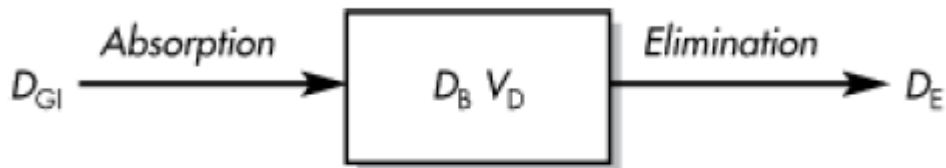


## PHARMACOKINETICS OF DRUG ABSORPTION

In pharmacokinetics, the overall rate of drug absorption may be described as either a first-order or zero-order input process. Most pharmacokinetic models assume first-order absorption unless an assumption of zero-order absorption improves the model significantly or has been verified experimentally.

The rate of change in the amount of drug in the body,  $dD_B/dt$ , is dependent on the relative rates of drug absorption and elimination. The net rate of drug accumulation in the body at any time is equal to the rate of drug absorption less the rate of drug elimination, regardless of whether absorption is zero-order or first order.

**Figure 7-1.**



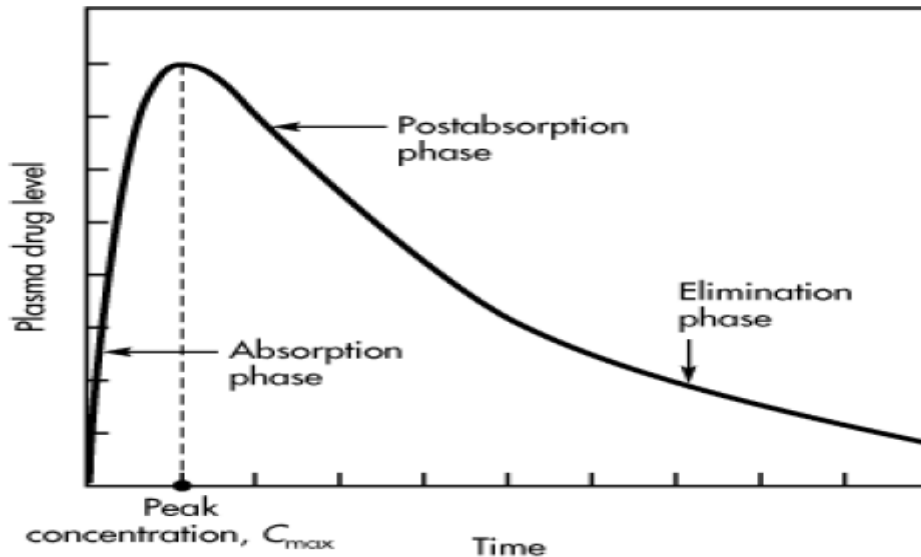
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Model of drug absorption and elimination.

$$\frac{dD_B}{dt} = \frac{dD_{GI}}{dt} - \frac{dD_E}{dt} \quad (7.1)$$

Where  $D_{GI}$  is amount of drug in the gastrointestinal tract and  $D_E$  is amount of drug eliminated. A plasma level time curve showing drug absorption and elimination rate processes is given in . During the *absorption phase* of a plasma level time curve, the rate of drug absorption is greater than the rate of drug elimination. Note that during the absorption phase, elimination occurs *whenever* drug is present in the plasma, even though absorption predominates.



Plasma level time curve for a drug given in a single oral dose. The drug absorption and elimination phases of the curve are shown.

$$\frac{dD_{GI}}{dt} > \frac{dD_E}{dt} \quad (7.2)$$

At the *peak drug concentration* in the plasma the rate of drug absorption just equals the rate of drug elimination, and there is no net change in the amount of drug in the body.

$$\frac{dD_{GI}}{dt} = \frac{dD_E}{dt} \quad (7.3)$$

Immediately after the time of peak drug absorption, some drug may still be at the absorption site (ie, in the GI tract or other site of administration). However, the rate of drug elimination at this time is faster than the rate of absorption, as represented by the ***postabsorption phase*** in .

