ONE-COMPARTMENT OPEN MODEL:
INTRAVENOUS BOLUS ADMINISTRATION: INTRODUCTION

The *one-compartment open model* offers the simplest way to describe the process of drug distribution and elimination in the body. This model assumes that the drug can enter or leave the body (ie, the model is "open"), and the body acts like a single, uniform compartment. The simplest route of drug administration from a modelling perspective is a rapid intravenous injection (IV bolus). **The simplest kinetic model that describes drug disposition in the body is to consider that the drug is injected all at once into a box, or compartment, and that the drug distributes instantaneously and homogenously throughout the compartment.**

Drug elimination also occurs from the compartment immediately after injection.

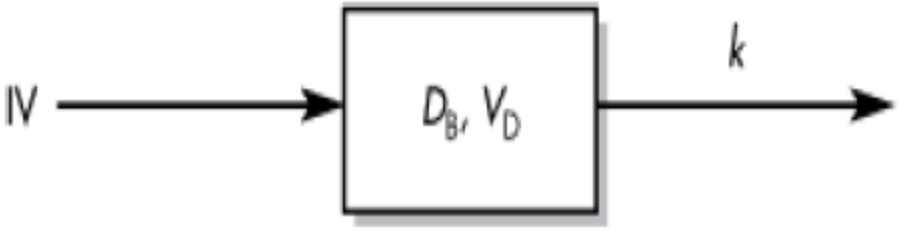
Of course, this model is a simplistic view of drug disposition in the body, **which in reality is infinitely more complex than a single compartment**. In the body, when a drug is given in the form of an **IV bolus**,1- the entire dose of drug enters the bloodstream immediately, and the drug absorption process is considered to be instantaneous. In most cases,2- the drug distributes via the circulatory system to potentially all the tissues in the body.

Uptake of drugs by various tissue organs will occur at varying rates, depending on the 1-blood flow to the tissue, 2-the lipophilicity of the drug, 3- the molecular weight of the drug, and the 4-binding affinity of the drug for the tissue mass. Most drugs are eliminated from the body either through the kidney and/or by being metabolized in the liver.

Because of rapid **drug equilibration between the blood and tissue**, drug elimination occurs as if the dose is all dissolved in a tank of uniform fluid (a single compartment) from which the drug is eliminated. The volume in which the drug is distributed is termed the *apparent volume of distribution*, *V*D. The apparent volume of distribution assumes that the drug is uniformly distributed in the body. The *V*D is determined from the preinjected amount of the dose in the syringe and the plasma drug concentration resulting immediately after the dose is injected.

1-The apparent volume of distribution is a parameter of the one-compartment model and governs the plasma concentration of the drug after a given dose. A second pharmacokinetic parameter is 2-**the *elimination rate constant*, *k***, which governs the rate at which the drug concentration in the body declines over time. The one compartment model that describes the distribution and elimination after an IV bolus dose is given in .

Figure 3-1.



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Pharmacokinetic model for a drug administered by rapid intravenous injection. D_B = drug in body; V_D = apparent volume of distribution; k = elimination rate constant.

The one-compartment open model does not predict actual drug levels in the tissues. However, the model assumes that changes in the plasma levels of a drug will result in proportional changes in tissue drug levels, since their kinetic profile is consistent with inclusion within the vascular compartment and the various drug concentrations within the compartment are in equilibrium. The *drug in the body*, *D*B, cannot be measured directly; however, accessible body fluids (such as blood) can be sampled to determine drug concentrations.

ELIMINATION RATE CONSTANT

The rate of elimination for most drugs from a tissue or from the body is a first-order process, in which the rate of elimination is dependent on the amount or concentration of drug present. The elimination rate constant, *k*, is a first-order elimination rate constant with units of time 1 (eg, hr^{-1} or 1/hr). Generally, the parent or active drug is measured in the vascular compartment. **Total removal or elimination of the parent drug from this compartment is effected by metabolism (biotransformation) and excretion**. The elimination rate constant represents the sum of each of these processes:

$$k = k_m + k_e \qquad (3.1)$$

where *k* m = **first-order rate process of metabolism and *k* e = first-order rate process of excretion.** There may be several routes of elimination of drug by metabolism or excretion. In such a case, each of these processes has its own first-order rate constant.

