

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

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

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

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

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 $1/\text{hr}$), 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.

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

$$\frac{dC_p}{dt} = -(Cl/V_D) \times C_p \quad (3.16)$$

For a first-order process,

$$\frac{dC_p}{dt} = -kC_p = \text{rate of drug administration} \quad (3.17)$$

Equating the two expressions yields:

$$kC_p = Cl/V_D \times C_p \quad (3.18)$$

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

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.

$$C_p = C_p^0 e^{-kt} \quad (3.20)$$

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

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:

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

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:

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

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.

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

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

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:

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

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.

$$\frac{dD_E}{dt} = kD_B = kC_p V_D \quad (3.31)$$

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:

$$Cl_T = \frac{kC_p V_D}{C_p} = kV_D \quad (3.32)$$

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 non compartment 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

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

MULTICOMPARTMENT MODELS: INTRAVENOUS BOLUS ADMINISTRATION:

INTRODUCTION

Compartmental models are classical pharmacokinetic models that simulate the kinetic processes of drug absorption, distribution, and elimination with little physiologic detail. In contrast, the more sophisticated physiologic model is. In compartmental models, drug tissue concentration is assumed to be **uniform within a given hypothetical compartment. Hence, all muscle mass and connective tissues may be lumped into one hypothetical tissue compartment that equilibrates with drug from the central (or plasma) compartment.** Since no data is collected on the tissue mass, the theoretical tissue concentration is unconstrained and cannot be used to forecast actual tissue drug levels. **However, tissue drug uptake and tissue drug binding from the plasma fluid is kinetically simulated by considering the presence of a tissue compartment.** Indeed, most drugs given by IV bolus dose decline rapidly soon after injection, **and then decline moderately as some of the drug initially distributes into the tissue moves back into the plasma.**

Multicompartment models were developed to explain this observation that, after a rapid IV injection, the plasma level time curve does not decline linearly as a single, first-order rate process. The plasma level time curve reflects first-order elimination of the drug from the body only after distribution equilibrium, or plasma drug equilibrium with peripheral tissues occurs. Drug kinetics after distribution is characterized by the first-order rate constant, b (or beta).

Nonlinear plasma level time curves occur because some drugs distribute at various rates into different tissue groups. Multicompartment models were developed to explain and predict plasma and tissue concentrations for the behavior of these drugs. In contrast, a one-compartment model is used when the drug appears to distribute into tissues instantaneously and uniformly.

For both one- and multicompartment models, the drug in the tissues that have the highest blood perfusion equilibrates rapidly with the drug in the plasma. These highly perfused tissues and blood make up the central compartment .

While this initial drug distribution is taking place, multicompartment drugs are delivered concurrently to one or more *peripheral compartments* composed of groups of tissues with lower blood perfusion and different affinity for the drug.

Because of these distribution factors, drugs will generally **concentrate unevenly** in the tissues, and different groups of tissues will accumulate the drug at different rates. A summary of the approximate blood flow to major human tissues is presented in . Many different tissues and rate processes are involved in the distribution of any drug. However, limited physiologic significance has been assigned to a few groups of tissues .

TABLE 4.1 Blood Flow to Human Tissues

TISSUE	PERCENT BODY WEIGHT	PERCENT CARDIAC OUTPUT	BLOOD FLOW (mL/100 g tissue per min)
Adrenals	0.02	1	550
Kidneys	0.4	24	450
Thyroid	0.04	2	400
Liver			
Hepatic	2.0	5	20
Portal		20	75
Portal-drained viscera	2.0	20	75
Heart (basal)	0.4	4	70
Brain	2.0	15	55
Skin	7.0	5	5
Muscle (basal)	40.0	15	3
Connective tissue	7.0	1	1
Fat	15.0	2	1

The nonlinear profile of plasma drug concentration versus time is the result of many factors interacting together,

