Biopharmaceutics–Lecture 9 & 10

Multicompartment models:

Two-compartment open model
Intravenous bolus administration

Introduction

- Most drugs given by IV bolus dose decline rapidly soon after injection, and then decline moderately as some of the drug initially distributes the tissue moves back into 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 single, first-order 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, β).

- 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 concentration for the behavior of these drugs.
- 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.

- Kinetic analysis of a multicompartment model assume that all transfer rate processes for the passage of drug into or out of individual compartments are first-order processes.
- On the basis of this assumption, the plasma level-time curve for a drug that follows a multicompartment model is best described by the summation of a series of exponential terms, each corresponding to first-order rate processes associated with a given compartment.

Two-compartment open model

- Many drugs given in a single intravenous bolus dose demonstrate a plasma level-time curve that does not decline as a single exponential (first-order) process.
- Figure 4-1 shows that the plasma drug concentration declines biexponentially as the sum of two first-order processes-distribution and elimination.

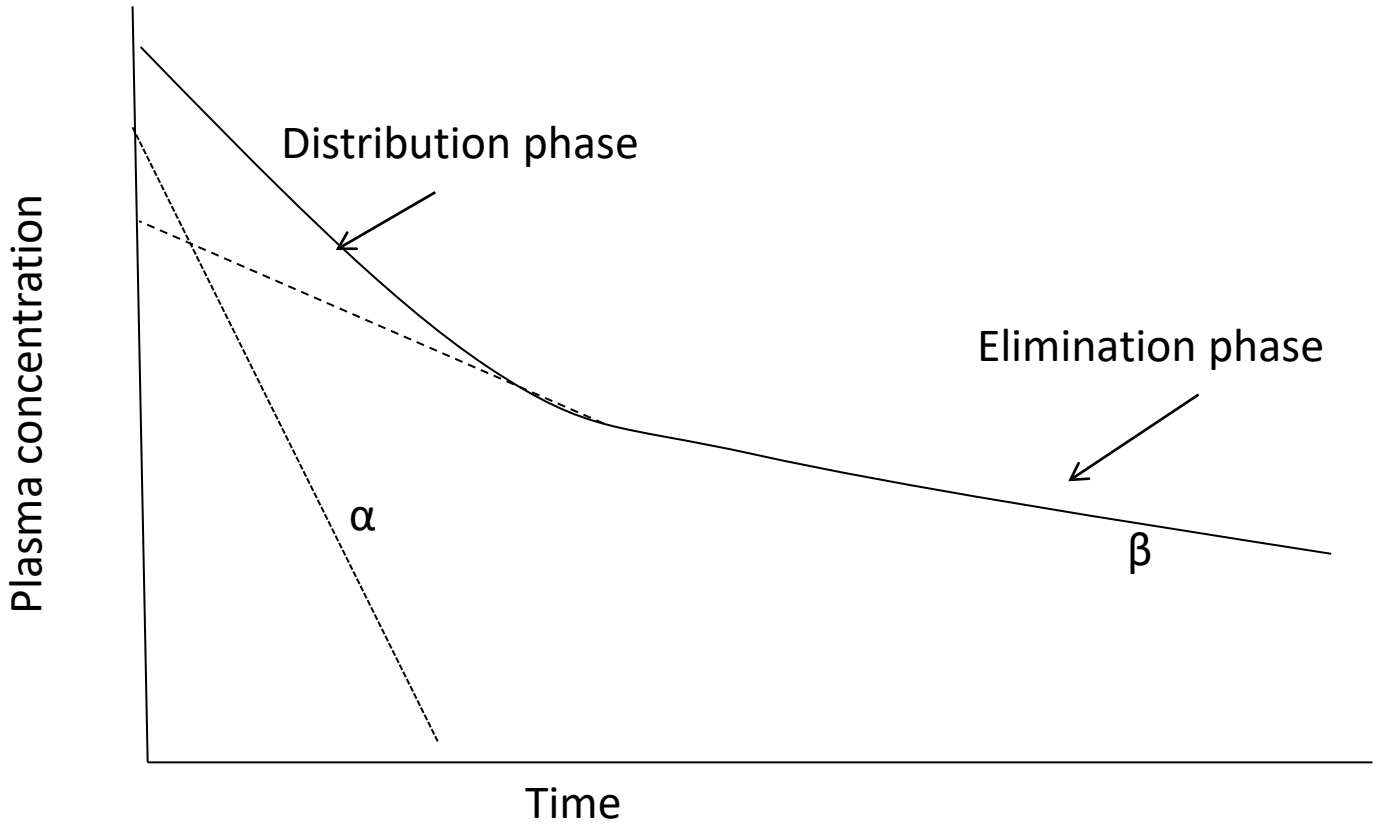


Figure 4.1 Two compartment model

1. A drug that follows the pharmacokinetics of a two-compartment model does not equilibrate rapidly throughout the body, as is assumed for a one-compartment model.
2. In this model, the drug distribute into two compartments, the central compartments, represent the blood, extracellular fluid, and highly perfused tissues.
3. The drug distributes rapidly and uniformly in the central compartment.
4. A second compartment, known as the tissue or peripheral compartment, contains tissues in which the drug equilibrates more slowly.
5. Drug transfer between the two compartments is assumed to take place by first-order processes.

