (diacetylmorphine).

Significance of Measuring Plasma Drug Concentrations

The intensity of the pharmacologic or toxic effect of a drug is often related to the concentration of the drug at the receptor site, usually located in the tissue cells. Because most of the tissue cells are richly perfused with tissue fluids or plasma, checking the plasma drug level is a responsive method of monitoring the course of therapy.

Clinically, individual variations in the pharmacokinetics of drugs are quite common. Monitoring the concentration of drugs in the blood or plasma ascertains that the calculated dose actually delivers the plasma level required for therapeutic effect. With some drugs, receptor sensitivity in individuals varies so that monitoring of plasma levels is needed to distinguish the patient who is receiving too much of a drug from the patient who is supersensitive to the drug. Moreover, the patient's physiologic functions may be affected by disease, nutrition, environment, concurrent drug therapy, and other factors. Pharmacokinetic models allow more accurate interpretation of the relationship between plasma drug levels and pharmacologic response. In the absence of pharmacokinetic information, plasma drug levels are relatively useless in dosage adjustment. For example, suppose a single blood sample from a patient was assayed and found to contain 10 μg/mL. According to the literature, the maximum safe concentration of this drug is 15 μg/mL. In order to apply this information properly, it is important to know when the blood sample was drawn, what dose of the drug was given, and the route of administration. If the proper information is available, the use of pharmacokinetic equations and models may describe the blood level–time curve accurately.

Monitoring of plasma drug concentrations allows for the adjustment of the drug dosage in order to individualize and optimize therapeutic drug regimens. In the presence of alteration in physiologic functions due to disease, monitoring plasma drug concentrations may provide a guide to the progress of the diseased state and enable the investigator to modify the drug dosage accordingly. Clinically, sound medical judgment and observation are most important. Therapeutic decisions should not be based solely on plasma drug concentrations.

In many cases, the pharmacodynamic response to the drug may be more important to measure than just the plasma drug concentration. For example, the electrophysiology of the heart including an electrocardiogram (ECG) is important to

assess in patients medicated with cardiotonic drugs such as digoxin. For an anticoagulant drug, such as dicumarol, prothrombin clotting time may indicate whether proper dosage was achieved. Most diabetic patients taking insulin will monitor their own blood or urine glucose levels.

For drugs that act irreversibly at the receptor site, plasma drug concentrations may not accurately predict pharmacodynamic response. Drugs used in cancer chemotherapy often interfere with nucleic acid or protein biosynthesis to destroy tumor cells. For these drugs, the plasma drug concentration does not relate directly to the pharmacodynamic response. In this case, other pathophysiologic parameters and side effects are monitored in the patient to prevent adverse toxicity.

BASIC PHARMACOKINETICS AND PHARMACOKINETIC MODELS

Basic pharmacokinetics involves the quantitative study of various kinetic processes of drug disposition in the body. The biological nature of drug distribution and disposition is complex, and drug events often happen simultaneously. Basic pharmacokinetics requires (1) a thorough knowledge of anatomy and physiology and (2) an understanding of the concepts and limitations of mathematical models.

Drugs are in a dynamic state within the body. A *model* is a *hypothesis* using mathematical terms to concisely describe quantitative relationships. Simplifying assumptions are made to describe a complex biologic system concerning the movement of drugs. Various mathematical models can be devised to simulate the rate processes of drug absorption, distribution, and elimination. These mathematical models make possible the development of equations to describe drug concentrations in the body as a function of time.

The predictive capability of a model lies in the proper selection and development of mathematical function(s) that parameterize the essential factors governing the kinetic process. The key parameters in a process is commonly estimated by fitting the model to the experimental data known as *variables*. A pharmacokinetic function relates an *independent* variable to a *dependent* variable. For example, a model may predict the drug concentration in the liver 1 hour after an oral administration of a 20 mg dose. The independent variable is time and the dependent variable is the drug concentration in the liver. Based on a set of time versus drug concentration data, a model equation is derived to predict the liver drug concentration with respect to time. The drug concentration depends on the time after the administration of the dose.

A model may be *empirically* or *physiologically* based. The model that simply interpolates the data and allows an empirical formula to estimate drug level over time is justified when limited information is available. Empirical models are practical but not very useful in explaining the mechanism of the actual process by which the drug is absorbed, distributed and eliminated in the body.

Physiologically based models also have limitations. Using the example above and apart from the necessity to sample tissue and monitor blood flow to the liver *in vivo*, the investigator needs to understand the following questions. What does liver drug concentration mean? Should the drug concentration in the blood within the tissue be determined and subtracted from the drug in the liver tissue? What type of cell is representative of the liver if a selective biopsy liver tissue sample can be collected without contamination from its surroundings? Indeed, depending on the

spatial location of the liver tissue from the hepatic blood vessels, tissue drug concentrations can differ. Moreover, changes in the liver blood perfusion will alter the tissue drug concentration. If the heterogeneous liver tissue is homogenized and assayed, the homogenized tissue only represents a hypothetical concentration that matches no real liver tissue. Most generated pharmacokinetic information depends on the method of tissue sampling, timing of the sample, drug analysis, and the predictive model selected. The need to approximate the real system (assuming uniformity within a given space or region) with a model is necessary and rational. Assumptions are inherent in all pharmacokinetic models even when a physiologic model is considered. A detailed physiologic model is more difficult but can reveal organ-specific or suborgan-regional information. In general, most pharmacokinetic models assume that the plasma drug concentration reflects drug concentrations globally within the body. Based on knowledge of the physiologic and biochemical composition of the body organs, the drug concentration in the liver may be estimated by knowing the liver extraction ratio for the drug.

A great number of models have been developed to estimate regional and global information about drug disposition in the body. Some physiologic pharmacokinetic models are discussed in Chapter 20. Pharmacokinetic processes are discussed in separate chapters under the topics of drug absorption, drug distribution, drug elimination, and pharmacokinetic drug interactions involving one or all the above processes. Theoretically, an unlimited number of models may be constructed to describe the kinetic processes of drug absorption, distribution, and elimination in the body depending on the degree of detailed information considered. Practical considerations have limited the growth of new pharmacokinetic models.

For example, assume a drug is given by intravenous injection and that the drug rapidly dissolves (distributes) in the body fluids. A pharmacokinetic model that describes this situation is a tank containing a volume of fluid that is rapidly equilibrated with the drug. In the human body, a fraction of the drug would be continually eliminated as a function of time (Fig. 2-4). The concentration of the drug in the tank after a given dose is governed by two parameters: (1) the fluid volume of the tank that will dilute the drug, and (2) the elimination rate of drug per unit of time. In pharmacokinetics, these parameters are assumed to be constants. If a known set of drug concentrations in the tank is determined at various time intervals, then the volume of fluid in the tank and the rate of drug elimination can be estimated.

Because drug concentrations is dependent on time, the two variables in this example, drug concentration and time, are called *dependent* and *independent* variables, respectively. In practice, pharmacokinetic parameters are determined experimentally from a set of drug concentrations collected over various times known as *data*. The number of parameters needed to describe the model depends on the complexity of the process and on the route of drug administration. In general, as the number of parameters that need to be evaluated increases, accurate estimation of these parameters becomes increasingly more difficult. With complex pharmacokinetic models, computer programs are used to facilitate parameter estimation.

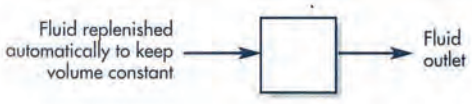


Figure 2-4. Tank with a constant volume of fluid equilibrated with drug. The volume of the fluid is 1.0 L. The fluid outlet is 10 mL/min. The fraction of drug removed per unit of time is 10/1000, or 0.01 min^{-1}.

However, for the parameters to be valid, the number of data points should always exceed the number of parameters in the model.

Pharmacokinetic models are used to:

1. Predict plasma, tissue, and urine drug levels with any dosage regimen.
2. Calculate the optimum dosage regimen for each patient individually.
3. Estimate the possible accumulation of drugs and/or metabolites.
4. Correlate drug concentrations with pharmacologic or toxicologic activity.
5. Evaluate differences in the rate or extent of availability between formulations (bioequivalence).
6. Describe how changes in physiology or disease affect the absorption, distribution, or elimination of the drug.
7. Explain drug interactions.

Because a model is based on a hypothesis and simplifying assumptions, a certain degree of caution is necessary when relying totally on the pharmacokinetic model to predict drug action. For some drugs, plasma drug concentrations are not useful in predicting drug activity. For other drugs, disease state and compensatory response from the body may modify the response of a drug. If a simple model does not fit accurately all the experimental observations, a new, more elaborate model may be proposed and subsequently tested. Since limited data are generally available in most clinical situations, pharmacokinetic data should be interpreted along with clinical observations rather than replacing sound judgment by the clinician. Development of pharmacometric, statistical models may help to improve prediction of drug levels among patients in the population (Sheiner and Beal, 1982; Mallet et al, 1988). However, it will be some time before these methods become generally accepted.

Compartment Models

The body can be represented as a series, or systems, of compartments that communicate reversibly with each other. A compartment is not a real physiologic or anatomic region but is considered as a tissue or group of tissues that have similar blood flow and drug affinity. Within each compartment, the drug is considered to be uniformly distributed. Mixing of the drug within a compartment is rapid and homogeneous and is considered to be "*well stirred*," so that the drug concentration represents an average concentration, and each drug molecule has an equal probability of leaving the compartment. Compartment models are based on linear assumptions using linear differential equations.

Conceptually, drugs move dynamically in and out of compartments. Rate constants are used to represent the overall rate processes of drug entry into and exit from the compartment. The model is an open system since drug can be eliminated from the system.

A compartmental model provides a simple way of grouping all the tissues into one or more compartments where drugs move to and from the central or plasma compartment. At any time, the amount of drug in the body is simply the sum of drug present in the central compartment plus the drug present in the tissue compartment. Although the tissue compartment does not represent a specific tissue, the mass balance accounts for the drug present in all the tissues. Knowing the parameters of the two-compartment model, one can estimate the amount of drug left in the body and the amount of drug eliminated from the body at any time. The compartmental models are particularly useful when there is little information known about the tissues.

If the tissue drug concentrations and binding are known, physiologic pharmacokinetic models, which are based on actual tissues and blood flow, describe the data more realistically. Physiologic pharmacokinetic models are frequently used in describing drug distribution in animals, because tissue samples are easily available for assay. On the other hand, tissue samples are often not available for human subjects, and approximations are often made in applying physiologic models to humans. Compartmental models form the basis of physiologic and other advanced models. Unlike physiological models, parameters, such as half-life, are kinetically determined from the data. In contrast, most physiological models assume an average set of blood flow for individual subjects, a major disadvantage in trying to predict individualized dosing.

Mammillary Model

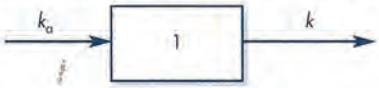
The mammillary model is the most common compartment model used in pharmacokinetics. The model consists of one or more peripheral compartments connected to a central compartment. The central compartment is assigned to represent plasma and highly perfused tissues which rapidly equilibrate with drug. The mammillary model is a strongly connected system since one can estimate the amount of drug in any compartment of the system after drug is introduced into a given compartment. When an intravenous dose of drug is given, the drug enters directly into the central compartment. Elimination of drug occurs from the central compartment since the organs involved in drug elimination, primarily kidney and liver, are well-perfused tissues.

Several types of compartment models are described in Figure 2-5. The pharmacokinetic rate constants are represented by the letter k. Compartment 1 represents the plasma or central compartment, and compartment 2 represents the tissue

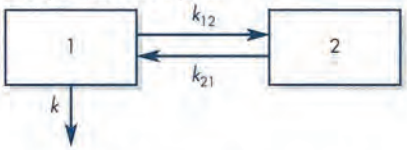
MODEL 1. One-compartment open model, IV injection.



MODEL 2. One-compartment open model with first-order absorption.



MODEL 3. Two-compartment open model, IV injection.



MODEL 4. Two-compartment open model with first-order absorption.

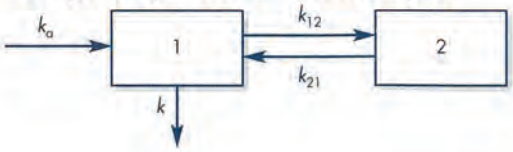


Figure 2-5. Various compartment models.

compartment. The drawing of models has three functions. The model (1) enables the pharmacokineticist to write differential equations to describe drug concentration changes in each compartment, (2) gives a visual representation of the rate processes, and (3) shows how many pharmacokinetic constants are necessary to describe the process adequately.



EXAMPLE

Two parameters are needed to describe model 1 (Fig. 2-5): the volume of the compartment and the elimination rate constant, k. In the case of model 4, the pharmacokinetic parameters consist of the volumes of compartments 1 and 2 and the rate constants—k_a, k, k_{12}, and k_{21}—for a total of six parameters.

In studying these models, it is important to know whether drug concentration data may be sampled directly from each compartment. For models 3 and 4 (Fig. 2-5), data concerning compartment 2 cannot be obtained easily because tissues are not easily sampled and may not contain homogeneous concentrations of drug. If the amount of drug absorbed and eliminated per unit time is obtained by sampling compartment 1, then the amount of drug contained in the tissue compartment 2 can be estimated mathematically. The appropriate mathematical equations for describing these models and evaluating the various pharmacokinetic parameters are given in the succeeding chapters.

Catenary Model

In pharmacokinetics, the mammillary model must be distinguished from another type of compartmental model called the *catenary* model. The catenary model consists of compartments joined to one another like the compartments of a train (Fig. 2-6). In contrast, the mammillary model consists of one or more compartments around a central compartment like satellites. Because the catenary model does not apply to the way most functional organs in the body are directly connected to the plasma, it is not used as often as the mammillary model.

Physiologic Pharmacokinetic Model (Flow Model)

Physiologic pharmacokinetic models, also known as blood flow or perfusion models, are pharmacokinetic models based on known anatomic and physiologic data. The models kinetically describe the data with the consideration that blood flow is

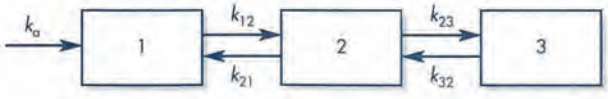


Figure 2-6. Example of catenary model.

responsible for distributing drug to various parts of the body. Uptake of drug into organs is determined by the binding of drug in these tissues. In contrast to an estimated tissue volume of distribution, the actual tissue volume is used. Because there are many tissue organs in the body, each tissue volume must be obtained and its drug concentration described. The model would potentially predict realistic tissue drug concentrations, which the two-compartment model fails to do. Unfortunately, much of the information required for adequately describing a physiologic pharmacokinetic model are experimentally difficult to obtain. In spite of this limitation, the physiologic pharmacokinetic model does provide a much better insight into how physiologic factors may change drug distribution from one animal species to another. Other major differences are described below.

First, no data fitting is required in the perfusion model. Drug concentrations in the various tissues are predicted by organ tissue size, blood flow, and experimentally determined drug tissue–blood ratios (ie, partition of drug between tissue and blood).

Second, blood flow, tissue size, and the drug tissue–blood ratios may vary due to certain pathophysiologic conditions. Thus, the effect of these variations on drug distribution must be taken into account in physiologic pharmacokinetic models.

Third, and most important of all, physiologically based pharmacokinetic models can be applied to several species, and, for some drugs, human data may be extrapolated. Extrapolation from animal data is not possible with the compartment models, because the volume of distribution in such models is a mathematical concept that does not relate simply to blood volume and blood flow. To date, numerous drugs (including digoxin, lidocaine, methotrexate, and thiopental) have been described with perfusion models. Tissue levels of some of these drugs cannot be predicted successfully with compartment models, although they generally describe blood levels well. An example of a perfusion model is shown in Figure 2-7.

The number of tissue compartments in a perfusion model varies with the drug. Typically, the tissues or organs that have no drug penetration are excluded from

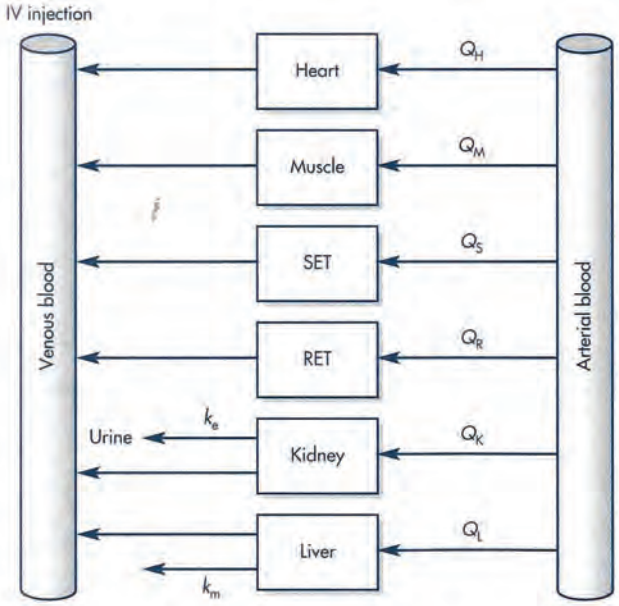


Figure 2-7. Pharmacokinetic model of drug perfusion. The *k*s represent kinetic constants: k_e is the first-order rate constant for urinary drug excretion and k_m is the rate constant for hepatic elimination. Each "box" represents a tissue compartment. Organs of major importance in drug absorption are considered separately, while other tissues are grouped as RET (rapidly equilibrating tissue) and SET (slowly equilibrating tissue). The size or mass of each tissue compartment is determined physiologically rather than by mathematical estimation. The concentration of drug in the tissue is determined by the ability of the tissue to accumulate drug as well as by the rate of blood perfusion to the tissue, represented by *Q*.

consideration. Thus, such organs as the brain, the bones, and other parts of the central nervous system are often excluded, as most drugs have little penetration into these organs. To describe each organ separately with a differential equation would make the model very complex and mathematically difficult. A simpler but equally good approach is to group all the tissues with similar blood perfusion properties into a single compartment. A perfusion model has been successfully used to describe the distribution of lidocaine in blood and various organs. In this case, organs such as lung, liver, brain, and muscle were individually described by differential equations, whereas other tissues were grouped as RET (rapidly equilibrating tissue) and SET (slowly equilibrating tissue), as shown in Figure 2-7. Figure 2-8 shows that the blood concentration of lidocaine declines biexponentially and was well predicted by the physiologic model based on blood flow. The tissue lidocaine level in the lung, muscle, and adipose and other organs is shown in Figure 2-9. The model shows that adipose tissue accumulates drugs slowly because of low blood supply. In contrast, vascular tissues, like the lung, equilibrate rapidly with the blood and start to decline as soon as drug level in the blood starts to fall. The physiologic pharmacokinetic model provides a realistic means of modeling tissue drug levels. Unfortunately, the simulated tissues levels in Figure 2-9 cannot be verified in humans because drug levels in tissues are not available. A criticism of physiologic pharmacokinetic models in general has been that there are fewer data points than parameters that one tries to fit. Consequently, the projected data are not well constrained.

The systems of different equations that describe drug distribution are usually solved by numerical integration. With the model as a base, the entire time course of drug levels in various tissue organs can be simulated.

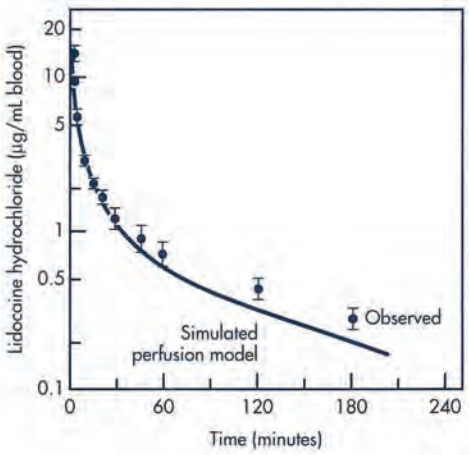


Figure 2-8. Observed mean (●) and simulated (—) arterial lidocaine blood concentrations in normal volunteers receiving 1 mg/kg per min constant infusion for 3 minutes.
(From Benowitz et al 1974, with permission; data from Tucker GT, Boas RA: *Anesthesiology* 34:538, 1971.)

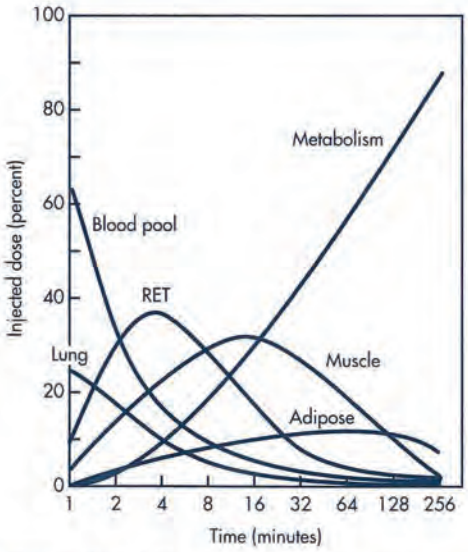


Figure 2-9. Perfusion model simulation of the distribution of lidocaine in various tissues and its elimination from humans following an intravenous infusion for 1 minute.
(From Benowitz et al 1974, with permission.)

The real significance of the physiologically based model is the potential application of this model in the prediction of human pharmacokinetics from animal data (Sawada et al, 1985). The mass of various body organs or tissues, extent of protein binding, drug metabolism capacity, and blood flow in humans and other species are often known or can be determined. Thus, physiologic and anatomic parameters can be used to predict the effects of drugs on humans from the effects on animals in cases where human experimentation is difficult or restricted.



FREQUENTLY ASKED QUESTIONS

1. Why is plasma or serum drug concentration used to monitor drug concentration in the body rather than blood concentration?
2. What are reasons to use multicompartment model instead of physiologic model?
3. At what time should plasma drug concentration be taken in order to best predict drug response and side effect?



LEARNING QUESTIONS

1. What is the significance of the plasma level–time curve? How does the curve relate to the pharmacologic activity of a drug?
2. What is the purpose of pharmacokinetic models?
3. Draw a diagram describing a three-compartment model with first-order absorption and drug elimination from compartment 1.
4. The pharmacokinetic model presented in Figure 2-10 represents a drug that is eliminated by renal excretion, biliary excretion, and drug metabolism. The metabolite distribution is described by a one-compartment open model. The following questions pertain to Figure 2-10.
   a. How many parameters are needed to describe the model if the drug is injected intravenously (ie, the rate of drug absorption may be neglected)?
   b. Which compartment(s) can be sampled?
   c. What would be the overall elimination rate constant for elimination of drug from compartment 1?
   d. Write an expression describing the rate of change of drug concentration in compartment 1 (dC_1/dt).
5. Give two reasons for the measurement of the plasma drug concentration, C_p assuming (a) the C_p relates directly to the pharmacodynamic activity of the drug and (b) the C_p does *not* relate to the pharmacodynamic activity of the drug.

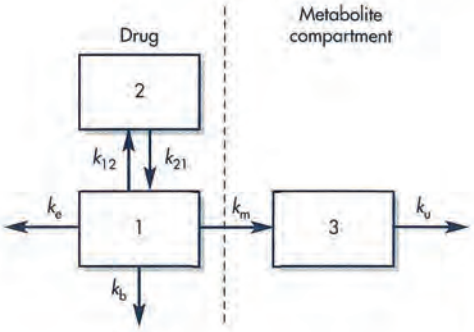


Figure 2-10. Pharmacokinetic model for a drug eliminated by renal and biliary excretion and drug metabolism. k_m = rate constant for metabolism of drug; k_u = rate constant for urinary excretion of metabolites; k_b = rate constant for biliary excretion of drug; and k_e = rate constant for urinary drug excretion.

6. Consider two biologic compartments separated by a biologic membrane. Drug A is found in compartment 1 and in compartment 2 in a concentration of c_1 and c_2, respectively.

a. What possible conditions or situations would result in concentration $c_1 > c_2$ at equilibrium?

b. How would you experimentally demonstrate these conditions given above?

c. Under what conditions would $c_1 = c_2$ at equilibrium?

d. The total amount of Drug A in each biologic compartment is A_1 and A_2, respectively. Describe a condition in which $A_1 > A_2$, but $c_1 = c_2$ at equilibrium.

Include in your discussion, how the physicochemical properties of Drug A or the biologic properties of each compartment might influence equilibrium conditions.

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is reached between the plasma and the tissue, the tissue drug concentration would be the same as the plasma. Do you agree?

e. Which tissues may be predicted by the tissue compartment?