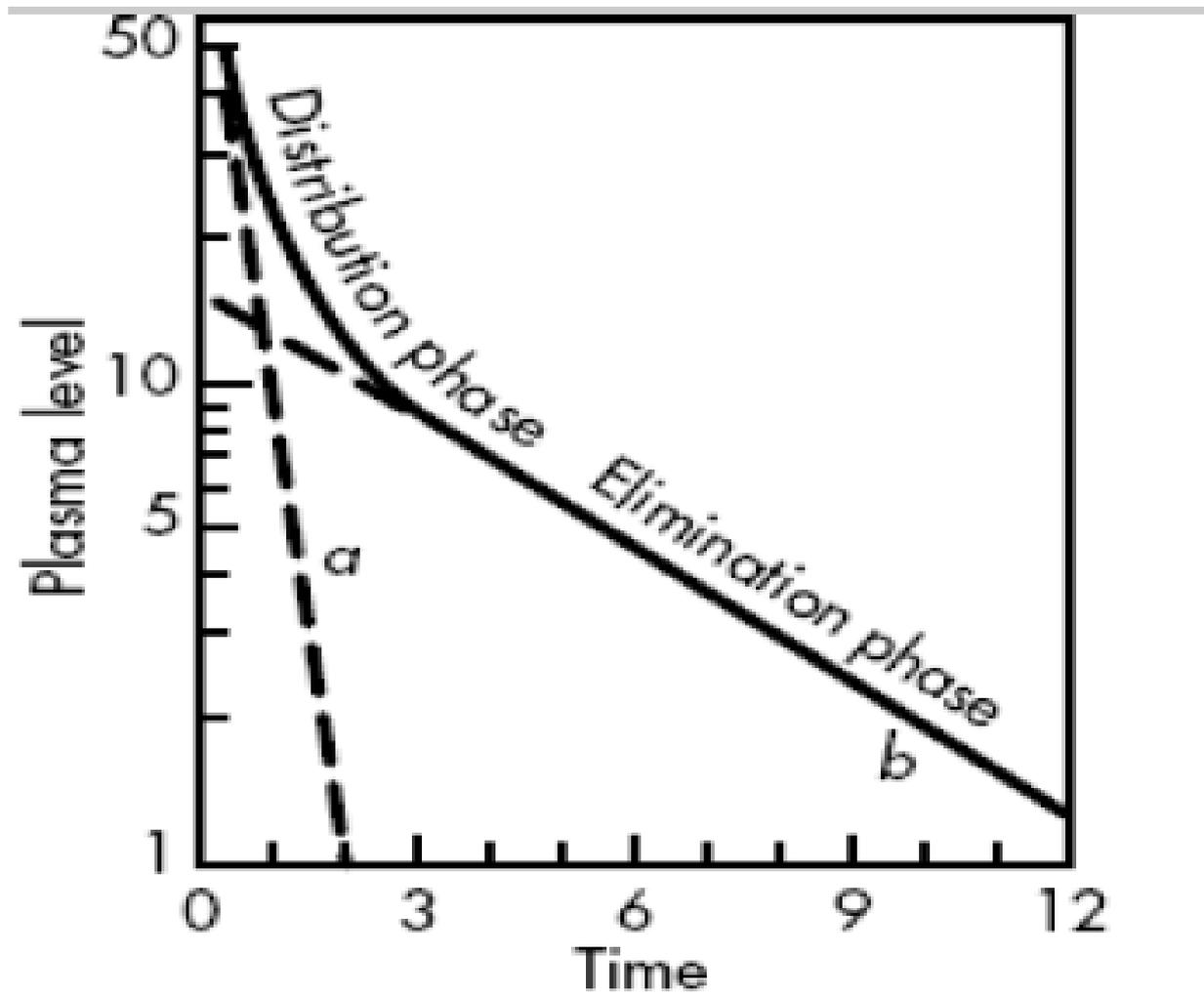
1-including blood flow to the tissues, 2- the permeability of the drug into the tissues, 3-the capacity of the tissues to accumulate drug, 4-and the effect of disease factors on these processes.

Impaired cardiac function may produce a change in blood flow and in the drug distributive phase, whereas impairment of the kidney or the liver may decrease drug elimination as shown by a prolonged elimination half-life and corresponding reduction in the slope of the terminal elimination phase of the curve. Frequently, multiple factors can complicate the distribution profile in such a way that the profile can only be described clearly with the assistance of a simulation model.

In this model, the drug distributes into two compartments, the central compartment and the tissue, or peripheral compartment.