- There are several possible two-compartment models (Fig. 4-2).
- Model A is used most often and discribes the plasma level-time curve observed in Figure 4-1

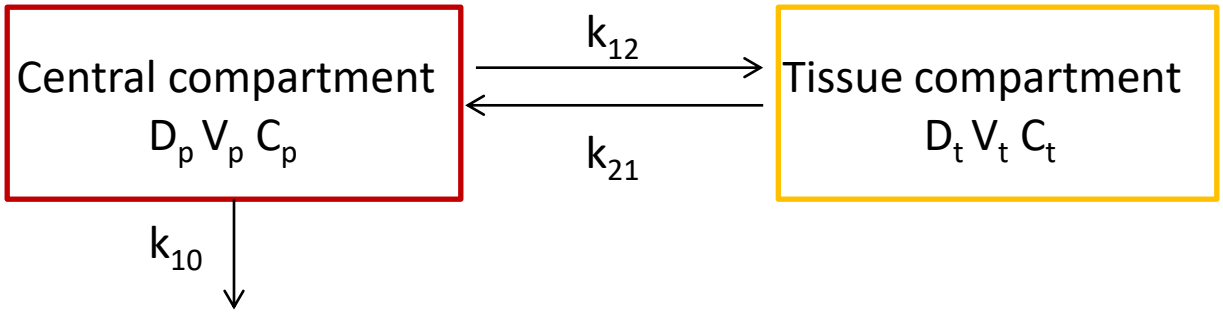


Figure 4.2 Model A

Model B

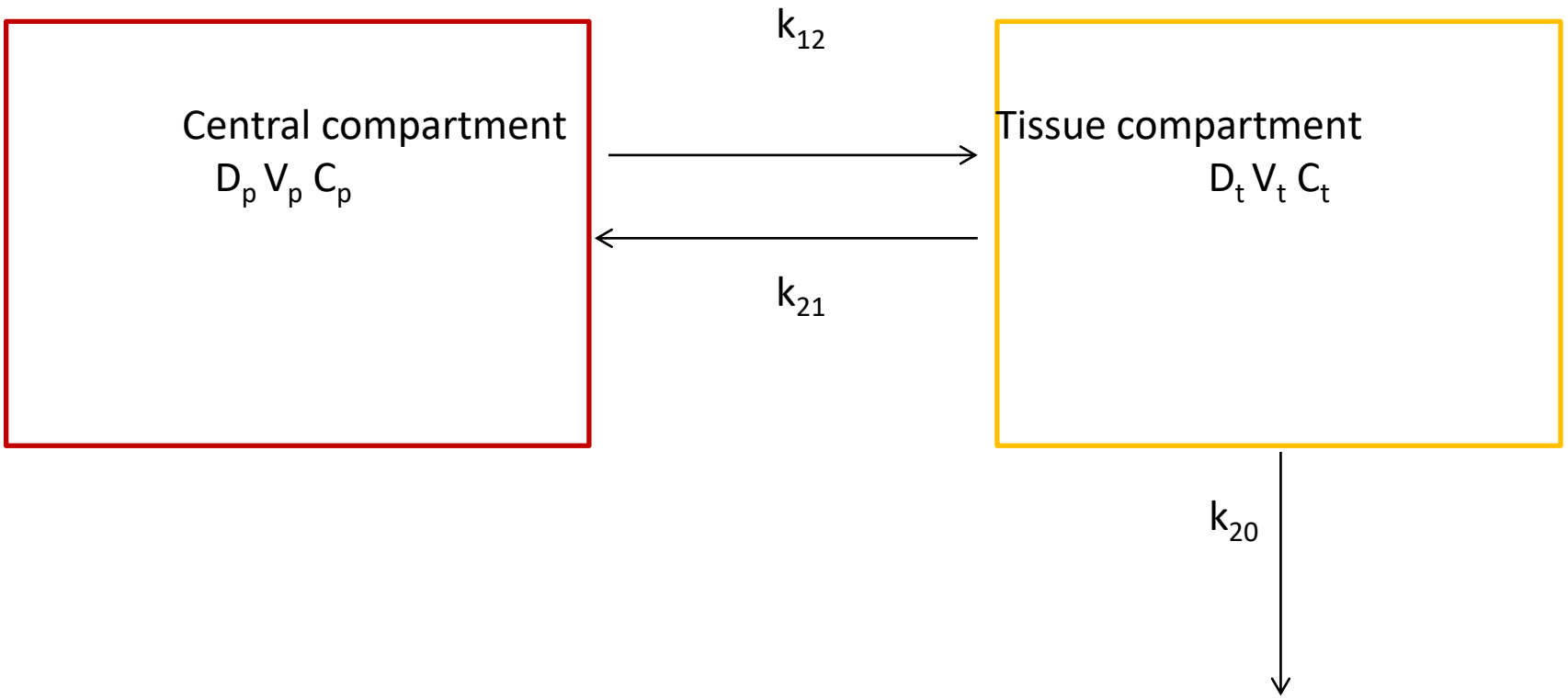


Figure 4.2 Model B

Model C

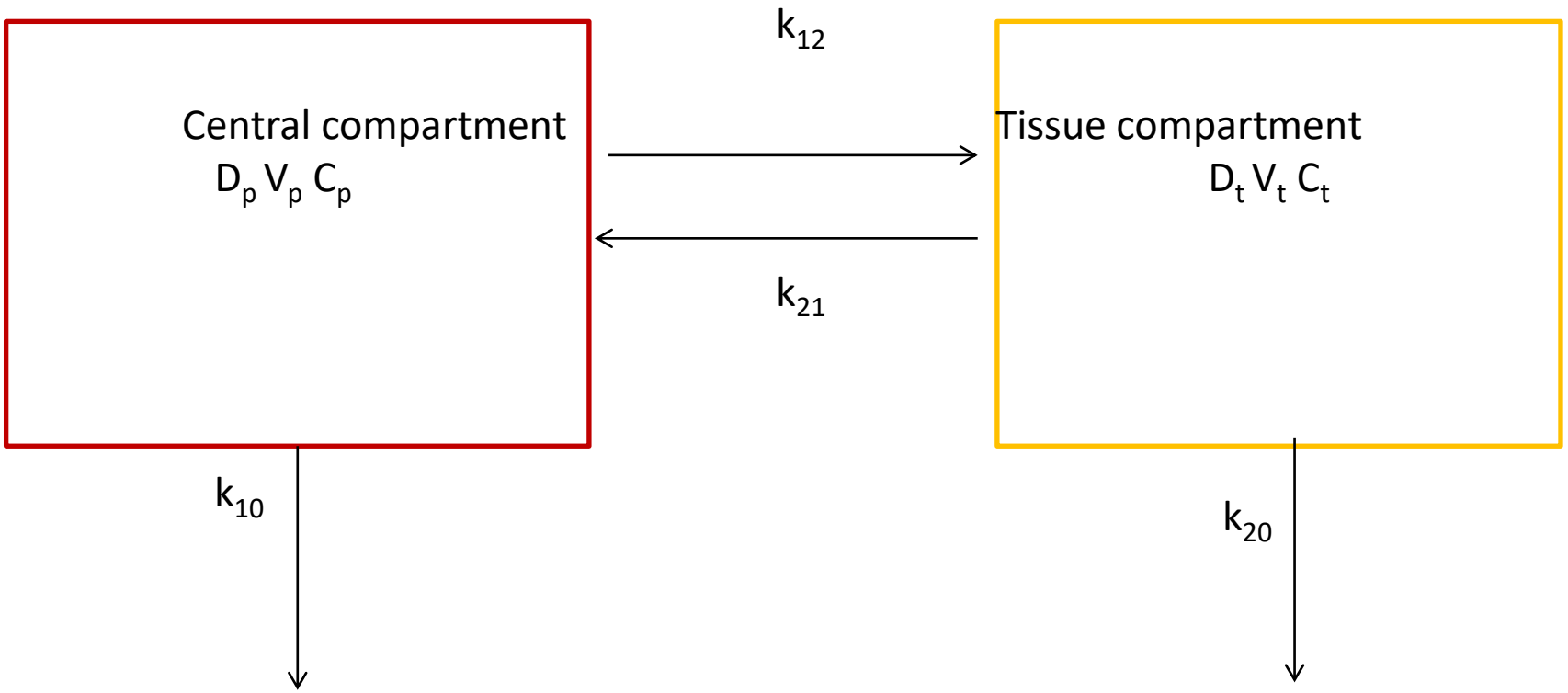


Figure 4.2 Model C

- 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 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, 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

- The plasma level-time curve for a drug that follows a two-compartment model may be divided into two parts (a) distribution phase and (b) an elimination phase.
- Two-compartment model assume 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 tissue compartment. (Figure 4-1, line a).
- Although drug elimination and distribution occur concurrently during 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 distribution phase increases up to a maximum in a given tissue, whose value may be greater or less than the plasma drug concentration .
- At a maximum tissue concentration, the rate of drug entry into the tissue equals the rate of drug exit from the tissue.

- The fraction of drug in tissue compartment is now in equilibrium (distribution equilibrium) with the fraction of drug in the central compartment (Fig. 4-3) 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 (β) phase (Fig. 4-1, line b).