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5

PHYSIOLOGIC FACTORS RELATED TO DRUG ABSORPTION

The systemic absorption of a drug is dependent upon (1) the physicochemical properties of the drug, (2) the nature of the drug product, and (3) the anatomy and physiologic functions at the site of drug absorption. All of these considerations are important in the manufacture and biopharmaceutic evaluation of drug products (Chapter 6). This chapter will focus on the anatomic and physiologic considerations for the systemic absorption of a drug. A thorough understanding of the physiologic and pathologic factors affecting drug absorption is important in drug product selection and in the avoidance of potential drug–drug and drug–nutrient interactions.

NATURE OF THE CELL MEMBRANE

For systemic absorption, a drug must pass from the absorption site through or around one or more layers of cells to gain access into the general circulation. The permeability of a drug at the absorption site into the systemic circulation is intimately related to the molecular structure of the drug and to the physical and biochemical properties of the cell membranes. For absorption into the cell, a drug must traverse the cell membrane.

Transcellular absorption is the process of a drug movement across a cell. Some polar molecules may not be able to traverse the cell membrane, but instead, go through gaps or "*tight junctions*" between cells, a process known as *paracellular drug absorption*. Figure 5-1 shows the difference of the two processes. Some drugs are probably absorbed by a mixed mechanism involving one or more processes.

Membranes are a major structure in cells, surrounding the entire cell (plasma membrane) and acting as a boundary between the cell and the interstitial fluid. In addition, membranes enclose most of the cell organelles (eg, the mitochondrion membrane). Functionally, membranes act as a selective barrier to the passage of molecules. Cell membranes are semipermeable membranes. Water, some selected small molecules, and lipid-soluble molecules pass through such membranes,

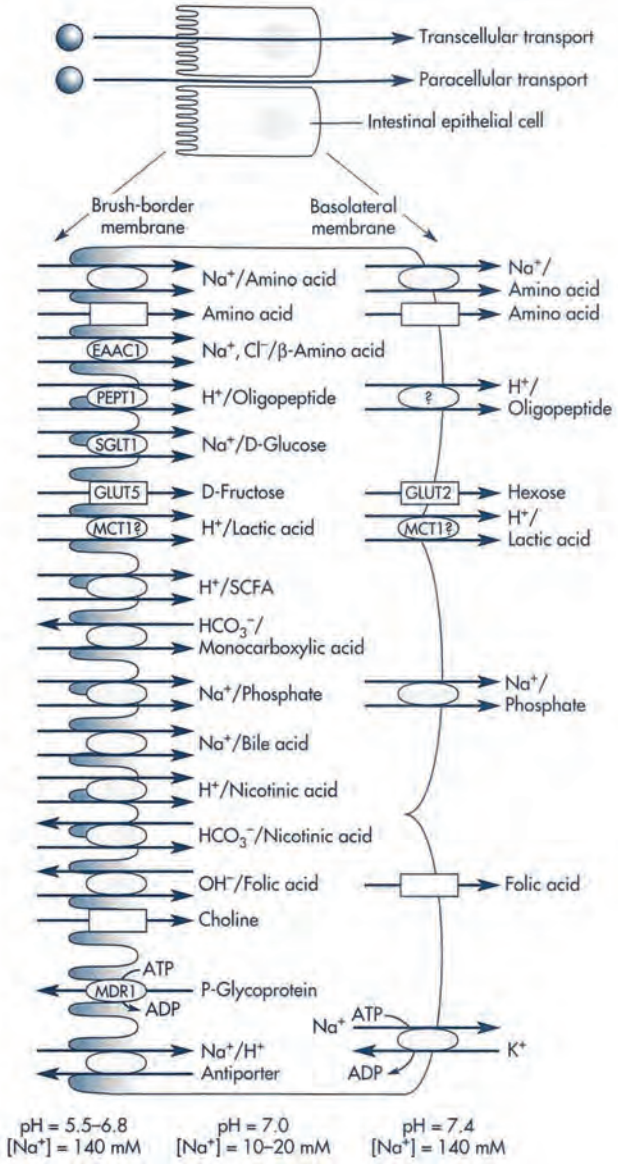


Figure 5-1. Summary of intestinal epithelial transporters. Transporters shown by square and oval shapes demonstrate active and facilitated transporters, respectively. Name of cloned transporters are shown with square or oval shapes. In the case of active transporter, arrows in the same direction represent symport of substance and the driving force. Arrows going in the reverse direction mean the antiport.
(From Tsuyi and Tamai, 1996, with permission.)

whereas highly charged molecules and large molecules, such as proteins and protein-bound drugs, do not.

The transmembrane movement of drugs is influenced by the composition and structure of the cell membranes. Cell membranes are generally thin, approximately 70 to 100Å in thickness. Cell membranes are primarily composed of phospholipids with interdispersed carbohydrates and integral protein groups in the form of a bilayer. There are several theories as to the structure of the cell membrane. The *lipid bilayer* or *unit membrane* theory, originally proposed by Davson and Danielli (1952), considers the cell membrane to be composed of two layers of phospholipid between two surface layers of proteins, with the hydrophilic "head" groups of the phospholipids facing the protein layers and the hydrophobic "tail" groups of the phospholipids aligned in the interior. The lipid bilayer theory explains the observation that

lipid-soluble drugs tend to penetrate cell membranes more easily than polar molecules. However, the bilayer cell membrane structure does not account for the diffusion of water, small-molecular-weight molecules such as urea, and certain charged ions.

The *fluid mosaic model*, proposed by Singer and Nicolson (1972), explains the transcellular diffusion of polar molecules. According to this model, the cell membrane consists of globular proteins embedded in a dynamic fluid, lipid bilayer matrix (Fig. 5-2). These proteins provide a pathway for the selective transfer of certain polar molecules and charged ions through the lipid barrier. As shown in Figure 5-2, transmembrane proteins are interdispersed throughout the membrane. Two types of pores of about 10 nm and 50 to 70 nm were inferred to be present in membranes based on capillary membrane transport studies (Pratt and Taylor, 1990). These small pores provide a channel through which water, ions, and dissolved solutes such as urea may move across the membrane.

PASSAGE OF DRUGS ACROSS CELL MEMBRANES

Passive Diffusion

Passive diffusion is the process by which molecules spontaneously diffuse from a region of higher concentration to a region of lower concentration. This process is

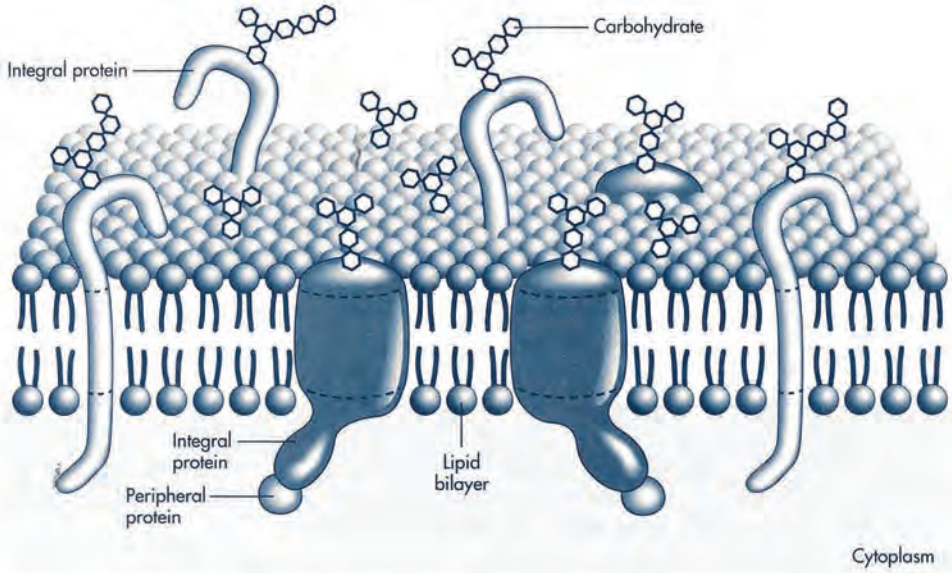


Figure 5-2. Model of the plasma membrane includes proteins and carbohydrates as well as lipids. Integral proteins are embedded in the lipid bilayer; peripheral proteins are merely associated with the membrane surface. The carbohydrate consists of monosaccharides, or simple sugars, strung together in chains that are attached to proteins (forming glycoproteins) or to lipids (forming glycolipids). The asymmetry of the membrane is manifested in several ways. Carbohydrates are always on the exterior surface and peripheral proteins are almost always on the cytoplasmic, or inner, surface. The two lipid monolayers include different proportions of the various kinds of lipid molecule. Most important, each species of integral protein has a definite orientation, which is the same for every molecule of that species.
(From Lodish and Rothman, 1979, with permission.)

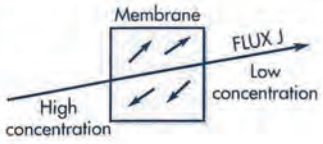


Figure 5-3. Passive diffusion of molecules. Molecules in solution diffuse randomly in all directions. As molecules diffuse from left to right and vice versa (small arrows), a net diffusion from the high-concentration side to the low-concentration side results. This results in a net flux (J) to the right side. Flux is measured in mass per unit area (eg, mg/cm^2).

passive because no external energy is expended. In Figure 5-3, drug molecules move forward and back across a membrane. If the two sides have the same drug concentration, forward-moving drug molecules will be balanced by molecules moving back, resulting in no net transfer of drug. When one side is higher in drug concentration, at any given time, the number of forward-moving drug molecules will be higher than the number of backward-moving molecules; the net result would be a transfer of molecules to the alternate side, as indicated in the figure by the big arrow. The rate of transfer is called *flux*, and is represented by a vector to show its direction in space. The tendency of molecules to move in all directions is natural because molecules possess kinetic energy and constantly collide with one another in space. Only left and right molecule movements are shown in Figure 5-3, because movement of molecules in other directions would not result in concentration changes because of the limitation of the container wall.

Passive diffusion is the major absorption process for most drugs. The driving force for passive diffusion is due to higher drug concentrations on the mucosal side over the blood. According to *Fick's law of diffusion*, drug molecules diffuse from a region of high drug concentration to a region of low drug concentration.

$$\frac{dQ}{dt} = \frac{DAK}{h}(C_{GI} - C_p) \qquad \textbf{(5.1)}$$

where dQ/dt = rate of diffusion; D = diffusion coefficient; K = lipid water partition coefficient of drug in the biologic membrane that controls drug permeation; A = surface area of membrane; h = membrane thickness; and $C_{GI} - C_p$ = difference between the concentrations of drug in the gastrointestinal tract and in the plasma.

Because the drug distributed rapidly into a large volume after entering the blood, the concentration of drug in the blood will be quite low with respect to the concentration at the site of drug absorption. For example, a drug is usually given in milligram doses, whereas plasma concentrations are often in the microgram per milliliter or nanogram per milliliter range. If the drug is given orally, then $C_{GI} >> C_p$ and a large concentration gradient is maintained, thus driving drug molecules into the plasma from the gastrointestinal tract.

Given Fick's law of diffusion, several other factors can be seen to influence the rate of passive diffusion of drugs. For example, the degree of lipid solubility of the drug will influence the rate of drug absorption. The partition coefficient, K, represents the lipid–water partitioning of a drug across the hypothetical membrane in the mucosa. Drugs that are more lipid soluble will have a larger value for K. The surface area of the membrane also influences the rate of absorption. Drugs may be absorbed from most areas of the gastrointestinal tract. However, the duodenal area of the small intestine shows the most rapid drug absorption due to such anatomic features as villi and microvilli, which provide a large surface area. These villi are less abundant in other areas of the gastrointestinal tract.

The thickness of the hypothetical model membrane, h, is a constant for any particular absorption site. Drugs usually diffuse very rapidly through capillary cell membranes in the vascular compartments, in contrast to diffusion through cell membranes of capillaries in the brain. In the brain, the capillaries are densely lined with glial cells, so that a drug diffuses slowly into the brain as if a thick lipid membrane existed. The term *blood–brain barrier* is used to describe the poor diffusion of water-soluble molecules across capillary cell membranes into the brain. However, in certain disease states these cell membranes may be disrupted or become more permeable to drug diffusion.

The diffusion coefficient, D, is a constant for each drug and is defined as the amount of a drug that diffuses across a membrane of a given unit area per unit time when the concentration gradient is unity. The dimensions of D are area per unit time—for example, cm^2/sec.

Because D, A, K, and h are constants under usual conditions for absorption, a combined constant P or permeability coefficient may be defined.

$$P = \frac{DAK}{h} \tag{5.2}$$

Furthermore, in Equation 5.1 the drug concentration in the plasma, C_p, is extremely small compared to the drug concentration in the gastrointestinal tract, C_{GI}. If C_p is negligible and P is substituted into Equation 5.1, the following relationship for Fick's law is obtained:

$$\frac{dQ}{dt} = P(C_{GI}) \tag{5.3}$$

Equation 5.3 is an expression for a first-order process. In practice, the extravascular absorption of most drugs tends to be a first-order absorption process. Moreover, due to the large concentration gradient between C_{GI} and C_p, the rate of drug absorption is usually more rapid than the rate of drug elimination.

Many drugs have both lipophilic and hydrophilic chemical substituents. Those drugs that are more lipid soluble tend to traverse cell membranes more easily than less lipid-soluble or more water-soluble molecules. For drugs that act as weak electrolytes, such as weak acids and bases, the extent of ionization influences the rate of drug transport. The ionized species of the drug contains a charge and is more water soluble than the nonionized species of the drug, which is more lipid soluble. The extent of ionization of a weak electrolyte will depend on both the pK_a of the drug and the pH of the medium in which the drug is dissolved. *Henderson and Hasselbalch* used the following expressions pertaining to weak acids and weak bases to describe the relationship between pK_a and pH.

For weak acids,

$$\text{Ratio} = \frac{(\text{salt})}{(\text{acid})} = \frac{(A^-)}{(HA)} = 10^{(pH\ -\ pKa)} \tag{5.4}$$

For weak bases,

$$\text{Ratio} = \frac{(\text{base})}{(\text{salt})} = \frac{(RNH_2)}{(RNH_3^+)} = 10^{(pH\ -\ pKa)} \tag{5.5}$$

With Equations 5.4 and 5.5, the proportion of free acid or free base existing as the nonionized species may be determined at any given pH, assuming the pK_a for

the drug is known. For example, at a plasma pH of 7.4, salicylic acid (pK_a 3.0) would exist mostly in its ionized or water-soluble form, as shown below:

$$\text{Ratio} = \frac{(\text{salt})}{(\text{acid})} = 10^{(7.4 - 3.0)}$$

$$\log \frac{(\text{salt})}{(\text{acid})} = 7.4 - 3.0 = 4.4$$

$$\frac{(\text{Salt})}{(\text{Acid})} = 2.51 \times 10^4$$

The total drug concentrations on either side of a membrane should be the same at equilibrium, assuming Fick's law of diffusion is the only distribution factor involved. For diffusible drugs, such as nonelectrolyte drugs or drugs that do not ionize, the drug concentrations on either side of the membrane are the same at equilibrium. However, for electrolyte drugs or drugs that ionize, the total drug concentrations on both sides of the membrane are not equal at equilibrium if the pH of the medium differs on respective sides of the membrane. For example, consider the concentration of salicylic acid (pK_a 3.0) in the stomach (pH 1.2) as opposed to its concentration in the plasma (pH 7.4) (Fig. 5-4).

According to the Henderson–Hasselbalch equation (Eq. 5.4) for weak acids, at pH 7.4 and at pH 1.2, salicylic acid would exist in the ratios that follow.

In the plasma, at pH 7.4:

$$\text{Ratio} = \frac{(\text{R COO}^-)}{(\text{R COOH})} = 2.51 \times 10^4$$

In gastric juice, at pH 1.2:

$$\text{Ratio} = \frac{(\text{R COO}^-)}{(\text{R COOH})} = 10^{(1.2 - 3.0)} = 1.58 \times 10^{-2}$$

The total drug concentration on either side of the membrane is determined as shown in Table 5.1. Thus, the pH affects distribution of salicylic acid (R COOH) and its salt ($R COO^-$) across cell membranes. It is assumed that the acid, R COOH, is freely permeable and the salt, $R COO^-$, is not permeable across the cell membrane. In this example the total concentration of salicylic acid at equilibrium is approximately 25,000 times greater in the plasma than in the stomach (Table 5.1). These calculations can also be applied to weak bases, using Equation 5.5.

According to the *pH–partition hypotheses*, if the pH on one side of a cell membrane differs from the pH on the other side of the membrane, then (1) the drug (weak acid or base) will ionize to different degrees on respective sides of the membrane; (2) the total drug concentrations (ionized plus nonionized drug) on either side of the membrane will be unequal; and (3) the compartment in which the drug is more highly ionized will contain the greater total drug concentration. For these

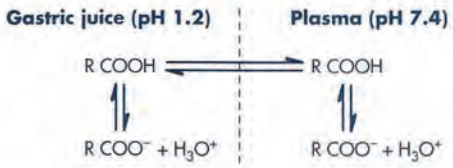


Figure 5-4. Model for the distribution of an orally administered weak electrolyte drug such as salicylic acid.

TABLE 5.1 Relative Concentrations of Salicylic Acid as Affected by pH

DRUG	GASTRIC JUICE (PH 1.2)	PLASMA (PH 7.4)
R COOH	1.0000	1
R COO^-	0.0158	25100
Total drug concentration	1.0158	25101

reasons, a weak acid (such as salicylic acid) would be rapidly absorbed from the stomach (pH 1.2), whereas a weak base (such as quinidine) would be poorly absorbed from the stomach.

Another factor that can influence drug concentrations on either side of a membrane is a particular *affinity* of the drug for a tissue component, which would prevent the drug from freely moving back across the cell membrane. For example, a drug may bind to plasma or tissue proteins. This drug–protein binding has been described for dicumarol, certain sulfonamides, and other drugs. Moreover, a drug such as chlordane, a lipid-soluble insecticide, might dissolve in the adipose (fat) tissue. In addition, a drug such as tetracycline might form a complex with calcium in the bones and teeth. Finally, a drug may concentrate in a tissue due to a specific uptake or active transport process. Such processes have been demonstrated for iodide in thyroid tissue, potassium in the intracellular water, and certain catecholamines in adrenergic storage sites.

Carrier-Mediated Transport

Theoretically, a lipophilic drug may pass through the cell or go around it. If the drug has a low molecular weight and is lipophilic, the lipid cell membrane is not a barrier to drug diffusion and absorption. In the intestine, molecules smaller than 500 MW may be absorbed by paracellular drug absorption. Numerous specialized carrier-mediated transport systems are present in the body, especially in the intestine for the absorption of ions and nutrients required by the body.

Active Transport

Active transport is a carrier-mediated transmembrane process that plays an important role in the gastrointestinal absorption and in renal and biliary secretion of many drugs and metabolites. A few lipid-insoluble drugs that resemble natural physiologic metabolites (such as 5-fluorouracil) are absorbed from the gastrointestinal tract by this process. Active transport is characterized by the transport of drug against a concentration gradient—that is, from regions of low drug concentrations to regions of high concentrations. Therefore, this is an energy-consuming system. In addition, active transport is a specialized process requiring a carrier that binds the drug to form a carrier–drug complex that shuttles the drug across the membrane and then dissociates the drug on the other side of the membrane (Fig. 5-5).

The carrier molecule may be highly selective for the drug molecule. If the drug structurally resembles a natural substrate that is actively transported, then it is likely to be actively transported by the same carrier mechanism. Therefore, drugs of similar structure may compete for sites of adsorption on the carrier. Furthermore, because only a fixed number of carrier is available, all the binding sites on the carrier may become saturated if the drug concentration gets very high. A comparison between the rate of drug absorption and the concentration of drug at the absorption

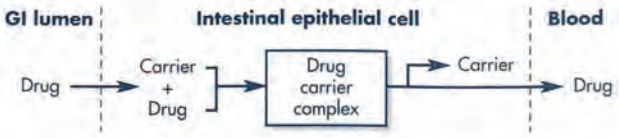


Figure 5-5. Hypothetical carrier-mediated transport process.

site is shown in Figure 5-6. Notice that for a drug absorbed by passive diffusion, the rate of absorption increases in a linear relationship to drug concentration. In contrast, when a drug is absorbed by a carrier-mediated process, the rate of drug absorption increases with drug concentration until the carrier molecules are completely saturated. At higher drug concentrations, the rate of drug absorption remains constant.

Facilitated Diffusion

Facilitated diffusion is also a carrier-mediated transport system, differing from active transport in that the drug moves along a concentration gradient (ie, moves from a region of high-drug concentration to a region of low-drug concentration). Therefore, this system does not require energy input. However, because this system is carrier mediated, it is saturable and structurally selective for the drug and shows competition kinetics for drugs of similar structure. In terms of drug absorption, facilitated diffusion seems to play a very minor role.

Carrier-Mediated Intestinal Transport

Various carrier mediated systems (*transporters*) are present at the intestinal brush border and basolateral membrane for the absorption of specific ions and nutrients essential for the body (Tsuji and Tamal, 1996). Many drugs are absorbed by these carriers because of the structural similarity to natural substrates (Table 5.2). A transmembrane protein, *P-glycoprotein* (P-gp) has been identified in the intestine. P-glycoprotein appears to reduce apparent intestinal epithelial cell permeability from lumen to blood for various lipophilic or cytotoxic drugs. Other transporters are present in the intestines (Tsuji and Tamal, 1996). For example, many oral cephalosporins are absorbed through the amino acid transporter. Cefazolin, a parenteral-only cephalosporin, is not available orally because it cannot be absorbed to a significant degree through this mechanism.

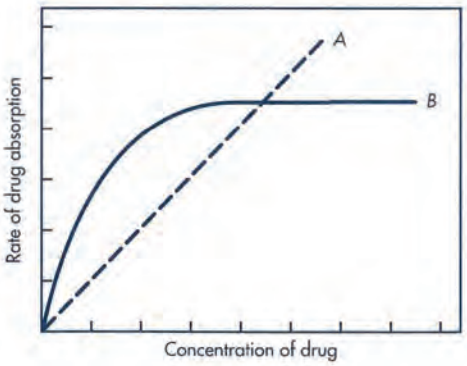


Figure 5-6. Comparison of the rates of drug absorption of a drug absorbed by passive diffusion (line *A*) and a drug absorbed by a carrier mediated system (line *B*).

TABLE 5.2 Intestine Transporters and Examples of Drugs Transported

TRANSPORTER	EXAMPLES	
Amino acid transporter	Gabapentin	D-cycloserine
	Methyldopa	Baclofen
	L-dopa	
Oligopeptide transporter	Cefadroxil	Cephradine
	Cefixime	Ceftibuten
	Cephalexin	Captopril
	Lisinopril	Thrombin inhibitor
Phosphate transporter	Fostomycin	Foscarnet
Bile acid transporter	S3744	
Glucose transporter	P-nitrophenyl-β-D-Glucopyranoside	
P-glycoprotein efflux	Etoposide	Vinblastine
	Cyclosporin A	
Monocarboxylic acid transporter	Salicylic acid	Benzoic acid
	Pravastatin	

Adapted from Tsuji and Tamai (1996).

Vesicular Transport

Vesicular transport is the process of engulfing particles or dissolved materials by the cell. *Pinocytosis* and *phagocytosis* are forms of vesicular transport that differ by the type of material ingested. Pinocytosis refers to the engulfment of small solutes or fluid, whereas phagocytosis refers to the engulfment of larger particles or macromolecules, generally by macrophages. *Endocytosis* and *exocytosis* are the processes of moving macromolecules into and out of a cell, respectively.

During pinocytosis or phagocytosis, the cell membrane invaginates to surround the material and then engulfs the material, incorporating it into the cell (Fig. 5-7).

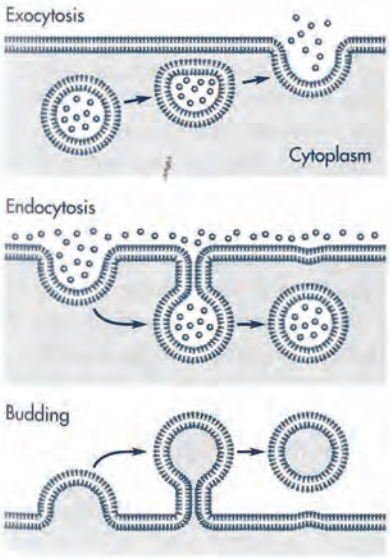


Figure 5-7. Diagram showing exocytosis and endocytosis. (From Alberts et al, 1988, with permission.)

Subsequently, the cell membrane containing the material forms a vesicle or vacuole within the cell. Vesicular transport is the proposed process for the absorption of orally administered Sabin polio vaccine and various large proteins.