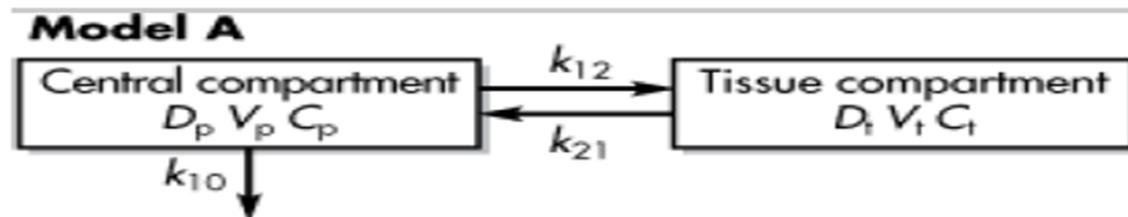
The central compartment represents the blood, extracellular fluid, and highly perfused tissues. The drug distributes rapidly and uniformly in the central compartment.

A second compartment, known as the *tissue or peripheral compartment*, contains tissues in which the drug equilibrates more slowly. Drug transfer between the two compartments is assumed to take place by first-order processes.

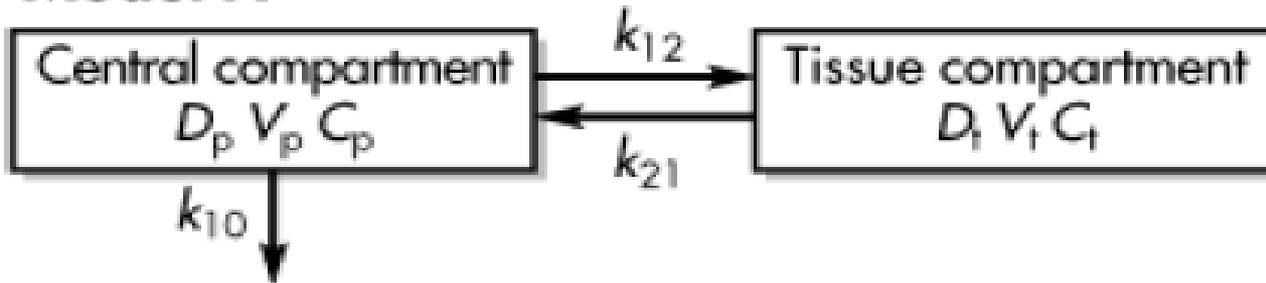


There are several possible two-compartment models. Model A is used most often and describes the plasma level time curve observed in . By convention, compartment 1 is the central compartment and compartment 2 is the tissue compartment. The rate constants k_{12} and k_{21} represent the first-order rate transfer constants for the movement of drug from compartment 1 to compartment 2 (k_{12}) and from compartment 2 to compartment 1 (k_{21}). The transfer constants are sometimes termed *microconstants*, and their values cannot be estimated directly.

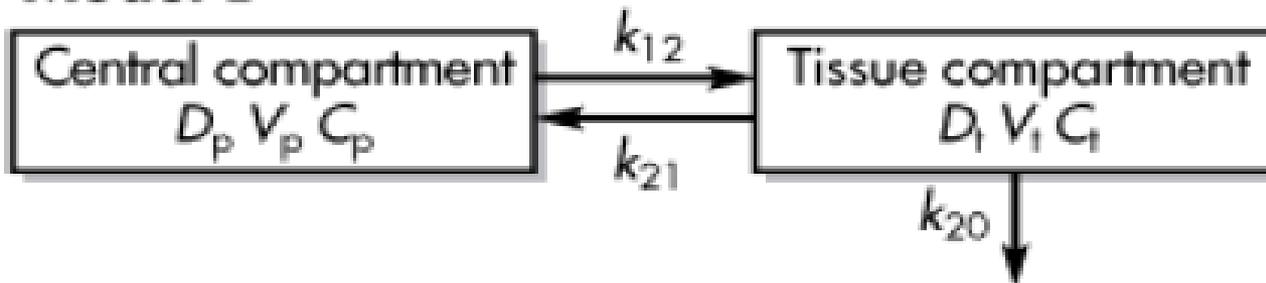
Most two-compartment models assume that elimination occurs from the central compartment model, as shown in (model A), unless other information about the drug is known. Drug elimination is presumed to occur from the central compartment, because the major sites of drug elimination (renal excretion and hepatic drug metabolism) occur in organs, such as the kidney and liver, which are highly perfused with blood.