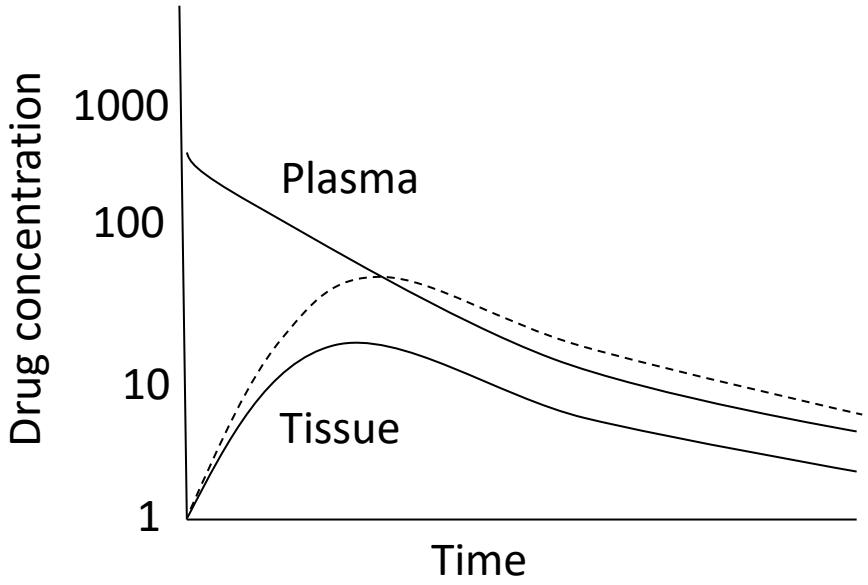


Figure 4-3 Relationship between tissue and plasma drug concentrations for a two-compartment open model. The maximum tissue drug concentration may be greater or less than Cp.

- Since plasma and tissue concentrations decline in parallel, plasma drug concentration provide some indication of the concentration of the 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 drug level curve after a single intravenous dose is shown in Figure 4-3.
- In term of pharmacokinetic model, the difference in tissue drug concentration is reflected in the k_{12}/k_{21} ratio. Thus, tissue drug concentrations 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 $k_{21}.C_t$ (rate into tissue> rate out of tissue), the tissue drug concentrations will increase and plasma drug concentrations will decrease.
- Tissue drug concentrations are theoretical only.
- 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. This information would not be available without pharmacokinetic models.

- In practice, a blood sample is removed periodically from the central compartment and the plasma is analysed 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.

  $dC_t/dt = k_{12} C_p - k_{21} C_t$ (4-1)

- The relationship between the amount of drug in each compartment and the concentration of drug in that compartment is shown by Equation 4-2 and 4-3

  $C_p = D_p / V_p$ (4-2)

  $C_t = D_t / V_t$ (4-3)

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

$$\frac{dC_p}{dt} = k_{21}\frac{D_t}{V_t} - k_{12}\frac{D_p}{V_p} - k\frac{D_p}{V_p} \qquad (4-4)$$