An example of *exocytosis* is the transport of a protein such as insulin from insulin-producing cells of the pancreas into the extracellular space. The insulin molecules are first packaged into intracellular vesicles, which then fuse with the plasma membrane to release the insulin outside the cell.

Pore (Convective) Transport

Very small molecules (such as urea, water, and sugars) are able to rapidly cross cell membranes as if the membrane contained channels or pores. Although such pores have never been directly observed by microscopy, the model of drug permeation through aqueous pores is used to explain renal excretion of drugs and the uptake of drugs into the liver.

A certain type of protein called a transport protein may form an open channel across the lipid membrane of the cell (Fig. 5-1). Small molecules including drugs move through the channel by diffusion more rapidly than at other parts of the membrane.

Ion Pair Formation

Strong electrolyte drugs are highly ionized or charged molecules, such as quaternary nitrogen compounds with extreme pK_a values. Strong electrolyte drugs maintain their charge at all physiologic pH values and penetrate membranes poorly. When the ionized drug is linked up with an oppositely charged ion, an ion pair is formed in which the overall charge of the pair is neutral. This neutral drug complex diffuses more easily across the membrane. For example, the formation of ion pairs to facilitate drug absorption has been demonstrated for propranolol, a basic drug that forms an ion pair with oleic acid, and quinine, which forms ion pair with hexylsalicylate (Nienbert, 1989).

ROUTE OF DRUG ADMINISTRATION

Drugs may be given by parenteral, enteral, inhalation, transdermal (percutaneous), and intranasal routes for systemic absorption. Each route of drug administration has certain advantages and disadvantages. Some characteristics of the more common routes of drug administration are listed in Table 5.3. Many drugs are not administered orally because of instability in the gastrointestinal tract or the degradation by the digestive enzymes in the intestine. For example, erythropoietin and human growth hormone (somatrophin) are administered intramuscularly, and insulin is administered subcutaneously or intramuscularly because the potential of degradation of the drugs in the intestine. Drug absorption after subcutaneous injection is slower than intravenous injection. The availability and onset of the drug administered by parenteral routes may be affected by blood flow to the administration site and by disease factors. The bioavailability of these products is discussed in Chapter 10. Biotechnology products are often too labile to be administered orally.

TABLE 5.3 Common Routes of Drug Administration

ROUTE	BIOAVAILABILITY	ADVANTAGES	DISADVANTAGES
Parenteral Routes			
Intravenous bolus (IV)	Complete (100%) systemic drug absorption. Rate of bioavailability considered instantaneous.	Drug is given for immediate effect.	Increased chance for adverse reaction. Possible anaphylaxis.
Intravenous infusion (IV inf)	Complete (100%) systemic drug absorption. Rate of drug absorption controlled by infusion pump.	Plasma drug levels more precisely controlled. May inject large fluid volumes. May use drugs with poor lipid solubility and/or irritating drugs.	Requires skill in insertion of infusion set. Tissue damage at site of injection (infiltration, necrosis, or sterile abscess).
Intramuscular injection (IM)	Rapid from aqueous solution. Slow absorption from nonaqueous (oil) solutions.	Easier to inject than intravenous injection. Larger volumes may be used compared to subcutaneous solutions.	Irritating drugs may be very painful. Different rates of absorption depending upon muscle group injected and blood flow.
Subcutaneous injection (SC)	Prompt from aqueous solution. Slow absorption from repository formulations.	Generally, used for insulin injection.	Rate of drug absorption depends upon blood flow and injection volume.
Enteral Routes			
Buccal or sublingual (SL)	Rapid absorption from lipid-soluble drugs.	No "first-pass" effects.	Some drugs may be swallowed. Not for most drugs or drugs with high doses.
Oral (PO)	Absorption may vary. Generally, slower absorption rate compared to IV bolus or IM injection.	Safest and easiest route of drug administration. May use immediate-release and modified-release drug products.	Some drugs may have erratic absorption, be unstable in the gastointestinal tract, or be metabolized by liver prior to systemic absorption.
Rectal (PR)	Absorption may vary from suppository. More reliable absorption from enema (solution).	Useful when patient cannot swallow medication. Used for local and systemic effects.	Absorption may be erratic. Suppository may migrate to different position. Some patient discomfort.
Other Routes			
Transdermal	Slow absorption, rate may vary. Increased absorption with occlusive dressing.	Transdermal delivery system (patch) is easy to use. Used for lipid-soluble drugs with low dose and low MW.	Some irritation by patch or drug. Permeability of skin variable with condition, anatomic site, age, and gender. Type of cream or ointment base affects drug release and absorption.
Inhalation	Rapid absorption. Total dose absorbed is variable.	May be used for local or systemic effects.	Particle size of drug determines anatomic placement in respiratory tract. May stimulate cough reflex. Some drug may be swallowed.



PRACTICAL FOCUS

The pharmacokinetics of erythropoietin (EPO) was investigated in uremic and healthy subjects (Jensen JD, 1994). After subcutaneous injection, the bioavailability was significantly lower in the patients (23.7 versus 38.5%; $P < 0.01$) than in the normal subjects, and the maximal s-EPO was lower (113 versus 153 U/L; $P < 0.05$) and delayed (15.4 versus 11.0 h; $P < 0.02$).

Subcutaneous administration offers an alternative route to oral administration for drugs with low bioavailability, for example, sumatriptine (Imitrex) has an oral bioavailability of about 14% due to extensive metabolism and low absorption. It is rapidly absorbed subcutaneously and gives prompt relief of migraine headache.

Oral Drug Absorption

Anatomic and Physiologic Considerations

The enteral system consists of the alimentary canal from the mouth to the anus (Fig. 5-8). The major physiologic processes that occur in the gastrointestinal (GI)

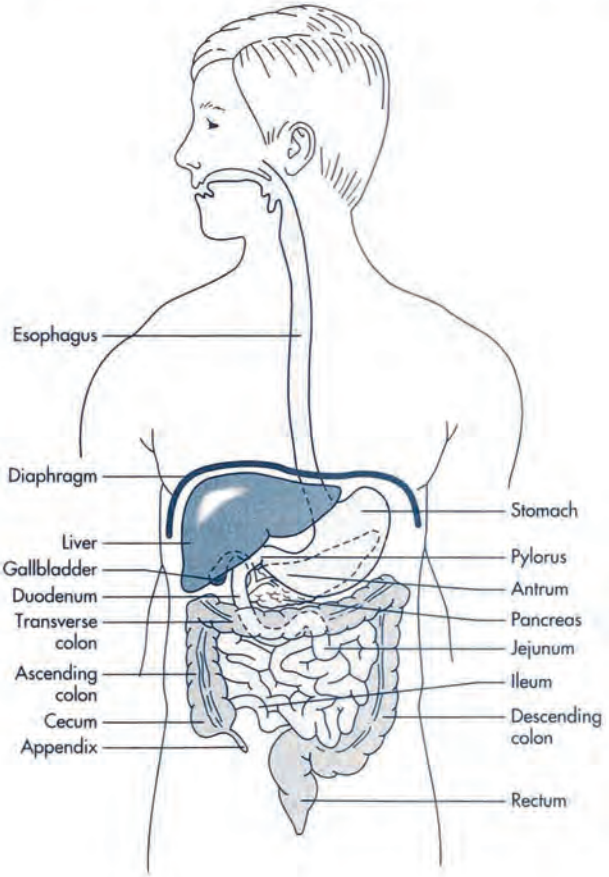


Figure 5-8. Gastrointestinal tract.

system are secretion, digestion, and absorption. *Secretion* includes the transport of fluid, electrolytes, peptides, and proteins into the lumen of the alimentary canal. Enzymes in saliva and pancreatic secretions are involved in the digestion of carbohydrates and proteins. Other secretions, such as mucus, protect the linings of the lumen of the GI tract. *Digestion* is the breakdown of food constituents into smaller structures in preparation for absorption. Food constituents are mostly absorbed in the proximal area (duodenum) of the small intestine. The process of *absorption* is the entry of constituents from the lumen of the gut into the body. Absorption may be considered as the net result of both lumen-to-blood and blood-to-lumen transport movements.

Drugs administered orally pass through various parts of the enteral canal, including the oral cavity, esophagus, and various parts of the gastrointestinal tract. Residues eventually exit the body through the anus. The total transit time, including gastric emptying, small intestinal transit, and colonic transit ranges from 0.4 to 5 days (Kirwan and Smith, 1974). The most important site for drug absorption is the small intestine. Small intestine transit time (SITT) ranges from 3 to 4 hours for most healthy subjects. If absorption is not completed by the time a drug leaves the small intestine, absorption may be erratic or incomplete. The small intestine is normally filled with digestive juices and liquids, keeping the lumen contents fluid. In contrast, the fluid in the colon is reabsorbed, and the lumenal content in the colon is either semisolid or solid, making further drug dissolution erratic and difficult. The lack of the solubilizing effect of the chyme and digestive fluid contributes to a less favorable environment for drug absorption.

The normal physiologic processes of the alimentary canal may be affected by diet, contents of the GI tract, hormones, the visceral nervous system, disease, and drugs. Thus, drugs given by the enteral route for systemic absorption may be affected by the anatomy, physiologic functions, and contents of the alimentary tract. Moreover, the physical, chemical, and pharmacologic properties of the drug itself will also affect its own absorption from the alimentary canal.

Oral Cavity. Saliva is the main secretion of the oral cavity, and has a pH of about 7. Saliva contains ptyalin (salivary amylase), which digests starches. Mucin, a glycoprotein that lubricates food, is also secreted and may interact with drugs. About 1500 mL of saliva is secreted per day.

Esophagus. The esophagus connects the pharynx and the cardiac orifice of the stomach. The pH of the fluids in the esophagus is between 5 and 6. The lower part of the esophagus ends with the esophageal sphincter, which prevents acid reflux from the stomach. Tablets or capsules may lodge in this area, causing local irritation. Very little drug dissolution occurs in the esophagus.

Stomach. The stomach is innervated by the vagus nerve. However, local nerve plexus, hormones, mechanoreceptors sensitive to the stretch of the GI wall, and chemoreceptors control the regulation of gastric secretions, including acid and stomach emptying. The fasting pH of the stomach is about 2 to 6. In the presence of food, the stomach pH is about 1.5 to 2, due to hydrochloric acid secreted by parietal cells. Stomach acid secretion is stimulated by gastrin and histamine. Gastrin is released from G cells, mainly in the antral mucosa and also in the duodenum. Gastrin release is regulated by stomach distension (swelling) and the presence of

peptides and amino acids. A substance called intrinsic factor for vitamin B-12 absorption and various gastric enzymes, such as pepsin that initiate protein digestion, are secreted into the gastric lumen to initiate digestion.

Basic drugs are solubilized rapidly in the presence of stomach acid. Mixing is intense and pressurized in the antral part of the stomach, a process of breaking down large food particles described as *antral milling*. Food and liquid are emptied by opening the pyloric sphincter into the duodenum. Stomach emptying is influenced by the food content and osmolality. Fatty acids and mono- and diglycerides delay gastric emptying (Hunt and Knox, 1968). High-density foods generally are emptied from the stomach more slowly. The relation of gastric emptying time to drug absorption is discussed more fully in the next section.

Duodenum. A common duct from the pancreas and the gallbladder enters into the duodenum. The duodenal pH is about 6 to 6.5 due to the presence of bicarbonate that neutralizes the acidic chyme emptied from the stomach. The pH is optimum for enzymatic digestion of protein and peptide food. Pancreatic juice containing enzymes is secreted into the duodenum from the bile duct. Trypsin, chymotrypsin, and carboxypeptidase are involved in the hydrolysis of proteins into amino acids. Amylase is involved in the digestion of carbohydrates. Pancreatic lipase secretion hydrolyzes fats into fatty acid. The complex fluid medium in the duodenum helps to dissolve many drugs with limited aqueous solubility.

The duodenum is a site where many ester prodrugs are hydrolyzed during absorption. The presence of proteolytic enzymes also makes many protein drugs unstable in the duodenum, preventing adequate absorption.

Jejunum. The jejunum is the middle portion of the small intestine in between the duodenum and the ileum. Digestion of protein and carbohydrates continues after receiving pancreatic juice and bile in the duodenum. This portion of the small intestine generally has fewer contractions than the duodenum and is preferred for in vivo drug absorption studies.

Ileum. The ileum is the terminal part of the small intestine. This site has fewer contractions than the duodenum and may be blocked off by catheters with an inflatable balloon and perfused for drug absorption study. The pH is about 7, with the distal part as high as 8. Due to the presence of bicarbonate secretion, acid drugs will dissolve. Bile secretion helps to dissolve fats and hydrophobic drugs. The ileocecal valve separates the small intestine from the colon.

Colon. The colon lacks villi and has limited drug absorption also due to the more viscous and semisolid nature of the lumen contents. The colon is lined with mucin functioning as lubricant and protectant. The pH in this region is 5.5 to 7. A few drugs, such as theophylline and metoprolol, are absorbed in this region. Drugs that are absorbed well in this region are good candidates for an oral sustained-release dosage form. The colon contains both aerobic and anaerobic microorganisms that may metabolize some drugs. For example, L-dopa and lactulose are metabolized by enteric bacteria. Crohn's disease affects the colon and thickens the bowel wall. The microflora also become more anaerobic. Absorption of clindamycin and propranolol are increased, whereas other drugs have reduced absorption with this disease (Rubinstein et al, 1988).

Rectum. The rectum is about 15 cm long, ending at the anus. In the absence of fecal material, the rectum has a small amount of fluid (approximately 2 mL) with a pH about 7. The rectum is perfused by the superior, middle, and inferior hemorrhoidal veins. The inferior hemorrhoidal vein (closest to the anal sphincter) and the middle hemorrhoidal vein feed into the vena cava and back to the heart. The superior hemorrhoidal vein joins the mesenteric circulation, which feeds into the hepatic portal vein and then to the liver.

Drug absorption after rectal administration may be variable depending upon the placement of the suppository or drug solution within the rectum. A portion of the drug dose may be absorbed via the lower hemorrhoidal veins, from which the drug feeds directly into the systemic circulation; some drugs may be absorbed via the superior hemorrhoidal vein, which feeds into the mesenteric veins to the hepatic portal vein to the liver, and metabolized prior to systemic absorption.

Drug Absorption in the Gastrointestinal Tract

Drugs may be absorbed by passive diffusion from all parts of the alimentary canal including sublingual, buccal, GI, and rectal absorption. For most drugs, the optimum site for drug absorption after oral administration is the upper portion of the small intestine or duodenum region. The unique anatomy of the duodenum provides an immense surface area for the drug to passively diffuse (Fig. 5-9). The large

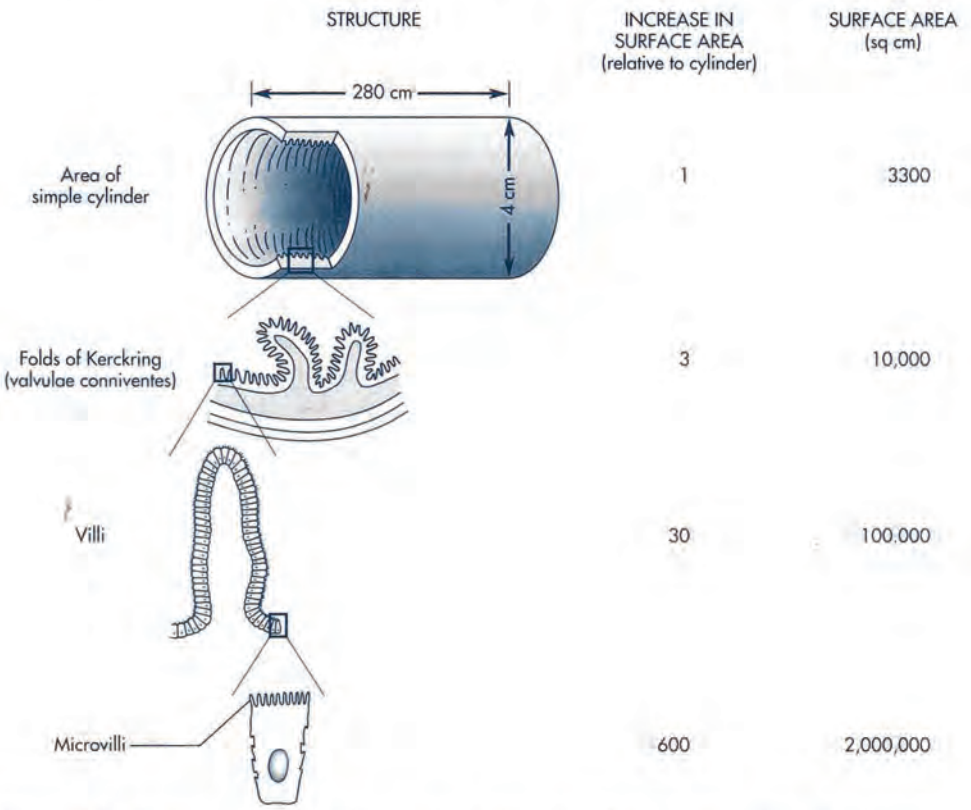


Figure 5-9. Three mechanisms for increasing surface area of the small intestine. The increase in surface area is due to folds of Kerkring, villi, and microvilli.
(From Wilson, 1962, with permission.)

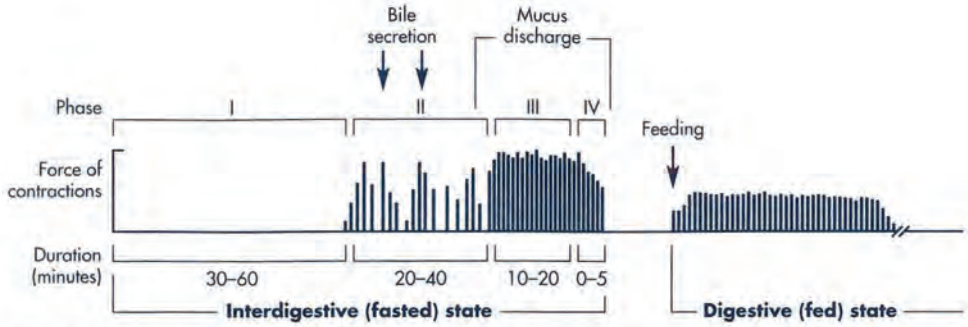


Figure 5-10. A pictorial representation of the typical motility patterns in the interdigestive (fasted) and digestive (fed) state.
(From Rubinstein et al, 1988, with permission.)

surface area of the duodenum is due to the presence of valvelike folds in the mucous membrane upon which are small projections known as *villi*. These villi contain even smaller projections known as *microvilli*, forming a brush border. In addition, the duodenal region is highly perfused with a network of capillaries, which helps to maintain a concentration gradient from the intestinal lumen and plasma circulation.

Gastrointestinal Motility

Once the drug is given orally, the exact location and/or environment of the drug product within the GI tract is difficult to discern. GI motility tends to move the drug through the alimentary canal so that the drug may not stay at the absorption site. For drugs given orally, an anatomic *absorption window* may exist within the GI tract in which the drug is efficiently absorbed. Drugs contained in a nonbiodegradable controlled-release dosage form must be completely released into this absorption window to be absorbed prior to the movement of the dosage form into the large bowel.

The transit time of the drug in the GI tract depends upon the pharmacologic properties of the drug, type of dosage form, and various physiologic factors. Physiologic movement of the drug within the GI tract depends upon whether the alimentary canal contains recently ingested food (*digestive* or *fed* state) or is in the *fasted* or *interdigestive* state (Fig. 5-10). During the fasted or interdigestive state, alternating cycles of activity known as the *migrating motor complex* (MMC) act as a propulsive movement that empties the upper GI tract to the cecum. Initially, the alimentary canal is quiescent. Then, irregular contractions followed by regular contractions with high amplitude (*housekeeper waves*) push any residual contents distally or farther down the alimentary canal. In the fed state, the migrating motor complex is replaced by irregular contractions, which have the effect of mixing intestinal contents and advancing the intestinal stream toward the colon in short segments (Table 5.4). The pylorus and ileocecal valves prevent regurgitation or movement of food from the distal to the proximal direction.

Gastric Emptying Time

Anatomically, the swallowed drug rapidly reaches the stomach. Eventually, the stomach empties its contents into the small intestine. Because the duodenum has the greatest capacity for the absorption of drugs from the GI tract, a delay in the *gas-*

TABLE 5.4 Characteristics of the Motility Patterns in the Fasted Dog

PHASE	DURATION	CHARACTERISTICS
Fasted State		
I	30–60 min	Quiescence.
II	20–40 min	▪ Irregular contractions. ▪ Medium amplitude but can be as high as phase III. ▪ Bile secretion begins. ▪ Onset of gastric discharge of administered fluid of small volume usually occurs before that of particle discharge. ▪ Onset of particle and mucus discharge may occur during the latter part of phase II.
III	5–15 min	▪ Regular contractions (4–5 contractions/min) with high amplitude. ▪ Mucus discharge continues. ▪ Particle discharge continues.
IV	0–5 min	▪ Irregular contractions. ▪ Medium descending amplitude. ▪ Sometimes absent.
Fed State		
One phase only	As long as food is present in the stomach	▪ Regular, frequent contractions. ▪ Amplitude is lower than phase III. ▪ 4–5 Contractions/min.

From Rubinstein et al (1988), with permission.

tric emptying time for the drug to reach the duodenum will slow the rate and possibly the extent of drug absorption, thereby prolonging the onset time for the drug. Some drugs, such as penicillin, are unstable in an acid and decompose if stomach emptying is delayed. Other drugs, such as aspirin, may irritate the gastric mucosa during prolonged contact.

A number of factors will affect gastric emptying time (Table 5.5). Some factors that tend to delay gastric emptying include consumption of meals high in fat, cold beverages, and anticholinergic drugs (Burks et al, 1985; Rubinstein et al, 1988). Liquids and small particles less than 1 mm are generally not retained in the stomach. These small particles are believed to be emptied due to a slightly higher basal pressure in the stomach over the duodenum. Different constituents of a meal will empty from the stomach at different rates. Feldman and associates (1984) observed that 10 ounces of liquid soft drink, scrambled egg (digestible solid), and a radiopaque (undigestible solid) were 50% emptied from the stomach in 30 minutes, 154 minutes, and 3 to 4 hours, respectively. Thus, liquids are generally emptied faster than digested solids from the stomach (Fig. 5-11). Large particles, including tablets and capsules, are delayed from emptying for 3 to 6 hours by the presence of food in the stomach. Indigestible solids empty very slowly, probably during the interdigestive phase, a phase in which food is not present and the stomach is less motile but periodically empties its content due to housekeeper wave contraction (Fig. 5-12).

Intestinal Motility

Normal peristaltic movements mix the contents of the duodenum, bringing the drug particles into intimate contact with the intestinal mucosal cells. The drug must have a sufficient time (*residence time*) at the absorption site for optimum absorption.

In the case of high motility in the intestinal tract, as in diarrhea, the drug has a very brief residence time and less opportunity for adequate absorption.

The average normal small intestine transit time (SITT) was about 7 hours in early studies using indirect methods based on the detection of hydrogen after an

TABLE 5.5 Factors Influencing Gastric Emptying

FACTOR	INFLUENCE ON GASTRIC EMPTYING
1. Volume	The larger the starting volume, the greater the initial rate of emptying; after this initial period, the larger the original volume, the slower the rate of emptying.
2. Type of meal	
Fatty acids	Reduction in rate of emptying is in direct proportion to their concentration and carbon chain length; little difference is detected from acetic to octanoic acids; major inhibitory influence is seen in chain lengths greater than 10 carbons (decanoic to stearic acids).
Triglycerides	Reduction in rate of emptying; unsaturated triglycerides are more effective than saturated ones; the most effective in reducing emptying rate were linseed and olive oils.
Carbohydrates	Reduction in rate emptying, primarily as a result of osmotic pressure; inhibition of emptying increases as concentration increases.
Amino acids	Reduction in rate of emptying to an extent directly dependent upon concentration, probably as a result of osmotic pressure.
3. Osmotic pressure	Reduction in rate of emptying to an extent dependent upon concentration for salts and nonelectrolytes; rate of emptying may increase at lower concentrations and then decrease at higher concentrations.
4. Physical state of gastric contents	Solutions or suspensions of small particles empty more rapidly than do chunks of material that must be reduced in size prior to emptying.
5. Chemicals	
Acids	Reduction in rate of emptying dependent upon concentration and molecular weight of the acid; lower molecular weight acids are more effective than those of higher molecular weight (in order of decreasing effectiveness: HCl, acetic, lactic, tartaric, citric acids).
Alkali ($NaHCO_3$)	Increased rate of emptying at low concentrations (1%), and decreased rate at higher concentrations (5%).
6. Drugs	
Anticholinergics	Reduction in rate of emptying.
Narcotic analgesics	Reduction in rate of emptying.
Metoclopramide	Increase in rate of emptying.
Ethanol	Reduction in rate of emptying.
7. Miscellaneous	
Body position	Rate of emptying is reduced in a patient lying on left side.
Viscosity	Rate of emptying is greater for less viscous solutions.
Emotional states	Aggressive or stressful emotional states increase stomach contractions and emptying rate; depression reduces stomach contraction and emptying.
Bile salts	Rate of emptying is reduced.
Disease states	Rate of emptying is reduced in some diabetics and in patients with local pyloric lesions (duodenal or pyloric ulcers; pyloric stenosis) and hypothyroidism; gastric emptying rate is increased in hyperthyroidism.
Exercise	Vigorous exercise reduces emptying rate.
Gastric surgery	Gastric emptying difficulties can be a serious problem after surgery.