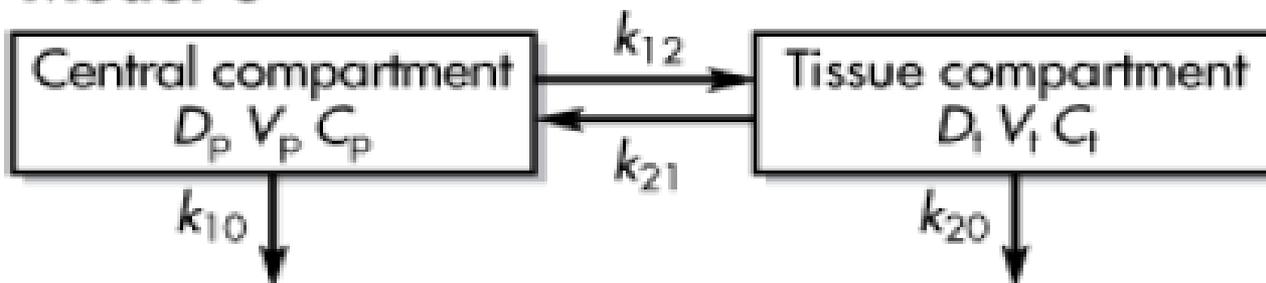
Model A



Model B



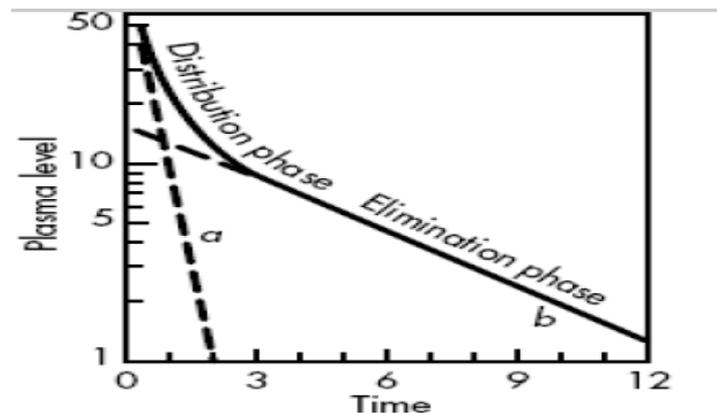
Model C



The plasma level time curve for a drug that follows a two-compartment model may be divided into two parts, (a) a distribution phase and (b) an elimination phase. The two-compartment model assumes that, at $t = 0$, no drug is in the tissue compartment. After an IV bolus injection, drug equilibrates rapidly in the central compartment.

The *distribution phase* of the curve represents the initial, more rapid decline of drug from the central compartment into the tissue compartment (, line a). Although drug elimination and distribution occur *concurrently* during the distribution phase, there is a net transfer of drug from the central compartment to the tissue compartment. The fraction of drug in the tissue compartment during the distribution phase increases up to a maximum in a given tissue, whose value may be greater or less than the plasma drug concentration.

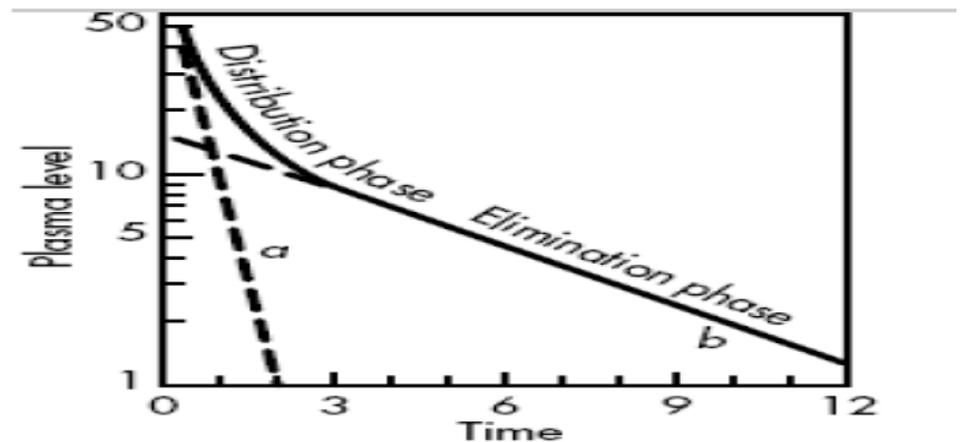
At maximum tissue concentrations, the rate of drug entry into the tissue equals the rate of drug exit from the tissue.