$$\frac{dD_{GI}}{dt} < \frac{dD_E}{dt} \quad (7.4)$$

When the drug at the absorption site becomes depleted, **the rate of drug absorption approaches zero, or  $dD_{GI}/dt = 0$** . The plasma level time curve (now the *elimination phase*) then represents only the elimination of drug from the body, usually **a first-order process**. Therefore, during the elimination phase the rate of change in the amount of drug in the body is described as a first-order process,

$$\frac{dD_B}{dt} = -kD_B \quad (7.5)$$

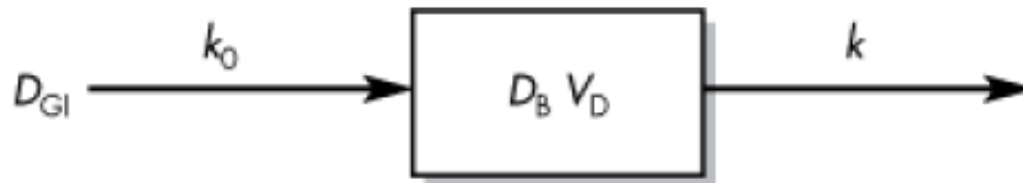
where  $k$  is the first-order elimination rate constant.

### ZERO-ORDER ABSORPTION MODEL

Zero-order drug absorption from the dosing site into the plasma usually occurs when either the drug is absorbed by a **saturable process** or a **zero-order controlled-release delivery system is used**. In this model, drug in the gastrointestinal tract,  $D_{GI}$ , is absorbed systemically at a **constant rate,  $k_0$** . Drug is simultaneously and immediately eliminated from the body by a first-order rate process defined by a first-order rate constant,  $k$ .

***This model is analogous to that of the administration of a drug by intravenous infusion.***

**Figure 7-3.**



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One-compartment pharmacokinetic model for zero-order drug absorption and first-order drug elimination.

The rate of first-order elimination at any time is equal to  $D_B k$ . The rate of input is simply  $k_0$ . Therefore, the net change per unit time in the body can be expressed as

$$\frac{dD_B}{dt} = k_0 - kD_B \quad (7.6)$$

Integration of this equation with substitution of  $V_D C_p$  for  $D_B$  produces

$$C_p = \frac{k_0}{V_D k} (1 - e^{-kt}) \quad (7.7)$$

The rate of drug absorption is constant until the amount of drug in the gut,  $DGI$ , is depleted. **The time for complete drug absorption to occur is equal to  $DGI/k_0$ .** After this time, the drug is no longer available for absorption from the gut, and Equation 7.7 no longer holds. The drug concentration in the plasma subsequently declines in accordance with a **first-order elimination rate process**.

### **FIRST-ORDER ABSORPTION MODEL**

Although zero-order absorption can occur, absorption is usually assumed to be a first-order process. This model assumes a first-order input across the gut wall and first-order elimination from the body. This model applies mostly to the oral absorption of drugs in **solution or rapidly dissolving dosage (immediate release) forms such as tablets, capsules, and suppositories**. In addition, drugs given by intramuscular or subcutaneous aqueous injections may also be described using a first-order process.

**Figure 7-4.**



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One-compartment pharmacokinetic model for first-order drug absorption and first-order elimination.

In the case of a drug given orally, **the dosage form first disintegrates if it is given as a solid, then the drug dissolves into the fluids of the GI tract.** Only drug in solution is absorbed into the body. The rate of disappearance of drug from the gastrointestinal tract is described by

$$\frac{dD_{GI}}{dt} = -k_a D_{GI} F \quad (7.8)$$

where  $k_a$  is the first-order absorption rate constant from the GI tract,  $F$  is the fraction absorbed, and  $D_{GI}$  is the amount of drug in solution in the GI tract at any time  $t$ .

Integration of the differential equation (7.8) gives

$$\frac{dD_{GI}}{dt} = -k_a D_{GI} F \quad (7.8)$$

$$\frac{dD_{GI}}{dt} = D_0 e^{-k_a t} \quad (7.9)$$

where  $D_0$  is the dose of the drug. The rate of drug elimination is described by a first-order rate process for most drugs and is equal to  $kD_B$ . The rate of drug change in the body,  $dD_B/dt$ , is therefore the rate of drug in, minus the rate of drug out as given by the differential equation, Equation 7.10:

