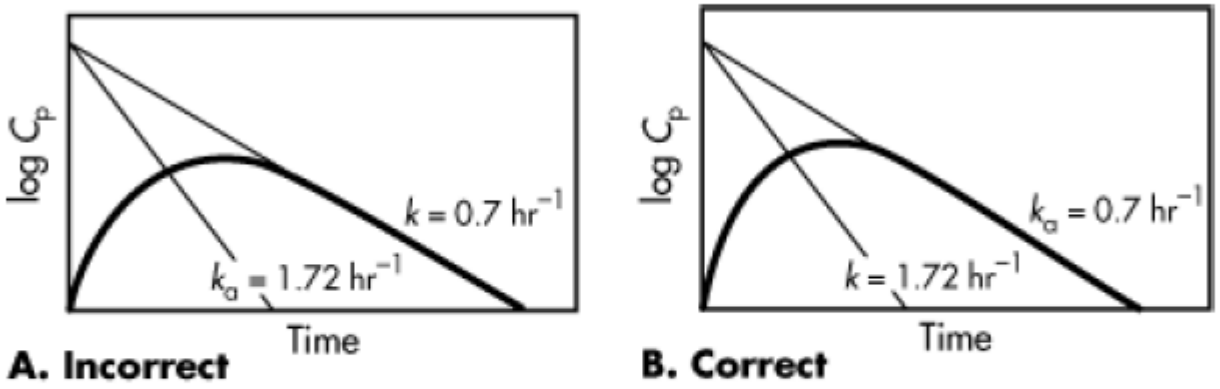
FLIP-FLOP OF KA AND K

In using the method of residuals to obtain estimates of *k*a and *k*, the terminal phase of an oral absorption curve is usually represented by *k* whereas the steeper slope is represented by *k*a. **In a few cases, the elimination rate constant *k* obtained from oral absorption data does not agree with that obtained after intravenous bolus injection**. For example, the *k* obtained after an intravenous bolus injection of a bronchodilator was 1.72 hr^{-1} , whereas the *k* calculated after oral administration was 0.7 hr^{-1}. When *k*a was obtained by the method of residuals, the rather surprising result was that the *k*a was 1.72 hr^{-1}

Figure 7-11.



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

Flip-flop of k_a and k. Because $k > k_a$, the right-hand figure and slopes represent the correct values for k_a and k.

For drugs that have a large elimination rate constant ($k > 0.69\ hr^{-1}$), the chance for flip-flop of *k*a and *k* is much greater. The drug isoproterenol, for example, has an oral elimination half-life of only a few minutes, and flip-flop of *k*a and *k* has been noted. Similarly, salicyluric acid was flip-flopped when oral data were plotted.

Apparently, **the *k*a and *k*** obtained by the method **of residuals** has been interchanged. This phenomenon is called ***flip-flop*** of the absorption and elimination rate constants. Flip-flop, or **the reversal of the rate constants**, may occur whenever *k*a and *k* are estimated from oral drug absorption data. In order to demonstrate unambiguously that the steeper curve represents the elimination rate for a drug given extravascularly, the drug must be given by intravenous injection into the same patient. After intravenous injection, the decline in plasma drug levels over time represents the true elimination rate.

Most of the drugs observed to have flip-flop characteristics are drugs with **fast elimination** (ie, $k > ka$

BIOAVAILABILITY AND BIOEQUIVALENCE: INTRODUCTION

A ***multisource drug product*** is a drug product that contains the same active drug substance in the same dosage form and is marketed by more than one pharmaceutical manufacturer. ***Single-source drug products*** **are drug products for which the patent has not yet expired or has certain exclusivities so that only one manufacturer can make it**. **Single-source drug products are usually brand-name (innovator) drug products.**

After the patent and other exclusivities for the brand-name drug expires, a pharmaceutical firm may manufacture a generic drug product that can be substituted for the branded drug product. Since the formulation and method of manufacture of the drug product can affect the bioavailability and stability of the drug, the generic drug manufacturer must demonstrate that the generic drug product is **bioequivalent and therapeutically equivalent** to the brand-name drug product.

