TWO-COMPARTMENT OPEN MODEL

A single intravenous bolus

Intravenous bolus administration: two compartment model

- The following assumptions are made:

1.Distribution, disposition and/or elimination of a drug follow the first-order process and passive diffusion.

2. The drug is being monitored in blood.

3. The organ responsible for removal of the drug is in the central compartment.

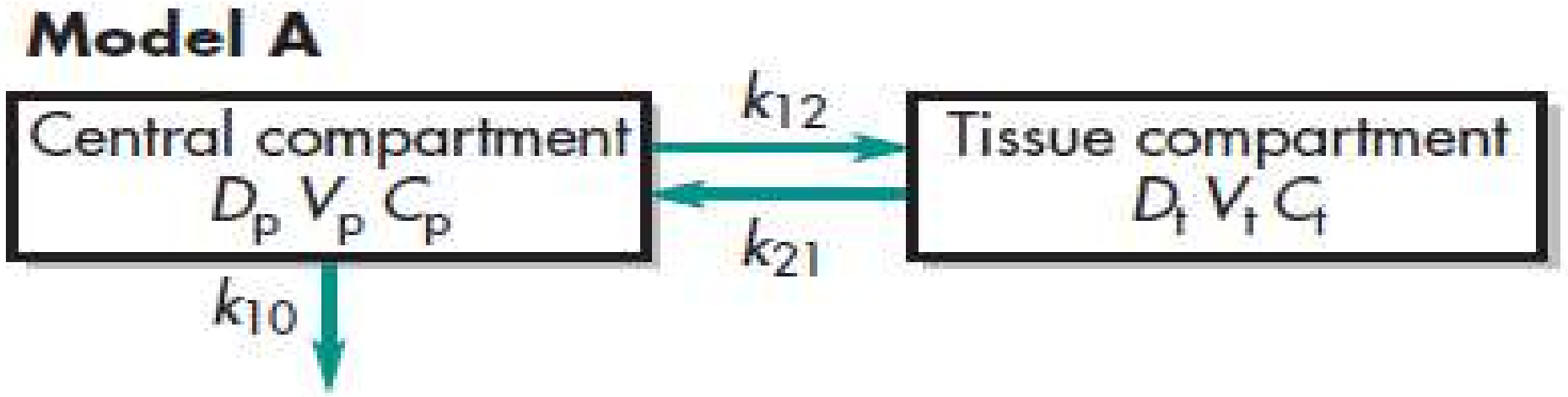


FIGURE 1-1 Two-compartment open models, intravenous injection.

- The rate constants k12 and k21 represent the first-order rate transfer constants for the movement of drug from compartment 1 to compartment 2 (k12) and from compartment 2 to compartment 1 (k21). K10 is elimination rate constant.
- The transfer constants are sometimes termed microconstants, and their values cannot be estimated directly.
- The elimination occurs from the central compartment model.