$$\frac{dD_B}{dt} = \text{rate in} - \text{rate out} \quad (7.10)$$

$$\frac{dD_B}{dt} = Fk_a D_{GI} - kD_B$$

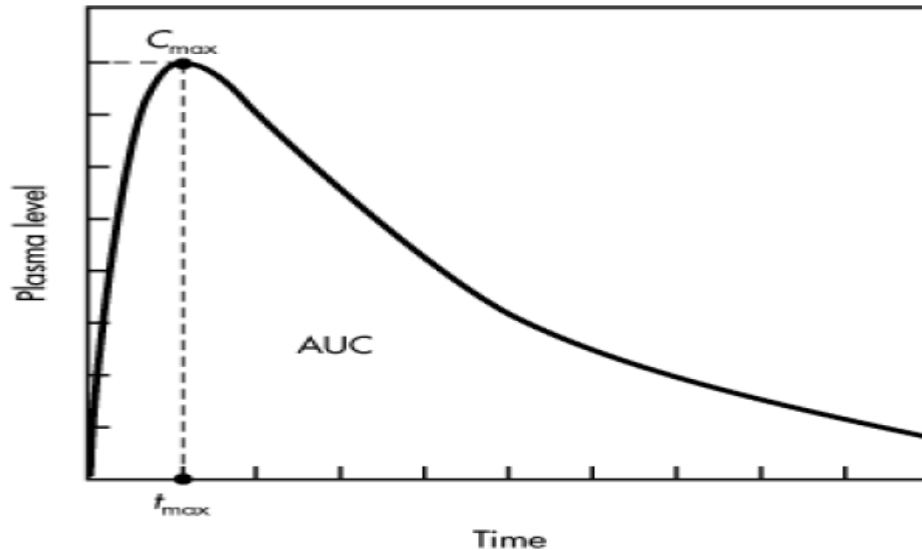
where  $F$  is the fraction of drug absorbed systemically. Since the drug in the gastrointestinal tract also follows a first-order decline (ie, the drug is absorbed across the gastrointestinal wall), the amount of drug in the gastrointestinal tract at any time  $t$  is equal to  $D_0 e^{-k_a t}$ .

$$\frac{dD_B}{dt} = Fk_a D_0 e^{-k_a t} - kD_B$$

The value of  $F$  may vary from 1 for a fully absorbed drug to 0 for a drug that is completely unabsorbed. This equation can be integrated to give the general oral absorption equation for calculation of the drug concentration ( $C_p$ ) in the plasma at any time  $t$ , as shown below.

$$C_P = \frac{Fk_a D_0}{V_D (k_a - k)} (e^{-kt} - e^{-k_a t}) \quad (7.11)$$

A typical plot of the concentration of drug in the body after a single oral dose is presented in



The maximum plasma concentration after oral dosing is  $C_{max}$ , and the time needed to reach maximum concentration is  $t_{max}$ . **The  $t_{max}$  is independent of dose and is dependent on the rate constants for absorption ( $k_a$ ) and elimination ( $k$ ) (Eq. 7.13a).** At  $C_{max}$ , sometimes called ***peak concentration***, the rate of drug absorbed is equal to the rate of drug eliminated. Therefore, the net rate of concentration change is equal to zero. **At  $C_{max}$ , the rate of concentration change can be obtained by differentiating Equation 7.12, as follows:**

$$C_P = \frac{Fk_a D_0}{V_D (k_a - k)} (e^{-kt} - e^{-k_a t}) \quad (7.11)$$

$$dC_P/dt = \frac{k_a D_0 F}{V_D (k_a - k)} (-ke^{-kt} + k_a e^{-k_a t}) = 0 \quad (7.12)$$

This can be simplified as follows:

$$-ke^{-kt} + k_a e^{-k_a t} = 0 \quad \text{or} \quad ke^{-kt} = k_a e^{-k_a t} \quad (7.13)$$

$$\ln k - kt = \ln k_a - k_a t$$

$$t_{\max} = \frac{\ln k_a - \ln k}{k_a - k} = \frac{\ln(k_a/k)}{k_a - k}$$

$$t_{\max} = \frac{2.3 \log(k_a/k)}{k_a - k} \quad (7.13a)$$

As shown in Equation 7.13a, the time for maximum drug concentration,  **$t_{\max}$** , is **dependent only on the rate constants  $k_a$  and  $k$** . In order to calculate  **$C_{\max}$** , the value for  **$t_{\max}$**  is determined via Equation 7.13a and then substituted into Equation 7.11, solving for  $C_{\max}$ . Equation 7.11 shows that  **$C_{\max}$  is directly proportional to the dose of drug given ( $D_0$ ) and the fraction of drug absorbed ( $F$ )**. Calculation of  $t_{\max}$  and  $C_{\max}$  is usually necessary, **since direct measurement of the maximum drug concentration may not be possible due to improper timing of the serum samples.**