Drug product selection and generic drug product substitution are major **responsibilities for physicians, pharmacists, and others who prescribe**, **dispense, or purchase drugs**. To facilitate such decisions, the U.S. Food and Drug Administration (FDA) publishes annually, in print and on the Internet, ***Approved Drug Products with Therapeutic Equivalence Evaluations***, also known as the ***Orange Book*** (www.fda.gov/cder/orange/default.htm). **The *Orange Book* identifies drug products approved on the basis of safety and effectiveness by the FDA and contains therapeutic equivalence evaluations for approved multisource prescription drug products**. These evaluations serve as public information and advice to state health agencies, prescribers, and pharmacists to promote public education in the area of drug product selection and to foster containment of health care costs. The following definitions are from the *2003 Orange Book, Code of Federal Regulations*, 21 CFR 320, and other sources.

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

On March 23, 2020, FDA removed from the Orange Book the listings for "biological products" that have been approved in applications under section 505 of the FD&C Act because these products are no longer "listed drugs" (see section 7002(e)(4) of the Biologics Price Competition and Innovation Act of 2009).

Additional information and resources for the Orange Book

Find Approved Drugs

Search by Proprietary Name, Active Ingredient or Application Number

Enter at least 3 characters Search

Search by Applicant (Company)

Search by Dosage Form (for example: *TABLET*)

Search by Route of Administration (for example: *ORAL*)

Find Patent Information

***Bioavailability*. Bioavailability means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.** For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

***Bioequivalence requirement*. A requirement imposed by the FDA for *in-vitro* and/or *in-vivo* testing of specified drug products, which must be satisfied as a <u>condition for marketing</u>**

Bioequivalent drug products. **This term describes pharmaceutical equivalent or pharmaceutical alternative products that display comparable bioavailability when studied under similar experimental conditions**. For systemically absorbed drugs, the test **(generic)** and reference listed drug **(brand-name)** shall be considered **bioequivalent** if: (1) the rate and extent of absorption of the test drug do not show a significant difference from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or (2) the extent of absorption of the test drug does not show a significant difference from the extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the reference drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

Brand name. **The trade name of the drug. This name is privately owned by the manufacturer or distributor and is used to distinguish the specific drug product from competitor's products (eg, Tylenol, McNeil Laboratories).**

***Chemical name*. The name used by organic chemists to indicate the chemical structure of the drug (eg, N-acetyl-*p*-aminophenol).**

RELATIVE AND ABSOLUTE AVAILABILITY

The area under the drug concentration time curve (AUC) is used as a measure of the total amount of unaltered drug that reaches the systemic circulation. The AUC is dependent on the total quantity of available drug, *FD*0, divided by the elimination rate constant, *k*, and the apparent volume of distribution, *V* D. *F* is the fraction of the dose absorbed. After IV administration, *F* is equal to unity, because the entire dose enters the systemic circulation. Therefore, the drug is considered to be completely available after IV administration.

After oral administration of a drug, *F* may vary from a value of 0 (no drug absorption) to 1 (complete drug absorption).

Relative Availability

Relative (apparent) availability is the availability of the drug from a drug product as compared to a recognized standard. The fraction of dose systemically available from an oral drug product is difficult to ascertain. The availability of drug in the formulation is compared to the availability of drug in a standard dosage formulation, usually a solution of the pure drug evaluated in a crossover study. **The relative availability of two drug products given at the same dosage level and by the same route of administration can be obtained using the following equation:**

$$\text{Relative availability} = \frac{[\text{AUC}]_A}{[\text{AUC}]_B} \qquad (15.1)$$

where drug product B is the recognized reference standard. This fraction may be multiplied by 100 to give percent relative availability.

When different doses are administered, a correction for the size of the dose is made, as in the following equation:

$$\text{Relative availability} = \frac{[\text{AUC}]_A/\text{dose A}}{[\text{AUC}]_B/\text{dose B}} \qquad (15.2)$$

Urinary drug excretion data may also be used to measure relative availability, as long as the total amount of intact drug excreted in the urine is collected. The percent relative availability using urinary excretion data can be determined as follows:

$$\text{Percent relative availability} = \frac{[D_u]_A^\infty}{[D_u]_B^\infty} \times 100 \qquad (15.3)$$

where $[D\ u]_A^\infty$ is the total amount of drug excreted in the urine.