The fraction of drug in the tissue compartment is now in equilibrium (*distribution equilibrium*) with the fraction of drug in the central compartment, and **the drug concentrations in both the central and tissue compartments decline in parallel and more slowly compared to the distribution phase.**

This decline is a first-order process and is called the *elimination phase* or the *beta phase* (line *b*). Since plasma and tissue concentrations decline in parallel, plasma drug concentrations provide some indication of the concentration of drug in the tissue. At this point, drug kinetics appear to follow a one-compartment model in which drug elimination is a first-order process described by *b* (also known as beta). A typical tissue drug level curve after a single intravenous dose is shown in .

Figure 4-3.



Tissue drug concentrations are theoretical only. The drug level in the theoretical tissue compartment can be calculated once the parameters for the model are determined. **However, the drug concentration in the tissue compartment represents the average drug concentration in a group of tissues rather than any real anatomic tissue drug concentration.** In reality, drug concentrations may vary among different tissues and possibly within an individual tissue. These varying tissue drug concentrations are due to differences in the partitioning of drug into the tissues. In terms of the pharmacokinetic model, the differences in tissue drug concentration is reflected in **the k_{12} / k_{21} ratio**. Thus, tissue drug concentration may be higher or lower than the plasma drug concentrations, depending on the properties of the individual tissue. Moreover, the elimination of drug from the tissue compartment may not be the same as the elimination from the central compartment. For example, **if $k_{12} C_p$ is greater than $k_{21} \cdot C_t$ (rate into tissue > rate out of tissue), the tissue drug concentrations will increase and plasma drug concentrations will decrease**

Real tissue drug concentration can sometimes be calculated by the addition of compartments to the model until a compartment that mimics the experimental tissue concentrations is found.

In spite of the hypothetical nature of the tissue compartment, the theoretical tissue level is still valuable information for clinicians. The theoretical tissue concentration, together with the blood concentration, gives an accurate method of calculating the total amount of drug remaining in the body at any time.

In practice, a blood sample is removed periodically from the central compartment and the plasma is analyzed for the presence of drug. The drug plasma level time curve represents a phase of initial rapid equilibration with the central compartment (the distribution phase) followed by an elimination phase after the tissue compartment has also been equilibrated with drug. The distribution phase may take minutes or hours and may be missed entirely if the blood is sampled too late or at wide intervals after drug administration. In the model depicted above, k_{12} and k_{21} are first-order rate constants that govern the rate of drug change in and out of the tissues:

$$\frac{dC_t}{dt} = k_{12}C_p - k_{21}C_t \quad (4.1)$$

The relationship between the amount of drug in each compartment and the concentration of drug in that compartment is shown by Equations 4.2 and 4.3:

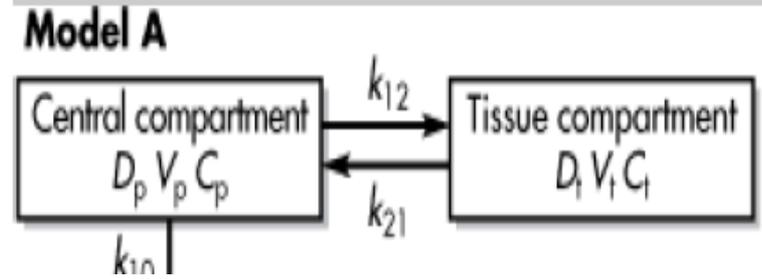
$$C_p = \frac{D_p}{V_p} \quad (4.2)$$

$$C_t = \frac{D_t}{V_t} \quad (4.3)$$

where D_p = amount of drug in the central compartment, D_t = amount of drug in the tissue compartment, V_p = volume of drug in the central compartment, and V_t = volume of drug in the tissue compartment.

$$\frac{dC_p}{dt} = k_{21} \frac{D_t}{V_t} - k_{12} \frac{D_p}{V_p} - k \frac{D_p}{V_p} \quad (4.4)$$

$$\frac{dC_t}{dt} = k_{12} \frac{D_p}{V_p} - k_{21} \frac{D_t}{V_t} \quad (4.5)$$



The rate constants for the transfer of drug between compartments are referred to as **microconstants or transfer constants**, and relate the amount of drug being transferred per unit time from one compartment to the other.