The first-order elimination rate constant may be determined from the elimination phase of the plasma level time curve. **At later time intervals, when drug absorption has been completed, ie,  $kat$** , Equation 7.11 reduces to

$$C_p = \frac{Fk_a D_0}{V_D(k_a - k)} e^{-kt} \quad (7.14)$$

Taking the natural logarithm of this expression,

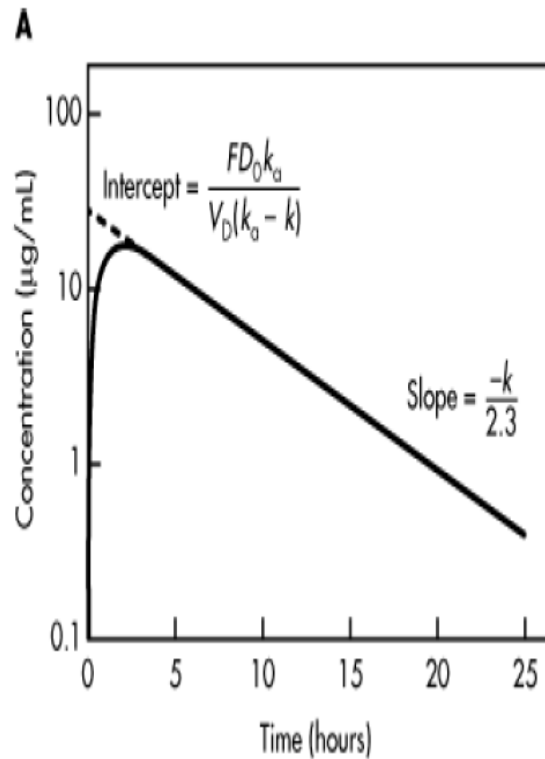
$$\ln C_p = \ln \frac{Fk_a D_0}{V_D(k_a - k)} - kt \quad (7.15)$$

Substitution of common logarithms gives

$$\log C_p = \log \frac{Fk_a D_0}{V_D(k_a - k)} - \frac{kt}{2.3} \quad (7.16)$$

With this equation, a graph constructed by plotting  $\log C_p$  versus time will yield a straight line with a slope of  $k/2.3$ .

Figure 7-6.



## Determination of Absorption Rate Constants from Oral Absorption Data

### METHOD OF RESIDUALS

Assuming  $k_a \gg k$  in Equation 7.11, the value for the second exponential will become insignificantly **small with time (ie,  $e^{-k_a t} \approx 0$ )** and can therefore be omitted. When this is the case, drug absorption is virtually complete. Equation 7.11 then reduces to Equation 7.22.