Absolute Availability

The absolute availability of drug is the systemic availability of a drug after extravascular administration (eg, oral, rectal, transdermal, subcutaneous) compared to IV dosing. The absolute availability of a drug is generally measured by comparing the respective AUCs after extravascular and IV administration. This measurement may be performed as long as *V*D and *k* are independent of the route of administration.

Absolute availability after oral drug administration using plasma data can be determined as follows:

$$\text{Absolute availability} = F = \frac{[\text{AUC}]_{\text{PO}}/\text{dose}_{\text{PO}}}{[\text{AUC}]_{\text{IV}}/\text{dose}_{\text{IV}}} \qquad (15.4)$$

Absolute availability, *F*, may be expressed as a fraction or as a percent by multiplying *F* x 100. Absolute availability using urinary drug excretion data can be determined by the following:

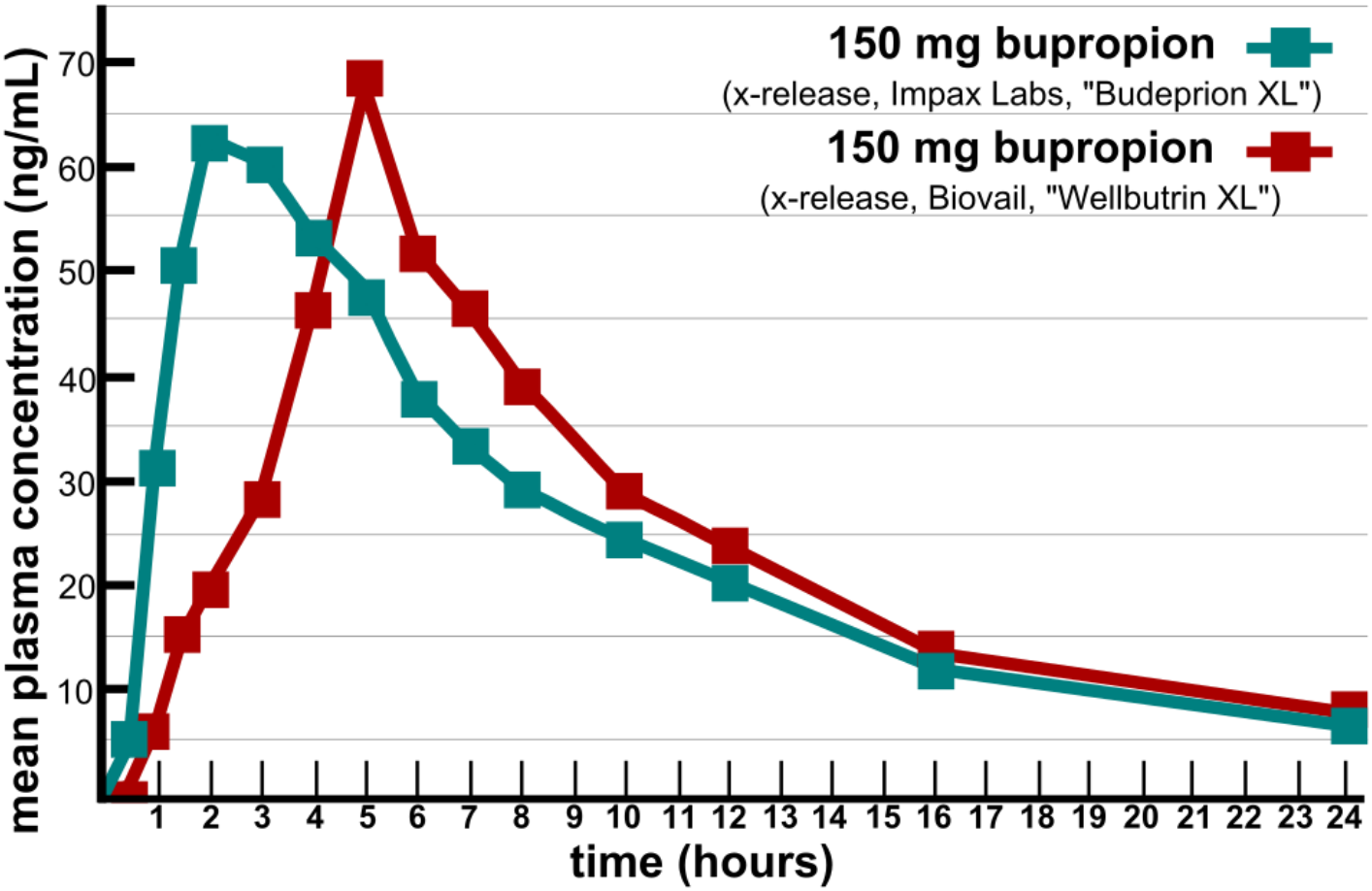
$$\text{Absolute availability} = \frac{[D_u]_{\text{PO}}^{\infty}/\text{dose}_{\text{PO}}}{[D_u]_{\text{IV}}^{\infty}/\text{dose}_{\text{IV}}} \qquad (15.5)$$