$$\frac{dC_t}{dt} = k_{12}\frac{D_p}{V_p} - k_{21}\frac{D_t}{V_t} \qquad (4-5)$$

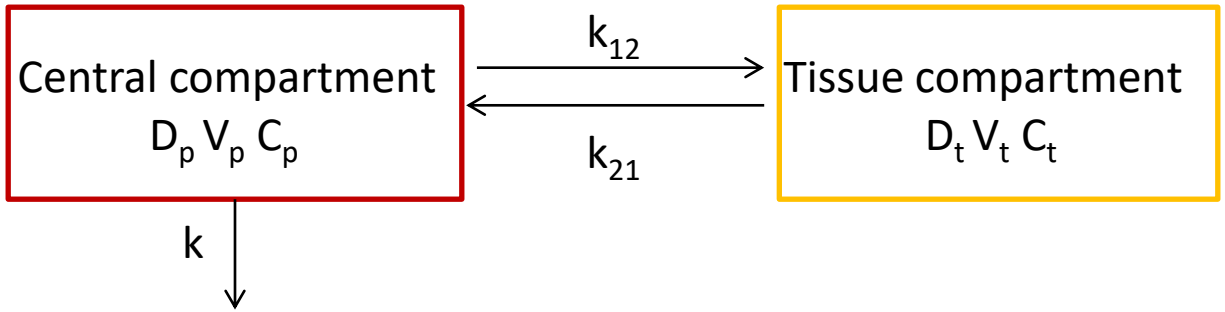


Figure 4.2 Model A

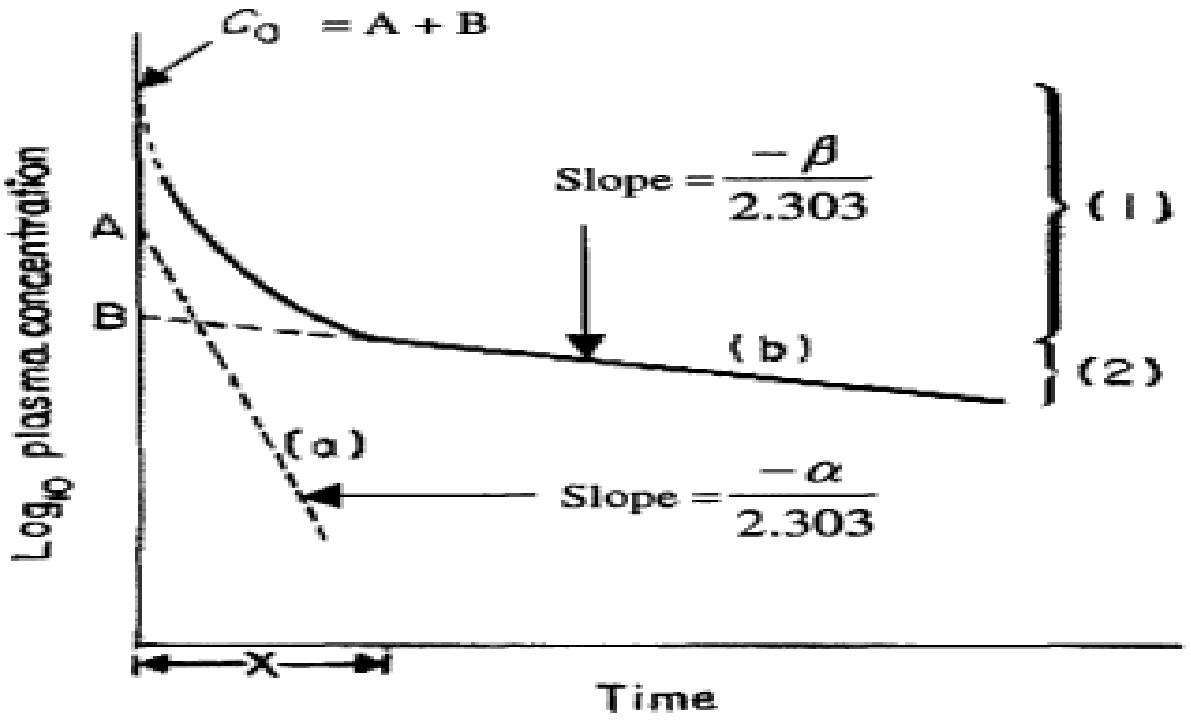
- The rate constants for the transfer of drug between compartments are referred to as microconstants or transfer constants, and relate the amount of drug being transferred per unit time from one compartment to the other.
- The values for these microconstants cannot be determined by direct measurement but can be estimated by a graphic method.

  $a + b = k_{12} + k_{21} + k$ (4-10)

  $ab = k_{21}\, k$ (4-11)
- The constants a and b are hybrid first-order constants for the distribution phase and elimination phase.
- 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.

Plasma level-time curve for two-compartment open model (single IV dose) described in Figure 4-2 (model A)

$$C_p = A\,e^{-at} + B\,e^{-bt} \qquad (4\text{-}12)$$



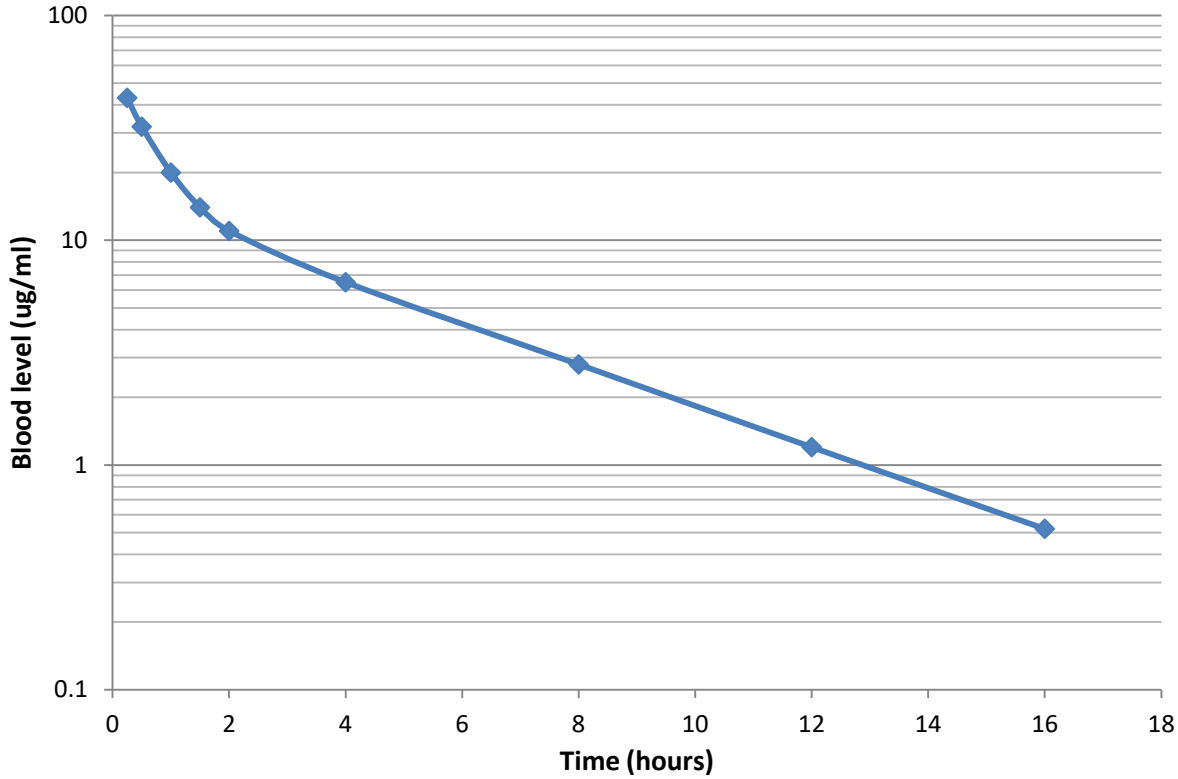
- The rate constants a and b are rate constants for the distribution phase and elimination phase, respectively.
- The constants A and B are intercepts on the y axis for each exponential segment of the curve in equation 4-12.
- These values may be obtained graphically by the method of residuals or by computer. Intercepts A and B do not have actual physiologic significance.