$$C_p = \frac{F k_a D_0}{V_D (k_a - k)} e^{-kt} \quad (7.22)$$

From this, one may also obtain the intercept of the y axis

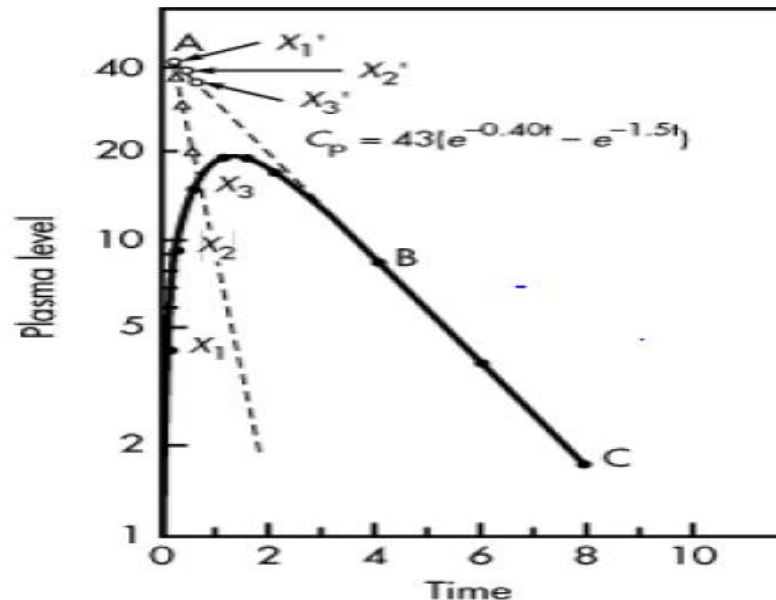
$$\frac{F k_a D_0}{V_D (k_a - k)} = A$$

where  $A$  is a constant. Thus, Equation 7.22 becomes

$$C_p = A e^{-kt} \quad (7.23)$$

This equation, which represents first-order drug elimination, will yield a linear plot on semilog paper. The slope is equal to  $-k/2.3$ . The value for  $k_a$  can be obtained by using the **method of residuals or a feathering** technique, as described in . The value of  $k_a$  is obtained by the following procedure:

1. Plot the drug concentration versus time on semilog paper with the concentration values on the logarithmic axis.
2. Obtain the slope of the terminal phase (line  $BC$ , ) by extrapolation.
3. Take any points on the upper part of line  $BC$  (eg,  $x'_1$ ,  $x'_2$ ,  $x'_3$ , . . .) and drop vertically to obtain corresponding points on the curve (eg,  $x_1$ ,  $x_2$ ,  $x_3$ , . . .).
4. Read the concentration values at  $x_1$  and  $x'_1$ ,  $x_2$  and  $x'_2$ ,  $x_3$  and  $x'_3$ , and so on. Plot the values of the differences at the corresponding time points 1, 2, 3, . . . . A straight line will be obtained with a slope of  $-k_a/2.3$ .



When using the method of residuals, **a minimum of three points should be used to define the straight line.**

Data points occurring shortly after  $t_{max}$  may not be accurate, because drug absorption is still continuing at that time. Because this portion of the curve represents **the postabsorption phase, only data points from the elimination phase should be used to define the rate of drug absorption as a first-order process.**

If drug absorption begins immediately after oral administration, **the residual lines obtained by feathering the plasma level time curve will intersect on the y axis at point A.**

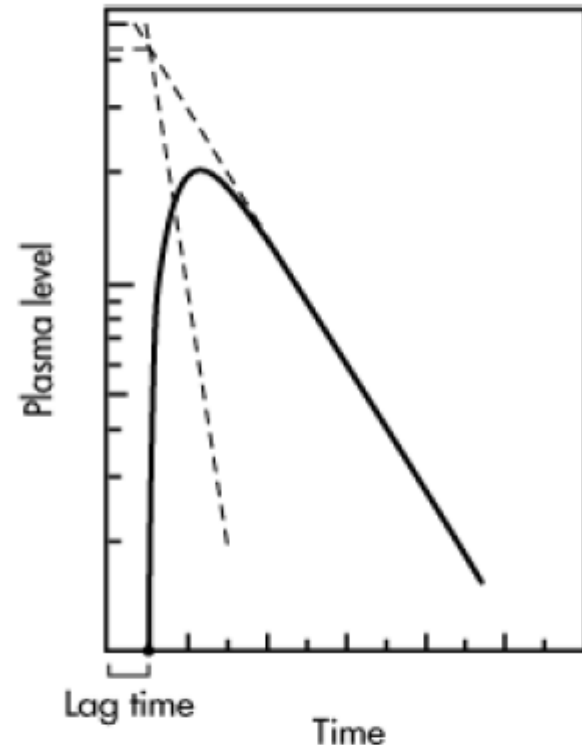
The value of this y intercept,  $A$ , represents **a hybrid constant composed** of  $k_a$ ,  $k$ ,  $V_D$ , and  $FD_0$ . The value of  $A$  has no direct physiologic meaning (see Eq. 7.23).

$$A = \frac{Fk_a D_0}{V_D (k_a - k)}$$

## LAG TIME

In **some individuals**, absorption of drug after a single oral dose does not start immediately, due to such physiologic factors as **stomach-emptying time and intestinal motility**. The time delay prior to the commencement of first-order drug absorption is known as ***lag time***.

The lag time for a drug may be observed if the two residual lines obtained by feathering the oral absorption plasma level time curve intersect at a point greater than  $t = 0$  on the x axis. The time at the point of intersection on the x axis is the lag time.



The lag time,  $t_0$ , represents the beginning of drug absorption and should not be confused with the pharmacologic term *onset time*, which represents latency, eg, the time required for the drug to reach minimum effective concentration.