The absolute bioavailability is also equal to *F*, the fraction of the dose that is bioavailable. Absolute availability is sometimes expressed as a percent, ie, $F = 1$, or 100%. For drugs given intravascularly, such as by IV bolus injection, $F = 1$ because all of the drug is completely absorbed. For all extravascular routes of administration, such as the oral route (PO), the absolute bioavailability *F* may not exceed 100% ($F > 1$). *F* is usually determined by Equation 15.4 or 15.5, where PO is the oral route or any other extravascular route of drug administration.

METHODS FOR ASSESSING BIOAVAILABILITY

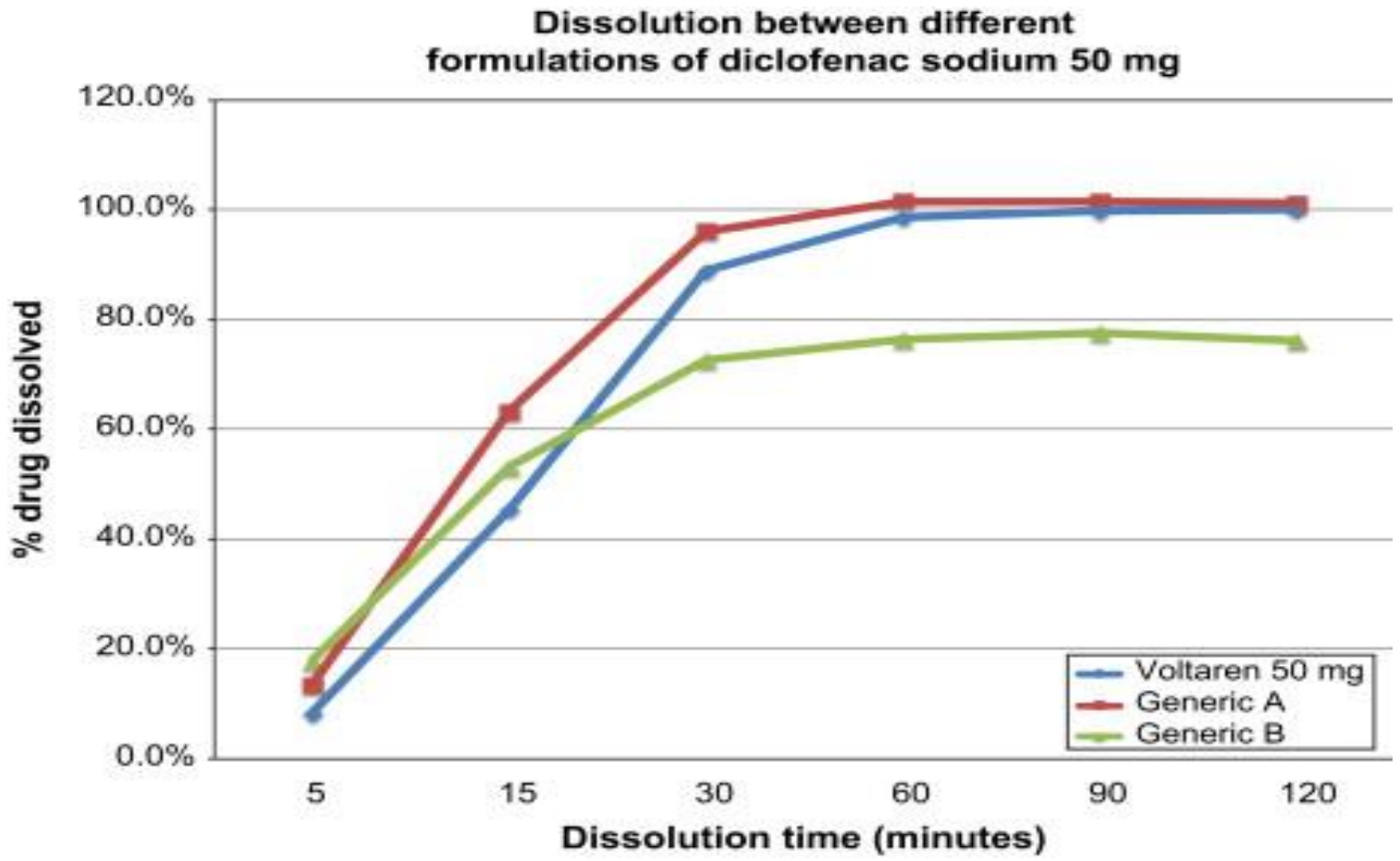
Table 15.1 Methods for Assessing Bioavailability and Bioequivalence
Plasma drug concentration
Time for peak plasma (blood) concentration (t_{max})
Peak plasma drug concentration (C_{max})
Area under the plasma drug concentrationâ€"time curve (AUC)
Urinary drug excretion
Cumulative amount of drug excreted in the urine (D_u)
Rate of drug excretion in the urine (dD_u/dt)
Time for maximum urinary excretion (t)
Acute pharmacodynamic effect
Maximum pharmacodynamic effect (E_{max})
Time for maximum pharmacodynamic effect
Area under the pharmacodynamic effectâ€"time curve
Onset time for pharmacodynamic effect
Clinical observations
Well-controlled clinical trials
***In-vitro* studies**