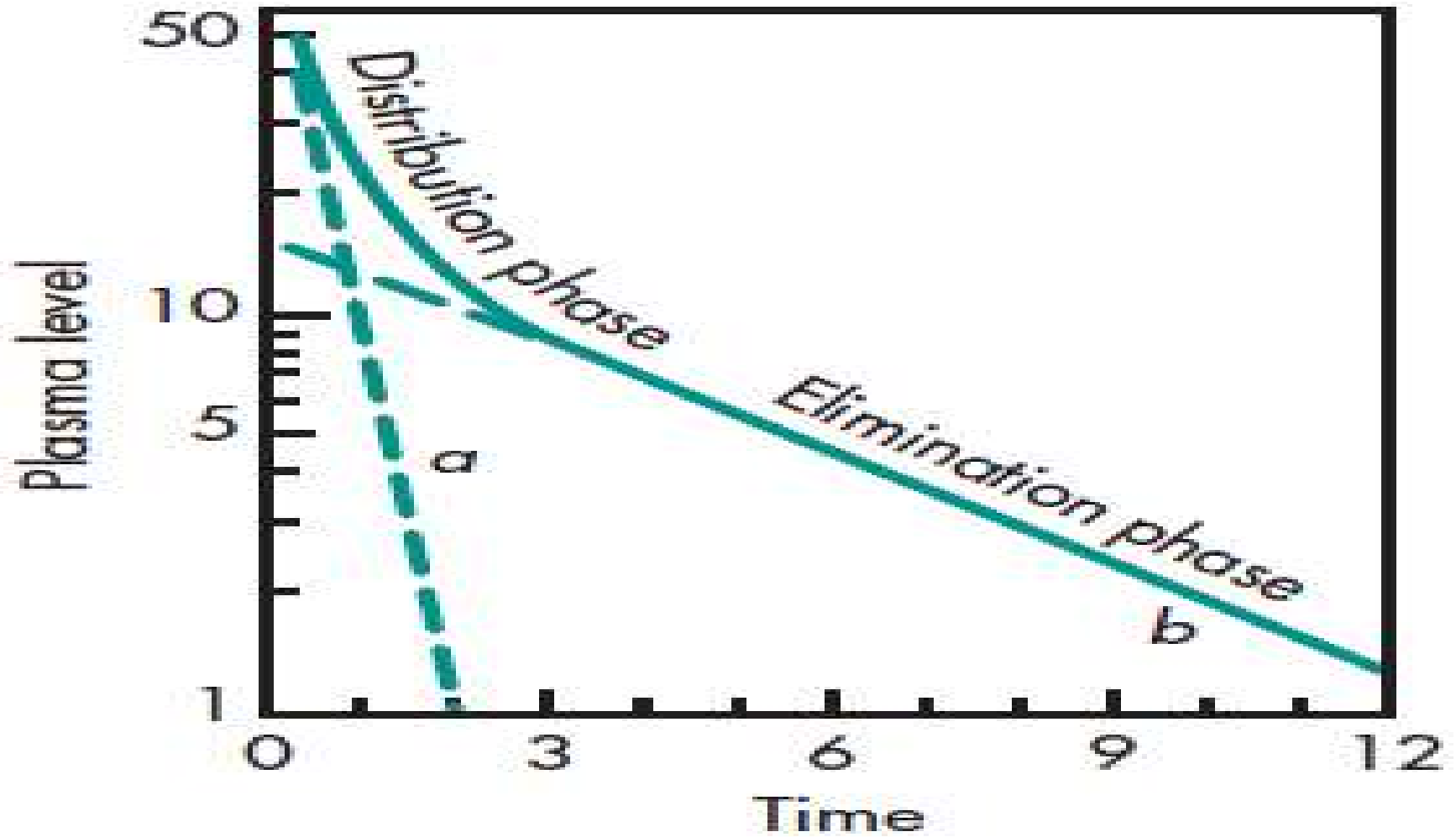
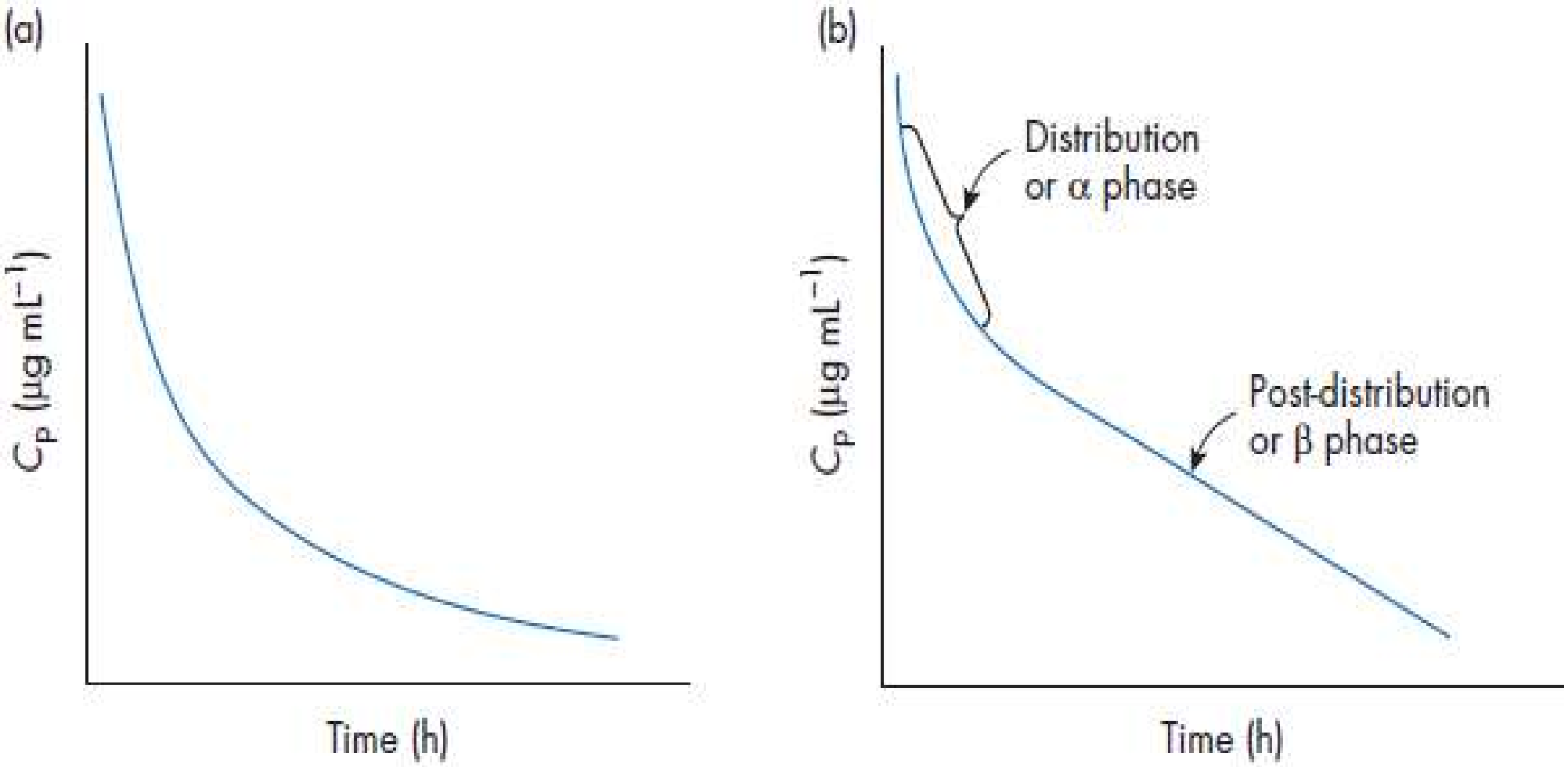