From Mayersohn (1979), with permission.

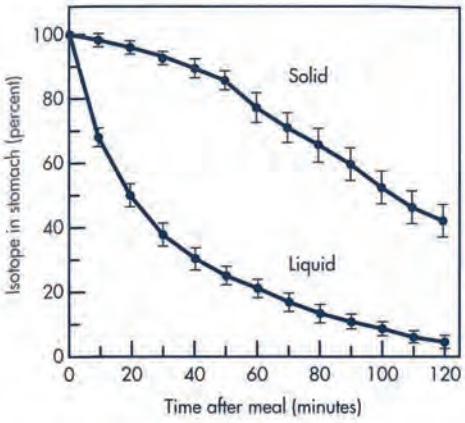


Figure 5-11. Gastric emptying of a group of normal subjects using the dual-isotope method. The mean and 1 SE of the fraction of isotope remaining in the stomach is depicted at various time intervals after ingestion of the meal. Note the exponential nature of liquid emptying and the linear process of solid emptying.
(From Minami and McCallum, 1984, with permission.)

oral dose of lactulose (fermentation of lactulose by colon bacteria yields hydrogen in the breath). Newer studies using gamma scintigraphy have shown SITT to be about 3 to 4 hours. Thus a drug may take about 4 to 8 hours to pass through the stomach and small intestine during the fasting state. During the fed state, SITT may take 8 to 12 hours. For modified-release or controlled-dosage forms, which slowly release the drug over an extended period of time, the dosage form must stay within a certain segment of the intestinal tract so that the drug contents are released and absorbed prior to loss of the dosage form in the feces. Intestinal transit is discussed further in the design of sustained-release products in Chapter 7.

Perfusion of the Gastrointestinal Tract

The blood flow to the GI tract is important in carrying the absorbed drug to the systemic circulation. A large network of capillaries and lymphatic vessels perfuse the duodenal region and peritoneum. The splanchnic circulation receives about 28% of the cardiac output and is increased after meals. Once the drug is absorbed from the small intestine, it enters via the mesenteric vessels to the hepatic–portal vein and the liver prior to reaching the systemic circulation. Any decrease in mesenteric blood flow, as in the case of congestive heart failure, will decrease the rate of drug removal from the intestinal tract, thereby reducing the rate of drug bioavailability (Benet et al, 1976).

The role of the lymphatic circulation in drug absorption is well established. Drugs are absorbed through the lacteal or lymphatic vessels under the microvilli. Absorption of drugs through the lymphatic system bypasses the first-pass effect due to liver metabolism, because drug absorption through the hepatic–portal vein is avoided. The lymphatics are important in the absorption of dietary lipids and may

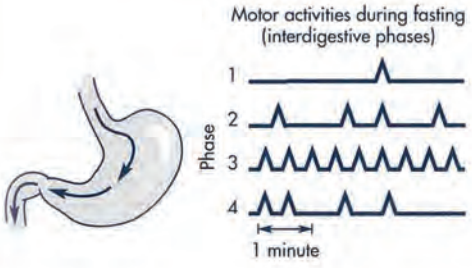


Figure 5-12. Motor activity responsible for gastric emptying of indigestible solids. Migrating myoelectric complex (MMC) usually initiated at proximal stomach or lower esophageal sphincter and contractions during phase 3 sweep indigestible solids through open pylorus.
(From Minami and McCallum, 1984, with permission.)

be partially responsible for the absorption for some lipophilic drugs. Many poorly water-soluble drugs are soluble in oil and lipids, which may dissolve in chylomicrons and be systemically absorbed via the lymphatic system. Bleomycin or aclarubicin were prepared in chylomicrons to improve oral absorption through the lymphatic system (Yoshikawa et al, 1983, 1989).

Effect of Food on Gastrointestinal Drug Absorption

The presence of food in the GI tract can affect the bioavailability of the drug. Digested foods contain amino acids, fatty acids, and many nutrients that may affect intestinal pH and solubility of drugs. The effects of food are not always predictable. The absorption of some antibiotics, such as penicillin and tetracycline, is decreased with food; whereas other drugs, such as griseofulvin, are better absorbed when given with food containing a high fat content (Fig. 5-13). The presence of food in the GI lumen stimulates the flow of bile. Bile contains bile acids, which are surfactants involved in the digestion and solubilization of fats, and also increases the solubility of fat-soluble drugs through micelle formation. For some basic drugs (eg, cinnarizine) with limited aqueous solubility, the presence of food in the stomach stimulates hydrochloric acid secretion, which lowers the pH, causing more rapid dissolution of the drug and better absorption. Absorption of this basic drug is reduced when gastric acid secretion is reduced (Ogata et al, 1986).

Generally, the bioavailability of drugs is better in patients in the fasted state and with a large volume of water (Fig. 5-14). However, drugs such as erythromycin, iron salts, aspirin, and nonsteroidal antiinflammatory agents (NSAID) are irritating to the GI mucosa and are given with food to reduce this irritation. For these drugs, the rate of absorption may be reduced in the presence of food, but the extent of absorption may be the same.

The dosage form of the drug may also be affected by the presence of food. Enteric-coated tablets may stay in the stomach for a longer period of time because food delays stomach emptying. Thus, the enteric-coated tablet does not reach the duodenum rapidly, delaying drug release and systemic drug absorption. In contrast, enteric-coated beads or microparticles disperse in the stomach, stomach emp-

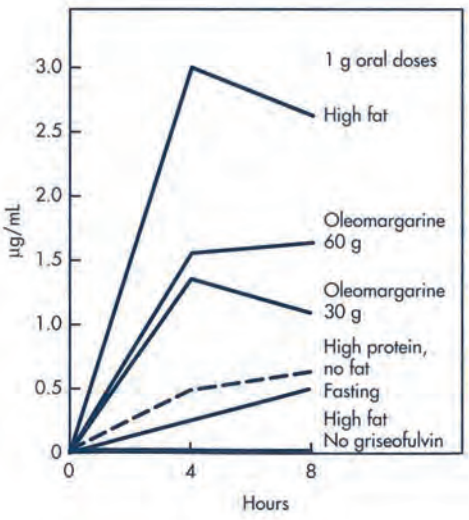


Figure 5-13. A comparison of the effects of different types of food intake on the serum griseofulvin levels following the 1.0-g oral dose.
(From Crounse, 1961, with permission.)

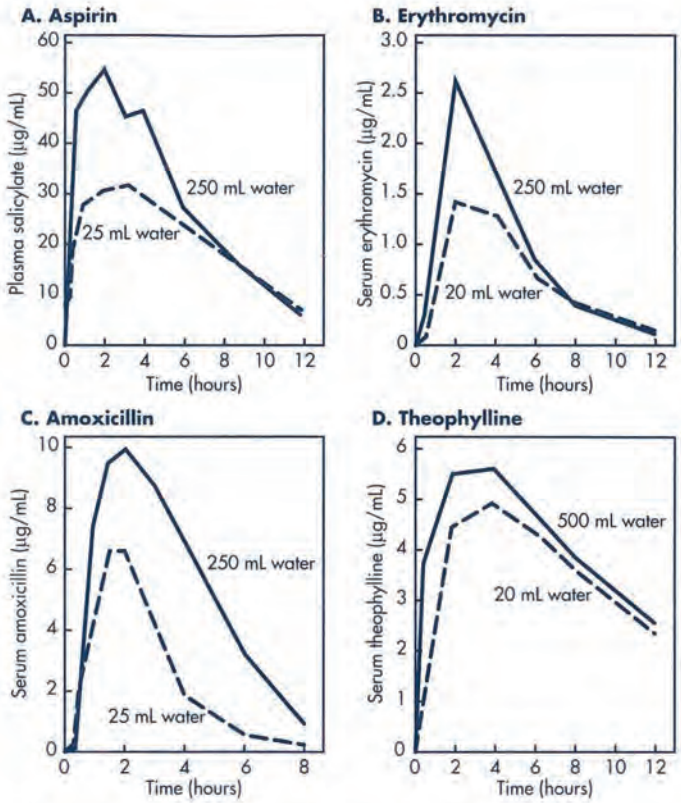


Figure 5-14. Mean plasma or serum drug levels in healthy, fasting human volunteers ($n = 6$ in each case) who received single oral doses of aspirin (650 mg) tablets, erythromycin stearate (500 mg) tablets, amoxicillin (500 mg) capsules, and theophylline (260 mg) tablets, together with large and small accompanying volumes of water.
(From Welling 1980, with permission.)

tying of the particles are less affected by food, and demonstrate more consistent drug absorption from the duodenum.

Food can also affect the integrity of the dosage form, causing an alteration in the release rate of the drug. For example, theophylline bioavailability from Theo-24 controlled-release tablets is much more rapid when given to a subject in the fed rather than fasted state (Fig. 5-15).

Double-Peak Phenomenon

Some drugs, such as ranitidine, cimetidine, and dipyridamole, after oral administration produce a blood concentration curve consisting of two peaks (Fig. 5-16). This double-peak phenomenon is generally observed after the administration of a single dose to fasted patients. The rationale for the double-peak phenomenon has been attributed to variability in stomach emptying, variable intestinal motility, presence of food, enterohepatic recycling, or failure of a tablet dosage form.

The double-peak phenomenon observed for cimetidine (Oberle and Amidon, 1987) may be due to variability in stomach emptying and intestinal flow rates during the entire absorption process after a single dose. For many drugs very little absorption occurs in the stomach. For a drug with high water solubility, dissolution

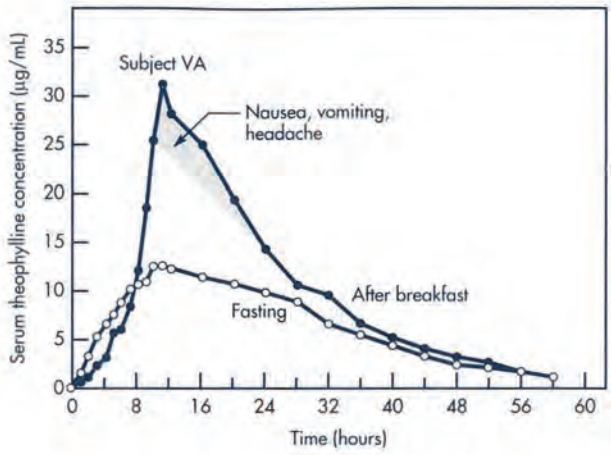


Figure 5-15. Theophylline serum concentrations in an individual subject after a single 1500 mg dose of Theo-24 taken during fasting and after breakfast. The shaded area indicates the period during which this patient experienced nausea, repeated vomiting, or severe throbbing headache. The pattern of drug release during the food regimen is consistent with "dose-dumping."
(From Hendeles et al 1985, with permission.)

of the drug occurs in the stomach, and partial emptying of the drug into the duodenum will result in the first absorption peak. A delay in stomach emptying results in a second absorption peak as the remainder of the dose is emptied into the duodenum.

In contrast, rantidine (Miller, 1984) produces a double peak after both oral or parenteral (IV bolus) administration. Ranitidine is apparently concentrated in the

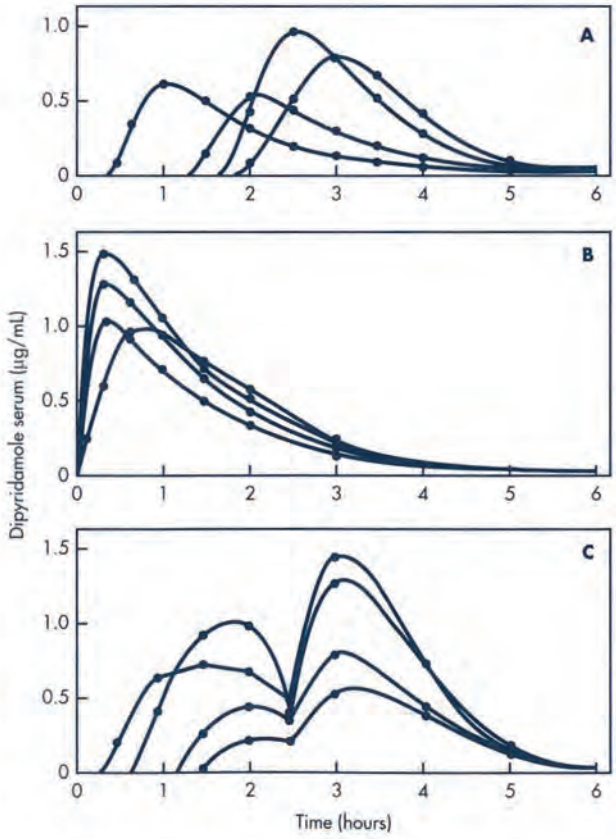


Figure 5-16. Serum concentrations of dipyridamole in 3 groups of 4 volunteers each. **A.** After taking 25 mg as tablet intact. **B.** As crushed tablet. **C.** As tablet intact 2 hours before lunch.
(From Mellinger and Bohorfoush 1966, with permission.)

bile within the gallbladder from the general circulation after IV administration. When stimulated by food, the gallbladder contracts and bile containing drug is released into the small intestine. The drug is then reabsorbed and recycled (enterohepatic recycling).

Tablet integrity may also be a factor in the production of double-peak phenomenon. Mellinger and Bohorfoush (1966) compared a whole tablet or a crushed tablet of dipyridamole in volunteers and showed that a tablet that does not disintegrate or incompletely disintegrates may have delayed gastric emptying, resulting in a second absorption peak.



PRACTICAL FOCUS

Effect of Food on Drug Administration

Many antibiotics (Table 5.6), such as penicillin and tetracycline, have delayed or reduced absorption when taken orally with food. Pharmacists regularly advise patients to take a medication either 1 hour before or 2 hours after meals to avoid any delay in drug absorption. Since fatty foods may delay stomach emptying time

TABLE 5.6 Drugs With Absorption Reduced, Delayed, Increased, or Not Affected by the Presence of Food

REDUCED	DELAYED	INCREASED	NOT AFFECTED
Amoxicillin	Acetaminophen	Canrenone	Cephradine
Ampicillin	Amoxicillin	Dicoumarol	Chlorpropamide
Aspirin	Aspirin	Griseofulvin	Digoxin (elixir)
Demethylchlortetracycline	Cefaclor	Hydralazine	Glibenclamide
Ethanol	Cephalexin	Hydrochlorothiazide	Glipizide
Isoniazid	Cephradine	Metoprolol	Melperone
Levodopa	Digoxin (solid)	Oxazepam	Metronidazole
Furosemide	Nitrofurantoin	Phenytoin	Penicillin V (acid)
Methacycline	Potassium ion	Propoxyphene	Prednisone
Oxytetracycline	Sulfadiazine	Propranolol	Propylthiouracil
Penicillin G	Sulfadimethoxine		Theophylline
Penicillin V (K)	Sulfanilamide	Slightly Increased	
Penicillin V (Ca)	Sulfisoxazole	Hetacillin	
Pencillin V (acid)			
Phenacetin			
Phenethicillin			
Phenylmercaptomethyl-pencillin			
Pivampicillin			
Propantheline			
Rifampin			
Tetracycline			
Slightly Reduced			
Doxycycline			

From Welling (1980), with permission.

beyond 2 hours, patients who have just eaten a heavy, fatty meal should take these drugs 3 hours or more after the meal, whenever possible. The presence of food may delay stomach emptying of enteric-coated tablets or nondisintegrating dosage forms for several hours. Fine granules (smaller than 1 to 2 mm in size) and tablets that disintegrate are not significantly delayed from emptying from the stomach in the presence of food.

Fluid volume tends to distend the stomach and speed up stomach emptying; however, large volume of nutrients with high caloric content supersedes that faster rate and delays stomach emptying time. Reduction in drug absorption may be caused by several factors. For example, tetracyline hydrochloride absorption is well known to be reduced by milk and food that contains calcium due to chelation. However, significant reduction may simply be the result of reduced dissolution due to increased pH. Coadministration of sodium bicarbonate raises the stomach pH and reduces tetracycline dissolution and absorption. Calcium was absent in the well-controlled experiment reported by Barr and Garrettson (1971).

Food may enhance the absorption of a drug beyond 2 hours after meals. For example, the timing of a fatty meal on the absorption of cefpodoxime proxetil was studied in 20 healthy adults (Borin et al, 1995). The area under the plasma concentration–time curve and peak drug concentration were significantly higher after administration of cefpodoxime proxetil tablets with a meal and 2 hours after a meal relative to dosing under fasted conditions or 1 hour before a meal. The time to peak concentration was not affected by food, which suggests that food increased the extent but not the rate of drug absorption. These results indicate that absorption of cefpodoxime proxetil is enhanced with food or if the drug is taken closely after a heavy meal.

Ticlopidine (Ticlid) is an antiplatelet agent commonly used to prevent thromboembolic disorders. Ticlopidine has enhanced absorption after a meal. The absorption of ticlopidine was compared in subjects who received either an antacid or food or were in a control group (fasting). Subjects who received ticlopidine 30 minutes after a fatty meal had an average of 20% increase in concentration over fasting subjects, whereas antacid reduced ticlopidine concentration by approximately the same amount. There was a higher gastrointestinal complaint in the fasting group. Many other drugs have reduced gastrointestinal side effects when taken with food. The decreased gastrointestinal side effects may greatly improve tolerance and compliance in patients.

Medications that cause gastric irritation, such as aspirin and potassium chloride, may be taken with food. In the case of enteric-coated aspirin tablets, the presence of food may delay drug absorption for several hours due to slower stomach emptying time; taking a granular or pellet enteric-coated product will reduce the delay. The patient should be advised of possible delay in onset of action of the drug when taking a drug with food.

Erythromycin has been recommended to be taken on an empty stomach, although in practice some patients cannot tolerate the drug on an empty stomach and vomit the medication. The presence of food sometimes makes the patient less nauseous with some drugs. A therapeutic alternative may be necessary at times. Oral absorption of the macrolide antibiotic dirithromycin, unlike erythromycin, is not significantly affected by antacid or food, both of which seem to slightly increase absorption.

Some drugs are recommended to be taken with food for special therapeutic purposes. For example, the drug lovastatin (Mevacor) is recommended to be taken

with food. Lovastatin inhibits (HMG-CoA reductase) cholesterol synthesis in the body and is taken long term to lower blood cholesterol.

Products that are used to curb stomach acid secretion are taken before meals in anticipation of acid secretion stimulated by food. Famotidine (Pepcid), and cimetidine (Tagamet) have been taken before meals to curb excessive acid production. Tagamet is recommended not to be taken with antacids since that may reduce its absorption. Iron supplements, and nonsteroidal antiinflammatory drugs (NSAIDS), such as ibuprofen, may be taken with food to decrease gastric irritation.

Timing of drug administration should not be based on absorption and onset information alone. Some drugs respond differently depending on the time of administration. Pravastatin is a drug for hypercholesterolemia recommended for twice a day (bid) or daily (qd) dosing. Interestingly, dosing once daily at bedtime is somewhat more effective than once in the morning. The observation is hypothesized to be related to peak cholesterol synthesis by the liver between midnight and 3 AM at night. With some anticancer drugs, time of administration may be critical, since responses have been shown to vary as related to the time of administration of the medication.

Most drugs should be taken with a full glass (approximately 8 fluid ounces) of water to ensure that drugs will wash down the esophagus. The solubility of many drugs is limited, and sufficient fluid is necessary for dissolution of the drug. Some patients may be on several drugs that are dosed frequently for months. These patients are often nauseous and are reluctant to take a lot of fluid. For example, HIV patients with active viral counts may be on an AZT or DDI combination with one or more of the protease inhibitors, Invirase (Hoffmann-La Roche), Crixivan (Merck), or Norvir (Abbott). These HIV treatments appear to be better than any previous treatment but depend on patient compliance in taking up to 12 to 15 pills daily for weeks. Any complications affecting drug absorption can influence the outcome of these therapies. With antibiotics, unabsorbed drug may influence the GI flora. Residual drug dose in the GI tract can potentially aggravate the incidence of diarrhea for drugs that cause GI disturbances.

Effect of Disease States on Drug Absorption

In theory, drug absorption may be affected by any disease that causes changes in (1) intestinal blood flow, (2) gastrointestinal motility, (3) changes in stomach emptying time, (4) gastric pH that affects drug solubility, (5) intestinal pH that affects the extent of ionization, (6) the permeability of the gut wall, (7) bile secretion, (8) digestive enzyme secretion, and (9) alteration of normal GI flora. Some factors may dominate, while other factors sometimes cancel the effect of each other. Pharmacokinetic studies comparing subjects with the disease to a control group is generally necessary to establish the effect of the disease on drug absorption.

Patients in an advanced stage of Parkinson's disease may have difficulty swallowing and greatly diminished gastrointestinal motility. A case was reported in which the patient could not be controlled with regular oral levodopa medication due to poor absorption. Infusion of oral levodopa solution using a *j*-tube gave adequate control of his symptoms. The patient was subsequently placed on this mode of therapy.

Patients on tricyclic antidepressants (imiprimine, amitriptyline, and nortriptyline) and antipsychotic drugs (phenothiazines) with anticholinergic side effects may have reduced gastrointestinal motility or even intestinal obstructions. Delay in drug absorption, especially with slow-release products have occurred.

Achlorhydric patients may not have adequate production of acids in the stomach; stomach HCl is essential for solubilizing insoluble free bases. Many weak base drugs that cannot form soluble salts will remain undissolved in the stomach when there is no hydrochloric acid present and are, therefore, unabsorbed. Salt forms of these drugs cannot be prepared since the free base readily precipitates out due to the weak basicity.

Crohn's Disease

Crohn's disease is an inflammatory disease of the distal small intestine and colon. The disease is accompanied by regions of thickening of the bowel wall, overgrowth of anaerobic bacteria, and sometimes obstruction and deterioration of the bowel occur. The effect on drug absorption is unpredictable, although impaired absorption may potentially occur because of reduced surface area and thicker gut wall for diffusion. In the case of propranolol administered orally, higher plasma propranolol concentration has been reported in patients with Crohn's disease. Alpha-1-acid glycoprotein level is increased in Crohn's disease patients. Higher alpha-1-acid glycoprotein may affect the protein binding and distribution of propranolol in the body and results in higher plasma concentration.

Celiac disease is an inflammatory disease affecting mostly the proximal small intestine. Celiac disease is caused by sensitization to gluten, a viscous protein found in cereals. Patients with celiac disease generally have an increased rate of stomach emptying and increased permeability of the small intestine. Cephalexin absorption appears to be increased in celiac disease although it is not possible to make general prediction in these patients. Other intestinal conditions that may potentially affect drug absorption include corrective surgery involving peptic ulcer, antrectomy with gastroduodenostomy, and selective vagotomy.

Drugs That Affect Absorption of Other Drugs

Propantheline bromide is an anticholinergic drug that may slow stomach emptying and motility of the small intestine. Anticholinergic drugs in general may reduce stomach acid secretion. Slower stomach emptying may cause delay in drug absorption. Tricyclic antidepressants and phenothiazines also have anticholinergic side effects that may cause slower peristalsis in the GI tract.

Metoclopramide is a drug that stimulates stomach contraction, relaxes the pyloric sphincter, and, in general, increases intestinal peristalsis which may reduce the effective time for the absorption of some drugs, and thereby reduce the peak drug concentration and the time for peak drug concentration. For example, digoxin absorption from a tablet is reduced due to metoclopramide but increased due to an anticholinergic drug, such as propantheline bromide. Allowing more time in the stomach for the tablet to dissolve generally helps with the dissolution and absorption of a poorly soluble drug but would not be helpful for a drug that is not soluble in stomach acid.

Cholestyramine is a nonabsorbable ion exchange resin for the treatment of hyperlipemia. Cholestyramine adsorbs warfarin, thyroxine, and loperamide similar to activated charcoal, thereby reducing absorption of these drugs.