The values for these microconstants cannot be determined by direct measurement but can be estimated by a graphic method.

$$a + b = k_{12} + k_{21} + k \quad (4.10)$$

$$ab = k_{21}k \quad (4.11)$$

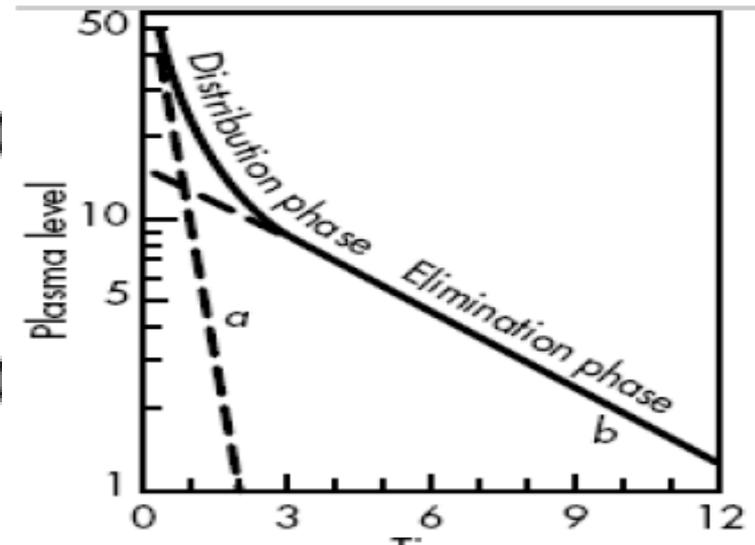
The **constants a and b are hybrid first-order** rate constants for the distribution phase and elimination phase, respectively. The mathematical relationship of a and b to the rate constants are given by Equations 4.10 and 4.11, which are derived after integration of Equations 4.4 and 4.5. Equation 4.6 can be transformed into the following expression:

$$C_p = Ae^{-at} + Be^{-bt} \quad (4.12)$$

The constants a and b are rate constants for the distribution phase and elimination phase, respectively. The constants A and B are intercepts on the y axis for each exponential segment of the curve in Equation 4.12. These values may be obtained graphically by the method of residuals or by computer. **Intercepts A and B are actually hybrid constants**, as shown in Equations 4.13 and 4.14, and do not have actual physiologic significance.