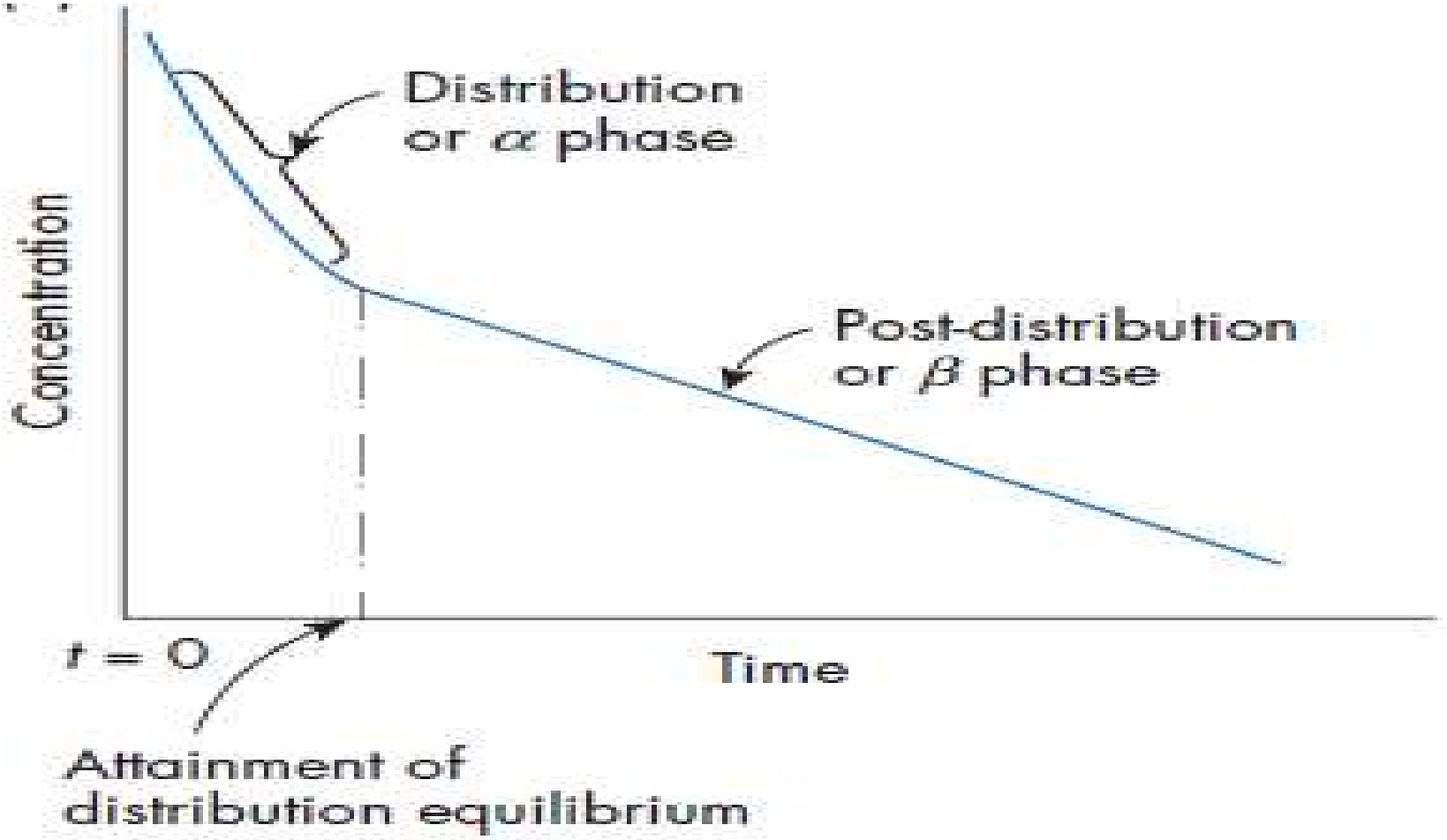