Absorption of calcium in the duodenum is an active process facilitated by vitamin D, with calcium absorption as much as four times more than that in vitamin

D deficiency states. It is believed that a calcium-binding protein, which increases after vitamin D administration, binds calcium in the intestinal cell and transfers it out of the base of the cell to the blood circulation.

Nutrients That Interfere with Drug Absorption

Many nutrients substantially interfere with the absorption or metabolism of drugs in the body (Anderson, 1988; Kirk, 1995). Food intake has been reported to enhance the bioavailability of several common drugs such as propranolol, metoprolol, nitrofurantoin, and hydrochlorothiazide. In contrast, food reduces the absorption of many antibiotics such as ampicillin, tetracycline, and rifampicin. Oral drug-nutrient interactions are drug specific and can result in either an increased or decreased drug absorption. Some nutrients may reduce the gastrointestinal irritation of drugs during absorption. Knowing the nature of drug-nutrient interactions can help the clinician to avoid a high concentration of irritating medications. Diet can change the blood levels of some drugs without altering their absorption. For example, a high protein diet may cause reduced theophylline drug level due to increased liver metabolism of the drug rather than a change in the extent of absorption from the gastrointestinal tract.

Absorption of water-soluble vitamins, such as vitamin B-12 and folic acid, are aided by special absorption mechanisms. Vitamin B-12 absorption is facilitated by intrinsic factors in the stomach, where it forms a complex with the factor and is carried in the intestinal stream to the ileum, where it binds to a specific receptor. Vitamin B-12 then ultimately disassociates from the complex and is absorbed.

Grapefruit juice was found to increase the plasma level of many drugs (see Chapter 13) due to naringin that inhibits their metabolism. This is an important example showing that an increase in the blood level of a drug should not be automatically interpreted as an increase in absorption. Many substances reduce the decomposition/metabolism of drugs in the GI tract and, therefore, indirectly increase the amount absorbed.



FREQUENTLY ASKED QUESTIONS

1. What is an "absorption window"?
2. Why are some drugs absorbed better with food and others retarded by food?
3. If a drug is administered orally as a solution, does it mean that all of the drug will be systemically absorbed?
4. What is the biggest biological factor that contributes to delay in drug absorption?



LEARNING QUESTIONS

1. A recent bioavailability study in adult human volunteers demonstrated that after the administration of a single enteric-coated aspirin granule product given with a meal, the plasma drug levels resembled the kinetics of a sustained-release drug product. In contrast, when the product was given to fasted subjects, the plasma drug levels resembled the kinetics of an immediate-release drug product. Give a plausible explanation for this observation.
2. The aqueous solubility of a weak base drug is poor. In an intubation (intestinal perfusion) study, the drug was not absorbed beyond the jejunum. Which of the following would be the correct strategy to improve drug absorption from the intestinal tract?
   a. Give the drug as a suspension and recommend that the suspension be taken on an empty stomach.
   b. Give the drug as a hydrochloride salt.
   c. Give the drug with milk.
   d. Give the drug as a suppository.
3. What is the primary reason that protein drugs like insulin are not given orally for systemic absorption?
4. Which of the following statements are true regarding an acidic drug with a pK_a of 4?
   a. The drug is more soluble in the stomach when food is present.
   b. The drug is more soluble in the duodenum than in the stomach.
   c. The drug is more soluble when dissociated.
5. Which region of the gastrointestinal tract is most populated by bacteria? What types of drugs might affect the gastrointestinal flora?
6. Discuss methods by which the first-pass effect (presystemic absorption) may be circumvented.
7. Misoprostol (Cytotec, GD Searle) is a synthetic prostaglandin E_1 analog. According to the manufacturer, the following information was obtained when misoprostol was taken with an antacid or high-fat breakfast.

Condition	C_{max} (pg/mL)	$AUC_{0-4\ hr}$ (pg hr/mL)	t_{max} (min)
Fasting	811 ± 317^a	417 ± 135	14 ± 8
With antacid	689 ± 315	349 ± 108^b	20 ± 14
With high-fat breakfast	303 ± 176^b	373 ± 111	64 ± 79^b

[a] Results are expressed as the mean ± SD (standard deviation).
[b] Comparisons with fasting results statistically significant, $P < .05$.

What is the effect of *antacid* and *high-fat breakfast* on the bioavailability of misoprostol? Comment on how these factors affect the rate and extent of systemic drug absorption.

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6

BIOPHARMACEUTIC CONSIDERATIONS IN DRUG PRODUCT DESIGN

Drugs are not generally given as a pure chemical drug substance but formulated into a finished dosage form (drug product), such as a tablet, capsule, etc, before administering to a patient for therapy. A formulated drug product usually includes the active drug substance and selected ingredients (excipients) that make up the dosage form. Common pharmaceutical dosage forms include liquid, tablet, capsule, injection, suppository, transdermal systems, and topical products. Formulating a drug product requires a thorough understanding of the biopharmaceutic principles of drug delivery.

Biopharmaceutics is the study of the *in vitro* impact of the physicochemical properties of the drug and drug product on drug delivery to the body under normal or pathologic conditions. A primary concern in biopharmaceutics is the bioavailability of drugs. *Bioavailability* refers to the measurement of the rate and extent of active drug that reaches the systemic circulation. Because the systemic blood circulation delivers the therapeutically active drug to the tissues and to the site of action of the drug, changes in bioavailability affect changes in the pharmacodynamics and toxicity of the drug. The aim of biopharmaceutics is to adjust the delivery of drug from the drug product in such a manner as to provide optimal therapeutic activity and safety for the patient.

Biopharmaceutic studies allow for the rational design of drug products based on (1) the physical and chemical properties of the drug substance, (2) route of drug administration including the anatomic and physiologic nature of the application site (eg, oral, topical, injectable, implant, transdermal patch, etc), and (4) desired pharmacodynamic effect (eg, immediate or prolonged activity), (5) toxicologic properties of the drug, (6) safety of excipients, and (7) effect of excipients and dosage form on drug delivery. For example, some drugs are intended for topical or local therapeutic action at the site of administration. For these drugs, systemic absorption is undesirable. Drugs intended for local activity are designed to

have a direct pharmacodynamic action without affecting other body organs. These drugs may be applied topically to the skin, nose, eye, mucous membranes, buccal cavity, throat, and rectum. A drug intended for local activity may be given intravaginally, into the urethral tract, intranasally, in the ear, on the eye, or orally. Examples of drugs used for local action include anti-infectives, antifungals, local anesthetics, antacids, astringents, vasoconstrictors, antihistamines, and corticosteroids. However, some systemic drug absorption may occur with drugs used for local activity.

Each route of drug application presents special biopharmaceutic considerations in drug product design. For example, the design of a vaginal tablet formulation for the treatment of a fungal infection must consider ingredients compatible with vaginal anatomy and physiology. An eye medication may require special biopharmaceutic considerations including appropriate pH, isotonicity, sterility, local irritation to the cornea, draining by tears, and concern for systemic drug absorption.

For a drug administered by extravascular route (eg, intramuscular injection), local irritation, drug dissolution, and drug absorption from the intramuscular site are some of the factors that must be considered. The systemic absorption of a drug from an extravascular site is influenced by the anatomic and physiologic properties of the site and the physicochemical properties of the drug and the drug product. If the drug is given by the intravascular route (eg, intravenous administration), systemic drug absorption is considered complete or 100% bioavailable because the drug is placed directly into the general circulation.

By carefully choosing the route of drug administration and properly designing the drug product, the bioavailability of the active drug can be varied from rapid and complete absorption to a slow, sustained rate of absorption or, even, virtually no absorption, depending on the therapeutic objective. Once the drug is systemically absorbed, normal physiologic processes for distribution and elimination occur, which usually are not influenced by the specific formulation of the drug. The rate of drug release from the product and the rate of drug absorption are important in determining the distribution, onset, intensity, and duration of the drug action.

Biopharmaceutic considerations often determine the ultimate *dose* and *dosage form* of a drug product. For example, the dosage for a drug intended for local activity, such as a topical dosage form, is often expressed in concentration or as percentage of the active drug in the formulation (eg, 0.5% hydrocortisone cream). The amount of drug applied is not specified because the concentration of the drug at the active site relates to the pharmacodynamic action. However, biopharmaceutic studies must be performed to ensure that the dosage form does not irritate, cause an allergic response, or allow systemic drug absorption. In contrast, the dosage of a drug intended for systemic absorption is given on the basis of mass, such as mg or g. In this case, dosage is based on the amount of drug that is absorbed systemically and dissolved in an apparent volume of distribution to produce a desired drug concentration at the target site. The dose may be based on the weight or surface area of the patient to account for the differences in the apparent volume of distribution. Thus, doses are expressed as mass per unit of body weight (mg/kg) or mass per unit of body surface area (mg/m^2).

RATE-LIMITING STEPS IN DRUG ABSORPTION

Systemic drug absorption from a drug product consists of a succession of rate processes (Fig. 6-1). For solid oral, immediate-release drug products (eg, tablet,

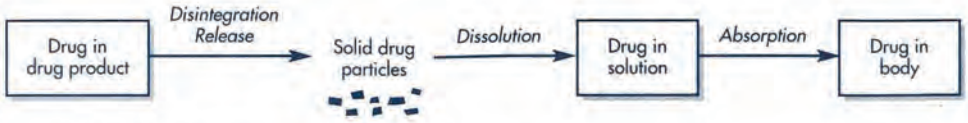


Figure 6-1. Rate processes of drug bioavailability.

capsule), the rate processes include (1) disintegration of the drug product and subsequent release of the drug; (2) dissolution of the drug in an aqueous environment; and (3) absorption across cell membranes into the systemic circulation. In the process of drug disintegration, dissolution, and absorption, the rate at which drug reaches the circulatory system is determined by the slowest step in the sequence.

The slowest step in a series of kinetic processes is called the *rate-limiting step.* Except for controlled release products, disintegration of a solid oral drug product is usually more rapid than drug dissolution and drug absorption. For drugs that have very poor aqueous solubility, the rate at which the drug dissolves (dissolution) is often the slowest step and, therefore, exerts a rate-limiting effect on drug bioavailability. In contrast, for a drug that has a high aqueous solubility, the dissolution rate is rapid, and the rate at which the drug crosses or permeates cell membranes is the slowest or rate-limiting step.

PHARMACEUTIC FACTORS AFFECTING DRUG BIOAVAILABILITY

Considerations in designing a drug product that will deliver the active drug with the desired bioavailability characteristics include (1) the type of drug product (eg, solution, suspension, suppository); (2) the nature of the excipients in the drug product; (3) the physicochemical properties of the drug molecule; and (4) the route of drug administration.

Disintegration

For immediate-release, solid oral dosage forms, the drug product must disintegrate into small particles and release the drug. For monitoring uniform tablet disintegration, the United States Pharmacopeia (USP) established an official disintegration test. Solid drug products exempted from disintegration tests include troches, tablets which are intended to be chewed, and drug products intended for sustained release or prolonged or repeat action. The process of disintegration does not imply complete dissolution of the tablet and/or the drug. Complete disintegration is defined by the USP (23rd edition) as "that state in which any residue of the tablet, except fragments of insoluble coating, remaining on the screen of the test apparatus in the soft mass have no palpably firm core." The official apparatus for the disintegration test and procedure is described in the USP. Separate specifications are given for uncoated tablets, plain coated tablets, enteric tablets, buccal tablets, and sublingual tablets.

Although disintegration tests allow for precise measurement of the formation of fragments, granules, or aggregates from solid dosage forms, no information is obtained from these tests on the rate of dissolution of the active drug. However, the

disintegration test serves as a component in the overall quality control of tablet manufacture.

Dissolution

Dissolution is the process by which a chemical or drug becomes dissolved in a solvent. In biologic systems, drug dissolution in an aqueous medium is an important prior condition of systemic absorption. The rate at which drugs with poor aqueous solubility dissolve from an intact or disintegrated solid dosage form in the gastrointestinal tract often controls the rate of systemic absorption of the drug. Thus, dissolution tests are discriminating of formulation factors that may affect drug bioavailability.

Noyes and Whitney (1897) and other investigators studied the rate of dissolution of solid drugs. According to their observations, the steps in dissolution include the process of drug dissolution at the surface of the solid particle, thus forming a saturated solution around the particle. The dissolved drug in the saturated solution known as the *stagnant layer* diffuses to the bulk of the solvent from regions of high drug concentration to regions of low drug concentration (Fig. 6-2).

The overall rate of drug dissolution may be described by the *Noyes–Whitney equation* (Eq. 6.1).

$$\frac{dC}{dt} = \frac{DA}{h}(C_S - C) \qquad \textbf{(6.1)}$$

where dC/dt = rate of drug dissolution at time t, D = diffusion rate constant, A = surface area of the particle, C_S = concentration of drug (equal to solubility of drug) in the stagnant layer, C = concentration of drug in the bulk solvent, and h = thickness of the stagnant layer.

The rate of dissolution, $\frac{dC}{dt}$ is the rate of drug dissolved per time expressed as concentration change in the dissolution fluid.

The Noyes–Whitney equation shows that dissolution in a flask may be influenced by the physicochemical characteristics of the drug, the formulation, and the solvent. Drug in the body, particularly in the gastrointestinal tract, is considered to be dissolving in an aqueous environment, permeation of drug across the gut wall (a model lipid membrane) is affected by the ability of the drug to diffuse (D) and to partition between the lipid membrane. A favorable partition coefficient ($K_{oil/water}$) will facilitate drug absorption.

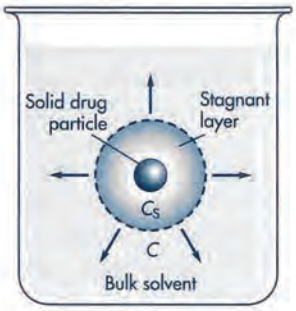


Figure 6-2. Dissolution of a solid drug particle in a solvent. (C_S = concentration of drug in the stagnant layer, C = concentration of drug in the bulk solvent.)

In addition to these factors, the temperature of the medium and the agitation rate also affect the rate of drug dissolution. *In vivo*, the temperature is maintained at a constant 37°C, and the agitation (primarily peristaltic movements in the gastrointestinal tract) is reasonably constant. In contrast, *in vitro* studies of dissolution kinetics require maintenance of constant temperature and agitation. Temperature is generally kept at 37°C, and the agitation or stirring rate is held to a specified rpm (revolutions per minute). An increase in temperature will increase the kinetic energy of the molecules and increase the diffusion constant, D. An increase in agitation of the solvent medium will reduce the thickness, h, of the stagnant layer, allowing for more rapid drug dissolution.

Factors that affect drug dissolution of a solid oral dosage form include (1) the physical and chemical nature of the active drug substance, (2) the nature of the ingredients, and (3) the method of manufacture.

PHYSICOCHEMICAL NATURE OF THE DRUG

The physical and chemical properties of the solid drug particles not only affect dissolution kinetics but are important considerations in designing the dosage form (Table 6.1). For example, intravenous solutions are difficult to prepare with drugs that have poor aqueous solubility. Drugs that are physically or chemically unstable may require special excipient, coating, or manufacturing process to protect the drug from degradation. The potent pharmacodynamic activity of drugs, such as estrogens and other hormones, penicillin antibiotics, cancer chemotherapeutic agents, and others, may cause adverse reactions to personnel who are exposed to these drugs during manufacture and also presents a problem.

Solubility, pH, and Drug Absorption

The *solubility–pH profile* is a plot of the solubility of the drug at various physiologic pH values. For designing oral dosage forms, the formulator must consider that the

TABLE 6.1 Physicochemical Properties for Consideration in Drug Product Design

pK_a and pH Profile	Necessary for optimum stability and solubility of the final product.
Particle Size	May affect the solubility of the drug and therefore the dissolution rate of the product.
Polymorphism	The ability of a drug to exist in various crystal forms may change the solubility of the drug. Also, the stability of each form is important, because polymorphs may convert from one form to another.
Hygroscopicity	Moisture absorption may affect the physical structure as well as stability of the product.
Partition Coefficient	May give some indication of the relative affinity of the drug for oil and water. A drug that has high affinity for oil may have poor release and dissolution from the foundation.
Excipient Interaction	The compatibility of the excipients with the drug and sometimes trace elements in excipients may affect the stability of the product. It is important to have specifications of all raw materials.
pH Stability Profile	The stability of solutions is often affected by the pH of the vehicle; furthermore, because the pH in the stomach and gut is different, knowledge of the stability profile would help to avoid or prevent degradation of the product during storage or after administration.

natural pH environment of the gastrointestinal tract varies from acidic in the stomach to slightly alkaline in the small intestine. A basic drug is more soluble in an acidic medium forming a soluble salt. Conversely, an acid drug is more soluble in the intestine, forming a soluble salt at the more alkaline pH. The solubility–pH profile gives a rough estimation of the completeness of dissolution for a dose of a drug in the stomach or in the small intestine. Solubility may be improved with the addition of an acidic or basic excipient. Solubilization of aspirin, for example, may be increased by the addition of an alkaline buffer. In the formulation of controlled-release drugs, buffering agents may be added to slow or modify the release rate of a fast-dissolving drug. To be effective, however, the controlled-release drug product must be a nondisintegrating dosage form. The buffering agent is released slowly rather than rapidly so that the drug does not dissolve immediately in the surrounding gastrointestinal fluid.

Stability, pH, and Drug Absorption

The *pH–stability profile* is a plot of the reaction rate constant for drug degradation versus pH. If drug decomposition occurs by acid or base catalysis, some prediction for degradation of the drug in the gastrointestinal tract may be made. For example, erythromycin has a pH-dependent stability profile. In acidic medium, as in the stomach, erythromycin decomposition occurs rapidly, whereas, in neutral or alkaline pH, the drug is relatively stable. Consequently, erythromycin tablets are enteric coated to protect against acid degradation in the stomach. This information also led subsequently to the preparation of a less water soluble erythromycin salt that is more stable in the stomach. The dissolution rate of erythromycin powder varied from 100% dissolved in 1 hour to less than 40% dissolved in 1 hour. The slow-dissolving raw drug material (active pharmaceutical ingredient) also resulted in slow-dissolving drug products. Therefore, the dissolution of powdered raw drug material is a very useful *in vitro* method for the prediction of a bioavailability problem of the erythromycin product in the body.

Particle Size and Drug Absorption

The effective surface area of the drug is increased enormously by a reduction in the particle size. Because dissolution is thought to take place at the surface of the solute (drug), the greater the surface area, the more rapid the rate of drug dissolution. The geometric shape of the particle also affects the surface area, and, during dissolution, the surface is constantly changing. In dissolution calculations, the solute particle is usually assumed to have retained its geometric shape.

Particle size and particle size distribution studies are important for drugs that have low water solubility. Many hydrophobic drugs are very active intravenously but are not very effective when given orally due to poor absorption. Griseofulvin, nitrofurantoin, and many steroids are drugs with low aqueous solubility; reduction of the particle size decreased by milling to a micronized form has improved the oral absorption of these drugs. Smaller particle size results in an increase in the total surface area of the particles, enhances water penetration into the particles, and increases the dissolution rates. With poorly soluble drugs, a disintegrant may be added to the formulation to ensure rapid disintegration of the tablet and release of the particles. The addition of surface-active agents may increase wetting as well as solubility of these drugs.

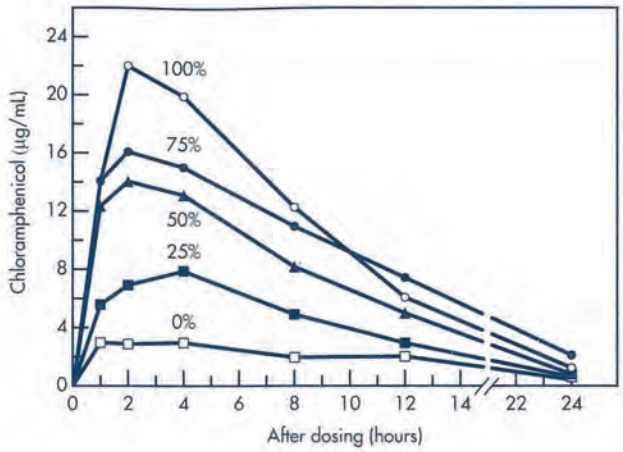


Figure 6-3. Comparison of mean blood serum levels obtained with chloramphenicol palmitate suspensions containing varying ratios of α and β polymorphs, following single oral dose equivalent to 1.5 g chloramphenicol. Percentage polymorph β in the suspension.
(From Aguiar et al, 1967, with permission.)

Polymorphic Crystals, Solvates, and Drug Absorption

Polymorphism refers to the arrangement of a drug in various crystal forms or polymorphs. Polymorphs have the same chemical structure but different physical properties, such as solubility, density, hardness, and compression characteristics. Some polymorphic crystals have much lower aqueous solubility than the amorphous forms, causing a product to be incompletely absorbed. Chloramphenicol, for example, has several crystal forms, and when given orally as a suspension, the drug concentration in the body was found to be dependent on the percent of β-polymorph in the suspension. The β-form is more soluble and better absorbed (Fig. 6-3). In general, the crystal form has the lowest free energy is the most stable polymorph. A drug that exists as an amorphous form (noncrystalline form) generally dissolves more rapidly than the same drug in a more structurally rigid crystalline form. Some polymorphs are metastable and may convert to a more stable form over time. A change in crystal form may cause problems in manufacturing the product. For example, a change in the crystal structure of the drug may cause cracking in a tablet or even prevent a granulation to be compressed into a tablet. Reformulation of a product may be necessary if a new crystal form of a drug is used. Some drugs interact with solvent during preparation to form a crystal called *solvate*. Water may form a special crystal with drugs called *hydrates*; for example, erythromycin hydrates have quite different solubility compared to the anhydrous form of the drug (Fig. 6-4). Ampicillin trihydrate, on the other hand, was reported to be less absorbed than the anhydrous form of ampicillin due to faster dissolution of the latter.

FORMULATION FACTORS AFFECTING DRUG DISSOLUTION

Excipients are added to a formulation to provide certain functional properties to the drug and dosage form. Some of these functional properties of the excipients are used

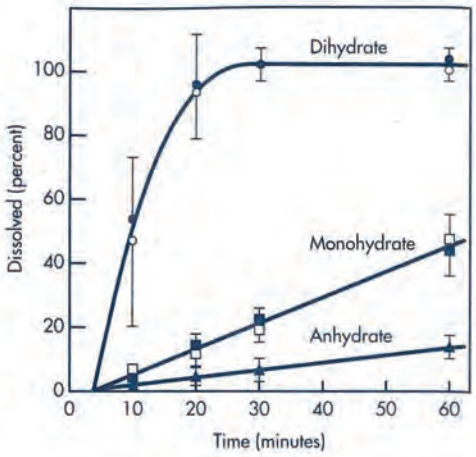


Figure 6-4. Dissolution behavior of erythromycin dihydrate, monohydrate, and anhydrate in phosphate buffer (pH 7.5) at 37°C.
(From Allen et al, 1978, with permission.)

to improve the compressibility of the active drug, stabilize the drug from degradation, decrease gastric irritation, control the rate of drug absorption from the absorption site, increase drug bioavailability, etc. Some of the excipients used in the manufacture of solid and liquid drug products are listed in Tables 6.2 and 6.3.