Method of Residuals

- The method of residuals (also known as feathering or peeling) is a useful procedure for fitting a curve to the experimental date 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 date were obtained

Time (hr)	Plasma concentration (ug/ mL)
0.25	43.0
0.5	32.0
1	20.0
1.5	14.0
2.0	11.0
4.0	6.5
8.0	2.8
12.0	1.2
16.0	0.52

1. When these data are plotted on semilogarithmic graph paper, a curved line is observed (Fig 4-4).



- 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.

$$C_p = A\,e^{-at} + B\,e^{-bt} \qquad (4\text{-}12)$$

- As shown in the biexponential curve in Figure 4-4, 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 $A e^{-at}$ will approach zero, while $B e^{-bt}$ will still have a value.
- At this later time Equation 4-12 will reduce to

  $C_p = B e^{-bt}$ (4-15)
- Which, in common logarithms, is

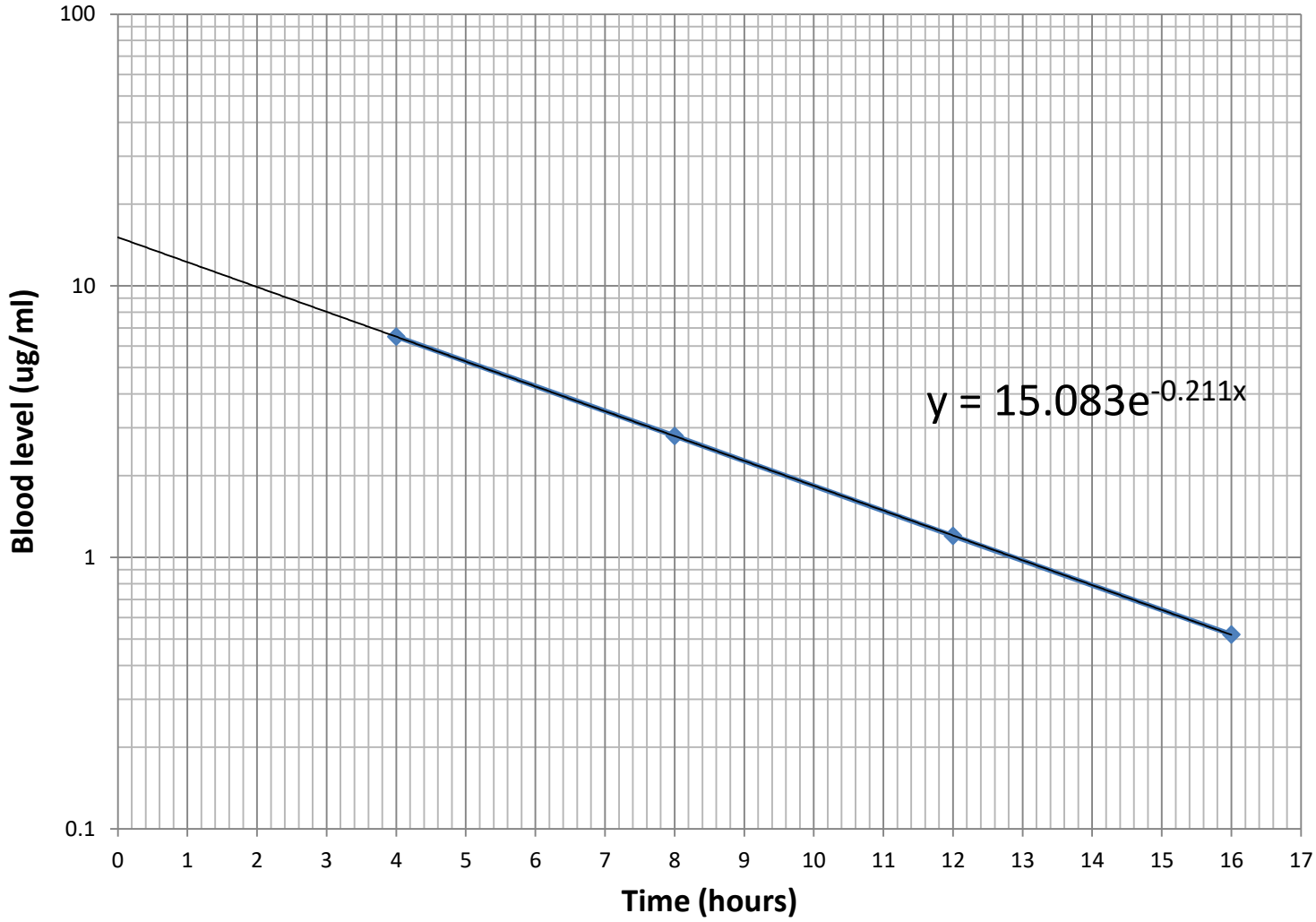
  $\log C_p = \log B - bt/2.3$ (4-16)

2. 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 (Fig 4-4)

- The $t_{1/2}$ for the elimination phase (beta half-life) can be derived from the following relationship:

  $t_{1/2} = 0.693/b$ (4-17)
- In the sample case considered here, b was found to be 0.21 hr^{-1}.