A rate expression for is

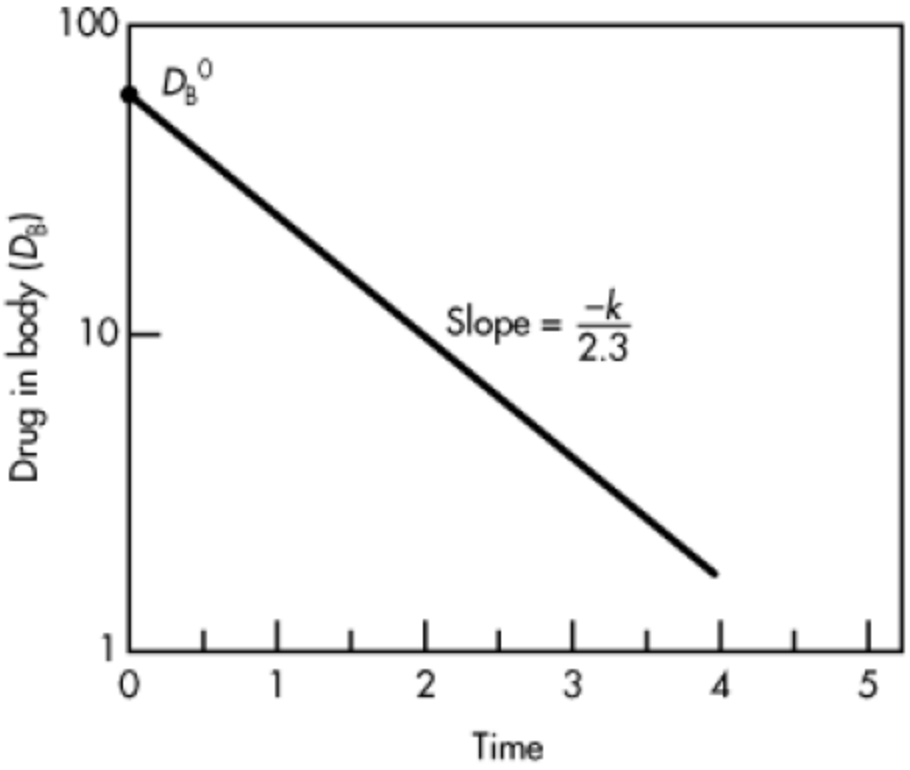
$$\frac{dD_B}{dt} = -kD_B \qquad (3.2)$$

This expression shows that the rate of elimination of drug in the body is a first-order process, depending on the overall elimination rate constant, *k*, and the amount of drug in the body, *D*B, remaining at any given time, *t*. Integration of Equation 3.2 gives the following expression:

$$\log D_B = \frac{-kt}{2.3} + \log D_B^0 \qquad (3.3)$$

where *D*B = drug in the body at time *t* and *D* B0 = drug in the body at *t* = 0. When log *D* B is plotted against *t*

for this equation, a straight line is obtained. In practice, instead of transforming values of *D*B to their corresponding logarithms, each value of *D*B is placed at logarithmic intervals on semilog paper.



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Semilog graph of the rate of drug elimination in a one-compartment model.

Equation 3.3 can also be expressed as

$$D_B = D_B^0 e^{-kt} \qquad (3.4)$$

APPARENT VOLUME OF DISTRIBUTION

In general, drug equilibrates rapidly in the body. When plasma or any other biologic compartment is sampled and analyzed for drug content, the results are usually reported in units of concentration instead of amount. Each individual tissue in the body may contain a different concentration of drug due to differences in drug affinity for that tissue. Therefore, the amount of drug in a given location can be related to its concentration by a proportionality constant that reflects the volume of fluid the drug is dissolved in. The *volume of distribution* represents a volume that must be considered in estimating the amount of drug in the body from the concentration of drug found in the sampling compartment. The volume of distribution is also the apparent volume (*V*D) in which the drug is dissolved (Eq. 3.5). Because the value of the volume of distribution does not have a true physiologic meaning in terms of an anatomic space, the term *apparent* volume of distribution is used.

The amount of drug in the body is not determined directly. Instead, a blood sample is removed at periodic intervals and analyzed for its concentration of drug. The *V*D relates the concentration of drug in plasma (*C* p) and the amount of drug in the body (*D*B), as in the following equation:

$$D_B = V_D C_p \qquad (3.5)$$

By substituting Equation 3.5 into Equation 3.3, a similar expression based on drug concentration in plasma is obtained for the first-order decline of drug plasma levels:

$$\log C_p = \frac{-kt}{2.3} + \log C_p^0 \qquad (3.6)$$

where *C* p = concentration of drug in plasma at time *t* and *C* p 0 = concentration of drug in plasma at *t* = 0.