Excipients in the drug product may also affect dissolution kinetics of the drug either by altering the medium in which the drug is dissolving or by reacting with the drug itself. Some of the more common manufacturing problems that affect dissolution are listed on Table 6.2. Other excipients include suspending agents that increase the viscosity of the drug vehicle and thereby diminish the rate of drug dissolution from suspensions. Tablet lubricants, such as magnesium stearate, may repel water and reduce dissolution when used in large quantities. Coatings, particularly shellac upon aging can decrease the dissolution rate. However, surfactants may affect drug dissolution in an unpredictable fashion. Low concentrations of surfactants decrease the surface tension and increase the rate of drug dissolution, whereas higher surfactants concentrations tend to form micelles with the drug and thus decrease the dissolution rate. Large drug particles have a smaller surface area and dissolve more slowly than smaller particles. High compression of tablets without

TABLE 6.2 Common Excipients Used in Solid Drug Products

EXCIPIENT	PROPERTY IN DOSAGE FORM
Lactose	Diluent
Dibasic calcium phosphate	Diluent
Starch	Disintegrant, diluent
Microcrystalline cellulose	Disintegrant, diluent
Magnesium stearate	Lubricant
Stearic acid	Lubricant
Hydrogenated vegetable oil	Lubricant
Talc	Lubricant
Sucrose (solution)	Granulating agent
Polyvinyl pyrrolidone (solution)	Granulating agent
Hydroxypropylmethylcellulose	Tablet-coating agent
Titinium dioxide	Combined with dye as colored coating
Methylcellulose	Coating or granulating agent
Cellulose acetate phthalate	Enteric coating agent

TABLE 6.3 Common Excipients Used in Oral Liquid Drug Products

EXCIPIENT	PROPERTY IN DOSAGE FORM
Sodium carboxymethylcellulose	Suspending agent
Tragacanth	Suspending agent
Sodium alginate	Suspending agent
Xanthan gum	Thixotropic suspending agent
Veegum	Thixotropic suspending agent
Sorbitol	Sweetener
Alcohol	Solubilizing agent, preservative
Propylene glycol	Solubilizing agent
Methyl, propylparaben	Preservative
Sucrose	Sweetener
Polysorbates	Surfactant
Sesame oil	For emulsion vehicle
Corn oil	For emulsion vehicle

sufficient disintegrant may cause poor disintegration of a compressed tablet. Some excipients, such as sodium bicarbonate, may change the pH of the medium surrounding the active drug substance. Aspirin, a weak acid when formulated with sodium bicarbonate will form a water-soluble salt in an alkaline medium in which the drug rapidly dissolves. The term for this process is *dissolution in a reactive medium.* The solid drug dissolves rapidly in the reactive solvent surrounding the solid particle. However, as the dissolved drug molecules diffuse outward into the bulk solvent, the drug may precipitate out of solution with a very fine particle size. These small particles have enormous collective surface area, dispersing and redissolving readily for more rapid absorption upon contact with the mucosal surface.

Excipients in a formulation may interact directly with the drug to form a water-soluble or water-insoluble complex. For example, if tetracycline is formulated with calcium carbonate, an insoluble complex of calcium tetracycline is formed that has a slow rate of dissolution and poor absorption.

Excipients may be added intentionally to the formulation to enhance the rate and extent of drug absorption or to delay or slow the rate of drug absorption (Table 6.4). For example, excipients that increase the aqueous solubility of the drug generally increase the rate of dissolution and drug absorption. Excipients may increase the retention time of the drug in the gastrointestinal tract and therefore increase

TABLE 6.4 Effect of Excipients on the Pharmacokinetic Parameters of Oral Drug Products[a]

EXCIPIENTS	EXAMPLE	K_A	T_{MAX}	AUC
Disintegrants	Avicel, Explotab	↑	↓	↑/—
Lubricants	Talc, hydrogenated vegetable oil	↓	↑	↓/—
Coating agent	Hydroxypropylmethyl cellulose	—	—	—
Enteric coat	Cellulose acetate phthalate	↓	↑	↓/—
Sustained-release agents	Methylcellulose, ethylcellulose	↓	↑	↓/—
Sustained-release agents (waxy agents)	Castorwax, Carbowax	↓	↑	↓/—
Sustained-release agents (gum/viscous)	Veegum, Keltrol	↓	↑	↓/—

[a] This may be concentration and drug dependent. ↑ = Increase, ↓ = decrease, — = no effect, k_a = absorption rate constant, t_{max} = time for peak drug concentration in plasma, AUC = area under the plasma drug concentration time curve.

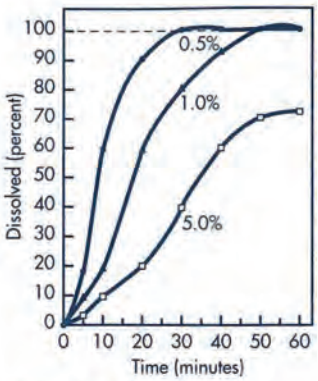


Figure 6-5. Effect of lubricant on drug dissolution. Percentage of magnesium stearate in formulation.

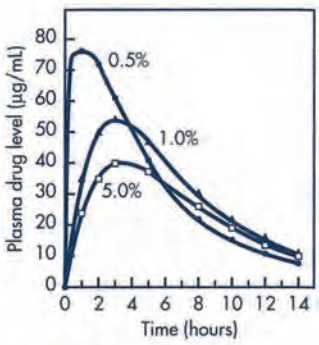


Figure 6-6. Effect of lubricant on drug absorption. Percentage of magnesium stearate in formulation. Incomplete drug absorption occurs for formulation with 5% magnesium stearate.

the total amount of drug absorbed. Excipients may act as carriers to increase drug diffusion across the intestinal wall. In contrast, many excipients may retard drug dissolution and thus reduce drug absorption. Common excipients found in oral drug products are listed in Table 6.2 and Table 6.3. Formulations contain various components (excipients) that are pharmacodynamically inert but that functionally enhance the drug and the dosage form. For solid oral dosage forms such as compressed tablets, excipients may include: (1) diluent (eg, lactose); (2) disintegrant (eg, starch); (3) lubricant (eg, magnesium stearate); and (4) other components such as binding and stabilizing agents. When improperly used in the formulation, the rate and extent of drug absorption may be affected. For example, Figure 6-5 shows that an excessive quantity of magnesium stearate (a hydrophobic lubricant) in the formulation may retard drug dissolution and slow the rate of drug absorption. The total amount of drug absorbed may also be reduced (Fig. 6-6). To prevent this problem, the lubricant level should be decreased or a different lubricant selected. Sometimes, increasing the amount of disintegrant may overcome the retarding effect of lubricants on dissolution. However, with some poorly soluble drugs an increase in disintegrant level has little or no effect on drug dissolution because the fine drug particles are not wetted. The influence of some common ingredients on drug absorption parameters is summarized in Table 6.4. These are general trends for typical preparations.

IN VITRO DISSOLUTION TESTING

Dissolution tests *in vitro* measure the rate and extent of dissolution of the drug in an aqueous medium in the presence of one or more excipients contained in the drug products. A bioavailability problem may be uncovered by a suitable dissolution method. However, the dissolution testing condition reveals that the bioavailability problem differs with each drug formulation. A reasonable approach involves selecting a dissolution method in which the acceptable and unacceptable drug formulation is distinguished by having different dissolution rates. Different agitation rates, different mediums (including different pH), and different types of dissolu-

TABLE 6.5 Dissolution of Erythromycin Stearate Bulk Drug and Corresponding Tablets

	PERCENT DISSOLUTION AFTER 1.0 HR		
CURVE NO.	BULK DRUG	500-MG TABLET	250-MG TABLET
4	49	44	
6	72	70	
7	75	70	
—	78	—	80
8	82	75	
9	92	85	

From Philip and Daly (1983), with permission.

tion apparatus should be tried. Once differences in dissolution rates are found, the formulation of the drug product may be matched with the dissolution rates to get an empirically acceptable criteria for the product. The composition and supplies of the raw materials may then be examined to reveal the problem. In one example, Philip and Daly (1983) devised a method using pH 6.6 phosphate buffer as the dissolution medium instead of 0.1 N HCL to avoid instability of the drug. Using the testing temperature at 22°C and the USP paddle method at 50 rpm, the dissolution of the various erythromycin tablets varied with the source of the bulk drug (as shown in Table 6.5 and Figure 6-7). There are a number of factors that must be considered when performing a dissolution test.

The size and shape of the dissolution vessel may affect the rate and extent of dissolution. For example, the vessel may range in size from several milliliters to several liters. The shape may be round-bottomed or flat, so that the tablet might lie in a different position in different experiments. The usual volume of the medium is 500 to 1000 mL. Drugs that are not very water soluble may require use of a very-large-capacity vessel (up to 2000 mL) to observe significant dissolution. *Sink con-*

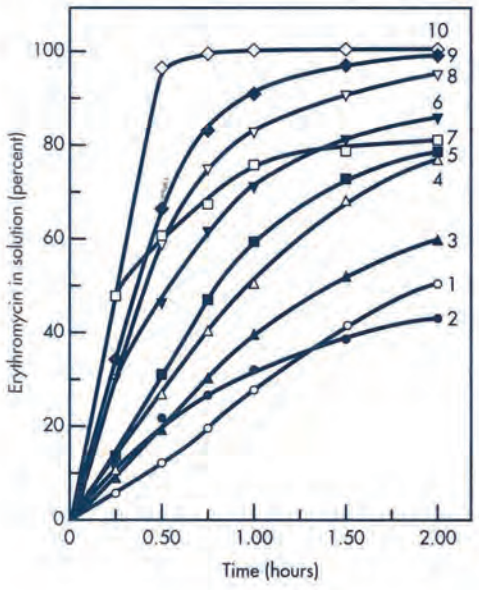


Figure 6-7. Dissolution profile of various lots of erythromycin stearate as a function of time (0.05 M pH 6.6 phosphate buffer).
(From Philip and Daly, 1983, with permission.)

ditions is a term referring an excess volume of medium that allows the solid drug to continuously dissolve. If the drug solution becomes saturated, no further net drug dissolution will take place. According to the USP (1995), "the quantity of medium used should be not less than 3 times that required to form a saturated solution of the drug substance."

The amount of agitation and the nature of the stirrer affect the dissolution rate. Stirring rates must be controlled, and specifications differ between drug products. Low stirring rates (50 to 100 rpm) are more discriminating of formulation factors affecting dissolution than higher stirring rates. The temperature of the dissolution medium must be controlled and variations in temperature must be avoided. Most dissolution tests are performed at 37°C.

The nature of the dissolution medium will also affect the dissolution test. The solubility of the drug must be considered as well as the amount of drug in the dosage form. The dissolution medium should not be saturated by the drug (ie, sink conditions are maintained). Usually, a volume of medium larger than the amount of solvent needed to completely dissolve the drug is used in such tests. Which medium is best is a matter of considerable controversy. The preferred dissolution medium in USP dissolution tests is deaerated water or if substantiated by the solubility characteristics of the drug or formulation, a buffered aqueous solution (typically pH 4 to 8) or dilute HCl may be used. The significance of deareation of the medium should be determined. Various investigators have used 0.1 N HCl, phosphate buffer, simulated gastric juice, water, and simulated intestinal juice, depending on the nature of the drug product and the location in the gastrointestinal tract where the drug is expected to dissolve.

The design of the dissolution apparatus, along with the factors described above, has a marked effect on the outcome of the dissolution test. No single apparatus and test can be used for all drug products. Each drug product must be tested individually with the dissolution test that best correlates to *in vivo* bioavailability.

Usually, the report on the dissolution test will state that a certain percentage of the labeled amount of drug product must dissolve within a specified period of time. In practice, the absolute amount of drug in the drug product may vary from tablet to tablet. Therefore, a number of tablets from each lot are usually tested to get a representative dissolution rate for the product.

COMPENDIAL METHODS OF DISSOLUTION

The USP-23 provides several official methods for carrying out dissolution tests of tablets, capsules and other special products such as transdermal preparations. Tablets are grouped into uncoated, plain-coated, and enteric-coated tablets. The selection of a particular method for a drug is usually specified in the monograph for a particular drug product. Buccal and sublingual tablets are tested applying the uncoated tablet procedure.

Rotating Basket Method (Apparatus 1)

The rotating basket method consists of a cylindrical basket held by a motor shaft. The basket holds the sample and rotates in a round flask containing the dissolution medium. The entire flask is immersed in a constant-temperature bath set at 37°C. The rotating speed and the position of the basket must meet specific re-

quirements set forth in the current USP. The most common rotating speed for the basket method is 100 rpm. Dissolution calibration standards are available to make sure that these mechanical and operating requirements are met. Calibration tablets containing prednisone are made specially for dissolution tests requiring disintegrating tablets, whereas salicylic acid calibration tablets are used as a standard requiring nondisintegrating tablets. Apparatus 1 is generally preferred for capsules and for dosage forms that tend to float or disintegrate slowly.

Paddle Method (Apparatus 2)

The paddle method, or Apparatus 2, consists of a special, coated paddle that minimizes turbulence due to stirring (Fig. 6-8). The paddle is vertically attached to a variable-speed motor that rotates at a controlled speed. The tablet or capsule is placed into the round-bottom dissolution flask, which minimizes turbulence of the dissolution medium. The apparatus is housed in a constant-temperature water bath

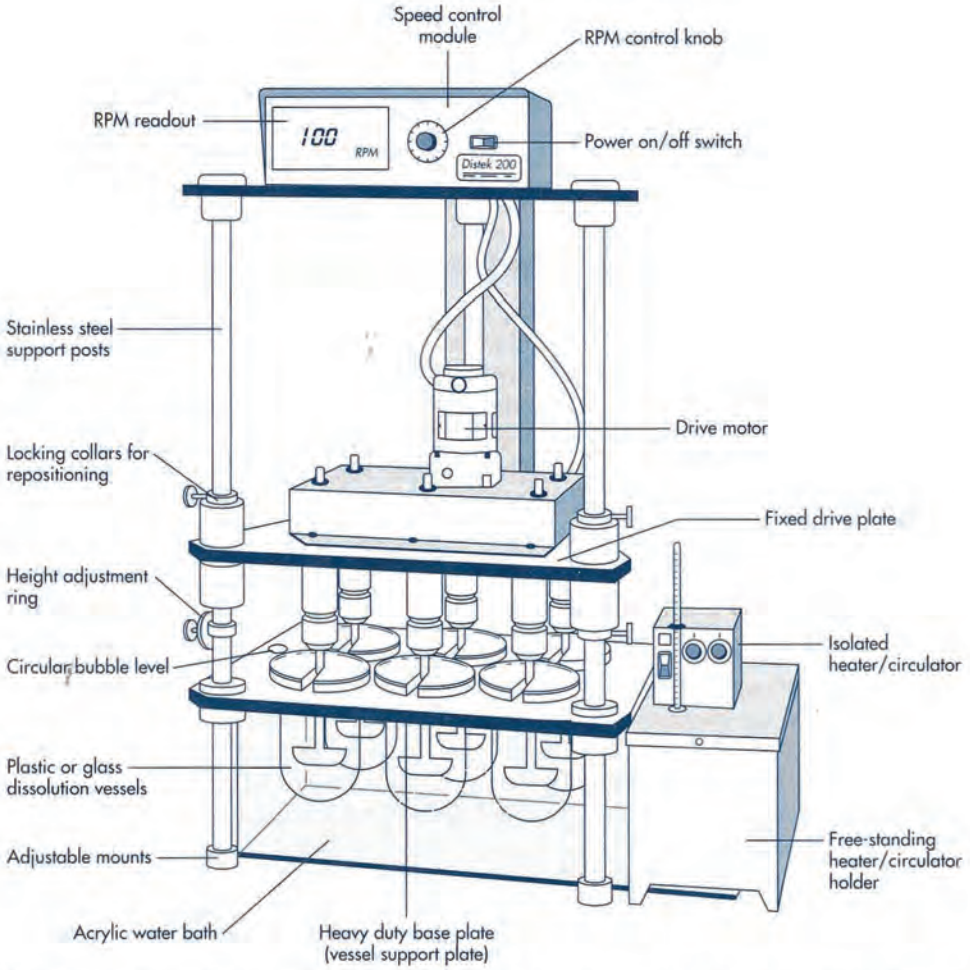


Figure 6-8. Typical set up for performing the USP dissolution test with the Distek 2000. The system is equipped with a height adjustment ring for easy adjustment of paddle height. (Drawing courtesy of Distek Inc, Somerset, NJ.)

maintained at 37°C similar to that of the rotating-basket method. The position and alignment of the paddle are specified in the USP. The paddle method is very sensitive to tilting. Improper alignment may drastically affect the dissolution results with some drug products. The same set of dissolution calibration standards is used to check the equipment before tests are run. The most common operating speeds for Apparatus 2 are 50 rpm for solid oral dosage forms and 25 rpm for suspensions. Apparatus 2 is generally preferred for tablets. A *sinker* such as a few turns of platinum wire may be used to prevent a capsule from floating. The sinker should not alter the dissolution characteristics of the dosage form.

Reciprocating Cylinder Method (Apparatus 3)

This apparatus consists of a set of cylindrical, flat-bottomed glass vessels equipped with reciprocating cylinders for dissolution testing of extended release products, particularly the bead-type modified release dosage forms. Six units are tested and the dissolution media is maintained at 37°C.

Flow-Through Cell Method (Apparatus 4)

The apparatus consists of a reservoir for the dissolution medium and a pump forcing dissolution medium through the cell that holds the test sample. Flow rate ranges from 4 to 16 mL/minute. Six samples are tested during the dissolution testing and the medium is maintained at 37°C. Apparatus 4 may be used for modified release dosage forms that contain active ingredients having very limited solubility.

Paddle Over Disk Method (Apparatus 5)

The USP-23 lists a "paddle over disk" method for testing the release of drugs from transdermal products. The apparatus consists of a sample holder or disk assembly that holds the product. The entire preparation is placed in a dissolution flask filled with specified medium maintained at 32°C. The paddle is placed directly over the disk assembly. Samples are drawn midway between the surface of the dissolution medium and the top of the paddle blade at specified times. Similar to dissolution testing with capsules and tablets, 6 units are tested during each run. Acceptance criteria are stated in the individual drug monographs.

Cylinder Method (Apparatus 6)

The cylinder method for testing transdermal preparation is modified from the basket method (Apparatus 1). In place of the basket, a stainless steel cylinder is used to hold the sample. The sample is mounted onto cuprophan (an inert porous cellulosic material) and the entire system adheres to the cylinder. Testing is maintained at 32°C. Samples are drawn midway between the surface of the dissolution medium and the top of the rotating cylinder for analysis.

Reciprocating Disk Method (Apparatus 7)

With the reciprocating disk method for testing transdermal products, a motor drive assembly is used to reciprocate the system vertically, and the samples are placed on disk-shaped holders using cuprophan supports. The test is also carried out at 32°C and reciprocating frequency is about 30 cycles per minute. The acceptance criteria are listed in the individual drug monographs.

METHODS FOR TESTING ENTERIC-COATED PRODUCTS

For testing enteric-coated products, USP-23 lists two methods.

Method A

Dissolution is carried out in the apparatus specified in the drug monograph (usually Apparatus 2 or 1). The product is first tested with 0.1 N HCl for 2 hours and then changed to pH 6.8 by adding 0.2 M tribasic sodium phosphate, fine-tuning pH either with 2 N NaOH or HCl if necessary. The buffer stage generally runs for 45 minutes. The test objective involves making sure that no significant dissolution occurs in the acid phase (less than 10% for any sample unit), and specified percent of drug must be released in the buffer phase. Specifications are set in the individual drug monographs.

Method B

This method involves testing the product in 0.1 N HCl for 2 hours, and then draining the acid and replacing it with a pH 6.8 buffer medium formed by mixing 0.2 M tribasic sodium phosphate with 0.1 N HCl. The temperature of the replaced medium must be preequilibrated to 37°C. The acceptance criteria are similar to those for method A.

MEETING DISSOLUTION REQUIREMENTS

Dissolution test times and specifications are usually established on the basis of an evaluation of dissolution profile data. The dissolution test time points should be selected to characterize adequately the ascending and plateau phases of the dissolution curve.

The USP–NF sets dissolution requirements for many products (see Table 6.6). The requirements apply to both the basket and the paddle methods. Amount of drug dissolved within a given time period (Q) is expressed as a percentage of label content. The Q is generally specified in the monograph for a drug product to pass the dissolution test. For each dissolution run, 6 tablets or capsules are tested, and the dissolution test continues until the criteria are met or the stages are exhausted.

For many products the passing of Q is set at 75% in 45 minutes. Some products are set at Q of 85% in 30 minutes, others at 75% in 60 minutes. For a new drug

TABLE 6.6 *Dissolution Acceptance*

STAGE	NUMBER TESTED	ACCEPTANCE CRITERIA
S_1	6	Each unit is not less than $Q + 5\%$
S_2	6	Average of 12 units ($S_1 + S_2$) is equal to or greater than Q, and no unit is less than $Q - 15\%$
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is equal to or greater than Q, not more than 2 units are less than $Q - 15\%$, and no unit is less than $Q - 25\%$

Adapted with permission from the United States Pharmacopeia (1995).

product, setting the dissolution specification requires a thorough consideration of the physical and chemical properties of the drug. In addition to the consideration that the dissolution test must ensure consistent bioavailability of the product, the test must provide for variation in manufacturing and testing variables so that a product may not be improperly rejected.

UNOFFICIAL METHODS OF DISSOLUTION TESTING

Rotating Bottle Method

This method was suggested in NF-XIII and has become less popular. The rotating bottle method was used mainly for controlled-release beads. For this purpose the dissolution media may be easily changed, such as from artificial gastric juice to artificial intestinal juice. The equipment consists of a rotating rack that holds the sample drug products in bottles. The bottles are capped tightly and rotated in a 37°C temperature bath. At various times, the samples are removed from the bottle, decanted through a 40-mesh screen, and the residues are assayed. To the remaining drug residues within the bottles are added an equal volume of fresh medium and the dissolution test is continued. A dissolution test with pH 1.2 medium for 1 hour, pH 2.5 medium for the next 1 hour, followed by pH 4.5 medium for 1.5 hours, pH 7.0 medium for 1.5 hours, and pH 7.5 medium for 2 hours was recommended to simulate condition of the gastrointestinal tract. The main disadvantage is that this procedure is manual and tedious. Moreover, it is not known if the rotating bottle procedure results in a better *in vitro–in vivo* correlation for drugs.

Flow-Through Dissolution Method

There are many variations of this method. Essentially, the sample is held in a fixed position while the dissolution medium is pumped through the sample holder dissolving the drug. Laminar flow of the medium is achieved by using a pulseless pump. Peristaltic or centrifugal pumps are not recommended. The flow rate is usually maintained between 10 and 100 mL/minute. The dissolution medium may be fresh or recirculated. In the case of fresh medium, the dissolution rate at any moment may be obtained, whereas in the official paddle or basket methods cumulative dissolution rates are monitored. A major advantage of the flow-through method is the easy maintenance of a sink condition for dissolution. A large volume of dissolution medium may also be used, and the mode of operation is easily adapted to automated equipment.

Intrinsic Dissolution Method

Most methods for dissolution deal with a finished drug product. Sometimes a new drug or substance may be tested for dissolution without the effect of excipients or the fabrication effect of processing. The dissolution of a drug powder by maintaining a constant surface area is called *intrinsic dissolution.* Intrinsic dissolution is usually expressed as mg/cm^2 min. In one method, the basket method is adapted to test dissolution of powder by placing the powder in a disk attached with a clipper to the bottom of the basket.

Peristalsis Method

This method attempts to simulate the hydrodynamic conditions of the gastrointestinal tract in an *in vitro* dissolution device. The apparatus consists of a rigid plastic cylindrical tubing fitted with a septum and rubber stoppers at both ends. The dissolution chamber consists of a space between the septum and the lower stopper. The apparatus is placed in a beaker containing the dissolution medium. The dissolution medium is pumped with peristaltic action through the dosage form.

PROBLEMS OF VARIABLE CONTROL IN DISSOLUTION TESTING

There are a number of equipment and operating variables associated with dissolution testing. Depending on the particular dosage form involved, the variables may or may not exert a pronounced effect on the rate of dissolution of the drug or drug product. Variations of 25% or more may occur with the same type of equipment and procedure. The centering and alignment of the paddle is critical in the paddle method. Turbulence can create increased agitation, resulting in a higher dissolution rate. Wobbling and tilting due to worn equipment should be avoided. The basket method is less sensitive to the tilting effect. However, the basket method is more sensitive to clogging due to gummy materials. Pieces of small particles can also clog up the basket screen and create a local nonsink condition for dissolution. Furthermore, dissolved gas in the medium may form air bubbles on the surface of the dosage form unit and can affect dissolution in both the basket and paddle methods.

The interpretation of dissolution data is probably the most difficult job for the pharmacist. In the absence of *in vivo* data, it is generally impossible to make valid conclusions about bioavailability from the dissolution data alone. The use of various testing methods makes it even more difficult to interpret dissolution results because there is no simple correlation among dissolution results obtained with various methods. For many drug products, the dissolution rates are higher with the paddle method. Dissolution results at 50 rpm with the paddle method may be equivalent to the dissolution at 100 rpm with the basket method. In a study of sustained theophylline tablets compressed at various degrees of hardness, Cameron et al (1983) found that, at 50 rpm, dissolution with the paddle method was faster than that of the basket method for tablets of 4.0 kg hardness. However, with tablets of 6.8 kg hardness, similar dissolution profiles were obtained at 125 rpm for the basket and paddle methods over a period of 6 hours. With both methods, increased dissolution rates were observed as the rates were increased. Apparently, the composition of the formulation as well as the process variables in manufacturing may be both important. No simple correlation can be made for dissolution results obtained with different methods.

In a comparison of the paddle and basket methods in evaluating sustained-release pseudoephedrine–guaifenesin preparation, Masih and coworkers (1983) found that the paddle method was more discriminating in demonstrating dissolution differences among drug products. At 100 rpm, the basket method failed to pick up formulation differences detected by the paddle method.