Drug dissolution



A bioequivalency profile comparison of 150 mg extended-release bupropion as produced by Impax Laboratories for Teva and Biovail for GlaxoSmithKline.

https://en.wikipedia.org/wiki/Bupropion#/media/File:Bupropion_bioequivalency_comparison.svg



https://www.researchgate.net/publication/235766465_The_differences_between_the_branded_and_generic_medicines_using_solid_dosage_forms_In-vitro_dissolution_testing/figures?lo=1

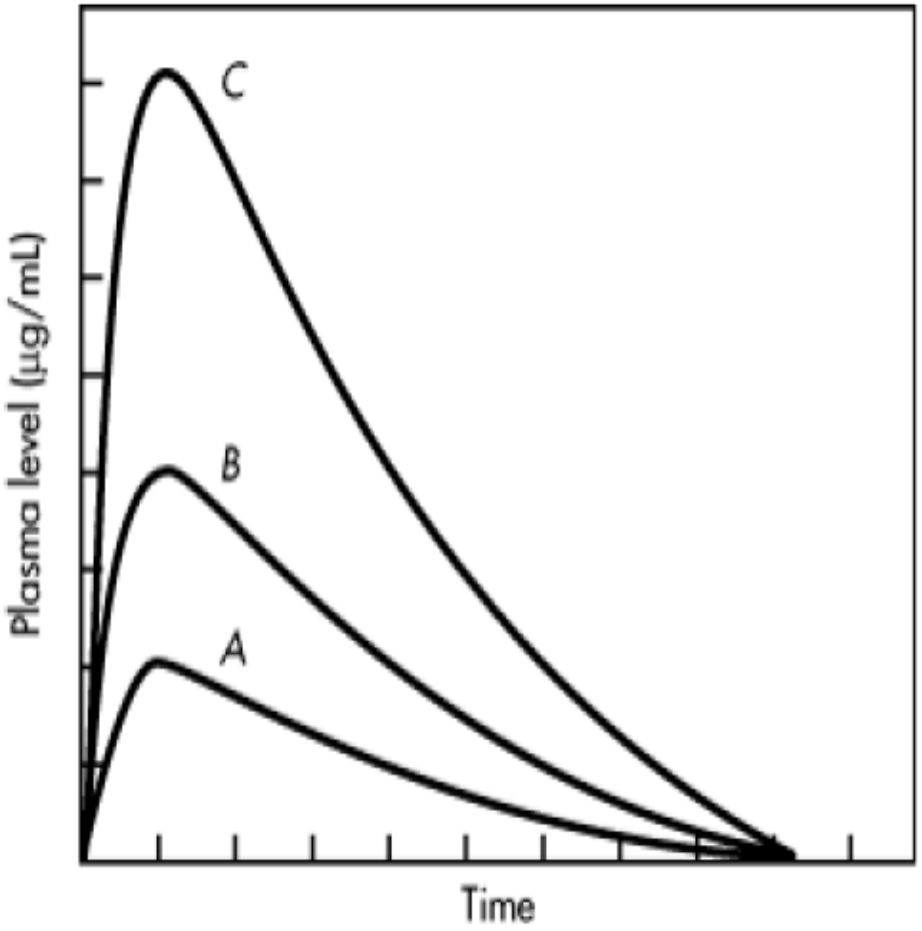
AUC. The *area under the plasma level time curve*, AUC, is a measurement of the *extent* of drug bioavailability . The AUC reflects the total amount of active drug that reaches the systemic circulation. The AUC is the area under the drug plasma level time curve from $t = 0$ to $t = \infty$, and is equal to the amount of unchanged drug reaching the general circulation divided by the clearance.

$$[\mathrm{AUC}]_0^\infty = \int_0^\infty C_\mathrm{P}\, dt \qquad (15.6)$$

$$[\mathrm{AUC}]_0^\infty = \frac{FD_0}{\mathrm{clearance}} = \frac{FD_0}{kV_\mathrm{D}} \qquad (15.7)$$

For many drugs, the AUC is directly proportional to dose. For example, if a single dose of a drug is increased from 250 to 1000 mg, the AUC will also show a fourfold increase.