Equation 3.6 can also be expressed as

$$C_p = C_p^0 e^{-kt} \qquad (3.7)$$

The relationship between apparent volume, drug concentration, and total amount of drug may be better understood by the following example.

Example

Exactly 1 g of a drug is dissolved in an unknown volume of water. Upon assay, the concentration of this

solution is 1 mg/mL. What is the original volume of this solution?

The original volume of the solution may be obtained by the following proportion, remembering that 1 g = 1000 mg:

$$\frac{1000\ \text{mg}}{x\ \text{mL}} = \frac{1\ \text{mg}}{\text{mL}} \qquad x = 1000\ \text{mL}$$

Therefore, the original volume was 1000 mL or 1 L.
If, in the above example, the volume of the solution is known to be 1 L, and the concentration of the solution is 1 mg/mL, then, to calculate the total amount of drug present,

$$\frac{x\ \text{mg}}{1000\ \text{mL}} = \frac{1\ \text{mg}}{\text{mL}} \qquad x = 1000\ \text{mg}$$

Therefore, the total amount of drug in the solution is 1000 mg, or 1 g.
From the preceding example, if the volume of solution in which the drug is dissolved and the drug concentration of the solution are known, then the total amount of drug present in the solution may be calculated. This relationship between drug concentration, volume in which the drug is dissolved, and total amount of drug present is given in the following equation:

$$V_D = \frac{\text{Dose}}{C_P^0} = \frac{D_B^0}{C_P^0} \qquad (3.8)$$

where D = total amount of drug, V = total volume, and C = drug concentration. From Equation 3.8, which is similar to Equation 3.5, if any two parameters are known, then the third term may be calculated

The body may be considered as a constant-volume system or compartment. Therefore, the apparent volume of distribution for any given drug is generally a constant. If both the concentration of drug in the plasma and the apparent volume of distribution for the drug are known, then the total amount of drug in the body (at the time in which the plasma sample was obtained) may be calculated from Equation 3.5.

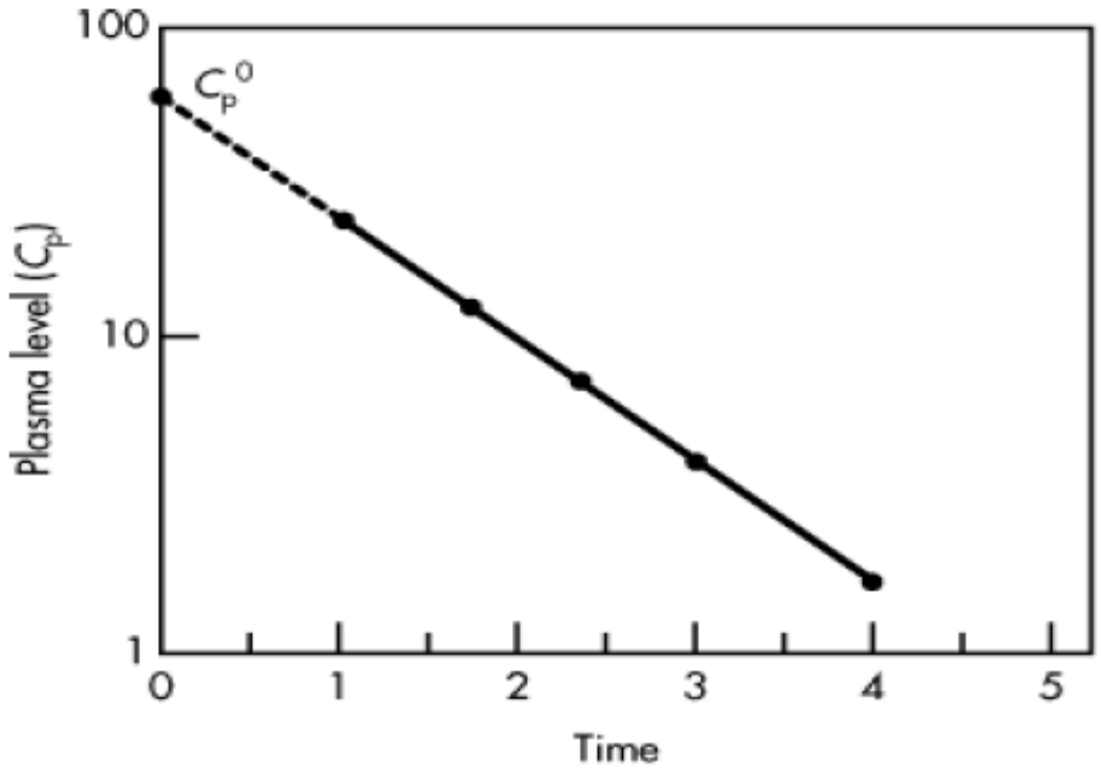
Calculation of Volume of Distribution

In a one-compartment model (IV administration), the *V*D is calculated with the following equation:

$$V_D = \frac{\text{Dose}}{C_P^0} = \frac{D_B^0}{C_P^0} \qquad (3.9)$$

When *C*p0 is determined by extrapolation, it represents the instantaneous drug concentration (concentration of drug at $t = 0$) after drug equilibration in the body. The dose of drug given by IV bolus (rapid IV injection) represents the amount of drug in the body, *D*B0, at $t = 0$. Because both *D*B0 and *C* p0 are known at $t = 0$, then the apparent volume of distribution, *V* D, may be calculated from Equation 3.9.

Figure 3-3.



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Semilog graph giving the value of C_p^0 by extrapolation.

From Equation 3.2 (repeated here), the rate of drug elimination is

From Equation 3.2 (repeated here), the rate of drug elimination is

$$\frac{dD_B}{dt} = -kD_B$$

By substitution of Equation 3.5, *D*B = *V*D *C*p, into Equation 3.2, the following expression is obtained:

$$\frac{dD_B}{dt} = -kV_D C_p \qquad (3.10)$$

Rearrangement of Equation 3.10 gives

$$dD_B = -kV_D C_p\, dt \qquad (3.11)$$

As both *k* and *V* D are constants, Equation 3.10 may be integrated as follows:

$$\int_{O}^{D_0} dD_B = -kV_D \int_{0}^{\infty} C_p\, dt \qquad (3.12)$$

Equation 3.12 shows that a small change in time (*dt*) results in a small change in the amount of drug in the body, *D*B.

The integral $\int_0^\infty C_p dt$ represents the AUC ∞0, which is the summation of the area under the curve from *t* = 0 to *t* = ∞ . Thus, the apparent *V* D may also be calculated from knowledge of the dose, elimination rate constant, and the area under the curve (AUC) from *t* = 0 to *t* = ∞. The AUC ∞ 0 is usually estimated by the trapezoidal rule (see chapter 12). After integration, Equation 3.12 becomes

$$D_0 = kV_D[AUC]_0^\infty$$

$$V_D = \frac{D_0}{k[AUC]_0^\infty} \qquad (3.13)$$

Significance of the Apparent Volume of Distribution

The apparent volume of distribution is not a true physiologic volume. Most drugs have an apparent volume of distribution smaller than, or equal to, the body mass. For some drugs, the volume of distribution may be several times the body mass. Equation 3.9 shows that the apparent *V* D is dependent on *C* p0. For a given dose, a very small *C*p0 may occur in the body due to concentration of the drug in peripheral tissues and organs. For this dose, the small *C* p0 will result in a large *V* D.

Drugs with a **large apparent *V*D** are more concentrated in **extravascular tissues** and less concentrated intravascularly. If a drug is highly bound to plasma proteins or remains in the vascular region, then *C* p0 will be higher, resulting in a smaller apparent *V*D. Consequently, binding of a drug to peripheral tissues or to plasma proteins will significantly affect *V*D.

The apparent *V*D is a volume term that can be expressed as a simple volume or in terms **of percent of body weight**. In expressing the apparent *V*D in terms of percent body weight, **a 1-L volume is assumed to be equal to the weight of 1 kg.** For example, if the *V*D is 3500 mL for a subject weighing 70 kg, the *V*D expressed as percent of body weight is

If $$\frac{3.5\ \text{kg}}{70\ \text{kg}} \times 100 = 5\%\ \text{of body weight}$$

If ***V*D is a very large number ie, >100%** of body weight then it may be assumed that the drug is concentrated in certain tissue compartments. Thus, the apparent *V* D is a useful **parameter in considering the relative amounts of drug in the vascular and in the extravascular tissues.**

Table 3.1 Fluid in the Body

Water Compartment	Percent of Body Weight	Percent of Total Body Water
Plasma	4.5	7.5
Total extracellular water	27.0	45.0
Total intracellular water	33.0	55.0
Total body water	60.0	100.0