3. From this information the regression line for the terminal or b (β) phase is extrapolated to the y axis, the y intercept is equal to B, or 15 ug/ mL.


100
10
1
0.1
Blood level (ug/ml)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
Time (hours)
y = 15.083e-0.211x

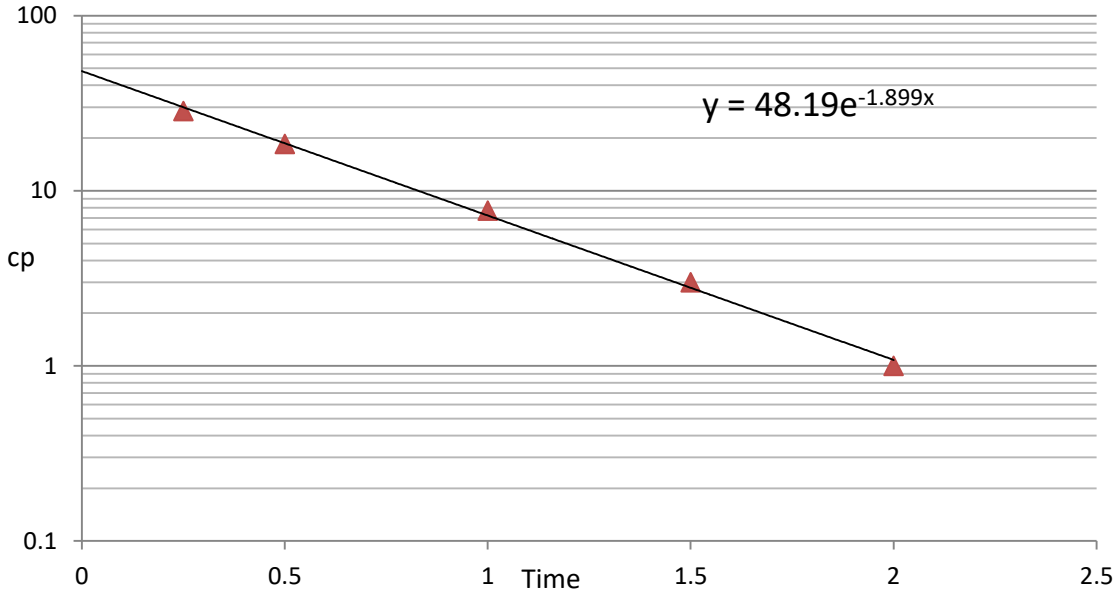
To obtain distribution phase rate constant b or α

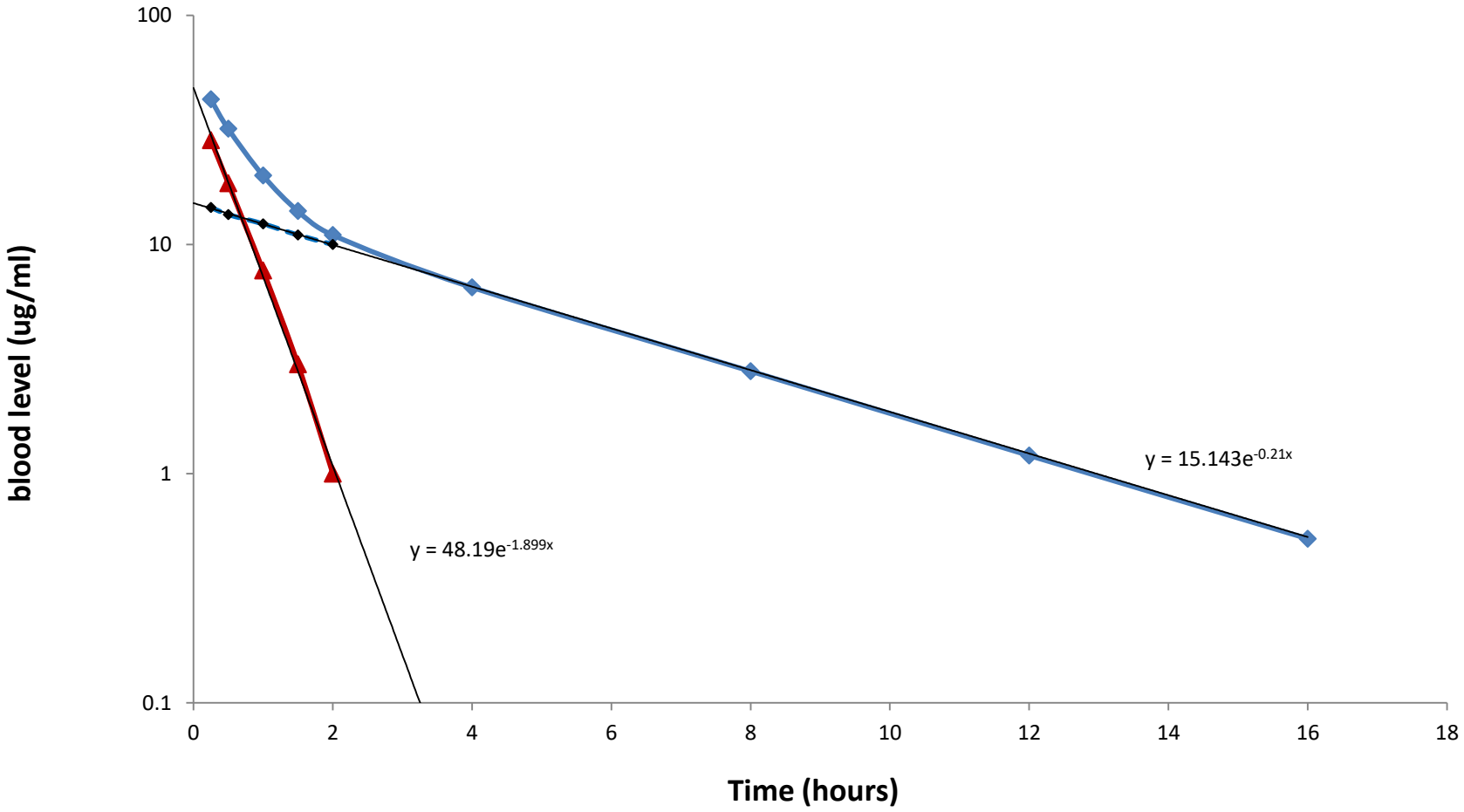
4. Values from the extrapolated line are then subtracted from the original experimental data points (table 4-3).