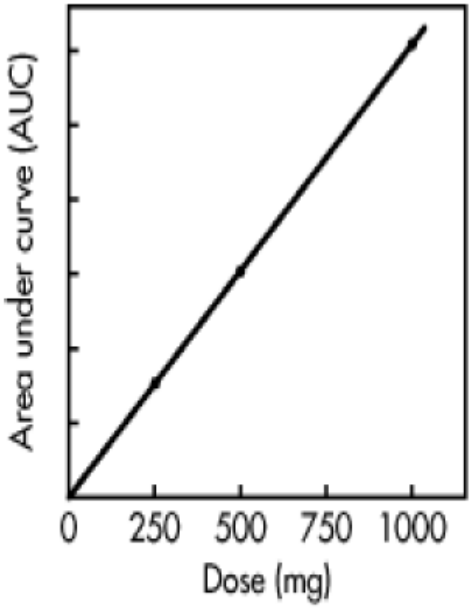
In some cases, the AUC is not directly proportional to the administered dose for all dosage levels. For example, as the dosage of drug is increased, one of the pathways for drug elimination may become saturated. Drug elimination includes the processes of metabolism and excretion. Drug metabolism is an enzyme-dependent process. **For drugs such as salicylate and phenytoin, continued increase of the dose causes saturation of one of the enzyme pathways for drug metabolism and consequent prolongation of the elimination half-life. The AUC thus increases disproportionally to the increase in dose, because a smaller amount of drug is being eliminated (ie, more drug is retained). When the AUC is not directly proportional to the dose, bioavailability of the drug is difficult to evaluate because drug kinetics may be dose dependent.**



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

Plasma levelâ€"time curve following administration of single doses of **(A)** 250 mg, **(B)** 500 mg, and **(C)** 1000 mg of drug.