Given the apparent *V*D for a particular drug, the total amount of drug in the body at any time after administration of the drug may be determined by the measurement of the drug concentration in the plasma (Eq. 3.5). Because the magnitude of the apparent *V*D is a useful indicator for the amount of drug outside the sampling compartment (usually the blood), **the larger the apparent *V*D, the greater the amount of drug in the extravascular tissues.** For each drug, the apparent *V*D is a constant. In certain pathologic cases, the apparent *V*D for the drug may be altered if the distribution of the drug is changed. For example, **in edematous conditions**, the total body water and total extracellular water increase; this is reflected in a larger apparent *V*D value for a drug that is highly water soluble. Similarly, changes in total body weight and lean body mass (which normally occur with age) may also affect the apparent *V*D.

CLEARANCE

***Clearance* is a measure of drug elimination from the body** without identifying the mechanism or process.

Drug Clearance in the One-Compartment Model

The body is considered as a system of organs perfused by plasma and body fluids. Drug elimination from the body is an **ongoing** process due to both metabolism (biotransformation) and drug excretion through the kidney and other routes. The mechanisms of drug elimination are complex, but collectively drug elimination from the body may be quantitated using the concept of drug clearance**.1- Drug clearance refers to the volume of plasma fluid that is cleared of drug per unit time. 2-Clearance may also be considered as the fraction of drug removed per unit time multiplied by the *V*D**.

DRUG ELIMINATION EXPRESSED AS AMOUNT PER TIME UNIT

The expression of drug elimination from the body in terms of mass per unit time (eg, mg/min, or mg/hr) is simple, absolute, and unambiguous. **For a zero-order elimination** process, expressing the rate of **drug elimination as mass per unit time is convenient** because the rate is constant. In contrast, the rate of **drug elimination for a first-order elimination process is not constant and changes with respect to the drug concentration in the body**. For a first-order elimination, drug clearance expressed as volume per unit time (eg, L/hr or mL/min) is convenient because it is a constant.

DRUG ELIMINATION EXPRESSED AS VOLUME PER TIME UNIT

The concept of expressing a rate in terms of volume per unit time is common in pharmacy. For example, a patient may be dosed at the rate **of 2 teaspoonsful (10 mL) of a liquid medicine (10 mg/mL) daily**, or alternatively, a dose (weight) of 100 mg of the drug daily.

Clearance is a concept that expresses "the rate of drug removal" in terms of volume of drug solution removed per unit time (at whatever drug concentration in the body prevailing at that time) . In contrast to a solution in a bottle, the drug concentration in the body will gradually decline by a first-order process such that the mass of drug removed over time is not constant. **The plasma volume in the healthy state is relatively constant because water lost through the kidney is rapidly replaced with fluid absorbed from the gastrointestinal tract.**

Since a constant volume of plasma (about 120 mL/min in humans) is filtered through the glomeruli of the kidneys, the rate of drug removal is dependent on the plasma drug concentration at all times. This observation is based on a first-order process governing drug elimination. **For many drugs, the rate of drug elimination is dependent on the plasma drug concentration, multiplied by a constant factor**

(*dC*/*dt* = *kC*).

When the plasma drug concentration is high, the rate of drug removal is high, and vice versa.

Clearance (volume of fluid removed of drug) for a first-order process is constant regardless of the drug concentration because clearance is expressed in volume per unit time rather than drug amount per unit time.

Mathematically, the rate of drug elimination is similar to Equation 3.10:

$$\frac{dD_B}{dt} = -kC_p V_D \qquad \textbf{(3.2a)}$$

Dividing this expression on both sides by C_p yields Equation 3.14:

$$\frac{dD_B/dt}{C_p} = \frac{-kC_p V_D}{C_p} \qquad \textbf{(3.14)}$$

$$\frac{dD_B/dt}{C_p} = -kV_D = -Cl \qquad \textbf{(3.15)}$$

where *dD* B/*dt* is the rate of drug elimination from the body (mg/hr), *C*p is the plasma drug concentration (mg/L), *k* is a first-order rate constant (hr- 1 or 1/hr), and *V*D is the apparent volume of distribution (L). *Cl* is clearance and has the units L/hr in this example. In the example in , *Cl* is in mL/min.