$$A = \frac{D_0(a - k_{21})}{V_p(a - b)} \quad (4.13)$$

$$B = \frac{D_0(k_{21} - b)}{V_p(a - b)} \quad (4.14)$$

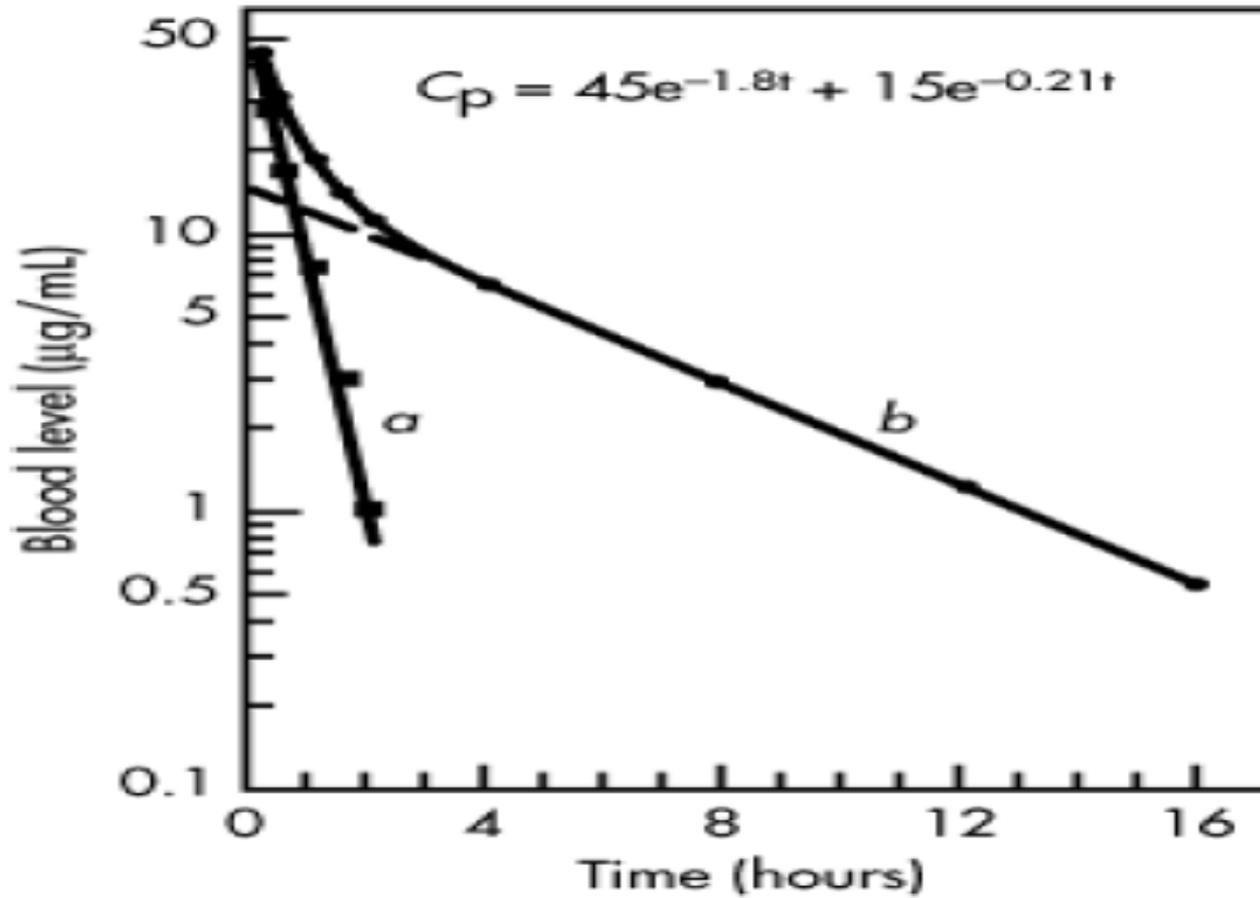


Method of Residuals

The *method of residuals* (also known as feathering or peeling) is a useful procedure for fitting a curve to the experimental data of a drug when the drug does not clearly follow a one-compartment model. For example, 100 mg of a drug was administered by rapid IV injection to a 70-kg, healthy adult male. Blood samples were taken periodically after the administration of drug, and the plasma fraction of each sample was assayed for drug. The following data were obtained:

Time (hr)	Plasma Concentration ($\mu\text{g/mL}$)
0.25	43.00
0.5	32.00
1.0	20.00
1.5	14.00
2.0	11.00
4.0	6.50
8.0	2.80
12.0	1.20
16.0	0.52

When these data are plotted on semilogarithmic graph paper, a curved line is observed. The curved-line relationship between the logarithm of the plasma concentration and time indicates that the drug is distributed in more than one compartment. From these data a biexponential equation, Equation 4.12, may be derived, either by computer or by the method of residuals



Plasma level time curve for a two-compartment open model. The rate constants and intercepts were calculated by the method of residuals

As shown in the **biexponential curve** in , the decline in the initial distribution phase is more rapid than the elimination phase. The rapid distribution phase is confirmed with the constant a being larger than the rate constant b . Therefore, at some later time the term Ae^{-at} will approach zero, while Be^{-bt} will still have a value.