FIGURE 1-1 Plasma level–time curve for the two-compartment open model (single IV dose)



Typical plasma concentration (C_p) versus time profiles for a drug that obeys a two-compartment model following intravenous bolus administration. (a) rectilinear plot; (b) semilogarithmic plot.



Semilogarithmic plots of drug concentration in the plasma for a two compartment drug.

- 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.

- The plasma level–time curve for a drug that follows a two-compartment model (Fig. 1-1) shows that the plasma drug concentration declines biexponentially as the sum of two first-order processes—distribution and elimination.
- A drug that follows the pharmacokinetics of a two-compartment model does not equilibrate rapidly throughout the body.
- The drug distributes into two compartments:
  - the central compartment 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.

- The plasma level–time curve may be divided into two parts:
  - (a) a distribution phase
  - (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 (Fig. 1-1, 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 rate of distribution is faster than the rate of elimination).

- The fraction of drug in the tissue compartment during the distribution phase increases up to a maximum in a given tissue.
- 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 (Fig. 1-2), 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 (**drug in both the central and peripheral compartments declining exponentially with the same rate constant **β)**.

- (Fig. 1-1, line b).

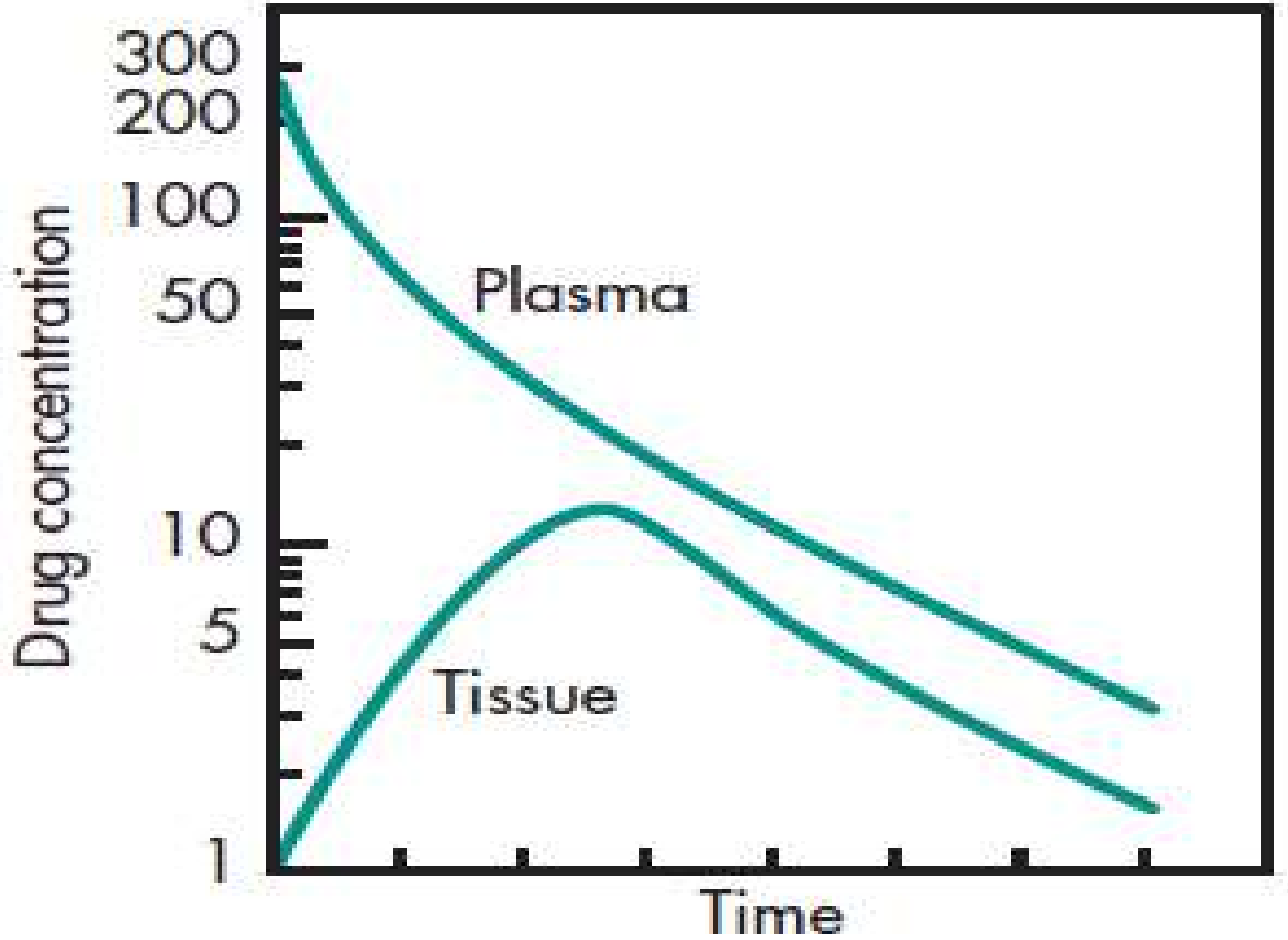
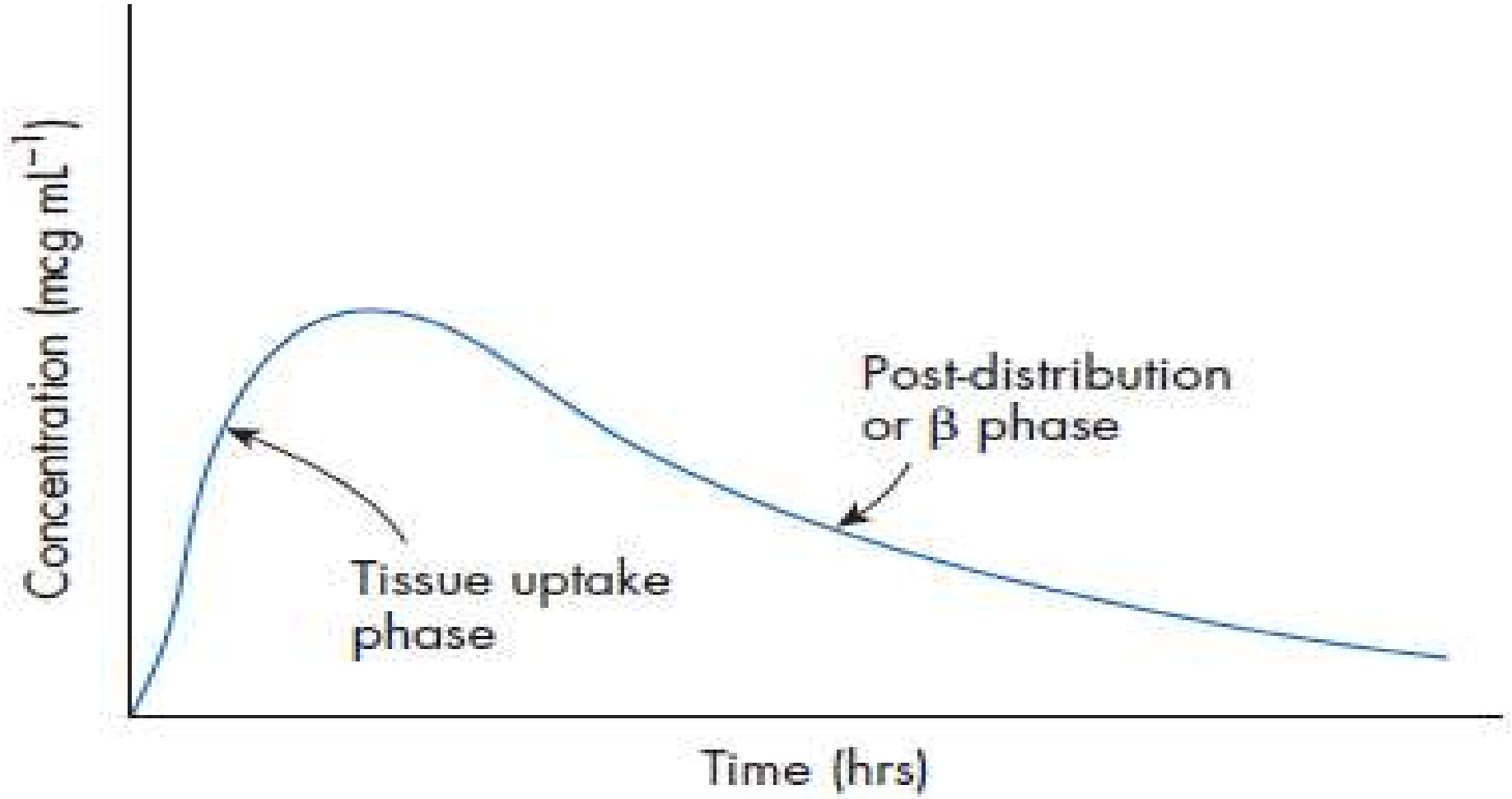