Two equations can adequately describe the curve in . In one, the lag time  $t_0$  is subtracted from each time point, as shown in Equation 7.24.

$$C_P = \frac{Fk_a D_0}{V_D(k_a - k)} (e^{-k(t-t_0)} - e^{-k_a(t-t_0)}) \quad (7.24)$$

where  $Fk_a D_0/V_D(k_a - k)$  is the y value at the point of intersection of the residual lines in Figure of lag time.

The second expression that describes the curve in the Figure of lag time omits the lag time, as follows:

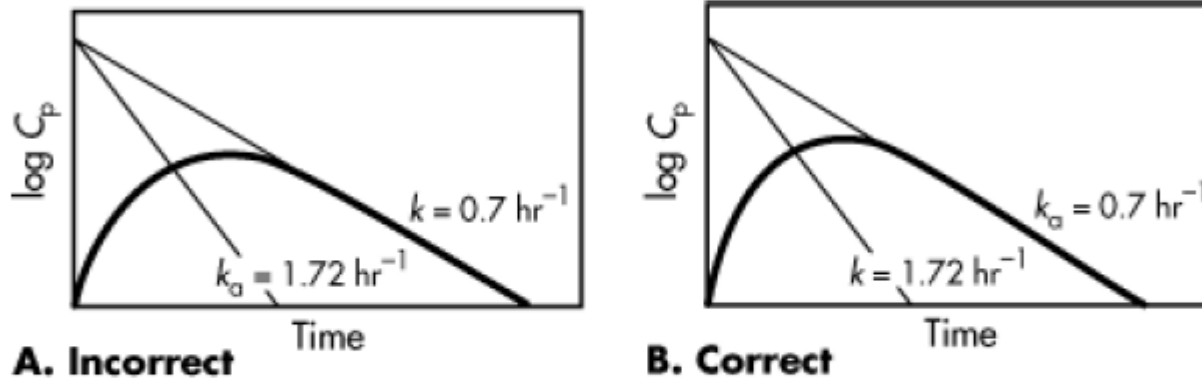
$$C_P = Be^{-kt} - Ae^{-k_a t} \quad (7.25)$$

where A and B represents the intercepts on the y axis after extrapolation of the residual lines for absorption and elimination, respectively.

## FLIP-FLOP OF $k_a$ 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  $1.72 \text{ hr}^{-1}$ , whereas the  $k$  calculated after oral administration was  $0.7 \text{ hr}^{-1}$ . When  $k_a$  was obtained by the method of residuals, the rather surprising result was that the  $k_a$  was  $1.72 \text{ hr}^{-1}$ .

**Figure 7-11.**



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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 ( $k > 0.69 \text{ hr}^{-1}$ ), 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, salicylic 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. Use of computer methods does not ensure against flip-flop of the two constants estimated. 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,  $k > k_a$ )

## **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](http://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.

**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 condition for marketing

**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,  $FDO$ , 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:

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

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:

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

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:

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

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:

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

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:

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

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 concentration–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 effect–time curve