In the absence of *in vivo* data, the selection of the dissolution method is based on the type of drug product to be tested. For example, a low-density preparation

may be poorly wetted in the basket method. A gummy preparation may clog up the basket screen; therefore the paddle method is preferred. A floating dosage form (eg, suppository) may be placed in a stainless steel coil so that the dosage form remains at the bottom of the dissolution flask. For many drugs, a satisfactory dissolution test may be obtained with more than one method by optimizing the testing conditions.

IN VITRO–IN VIVO CORRELATION OF DISSOLUTION

In vitro drug dissolution studies are most useful for monitoring drug product stability and manufacturing process control. Thus, dissolution testing is of immense value as a tool for quality control. Dissolution tests are discriminating of formulation factors that may affect bioavailability of the drug. In some cases, dissolution tests for immediate-release solid oral drug products are very discriminating and a clinically acceptable product might perform poorly in the dissolution test. When a proper dissolution method is chosen, the rate of dissolution of the product may be correlated to the rate of absorption of the drug into the body. Well defined *in vitro–in vivo* correlations have been reported for modified release drug products (Chapter 7) but have been more difficult to predict for immediate release preparations.

This dissolution test then becomes a part of the standard quality control procedure for the drug product. For example, USP-23 has separate and distinct dissolution test requirements for the two different phenytoin sodium capsules. Regarding the extended phenytoin sodium capsules, USP states that "not more than 35%, between 30% and 70% and not less than 85% of the labeled amount of $C_{15}H_{11}N_2NaO_2$ in the Extended Capsules dissolves in 30 minutes, 60 minutes, and 120 minutes, respectively, under the specified dissolution conditions." In contrast, about tolerances for the prompt phenytoin sodium capsules USP states that "not less than 85% of the labeled amount of $C_{15}H_{11}N_2NaO_2$ in the Prompt Capsules dissolves in 30 minutes." There are several ways of checking for *in vitro–in vivo* correlation. *In vitro–in vivo* correlation for modified release drug products is discussed in Chapter 7.

Biopharmaceutic Drug Classification System

A theoretical basis for correlating *in vitro* drug dissolution with *in vivo* bioavailability was developed by Amidon et al, 1995. This approach is based upon the aqueous solubility of the drug and the permeation of the drug through the gastrointestinal tract. This classification system was based on *Fick's First Law* applied to a membrane:

$$J_w = P_w\, C_w$$

where J_w is the drug flux (mass/area/time) through the intestinal wall at any position and time, P_w is the permeability of the membrane, and C_w is the drug concentration at the intestinal membrane surface.

This approach assumes that no other components in the formulation affect the membrane permeability and/or intestinal transport. Using this approach, Amidon et al (1995) studied the solubility and permeability characteristics of various representative drugs and obtained a biopharmaceutic drug classification (Table 6.7)

for predicting the *in vitro* drug dissolution of immediate release solid oral drug products with *in vivo* absorption. As shown in Table 6.7, drugs that fall in class 1, *high solubility* and *high permeability* are drugs that are well absorbed after oral administration, whereas drugs that fall into class 4, *low solubility* and *low permeability* are drugs that present significant problems for complete oral absorption and an *in vitro–in vivo* correlation is not expected. Using this biopharmaceutics classification system, the FDA has developed a guidance "Dissolution Testing of Immediate Release Oral Dosage Forms" (August 1997). (FDA draft Guidances are available at *http://www.fda.gov/cder/index.html* on the Internet.) This draft guidance provides general recommendations for dissolution testing, approaches for setting dissolution specifications related to the biopharmaceutics characteristics of the drug substance, statistical methods for comparing dissolution profiles and a process to help determine when dissolution testing is sufficient to grant a waiver for an *in vivo* bioequivalence study.

Dissolution Rate Versus Absorption Rate

If dissolution of the drug is rate limiting, a faster dissolution rate may result in a faster rate of appearance of the drug in the plasma. It may be possible to establish a correlation between rate of dissolution and rate of absorption of the drug.

The absorption rate is usually more difficult to determine than peak-absorption time. Therefore, the absorption time may be used in correlating dissolution data to absorption data. In the analysis of *in vitro–in vivo* drug correlation, rapid drug absorption may be distinguished from the slower drug absorption by observation of the absorption time for the preparation. The absorption time refers to the time for a constant amount of drug to be absorbed. In one study involving three sustained-release aspirin products, the dissolution time for the preparations were linearly correlated to the absorption times for various amounts of aspirin absorbed (Fig. 6-9). The results from this study demonstrated that aspirin was rapidly absorbed and was very much dependent on the dissolution rate for absorption.

TABLE 6.7 Biopharmaceutic Drug Classification for Predicting the Correlation of *in Vitro* Drug Dissolution of Immediate Release Solid Oral Drug Products with *in Vivo* Bioavailability

CLASS	SOLUBILITY	PERMEABILITY	COMMENTS
1	High	High	*In vitro–in vivo* correlation expected if dissolution rate is slower than the gastric emptying rate
2	Low	High	*In vitro–in vivo* correlation expected if the *in vitro* dissolution rate is similar to the *in vivo* dissolution rate, unless dose is very high
3	High	Low	Drug absorption (permeability) is rate determining and an *in vitro–in vivo* correlation may not be demonstrated
4	Low	High	*In vitro–in vivo* correlation is not expected

Adapted from Amidon et al, 1995

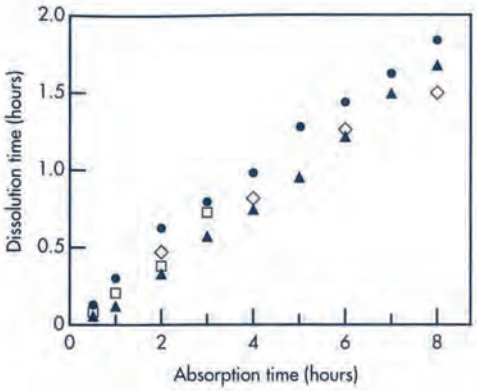


Figure 6-9. An example of correlation between time required for a given amount of drug to be absorbed and time required for the same amount of drug to be dissolved *in vitro* for three sustained-release aspirin products.
(From Wood, 1966, with permission.)

Percent of Drug Dissolved Versus Percent of Drug Absorbed

If a drug is absorbed completely after dissolution, a linear correlation may be obtained by comparing the percent of drug absorbed to the percent of drug dissolved. In choosing the dissolution method, one must consider the appropriate dissolution medium and use a slow dissolution stirring rate so that *in vivo* dissolution is approximated.

Aspirin is absorbed rapidly, and a slight change in formulation may be reflected in a change in the amount and rate of drug absorption during the period of observation (Figs. 6-9 and 6-10). If the drug is slow absorbing, which occurs when absorption is the rate-limiting step, a difference in dissolution rate of the product may not be observed. In this case, the drug would have been absorbed very slowly independent of the dissolution rate.

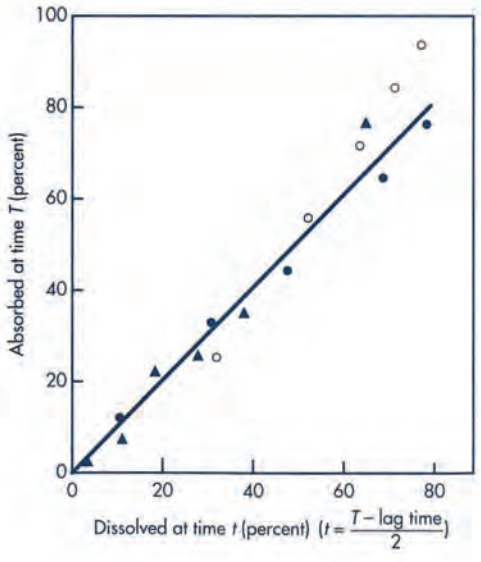


Figure 6-10. An example of continuous *in vivo–in vitro* correlation of aspirin.
(From Levy et al, 1965, with permission.)

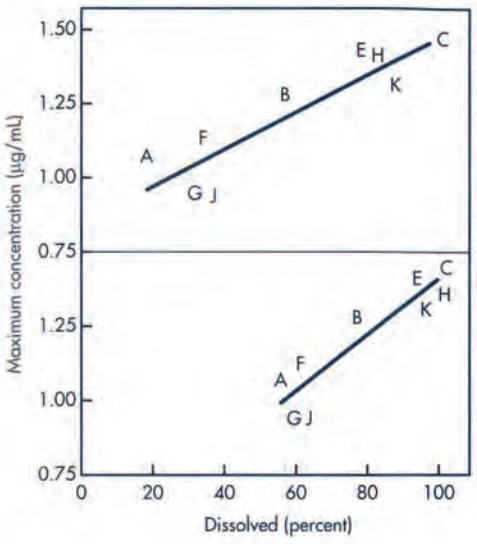


Figure 6-11. *In vitro–in vivo* correlation between C_{max} and percent drug dissolved. Top, 30 min (slope = 0.06, $r = 0.902$, $P < .001$). Bottom, 60 min (slope = 0.10, $r = 0.940$, $P < .001$). (Letters on graph indicate different products.)
(From Shah et al, 1983, with permission.)

Maximum Plasma Concentrations Versus Percent of Drug Dissolved *In Vitro*

When different drug formulations are tested for dissolution, a poorly formulated drug will not be completely dissolved and released, resulting in lower plasma drug concentrations. The percent of drug released at any time interval will be greater for the more available drug product. When such drug products are tested *in vivo*, the peak drug serum concentration will be higher for the drug product that shows the highest percent of drug dissolved. An example of *in vitro–in vivo* correlation for 100 mg phenytoin sodium capsules is shown in Figure 6-11. Several products were tested. A linear correlation was observed between the maximum drug concentration in the body and the percent of the drug dissolved *in vitro*.

The dissolution study on the phenytoin sodium products showed that the fastest dissolution rate was product *C*, for which about 100% of the labeled contents dissolved in the test (Fig. 6-12). Interestingly, these products also show the shortest time to reach peak concentration (t_{max}). The t_{max} is dependent on the absorption

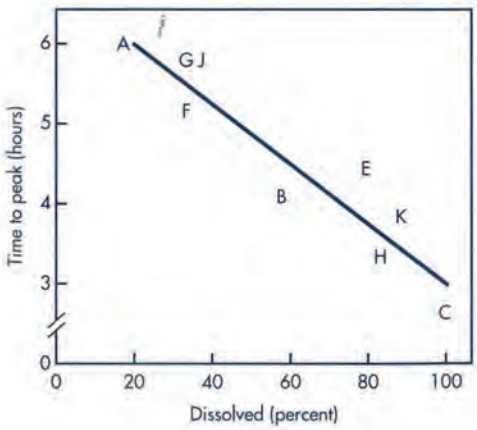


Figure 6-12. *In vitro–in vivo* correlation between t_{max} and percent drug dissolved in 30 minutes by basket method. Letters on graph indicate different products.
(From Shah et al, 1983, with permission.)

rate constant. In this case, the fastest absorption would also result in the shortest t_{max} (see Chapter 9).

Serum Drug Concentration Versus Percent of Drug Dissolved

In a study on aspirin absorption the serum concentration of aspirin was correlated to the percent of drug dissolved using an *in vitro* dissolution method. The dissolution medium was simulated gastric juice. Because aspirin is rapidly absorbed from the stomach, the dissolution of the drug is the rate-limiting step, and various formulations with different dissolution rates would cause differences in the serum concentration of aspirin by minutes (Fig. 6-13).

FAILURE OF CORRELATION OF *IN VITRO* DISSOLUTION TO *IN VIVO* ABSORPTION

Although there are many published examples of drugs with dissolution data that correlate well with drug absorption in the body, there are also many examples indicating poor correlation of dissolution to drug absorption. There are also instances where a drug has failed the dissolution test and yet is well absorbed. The problem of no correlation between bioavailability and dissolution may be due to the complexity of drug absorption and the weakness of the dissolution design. For example, a product that involves fatty components may be subjected to longer retention in the gastrointestinal tract. The effect of digestive enzymes may also play an important role in the dissolution of the drug *in vivo*. These factors may not be adequately simulated with a simple dissolution medium. An excellent example showing the importance of dissolution design is shown in Figure 6-14. Dissolution tests using four different dissolution media were performed for

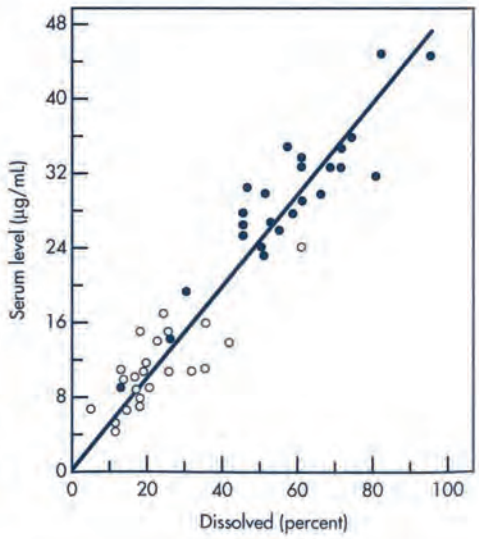


Figure 6-13. Example of *in vivo–in vitro* two-point correlation between 10-minute serum level and percent dissolved at 1.2 minutes (○) and the 20-minute serum level and percent dissolved 4.2 minutes (●). (From Wood, 1966, with permission.)

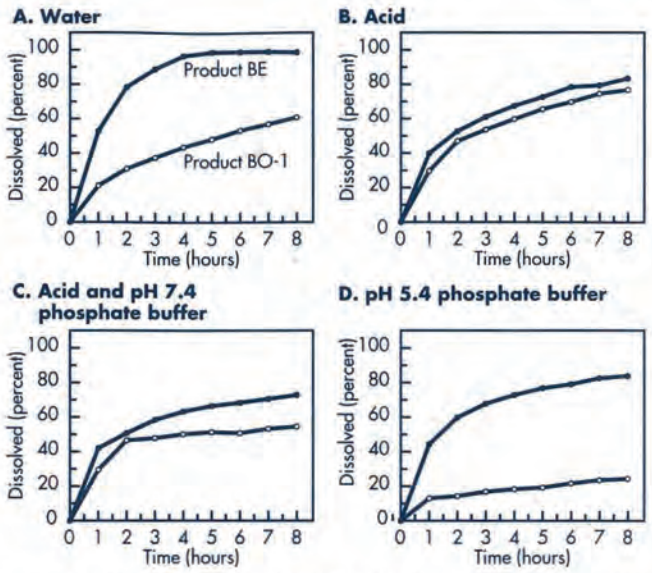


Figure 6-14. Dissolution profile of two quinidine gluconate sustained release products in different dissolution media. Each data point is the mean of 12 tablets. (● = product BE, ○ = product BO-1.) (From Prasad et al, 1983, with permission.)

two quinidine gluconate sustained-release tablets. Brand BE was known to be bioavailable, whereas product BO-1 was known to be incompletely absorbed. It is interesting to see that using acid media as well as acid followed by pH 7.4 buffer did not distinguish the two products well, whereas using water or pH 5.4 buffer as dissolution media clearly distinguishes the "good" product from the one that is not completely available. In this case, the use of an acid medium is consistent with the physiologic condition in the stomach, but this procedure would be misleading as a quality control tool. It is important that any new dissolution test be carefully researched before being adopted as a method for predicting drug absorption.

BIOPHARMACEUTIC CONSIDERATIONS

Some of the major biopharmaceutic considerations in the design of a drug product are given in Table 6.8. The prime considerations in the design of a drug product are safety and efficacy. The drug product must effectively deliver the active drug at an appropriate rate and amount to the target receptor site so that the intended therapeutic effect is achieved. The finished dosage form should not produce any additional side effects or discomfort due to the drug and/or excipients. Ideally, all excipients in the drug product should be inactive ingredients alone or in combination in the final dosage form.

The finished drug product is a compromise of various factors including therapeutic objectives, pharmacokinetics, physical and chemical properties, manufacturing, cost, and patient acceptance. Most importantly, the finished drug product should meet the therapeutic objective by delivering the drug with maximum bioavailability and minimum adverse effects.

TABLE 6.8 Biopharmaceutic Considerations in Drug Product Design

Pharmacodynamic Considerations	Patient Considerations
Therapeutic objective	Compliance and acceptability of drug product
Toxic effects	Cost
Adverse reactions	Manufacturing Considerations
Drug Considerations	Cost
Chemical and physical properties of drug	Availability of raw materials
Drug Product Considerations	Stability
Pharmacokinetics of drug	Quality control
Bioavailability of drug	
Route of drug administration	
Desired drug dosage form	
Desired dose of drug	

PHARMACODYNAMIC CONSIDERATIONS

Therapeutic considerations are concerned with the pharmacodynamic and pharmacologic properties of the drug, including the desired therapeutic response as well as the type and frequency of toxic and/or adverse reactions of the drug. The *therapeutic objective* will influence the type of drug product to be manufactured. A drug used to treat an acute illness should be formulated to release the drug rapidly, allowing for quick absorption and rapid onset. For example, nitroglycerin is formulated in a sublingual tablet for the treatment of angina pectoris. For prophylactic use in the treatment of certain chronic diseases such as asthma, an extended- or controlled-release dosage form is preferred. The extended-release dosage form releases the drug slowly, thereby controlling the rate of drug absorption and allowing for more constant plasma drug concentrations. In some cases, an immediate drug release component is included in the extended-release dosage form, to allow for both rapid onset followed by a slower sustained release of the drug. Controlled release and modified release dosage forms are discussed in Chapter 7.

DRUG CONSIDERATIONS

As discussed earlier, the *physicochemical properties* of the drug (Table 6.1) are major factors that are controlled or modified by the formulator. These physicochemical properties influence the type of dosage form and the process for the manufacture of the dosage form. Physical properties of the drug—such as dissolution, particle size, and crystalline form—are influenced by methods of processing and manufacturing. If the drug has low aqueous solubility and an intravenous injection is desired, then a soluble salt of the drug may be prepared. Chemical instability or chemical interactions with certain excipients will also affect the type of drug product and its method of fabrication. There are many creative approaches to improve the product. Only a few are discussed in this chapter.

DRUG PRODUCT CONSIDERATIONS

Pharmacokinetics of the Drug

Knowledge of the pharmacokinetic profile of the drug is important for the estimate of the appropriate amount (dose) of drug in the drug product and the re-

lease rate that will maintain a desired drug level in the body. The *therapeutic window* determines the desired or *target plasma drug concentration* that will be effective with minimal adverse effects. Drug concentrations higher than the therapeutic window (eg, minimum toxic concentration) may cause more intense pharmacodynamic and/or toxic response; drug concentrations below the therapeutic window (eg, minimum effective concentration) may be subtherapeutic. For drugs with a narrow therapeutic window, knowledge of the pharmacokinetic profile enhances drug therapy for many products through the development of an appropriate dosage regimen, including the *size of the dose* and the *dosing frequency*, that will achieve and maintain the target drug concentration.

Bioavailability of the Drug

The stability of the drug in the gastrointestinal tract, including the stomach and intestine, is another consideration. Some drugs, such as penicillin G, are unstable in the acid media of the stomach. The addition of buffering in the formulation or the use of an enteric coating on the dosage form protects the drug from degradation at a low pH. Some drugs have poor bioavailability because of first-pass effects (presystemic elimination). If oral drug bioavailability is poor due to metabolism by enzymes in the gastrointestinal tract or in the liver, then a higher dose may be needed, as in the case of propranolol or an alternative route of drug administration as in the case of insulin. Drugs which are only partially absorbed after oral administration usually leave residual drug in the gastrointestinal tract, which may cause local bowel irritation or alter the normal gastrointestinal flora. Unabsorbed drug always runs the risk of being completely absorbed under unusual situations (eg, change in diet or disease condition), leading to excessive drug bioavailability and toxicity. If the drug is not absorbed after the oral route or a higher dose causes toxicity, then the drug must be given by an alternate route of administration, and a different dosage form such as a parenteral drug product might be needed.

Dose Considerations

The size of the dose in the drug product is based on the inherent potency of the drug and its apparent volume of distribution which determines the target plasma drug concentration needed for the desired therapeutic effect. For some drugs, wide variation in the size of the dose is needed for different patients due to large intersubject differences in the pharmacokinetics and bioavailability of the drug. Therefore, the drug product must be available in several dose strengths to allow for individualized dosing. Some tablets are also scored for breaking to allow the administration of fractional doses.

The *size* and *shape* of the solid oral drug product are designed for easy swallowing. The total size of a drug product is determined by the dose of the drug and any additional excipients needed to manufacture the desired dosage form. For oral dosage forms, if the required dose is large (1 g or more), then the patient may have difficulty in swallowing the drug product. For example, many patients may find a capsule-shaped tablet (caplet) more easy to swallow than a large round tablet. Large or oddly shaped tablets, which may become lodged in the esophageal sphincter during swallowing, are generally not manufactured. Some esophageal injuries due to irritating drug lodged in the esophagus have been reported with potassium chloride tablets and other drugs. Older patients may have more difficulties in swal-

lowing large tablets and capsules. Most of these swallowing difficulties may be overcome by taking the product with a large amount of fluid.

Dosing Frequency

The dosing frequency is related to the clearance of the drug and the target plasma drug concentration. If the pharmacokinetics show that the drug has a short duration of action due to a short elimination half-life or rapid clearance from the body, the drug must be given more frequently. To minimize fluctuating plasma drug concentrations and improve patient compliance, an extended release drug product may be preferred. An extended-release product contains two or more doses of the drug that are released over a prolonged period.

PATIENT CONSIDERATIONS

The drug product must be acceptable to the patient. Poor patient compliance may be the result of poor product attributes, such as difficulty in swallowing, disagreeable odor, bitter medicine taste, or two frequent and/or unusual dosage requirements. In recent years, creative packaging has allowed the patient to remove 1 tablet each day from a specially designed package so that the daily doses are not missed. This innovation improves compliance. Of course, pharmacodynamic factors, such as side effects of the drug or an allergic reaction, also influence patient compliance.

ROUTE OF DRUG ADMINISTRATION

The route of drug administration (Chapter 5) affects the bioavailability of the drug, thereby affecting the onset and duration of the pharmacologic effect. In the design of a drug dosage form, the pharmaceutical manufacturer must consider (1) the intended route of administration; (2) the size of the dose; (3) the anatomic and physiologic characteristics of the administration site, such as membrane permeability and blood flow; (4) the physicochemical properties of the site, such as pH, osmotic pressure, and presence of physiologic fluids; and (5) the interaction of the drug and dosage form at the administration site, including alteration of the administration site due to the drug and/or dosage form.

Although drug responses are quite similar with different routes of administration, there are examples where severe differences in response may occur. For example, with the drug isoproterenol, a difference in activity of a thousand-fold has been found, attributed to different routes of administration. Figure 6-15 shows the change in heart rate due to isoproterenol with different routes of administration. Studies have shown that isoproterenol is metabolized in the gut and during the passage through the liver. The rate and types of metabolite formed are found to be different depending on the routes of administration.

Oral Preparations

The major advantages of oral preparations are the convenience of administration, safety, and the elimination of discomforts involved with injections. The hazard of

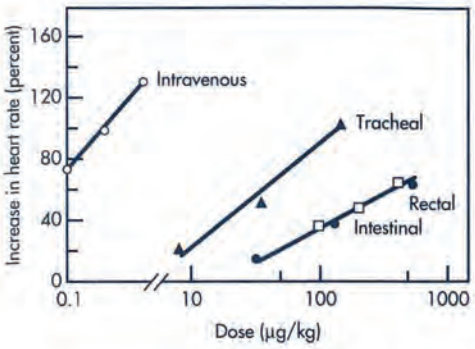


Figure 6-15. Dose response curve to isoproterenol by various routes in dogs.
(From Gillette and Mitchell, 1975, with permission.)

rapid intravenous administration causing toxic high concentration of drug in the blood is avoided. The main disadvantages of oral preparations are the potential problems of reduced and erratic bioavailability due to either incomplete absorption or drug interactions. Nausea or gastrointestinal discomfort may occur with some drugs that cause local irritation. Poor oral bioavailability or reduced absorption may be due to antacids or food interaction. Many drugs are adsorbed to antacids or food substances (see Chapter 5). These drugs would not diffuse effectively across the gastrointestinal tract to be absorbed. Drug molecules do not get absorbed easily when ionized. The ganglion-blocking drugs, hexamethonium, pentolinium, and bretylium, are ionized at intestinal pH. Therefore, they are not absorbed orally to be effective. Neomycin, gentamicin, and cefamandole are not well absorbed orally. In the case of neomycin, after oral administration the drug will concentration in the gastrointestinal tract to exert its local antibacterial effect.