FIGURE 1-2 Relationship between tissue and plasma drug concentrations for a two-compartment open model.



A typical concentration versus time profile for a drug in the peripheral compartment (also called the tissue compartment or compartment 2) and that obeys a two-compartment model following intravenous bolus administration.

- 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 appears to follow a one-compartment model in which drug elimination is a first-order process described by β.

- In the model depicted above, k12 and k21 are first-order rate constants that govern the rate of drug distribution into and out of the tissues and plasma:

$$\frac{dC_t}{dt} = k_{12}C_p - k_{21}C_t \qquad (1.1)$$

$$\frac{dC_p}{dt} = k_{21}C_t - k_{12}C_p - k_{10}C_p \qquad (1.2)$$

- The relationship between the amount of drug in each compartment and the concentration of drug in that compartment is shown by Equations 1.3 and 1.4:

$$C_p = \frac{D_p}{V_p} \qquad (1.3)$$

$$C_t = \frac{D_t}{V_t} \qquad (1.4)$$

- where Dp = amount of drug in the central compartment, Dt = amount of drug in the tissue compartment, Vp = volume of drug in the central compartment, and Vt = volume of drug in the tissue compartment.

$$\frac{dC_p}{dt} = k_{21}\frac{D_t}{V_t} - k_{12}\frac{D_p}{V_p} - k_{10}\frac{D_p}{V_d} \qquad (1.5)$$

$$\frac{dC_t}{dt} = k_{12}\frac{D_p}{V_p} - k_{21}\frac{D_t}{V_t} \qquad (1.6)$$

Solving Equations 1.5 and 1.6 using **Laplace transforms** and **matrix algebra** will give Equations 1.7 and 1.8, which describe the change in drug concentration in the blood and in the tissue with respect to time:

Equations 1.7 and 1.8 for knowledge only

$$C_p = \frac{D_p^0}{V_p}\left(\frac{k_{21}-\alpha}{\beta-\alpha}e^{-\alpha t} + \frac{k_{21}-\beta}{\alpha-\beta}e^{-\beta t}\right) \qquad (1.7)$$

$$C_t = \frac{k_{21}D_P^0}{V_t(\alpha-\beta)}\left(e^{-\beta t} - e^{-\alpha t}\right) \qquad (1.8)$$

where $DP0$ = dose given intravenously,

t = time after administration of dose,

α and β are constants that depend solely on k12, k21, and k10.

- The amount of drug remaining in the plasma and tissue compartments at any time may be described realistically by Equations 1.9 and 1.10.

$$D_P = D_P^0\left(\frac{k_{21}-\alpha}{\beta-\alpha}e^{-\alpha t}+\frac{k_{21}-\beta}{\alpha-\beta}e^{-\beta t}\right) \qquad \textbf{(1.9)}$$

$$D_t = \frac{k_{21}D_P^0}{(\alpha-\beta)}\left(e^{-\beta t}-e^{-\alpha t}\right) \qquad \textbf{(1.10)}$$

Equations 1.9 and 1.10 for knowledge only

- The rate constants for the transfer of drug between compartments are referred to as microconstants or transfer constants.
- They 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 they can be estimated by a graphic method.
- The mathematical relationships of α and β to the rate constants are given by Equations 1.11 and 1.12, which are derived after integration of Equations 1.5 and 1.6.

$$\alpha + \beta = k_{12} + k_{21} + k_{10} \qquad (1.11)$$ ☺ ☺ ☺

$$\alpha\,\beta = k_{21}\,k_{10} \qquad (1.12)$$ ☺ ☺ ☺

- The constants α and β are hybrid first-order rate constants for the distribution phase and elimination phase, respectively.

- Equation 1.7 can be transformed into the following expression:

$$C_p = Ae^{-\alpha t} + Be^{-\beta t} \qquad (1.13)$$

- The constants α and β 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 1.13.
- These values may be obtained graphically by the method of residuals.

- Intercepts A and B are actually hybrid constants, as shown in Equations 1.14 and 1.15.

$$A = \frac{D_0(\alpha - k_{21})}{V_P(\alpha - \beta)}$$

(1.14)

$$B = \frac{D_0(k_{21} - \beta)}{V_P(\alpha - \beta)}$$

(1.15)

Equations 1.14 and 1.15 for knowledge only

- The values of A and B are empirical constants directly proportional to the dose administered, with units of concentration.

- **Determination of the post-distribution rate constant (β) and the coefficient (B)**

- The rapid distribution phase constant α being larger than the rate constant β→at some later time (generally at a time following the attainment of distribution equilibrium)→ the term