At this later time Equation 4.12 will reduce to

$$C_p = Be^{-bt} \quad (4.15)$$

which, in common logarithms, is

$$\log C_p = \frac{-bt}{2.3} + \log B \quad (4.16)$$

From Equation 4.16, the rate constant can be obtained from the slope ($-b/2.3$) of a straight line representing the terminal exponential phase. The $t_{1/2}$ for the elimination phase (beta half-life) can be derived from the following relationship:

$$t_{1/2} = \frac{0.693}{b}$$

In the sample case considered here, b was found to be 0.21 hr^{-1} . From this information the regression line for the terminal exponential or b phase is extrapolated to the y axis; the y intercept is equal to B , or 15 g/mL .

Values from the extrapolated line are then subtracted from the original experimental data points and a straight line is obtained. This line represents the rapidly distributed a phase.

The new line obtained by graphing the logarithm of the residual plasma concentration ($C_p - C'_p$) against time represents the a phase. The value for a is 1.8 hr^{-1} , and the y intercept is 45 g/mL . The elimination $t_{1/2}$ is computed from b by use of Equation 4.17 and has the value of 3.3 hr .

Apparent Volumes of Distribution

As discussed in , the apparent VD is a useful parameter that relates plasma concentration to the amount of drug in the body. For drugs with large extravascular distribution, the apparent volume of distribution is generally large.

Conversely, for **polar drugs** with low lipid solubility, the apparent VD is generally small. Drugs with high peripheral tissue binding also contribute to a large apparent VD . In **multiple-compartment kinetics**, such as the two compartment model, several volumes of distribution can be calculated. Volumes of distribution generally reflect the extent of drug distribution in the body on a relative basis, and the calculations depend on the availability of data.

In general, it is important to refer to the same volume parameter when comparing kinetic changes in disease states. Unfortunately, values of apparent volumes of distribution of drugs from tables in the clinical literature are often listed without specifying the underlying kinetic processes, model parameter, or method of calculation.

VOLUME OF THE CENTRAL COMPARTMENT

The volume of the central compartment is useful for determining the drug concentration directly after an IV injection into the body. In clinical pharmacy, this volume is also referred to as V_i or the initial volume of distribution as the drug distributes within the plasma and other accessible body fluids. This volume is generally smaller than the terminal volume of distribution after drug distribution to tissue is completed. The volume of the central compartment is generally greater than 3 L, which is the volume of the plasma fluid for an average adult.

For many polar drugs, an initial volume of 7- 10 L may be interpreted as rapid drug distribution within the plasma and some extracellular fluids. For example, the V_p of moxalactam ranges from 0.12 to 0.15 L/kg, corresponding to about 8.4 to 10.5 L for a typical 70-kg patient. In contrast, V_p of hydromorphone is about 24 L, possibly because of its rapid exit from the plasma into tissues even during the initial phase.

As in the case of the one-compartment model, V_p may be determined from the dose and the instantaneous plasma drug concentration, C_0 . V_p is also useful in the determination of drug clearance if k is known. In the two-compartment model, V_p may also be considered as **a mass balance** factor governed by the mass balance between **dose and concentration**, ie, **drug concentration multiplied by the volume of the fluid must equal to the dose at time zero. At time zero, no drug is eliminated, $D_0 = V_p C_p$.**

The basic model assumption is that Plasma drug concentration is representative of drug concentration within the distribution fluid. If this statement is true, then the volume of distribution will be 3 L; if it is not, then distribution of drug may also occur outside the vascular pool.

$$V_p = \frac{D_0}{C_p^0} \quad (4.21)$$

At zero time ($t = 0$), all of the drug in the body is in the central compartment. C_0 can be shown to be equal to $A + B$ by the following equation.

$$C_p = Ae^{-at} + Be^{-bt} \quad (4.22)$$

At $t = 0$, $e_0 = 1$. Therefore,

$$C_P^0 = A + B \quad (4.23)$$

V_P is determined from Equation 4.24 by measuring A and B after feathering the curve, as discussed previously:

$$V_P = \frac{D_0}{A + B} \quad (4.24)$$

Alternatively, the volume of the central compartment may be calculated from the $[AUC]_0^\infty$ in a manner similar to the calculation for the apparent V_D in the one-compartment model. For a one-compartment model,

$$[AUC]_0^\infty = \frac{D_0}{kV_D} \quad (4.25)$$

Rearrangement of this equation yields

$$V_P = \frac{D_0}{k[AUC]_0^\infty} \quad (4.27)$$