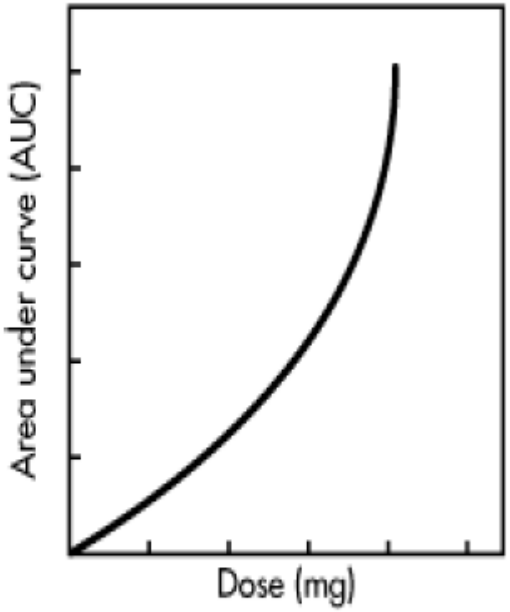
Figure 15-3.



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

Linear relationship between AUC and dose (data from).

Figure 15-4.



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

Relationship between AUC and dose when metabolism is saturable.

Drug elimination and Hepatic clearance
Chapter 6

DRUG ELIMINATION

Drugs are removed from the body by various elimination processes. ***Drug elimination*** **refers to the irreversible removal of drug from the body by all routes of elimination. Drug elimination is usually divided into two major components: excretion and biotransformation.**

Drug excretion is the removal of the intact drug. **Nonvolatile drugs are excreted mainly by renal excretion, a process in which the drug passes through the kidney to the bladder and ultimately into the urine.** Other pathways for drug excretion may include the excretion of drug into bile, sweat, saliva, milk (via lactation), or other body fluids. Volatile drugs, such as gaseous anesthetics or drugs with high volatility, are excreted via the lungs into expired air.

Biotransformation* or *drug metabolism is the process by which the drug is chemically converted in the body to a metabolite. Biotransformation is usually an enzymatic process. A few drugs may also be changed chemically by a nonenzymatic process (eg, ester hydrolysis). The enzymes involved in the biotransformation of drugs are located mainly in the liver. Other tissues such as kidney, lung, small intestine, and skin also contain biotransformation enzymes.

Drug elimination in the body involves many complex rate processes. Although organ systems have specific functions, the tissues within the organs are not structurally homogeneous, and elimination processes may vary in each organ. In elimination was modeled by an overall first-order elimination rate process.

In this chapter, drug elimination is described in terms of clearance from a well-stirred compartment containing uniform drug distribution. The term *clearance* describes the process of drug elimination from the body or from a single organ without identifying the individual processes involved. Clearance may be defined as the volume of fluid cleared of drug from the body per unit of time. The units for clearance are milliliters per minute (mL/min) or liters per hour (L/hr). The volume concept is simple and convenient, because all drugs are dissolved and distributed in the fluids of the body.

THE KIDNEY

The liver and kidney are the two major drug elimination organs in the body, though drug elimination can also occur almost anywhere in the body. **The kidney is the main excretory organ for the removal of metabolic waste products and plays a major role in maintaining the normal fluid volume and electrolyte composition in the body.** To maintain salt and water balance, the kidney excretes excess electrolytes, water, and waste products while conserving solutes necessary for proper body function.

In addition, the kidney has two endocrine functions:

(1) secretion of renin, which regulates blood pressure; and (2) secretion of erythropoietin, which stimulates red blood cell production.

Anatomic Considerations

The kidneys are located in the peritoneal cavity. The outer zone of the kidney is called the *cortex* , and the inner region is called the *medulla* . The *nephrons* are the basic functional units, collectively responsible for the removal of metabolic waste and the maintenance of water and electrolyte balance. Each kidney contains 1 to 1.5 million nephrons. The *glomerulus* of each nephron starts in the cortex. *Cortical nephrons* have short *loops of Henle* that remain exclusively in the cortex; *juxtamedullary nephrons* have long loops of Henle that extend into the medulla. The longer loops of Henle allow for a greater ability of the nephron to reabsorb water, thereby producing a more concentrated urine.