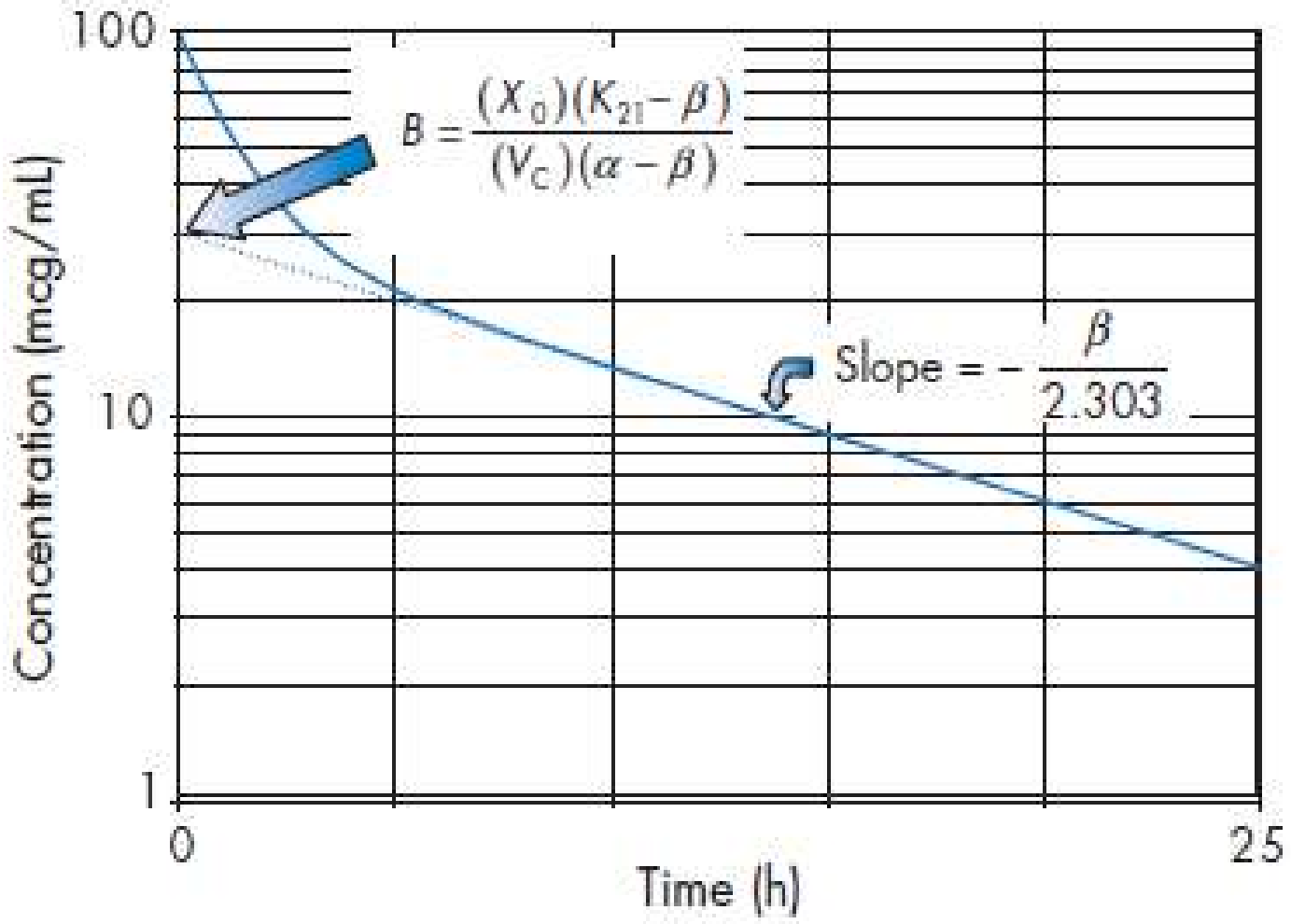
$Ae^{-\alpha t}$ will approach 0, while $Be^{-\beta t}$ will still have a finite value.

At this later time Equation 1.13 will reduce to:

$$C_p = Be^{-\beta t} \qquad (1.16)$$

Which in common logarithm

$$\log C_p = \log B - \frac{\beta t}{2.3} \qquad (1.17)$$



A plasma concentration (Cp) versus time profile for a drug that obeys a two-compartment model following intravenous bolus administration plotted on semilogarithmic paper. β, slow disposition, or post-distribution, rate constant; B, empirical constant; Vc, apparent volume of distribution for the central compartment; K21, transfer rate constant; X0, administered dose; a, distribution rate constant.

- **Determination of the post-distribution rate constant (β) and the coefficient (B)**

  - The rate constant (β) can be obtained from the slope (−β/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:

$$t_{1/2\beta} = \frac{0.693}{\beta} \qquad (1.18)$$

    - From the graph
  - The y intercept is equal to B (e.g. μg/mL).

➢ Determination of the distribution rate constant (α) and the coefficient (A)

- **Method of Residuals**
  The method of residuals (also known as feathering, peeling, or curve stripping) is a commonly employed technique for resolving a curve into various exponential terms.
- This method allows the separation of the monoexponential constituents of a biexponential plot of plasma concentration against time.
- See the table in the next slide.
- The difference between plasma concentrations measured and those obtained by extrapolation:

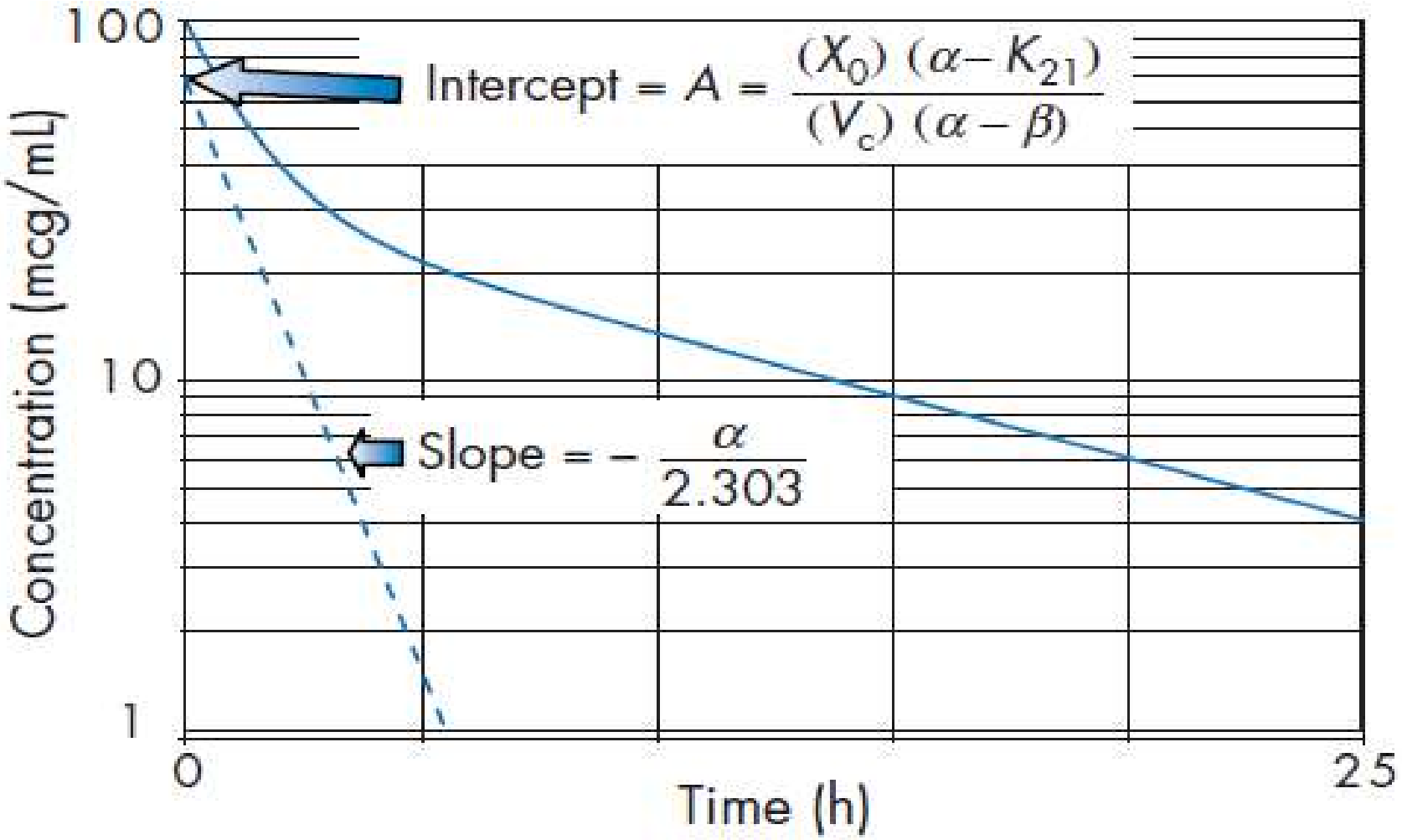
(Cp)diff (values from column 4) versus time (values from column 1) are then plotted on the the same or separate semilogarithmic paper.

➢ Determination of the distribution rate constant (α) and the coefficient (A)

Table [redacted] Method of residuals to calculate the difference between the extrapolated and observed plasma concentrations values

Time (h)	$(C_p)_{obs}$ ($\mu g\ mL^{-1}$)	$(C_p)_{extrap}$ ($\mu g\ mL^{-1}$)	$(C_p)_{diff}$ ($\mu g\ mL^{-1}$)
0.25			
0.50			
0.75			
1.0			

$(C_p)_{extrap}$, extrapolated plasma concentrations; $(C_p)_{obs}$, observed plasma concentrations; $(C_p)_{diff}$, difference between extrapolated and observed values for each time in the absorption phase.



A semilogarithmic plot of the difference between plasma concentrations measured and those obtained by extrapolation [(Cp)diff] for a drug that obeys a two-compartment model following intravenous bolus administration.

➢ Determination of the distribution rate constant (α) and the coefficient (A)

$$C_{p\ diff} = Ae^{-\alpha t} \qquad (1.19)$$

- The rate constant (**α**) can be obtained from the slope (− **α** /2.3) of a residual line.
- The $t_{1/2}$ for the distribution phase (alpha half-life) can be derived:
  - From the following relationship:

$$t_{1/2\ \alpha} = \frac{0.693}{\alpha} \qquad (1.20)$$

  - From the graph

- The y intercept is equal to A (e.g. μg/mL).

❖ **Determination of micro rate constants: the inter-compartmental rate constants (K21 and K12) and the pure elimination rate constant (K10)**

- A number of pharmacokinetic parameters may be derived by proper substitution of rate constants α and β and y intercepts A and B into the following equations

$$k_{10} = \frac{\alpha\beta(A + B)}{A\beta + B\alpha}$$

$$k_{12} = \frac{AB(\beta - \alpha)^2}{(A + B)(A\beta + B\alpha)}$$

$$k_{21} = \frac{A\beta + B\alpha}{A + B}$$

Note ☺

When an administered drug exhibits the characteristics of a two-compartment model, the difference between the distribution rate constant (α) and the slow (post-) distribution rate constant (β) plays a critical role. The greater the difference between these, the more conspicuous is the existence of a two-compartment model and, therefore, the greater is the need to apply all the equations for a two-compartment model.