Onset time for pharmacodynamic effect

### **Clinical observations**

Well-controlled clinical trials

### ***In-vitro* studies**

Drug dissolution

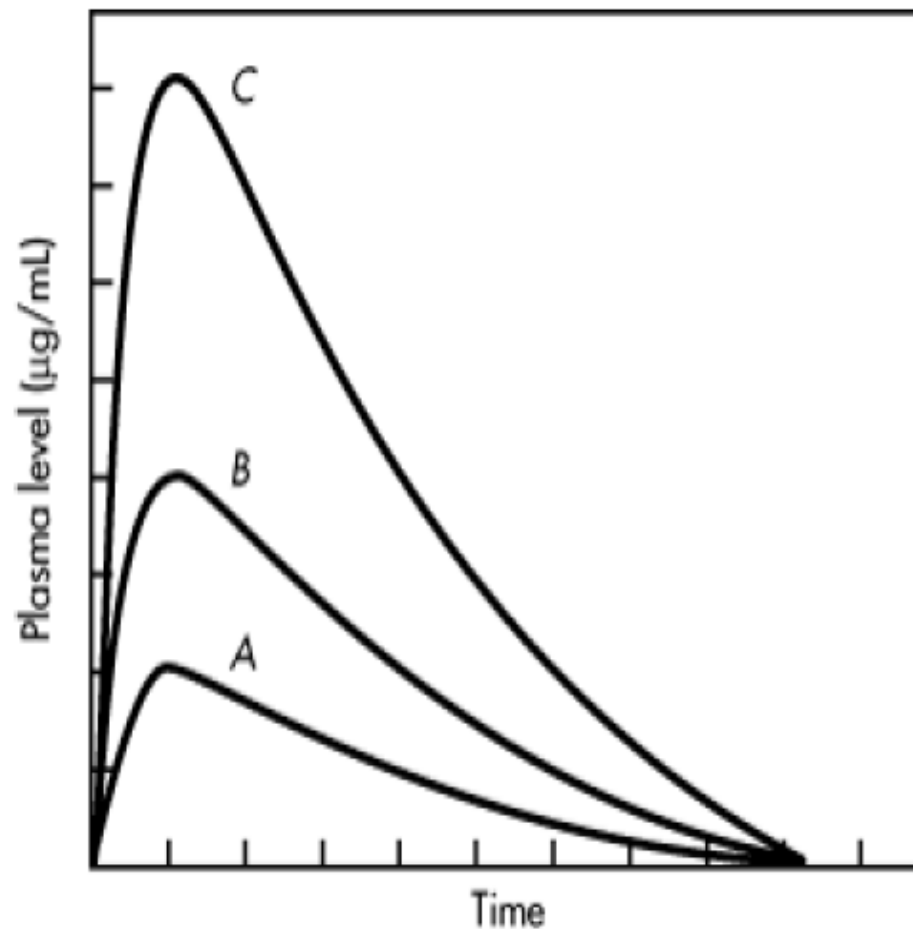
**AUC.** The *area under the plasma level time curve*, AUC, is a measurement of the *extent* of drug bioavailability . The AUC reflects the total amount of active drug that reaches the systemic circulation. The AUC is the area under the drug plasma levelime curve from  $t = 0$  to  $t = \infty$ , and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

$$[\text{AUC}]_0^\infty = \int_0^\infty C_P dt \quad (15.6)$$

$$[\text{AUC}]_0^\infty = \frac{FD_0}{\text{clearance}} = \frac{FD_0}{kV_D} \quad (15.7)$$

**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 disproportionately 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.

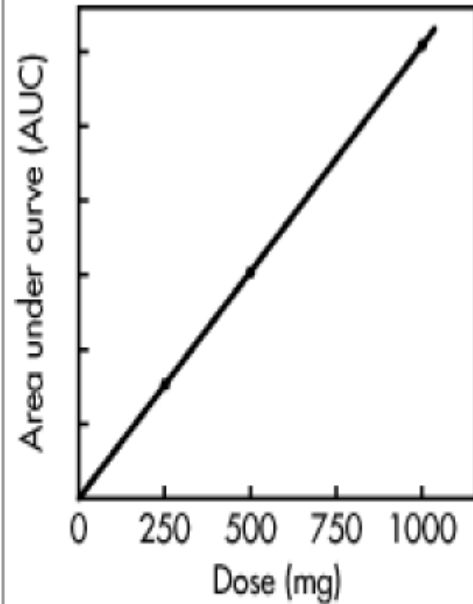


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Plasma level–time curve following administration of single doses of **(A)** 250 mg, **(B)** 500 mg, and **(C)** 1000 mg of drug.

**Figure 15-3.**

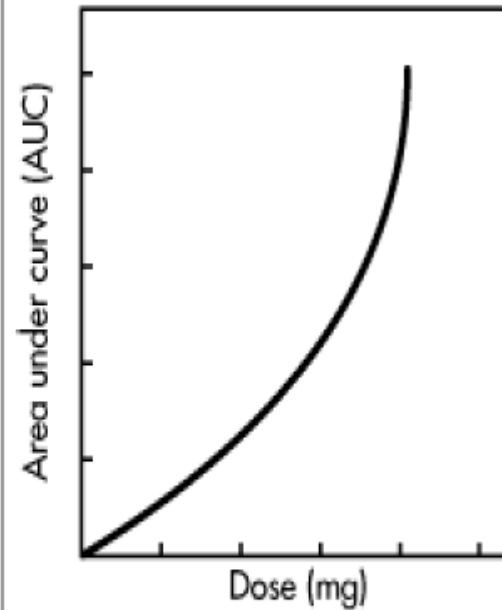


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Linear relationship between AUC and dose (data from ).

**Figure 15-4.**



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

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Relationship between AUC and dose when metabolism is saturable.