Drugs with large molecular weights may not be well absorbed when given orally. There is some evidence that large drug molecules may be absorbed through the lymphatic system when formulated with a "carrier." The mechanism is not known. Some large molecules are absorbed when administered in solution with a surface-active agent. For example, the drug cyclosporin has been given orally with good absorption when formulated with a surfactant in oil. A possible role of the oil is to stimulate the flow of lymph as well as to delay the retention of the drug. Oily vehicles have been used to lengthen the gastrointestinal transit time of oral preparations.

Absorption of Lipid-Soluble Drugs

Most hydrophobic drugs are poorly soluble in water and generally are not well absorbed orally because of failure of the drug to dissolve in the fluids of the gastrointestinal (GI) tract. These lipophilic drugs are more soluble in lipids or oily vehicles. Lipid-soluble drugs given with fatty excipients mix with digested fatty acids, which are emulsified by bile in the small intestine. The emulsified drug is then absorbed through the GI mucosa or through the lymphatic system. A normal digestive function of the small intestine is the digestion and absorption of fats such as triglycerides. These fats are first hydrolyzed into monoglycerides and fatty acids by pancreatic lipase. The fatty acids then react with carrier lipoproteins to form *chylomicrons*, which are absorbed through the lymph. The chylomicrons eventually release the fatty acids and any lipophilic drugs are incorporated in the oil phase. Fat substances trigger receptors in the stomach to delay stomach emptying and reduce GI transit rates. Prolonged transit time would allow more contact time for increased drug absorption.

When griseofulvin or phenytoin was given orally in corn oil suspensions, an increase in drug absorption was demonstrated (Bates and Equeira, 1975). The increase in absorption was attributed to the formation of mixed micelles with bile secretions, which aid drug dissolution. In addition, stomach emptying may be delayed depending on the volume and nature of the oil. Long-chain fatty acids (above C-10) are more effective than short-chain acids in delaying stomach emptying. Unsaturated fatty acids are more effective than saturated straight-chain fatty acids; triglycerides are not as effective as fatty acids. Oleic acid, arachis oil, and myristic acid also delay stomach emptying. For example, the bioavailability of a water-insoluble antimalarial drug was increased in dogs when oleic acid was incorporated as part of a vehicle into a soft gelatin capsule (Stella et al, 1978).

Calcium carbonate, a source of calcium for the body, was only about 30% available in a solid dosage form, but was almost 60% bioavailable when dispersed in a special vehicle as a soft gelatin capsule (Fordtran et al, 1986). Bleomycin, an anticancer drug (MW 1500), is poorly absorbed orally and, therefore, was formulated for absorption through the lymphatic system. The lymphotropic carrier was dextran sulfate. Bleomycin was linked ionically to the carrier to form a complex. The carrier dextran (MW 500,000) was too large to be absorbed through the membrane and pass into the lymphatic vessels (Yoshikawa et al, 1989).

Gastrointestinal Side Effects

Many orally administered drugs are irritating to the stomach. These drugs may cause nausea or stomach pain when taken on an empty stomach. In some cases, food or antacids may be given together with the drug to reduce stomach irritation. Alternatively, the drug may be enteric-coated to reduce gastric irritation. A common drug that causes irritation is aspirin. Buffered aspirin tablets, enteric-coated tablets, and granules are available. However, enteric coating may sometimes delay or reduce the amount of drug absorbed. Furthermore, enteric coating may not abolish gastric irritation completely, because the drug may occasionally be regurgitated back to the stomach after the coating dissolves in the intestine. Enteric-coated tablets may be greatly affected by the presence of food in the stomach. The drug may not be released from the stomach for several hours when stomach emptying is delayed by food.

Buffering material or antacid ingredients have also been used with aspirin to reduce stomach irritation. When a large amount of antacid or buffering material is included in the formulation, dissolution of aspirin may occur quickly, leading to reduced irritation to the stomach. However, many buffered aspirin formulations do not contain sufficient buffering material to make a difference in dissolution in the stomach.

Certain drugs have been formulated into soft gelatin capsules to improve drug bioavailability and reduce gastrointestinal side effects. If the drug is formulated in the soft gelatin capsule as a solution, the drug may disperse and dissolve more rapidly, leaving less residual drug in the gut and causing less irritation. This approach may be useful for a drug that causes local irritation but would be ineffective if the drug is inherently ulcerogenic. Indomethacin, for example, may cause ulceration even when administered parenterally to animals.

There are many options available to the formulator to improve the tolerance of the drug and minimize gastric irritation. The nature of excipients and the physical state of the drugs are important and must be carefully assessed before a drug product is formulated. Some excipients may improve the solubility of the drug and

facilitate absorption, whereas others may physically adsorb the drug to reduce irritation. Often, a great number of formulations must be tested before an acceptable one is chosen.

Buccal and Sublingual Tablets

A drug that diffuses and penetrates rapidly across mucosal membranes may be placed under the tongue and be rapidly absorbed. A tablet designed for release under the tongue is called a *sublingual tablet.* Nitroglycerin, isoproterenol, erythrityl tetranitrate and isosorbide dinitrate are common examples. Sublingual tablets usually dissolve rapidly.

A tablet designed for release and absorption of the drug in the buccal pouch is called a *buccal tablet.* The buccal (cheek) cavity refers to the space in between the mandibular arch and the oral mucosa, an area well supplied with blood vessels for efficient drug absorption. A buccal tablet may release drug rapidly or may be designed to release drug slowly for a prolonged effect. For example, Sorbitrate sublingual tablet, Sorbitrate chewable tablet, and Sorbitrate oral tablet (Zeneca) are three different dosage forms of isosorbide dinitrate for the relief and prevention of angina pectoris. The sublingual tablet is a lactose formulation that rapidly dissolves under the tongue and absorbed. The *chewable tablet* is chewed, and some drug is absorbed in the buccal cavity while the oral tablet is simply a conventional product for GI absorption. The chewable tablet contains flavor, confectioner's sugar, and mannitol, which are absent in both the oral and sublingual tablet. The sublingual tablet contains lactose and starch for rapid dissolution. The onset of sublingual nitroglycerin is rapid, much faster than when taken orally or absorbed through the skin. The duration of action, however, is shorter than with the other two routes. Drug absorbed through the buccal mucosa will not pass through the liver before general distribution. Consequently, for a drug with significant first-pass effect, buccal absorption may provide better bioavailability over oral administration. Some peptide drugs have been reported to be absorbed by buccal route, which provide a route of administration without the drug being destroyed by enzymes in the GI tract.

A newer approach to drug absorption from the oral cavity has been the development of a *translingual* nitroglycerin spray (Nitrolinqual). The spray, containing 0.4 mg per metered dose, is given by spraying 1 or 2 metered doses onto the oral mucosa at the onset of an acute angina attack.

Nasal Preparations

Nasal products provide a simple means of local and/or systemic drug delivery. The vehicle used for a nasal administration must be nonirritating and well tolerated. The most common drug products for local activity are the nasal vasoconstrictors phenylephrine and naphazoline. An example of a new nasal delivery for both local and systemic effect is ipratropium bromide, a drug used for rhinitis and the common cold. In patients with perennial rhinitis, about 10% of the drug was absorbed intranasally (Wood, 1995).

Nasacort AQ nasal spray (Rhone-Poulenc-Rorer) is triamcinolone acetonide delivered to the nasal area by spray. Each puff delivers about 50 mcg of the drug. It is useful for allergic rhinitis. The action is partially systemic and local. Another example is levocabastine, a histamine H_1-receptor antagonist developed as levocabastine nasal spray. Peak plasma concentrations (C_{max}) occur within 1 to 2 hours, with systemic availability ranging from 60% to 80% (Heykants, 1995). Benefits of

levocabastine are predominantly mediated through local antihistaminic effects with some systemic contribution. Butorphanol tartrate nasal spray (Stadol NS) is an opioid analgesic available as a nasal spray for the treatment of pain as a preoperative or preanesthetic medication, as well as for pain relief during labor and migraine headache. The nasal route offers an alternative to injection. Some biological products such as peptides and proteins have been suggested for nasal delivery since they are not digested by enzymes as they were in the GI tract. The luteinizing hormone-releasing hormone agonist, buserelin, has been formulated with oleic acid for systemic nasal delivery in an experimental formulation. Therapeutic proteins, such as recombinant interferon-alpha/D, has also be been investigated for nasal delivery. Detectable levels of interferon-alpha β/D in the serum were achieved via nasal route and in the lung. Drug bioavailability was 6.8% from the lung in the rat, and 2.9% from the nasal cavity in the rabbit (Bayley et al, 1995). Other examples of nasal delivery drug products for systemic drug absorption are Nicotrol for the delivery of nicotine to aid smokers in quitting smoking and of Miacalcin for the delivery of calcitonin salmon, a parathyroid agent for the treatment of postmenopausal osteoporosis.

An *in vitro* human nasal model (De Fraissinettea et al, 1995) was developed as a tool to study the local tolerability of nasal powder forms using excised nasal mucosa in a diffusion chamber. The suitability of this model was tested using Sandostatin, an octapeptide analog of somatostatin. The drug is also used for ocular treatment of allergic rhinoconjunctivitis as eye drops; it was about 30 to 60% was available systemically by that route.

Colonic Drug Delivery

There has been considerable research in the delivery of drugs specifically to the colon after oral administration. Crohn's disease or chronic inflammatory colitis may be more effectively treated by direct drug delivery to the colon. One such drug, mesalamine ((5-aminosalicylic acid, Asacol) is available in a delayed-release tablet coated with an acrylic-based resin that delays the release of the drug until it reaches the distal ileum and beyond. Protein drugs are generally unstable in the acidic environment of the stomach and are also degraded by proteolytic enzymes present in the stomach and small intestine. Researchers are investigating the oral delivery of protein and peptide drugs by protecting them against enzymatic degradation for later release in the colon.

Over 500 different bacterial species inhabit the colon, although five frequent species dominate the microflora. Within the caecum and colon, anaerobic species dominate and bacterial counts of 10^{12}/mL has been reported. Drugs such as the β-blockers, oxprenolol and metoprolol, and isosorbide-5-mononitrate are well absorbed in the colon similar to absorption in the small intestine. Thus, these drugs are suitable candidates for colonic delivery. The nonsteroidal antiinflammatory drug, naproxen has been formed into a prodrug naproxen-detran that survives intestinal enzyme and intestinal absorption. The prodrug reaches the colon where it is enzymatically decomposed into naproxen and detran.

Rectal and Vaginal Drug Delivery

Products for rectal or vaginal drug delivery may be administered either in solid or liquid dosage forms. Rectal drug administration can be for either local or systemic

drug delivery. Rectal drug delivery for systemic absorption is preferred to drugs that can not be tolerated orally (eg, when a drug causes nausea) or in situations where the drug cannot be given orally. A sustained-release preparation may be prepared for rectal administration. The rate of release of the drug from this preparation is dependent on the nature of the base composition and on the solubility of the drug involved. Rectal drug absorption may partially bypass the first-pass effects due to enzymes in the liver. The drug absorbed in the lower rectal region does not pass through the liver, whereas the drug absorbed in the upper rectal region passes through the hepatic portal vein. Release of drug from a suppository depends on the composition of the suppository base. A water-soluble base, such as PEG and glycerin, generally dissolve and release the drug; on the other hand, an oleaginous base with a low melting point may melt at body temperature and release the drug. Some suppositories contain an emulsifying agent that keeps the fatty oil emulsified and the drug dissolved in it.

Vaginal drug delivery is generally for local drug delivery, but some systemic drug absorption can occur. Progesterone vaginal suppositories have been evaluated for the treatment of premenstrual symptoms of anxiety and irritability. Antifungal agents are often formulated into suppositories for treating vaginal infections. Fluconazole, a triazole antifungal agent has been formulated to treat vulvovaginal candidiasis. The result of oral doses are compared with that of a clotrimazole vaginal suppository. Many vaginal preparations are used for the delivery of antifungal agents.

Parenteral Products

In general, intravenous (IV) bolus administration of a drug provides the most rapid onset of drug action. After IV bolus injection, the drug is distributed via the circulation to all parts of the body within a few minutes. After intramuscular (IM) injection, drug is absorbed from the injection site into the bloodstream (Figure 6-16). Plasma drug input after oral and IM administration involve an absorption phase in which the drug concentration rises slowly to a peak and then declines according to the elimination half-life of the drug. (Note that the systemic elimination of all products are essentially similar, only the rate and extent of absorption may be modified by formulation). The plasma drug level peaks instantaneously after an IV bolus injection so that a peak is usually not visible. After 3 hours, however, the plasma level of the drug after intravenous administration has declined to a lower level than that of the oral and intramuscular administration. In this example (Fig. 6-16), the areas under the plasma curves are all approximately equal, indicating that the oral and intramuscular preparations are both well formulated and are 100% available. Frequently, because of incomplete absorption or metabolism, oral preparations may have a lower area under the curve.

Drug absorption after an intramuscular injection may be faster or slower absorption than after oral drug administration. Intramuscular preparations are generally injected into a muscle mass such as in the buttocks (gluteus muscle) or in the deltoid muscle. Drug absorption occurs as the drug diffuses from the muscle into the surrounding tissue fluid and then into the blood. Different muscle tissues have different blood flow. For example, blood flow to the deltoid muscle is higher than blood flow to the gluteus muscle. Intramuscular injections may be formulated to have a faster or slower drug release by changing the vehicle of the injection

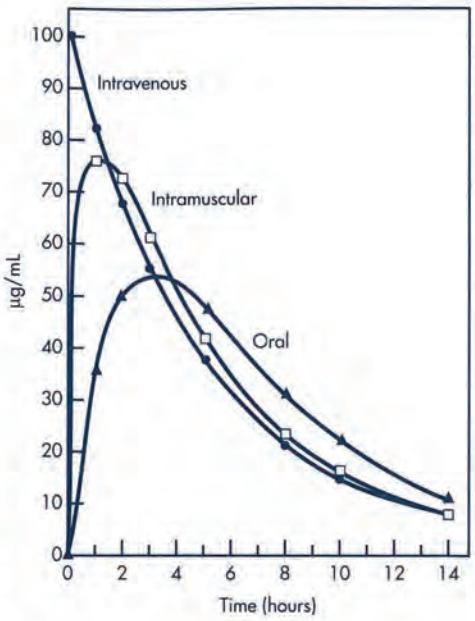


Figure 6-16. Plasma concentration of a drug after the same dose is administered by three different routes.

preparation. Aqueous solutions release drug more rapidly, and the drug more rapidly absorbed from the injection site, whereas a viscous, oily, or suspension vehicle may result in a slow drug release and consequently slow and sustained drug absorption. Viscous vehicles generally slow down drug diffusion and distribution. A drug in an oily vehicle must partition into an aqueous phase before systemic absorption. A drug that is very soluble in the oil and relatively insoluble in water may have a relatively long and sustained release from the absorption site because of slow partitioning.

CLINICAL EXAMPLE

Haloperidol (Haldol) is a butyrophenone antipsychotic agent with pharmacologic effects similar to the piperazine phenothiazines. Haloperidol is available for oral and IM administration. Two IM preparations of haloperidol are available, including haloperidol lactate in an aqueous vehicle and haloperidol deconate in a nonaqueous sesame oil vehicle. The following Table 6.9 shows the T_{max} and elimination half-life of haloperidol after the oral, IM, or IV administration.

Haloperidol lactate is in an aqueous solution and after intramuscular injection has a time for peak drug concentration of 20 minutes and an elimination half-life of 21 days. In contrast, haloperidol deconate, the deconate ester of the butyrophenone, is lipid soluble and is formulated in sesame oil. Due to the slow drug release from the oil after IM administration, the time for peak drug concentration is 4 to 11 days and the elimination half-life is about 3 weeks. Thus, the suggested dosage interval between intramuscular injections for haloperidol deconate is 4 weeks. Table 6.9 lists some of the pharmacokinetics of haloperidol after oral, IM and IV administration.

TABLE 6.9 Pharmacokinetic Parameters for Haloperidol After Oral and Parenteral Administration

ROUTE	PERCENT ABSORPTION	TIME FOR PEAK CONCENTRATION, t_{max}	ELIMINATION HALF-LIFE
Oral	60	3–5 hr	24 (12–38) hr
IM	75	0.33 hr	21 (13–36) hr
Deconate		6th day (4 to 11 days)	3 weeks
IV	100	immediate	14 (10–19) hr

Adapted from *Facts and Comparisons*, 1997

A major advantage of the intramuscular injection compared to intravenous bolus injection is the flexibility of formulation. A drug that is not water soluble cannot be easily administered by intravenous route. A nonaqueous injection for intravenous administration must be given very slowly to avoid any drug precipitation in the vein. Propylene glycol and PEG 400 in combination with other solvents have been used in intravenous preparations.

Parenteral dosage forms for intravenous administration containing suspensions, liposomes, or nanoparticles have been developed for the administration of antineoplastic drugs. In this case, the dosage form may alter the distribution of the drug, because small particles are engulfed by macrophages of the reticuloendothelial system resulting in drug concentration in the liver and spleen.

Inhalation Preparations

Drugs administered into the respiratory system, such as bronchodilators and corticosteroids, may be formulated as an aerosol or inhalation solution. An aerosol preparation with suitable propellant can administer drug rapidly into the bronchial region. The advantages of drugs given by inhalation include (1) rapid absorption and rapid onset of activity (eg, bronchodilators), (2) avoidance of first-pass effects or metabolism prior to systemic absorption (eg, isoproterenol, bitolterol), and (3) localize drug activity to the lung and minimize systemic toxicity (eg, dexamethasone).

The particle size of the suspension (or in the case of a solution, the size of the mist particles) is important in determining the extent of penetration into the bronchioles. For coarse particles, the inertia carries the drug for a short distance up the nasal cavity. Drugs with small particles move by sedimentation or brownian movements deeper into the bronchioles.

Many aerosol products are designed for drug therapy of chronic obstructive pulmonary disease (COPD), particularly asthma. For example, Intal (Rhone-Poulenc-Rorer) delivers sodium cromolyn to a patient through inhalation. The propellants for aerosols have been the chlorinated-fluorocarbons (CFCs, such as Freons—DuPont). Freons commonly used include dichlorodifluoromethane (Freon 12) and dichlortetrafluoroethane (Freon 114). However, these compounds deplete the ozone layer of the stratosphere and other propellants are now being investigated to replace CFCs. The new propellants include classes of hydrofluoroalkane (HFAs) which do not contain chlorines. HFA-227 and HFA-134a show promise as new propellents for medical inhalers since they are nonflammable, not chemically reactive,

TABLE 6.10 Examples of Aerosol Products

Alupent (metaproterenol sulfate)
Proventil (albuterol)
Alupent (metaproterenol)
Bronkosol (isoetharine)
Vaponefrin (racepinephrine)

and do not have ozone-depleting potential. Some examples of aerosol products are shown in Table 6.10.

Transdermal Preparations

Transdermal administration delivers a drug into the patient's systemic circulation through the skin for systemic activity. For example, scopolamine was delivered through the skin of the ear for motion sickness. Transdermal administration may release the drug over an extended period of several hours or days without the discomforts of gastrointestinal side effects or first-pass effects. For example, Estraderm delivers estradiol for estrogen replacement therapy in postmenopausal women and is applied twice a week. Many transdermal products deliver drug at a constant rate to the body similar to a zero-order infusion process. As a result, a stable, plateau level of the drug may be maintained. Many therapeutic categories of drugs are now available as transdermal products (Table 6.11).

Transdermal products vary in design. In general, the patch contains several parts: (1) a backing or support layer; (2) a drug layer (reservoir containing the dose); (3) a release-controlling layer (usually a semipermeable film), (4) a pressure sensitive adhesive (PSA); and (5) a protective strip, which must be removed prior to application. (See Fig. 7-13, Chapter 7.) The release controlling membrane could be a polymeric film such as ethylvinyl copolymer, which controls the release rate of the dose and its duration of action. The PSA layer is important for maintaining uninterrupted skin contact for drug diffusion through the skin. In some cases, the drug is directly blended into an adhesive, such as acrylate or silicone; performing the dual functions of release control and adhesion, this product is known as "drug in adhesive." In other products, the drug dose may be placed in a separate insoluble matrix layer which helps controlling the release rate. This is generally known as a "matrix patch," which gains a little more control of the release rate as com-

TABLE 6.11 Transdermal Products

DRUG	PRODUCT	DRUG CLASS
Estradiol	Vivelle	Estrogen
Fentanyl	Duragesic	Opiate agonist
Nicotine	Habitrol Tran	Smoking control
	Nicoderm	Smoking control
	Nicotrol	Smoking control
	Prostep patch	Smoking control
Naftifine HCl	Naftin	Antifungal
Nifedipine	Adalat	Calcium channel blocker
Nitroglycerin	Nitrodisc	Antiangina
	Nitro-Dur	Antiangina

pared with the simple "reservoir" type of patch. Multilayers of drugs may be involved in other transdermal products using the "laminate design." In many cases, drug permeation through the skin is the slowest step in the transdermal delivery of drug into the body. See Chapter 7 for modified-release patches.

Scale-Up and Post-Approval Changes (SUPAC)

Any changes in a drug product after it has been approved for marketing by the FDA is known as a *post-approval change*. A major concern by industry and FDA is that if a pharmaceutical manufacturer makes any change in the formulation; scales up the formulation to a larger batch size; changes the process, equipment, or manufacturing site; and whether these changes will affect the identity, strength, purity, quality, safety, and efficacy of the approved drug product. In addition any changes in the raw material (ie, active pharmaceutical ingredient), excipients or packaging (including container closure system) should also be shown not to affect the quality of the drug product.

FDA has been publishing draft guidances for the pharmaceutical industry that addresses the following issues:

- components and composition of the drug product
- manufacturing site change
- scale-up of drug product
- manufacturing equipment
- manufacturing process
- packaging
- active pharmaceutical ingredient

In these documents, FDA describes the (1) level of change, (2) recommended chemistry, manufacturing and controls tests for each level of change, (3) *in vitro* dissolution tests and/or bioequivalence tests for each level of change, and (4) documentation that should support the change. The level of change is classified as to the likelihood that a change in the drug product as listed above might affect the quality of the drug product. The level of changes as described by the FDA are listed in Table 6.12.

As noted in Table 6.12, a Level 1 change which could be a small change in the excipient amount (eg, starch, lactose) would be unlikely to alter the quality or performance of the drug product, whereas a Level 3 change which may be a qualitative or quantitative change in the excipients beyond an allowable range, particularly for drug products containing a narrow therapeutic drug, might require an *in vivo*

TABLE 6.12 FDA Definitions of Level of Changes That May Affect the Quality of an Approved Drug Product

CHANGE LEVEL	DEFINITION OF LEVEL
Level 1	Level 1 changes are those that are unlikely to have any detectable impact on the formulation quality and performance.
Level 2	Level 2 changes are those changes that could have a significant impact on formulation quality and performance.
Level 3	Level 3 changes are those changes that are likely to have a significant impact on formulation quality and performance.

bioequivalence study to demonstrate that drug quality and performance was not altered by the change.



FREQUENTLY ASKED QUESTIONS

1. What physical or chemical properties of a drug substance are important in designing a drug for **(a)** oral administration or **(b)** parenteral administration?
2. For a lipid soluble drug that has very poor aqueous solubility, what strategies could be used to make this drug more bioavailable after oral administration?
3. For a weak ester drug that is unstable in highly acid or alkaline solutions, what strategies could be used to make this drug more bioavailable after oral administration?
4. How do excipients in a drug product that are physically inert, chemically inert, and nontoxic change the bioavailability of the active drug substance?



LEARNING QUESTIONS

1. What are the two rate-limiting steps possible in the oral absorption of a solid drug product? Which one would apply to a soluble drug? Which one could be altered by the pharmacist? Give examples.
2. What is the physiologic transport mechanism for the absorption of most drugs from the gastrointestinal tract? What area of the gastrointestinal tract is most favorable for the absorption of drugs? Why?
3. Explain why the absorption rate of a soluble drug tends to be greater than the elimination rate of the drug.
4. What type of oral dosage form generally yields the greatest amount of systemically available drug in the least amount of time? (Assume that the drug can be prepared in any form.) Why?
5. What effect does the oral administration of an anticholinergic drug, such as atropine sulfate, have on the bioavailability of aspirin from an enteric-coated tablet? (Hint: Atropine sulfate decreases gastrointestinal absorption.)
6. Drug formulations of erythromycin, including its esters and salts, have significant differences in bioavailability. Erythromycin is unstable in an acidic medium. Suggest a method for preventing a potential bioavailability problem for this drug.

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