Time	Concentration (Observed)	Concentration (extrapolated)	Concentration (Observed-extrapolated)
0.25	43	14.5	28.5
0.5	32	13.5	18.5
1	20	12.3	7.7
1.5	14	11	3
2	11	10	1

5. The new line obtained by graphing the logarithm of the residual plasma concentration (Cp-Cṕ) against time represents the a phase. The value for a or (α) is 1.8 hr^{-1}, and the y intercept is 48 ug/mL.

- The elimination $t_{1/2}$ is computed from b by using of Equation 4-17 and has the value of 3.3 hr.




100
10
1
0.1
blood level (ug/ml)
0
2
4
6
8
10
12
14
16
18
Time (hours)
y = 15.143e-0.21x
y = 48.19e-1.899x

Lecture-10
Apparent Volume of Distribution
(Multi-compartment model)

- Apparent V_D is a useful parameter that

1. Relates plasma drug concentration to the amount of drug in the body.
2. For drug with large extravascular distribution, the apparent volume of distribution is generally large.
3. Conversely, for polar drug with low lipid solubility, the apparent V_D is generally small.
4. Drug with high peripheral tissue binding also contribute to a large apparent V_D .

- 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.

Volume of central compartment

- The volume of central compartment is useful for determining the drug concentration directly after an IV injection into body.

- Notes:

1. In clinical pharmacy, this volume is also referred to as V_1 or the initial volume of distribution as the drug distribute within the plasma and other accessible body fluid.
2. This volume is generally smaller than the terminal volume of distribution after drug distribution to tissue is completed.
3. The volume of the central compartment is generally greater than 3 L, which is the volume of the plasma fluid for an average adult.
4. For many polar drugs, an initial volume of 7-10 L may be interpreted as rapid drug distribution within the plasma and some extravascular fluids.

Examples:

1. The volume of distribution 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 (Table 4-6)
2. 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.

Calculation the value of V_p

- As in the case of one-compartment model, V_p may be determined from the dose and the instantaneous plasma-drug concentration, Cp^0.

  $V_D = D_0 / Cp^0$

- V_p is also useful in determination of drug clearance if k is known.
- In one compartment model $CL = k\ V_D$
- In the two-compartment model, V_p may also be considered as a mass balance factor governed by the mass balance between dose and drug concentration, i.e., 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.

$V_p = D_0 / C_p$ (4-21)

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

$$C_p = A\, e^{-at} + B\, e^{-bt} \qquad (4\text{-}22)$$

At t = 0, $e^0 = 1$. therefore,

$$Cp^0 = A + B \qquad (4\text{-}23)$$

V_p is determined from Equation (4-24) by measuring A and B after feathering the curve, as discussed previously

$$V_p = D_0 / A + B \qquad (4\text{-}24)$$

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

$$[\mathbf{AUC}]_0^\infty = \frac{D_0}{\mathbf{k}\,\mathbf{V_D}} \qquad (4-25)$$

- In contrast, $[\mathbf{AUC}]_0^\infty$ for the two-compartment model is

$$[\mathbf{AUC}]_0^\infty = \frac{D_0}{\mathbf{k}\,\mathbf{V_p}} \qquad (4-26)$$

- Rearrangement of this equation yields

$$V_p = \frac{D_0}{K[AUC]_0^\infty} \qquad (4-27)$$