Clearance, *Cl*, is expressed as volume/time. Equation 3.15 shows that clearance is a constant because *V*D and *k* are both constants. *D*B is the amount of drug in the body, and *dD* B/*dt* is the rate of change (of amount) of drug in the body with respect to time. The negative sign refers to the drug exiting from the body.

$$\frac{dC_P}{dt} = -(Cl/V_D) \times C_P \qquad (3.16)$$

For a first-order process,

$$\frac{dC_P}{dt} = -kC_P = \text{rate of drug administration} \qquad (3.17)$$

Equating the two expressions yields:

$$kC_P = Cl/V_D \times C_P \qquad (3.18)$$

$$k = \frac{Cl}{V_D} \qquad (3.19)$$

One-Compartment Model Equation in Terms of *Cl* and *V* D

Equation 3.20 may be rewritten in terms of clearance and volume of distribution by substituting *Cl*/*V* D for *k*.

The clearance concept may also be applied a biologic system in physiologic modeling without the need of a theoretical compartment.

$$C_P = C_P^0 e^{-kt} \qquad (3.20)$$

$$C_P = D_0 / V_D e^{-(Cl/V_D)t} \qquad (3.21)$$

Clearance from Drug-Eliminating Tissues

Clearance may be applied to any organ that is involved in drug elimination from the body. As long as first order elimination processes are involved, clearance represents the sum of the clearances for each drug eliminating organ as shown in Equation 3.26:

$$Cl_T = Cl_R + Cl_{NR} \qquad (3.26)$$

where *Cl* R is renal clearance or drug clearance through the kidney, and *Cl* NR is nonrenal clearance through other organs. Generally, clearance is considered as the sum of renal, *Cl* R, and nonrenal drug clearance, *Cl* NR.

Cl NR is assumed to be due primarily to hepatic clearance (*Cl* H) in the absence of other significant drug clearances, such as elimination through the lung or the bile, as shown in Equation 3.27:

$$Cl_T = Cl_R + Cl_H \qquad (3.27)$$

Drug clearance considers that the drug in the body is uniformly dissolved in a volume of fluid (apparent volume of distribution, *V*D) from which drug concentrations can be measured easily. Typically, plasma fluid concentration is measured and drug clearance is then calculated as the fixed volume of plasma fluid (containing the drug) cleared of drug per unit of time. The units for clearance are volume/time (eg, mL/min, L/hr).

Alternatively, *Cl* T may be defined as the rate of drug elimination divided by the plasma drug concentration.

Thus, clearance is expressed in terms of the volume of plasma containing drug that is eliminated per unit time. This clearance definition is equivalent to the previous definition and provides a practical way to calculate clearance based on plasma drug concentration data.

$$Cl_T = \frac{\text{elimination rate}}{\text{plasma concentration } (C_p)} \qquad (3.28)$$

$$Cl_T = \frac{(dD_E/dt)}{C_p} = (\mu g/\text{min})/(\mu g/\text{mL}) = \text{mL/min} \qquad (3.29)$$

where D_E is the amount of drug eliminated and dD_E/dt is the rate of drug elimination.

Rearrangement of Equation 3.29 gives Equation 3.30:

$$\text{Drug elimination rate} = \frac{dD_E}{dt} = C_p Cl_T \qquad (3.30)$$

Therefore *Cl* T is a constant for a specific drug and represents the **slope of the line obtained by plotting *dD* E/*dt* versus *C* p, as shown in Equation 3.30.**

For drugs that follow first-order elimination, the rate of drug elimination is dependent on the amount of drug remaining in the body.

$$\frac{dD_E}{dt} = kD_B = kC_pV_D \qquad (3.31)$$

Substituting the elimination rate in Equation 3.30 for *kC* p*V* D in Equation 3.31 and solving for *Cl* T gives Equation 3.32:

$$Cl_T = \frac{kC_pV_D}{C_p} = kV_D \qquad (3.32)$$

Equation 3.32 shows that clearance, *Cl* T, is the product of *V* D and *k*, both of which are constant. This Equation 3.32 is similar to Equation 3.19 shown earlier. As the plasma drug concentration decreases during elimination, the rate of drug elimination, *dD* E/*dt*, will decrease accordingly, but clearance will remain constant. Clearance will be constant as long as the rate of drug elimination is a first-order process.

For some drugs, the elimination rate process is more complex and a nonc ompartment method may be used to calculate certain pharmacokinetic parameters such as clearance. In this case, clearance can be determined directly from the plasma drug concentration-versus-time curve by

$$Cl_T = \frac{D_0}{[\mathrm{AUC}]_0^\infty} \qquad (3.33)$$