Biopharmaceutics

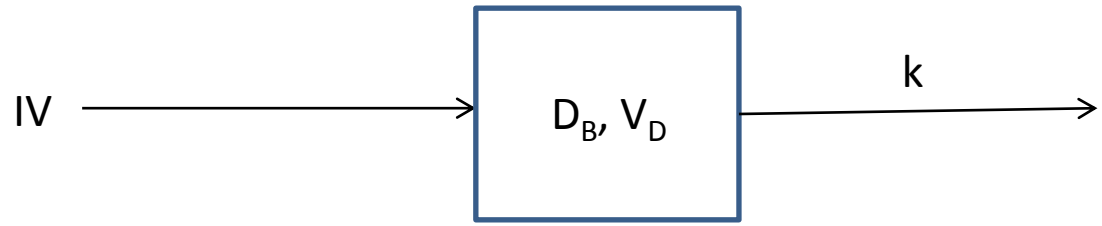
One-compartment open model: intravenous bolus administration

Introduction

- The one-compartment open model offers the simplest way to describe the process of drug distribution and elimination in the body.
- This model assume that the drug can enter or leave the body (i.e., the model is “open”), and the body acts like a single, uniform compartment.
- 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.

- 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.
- 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.
- 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 the elimination rate constant, k, which governs the rate at which the drug concentration in the body declines over time.



- Figure 3-1 pharmacokinetic model for a drug administration by rapid intravenous injection. D_B = drug in body; V_D = apparent volume of distribution; k = elimination rate constant.

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} (e.g., 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:

$k = k_m + k_e$ (3.1)

Where k_m = first-order rate process of metabolism and k_e = first-order rate process of excretion.

A rate expression for is

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

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

$$\frac{dD_B}{D_B} = -k\,dt$$

$$\int_{D_B^0}^{D_B} \frac{dD_B}{D_B} = -k \int_0^t dt$$

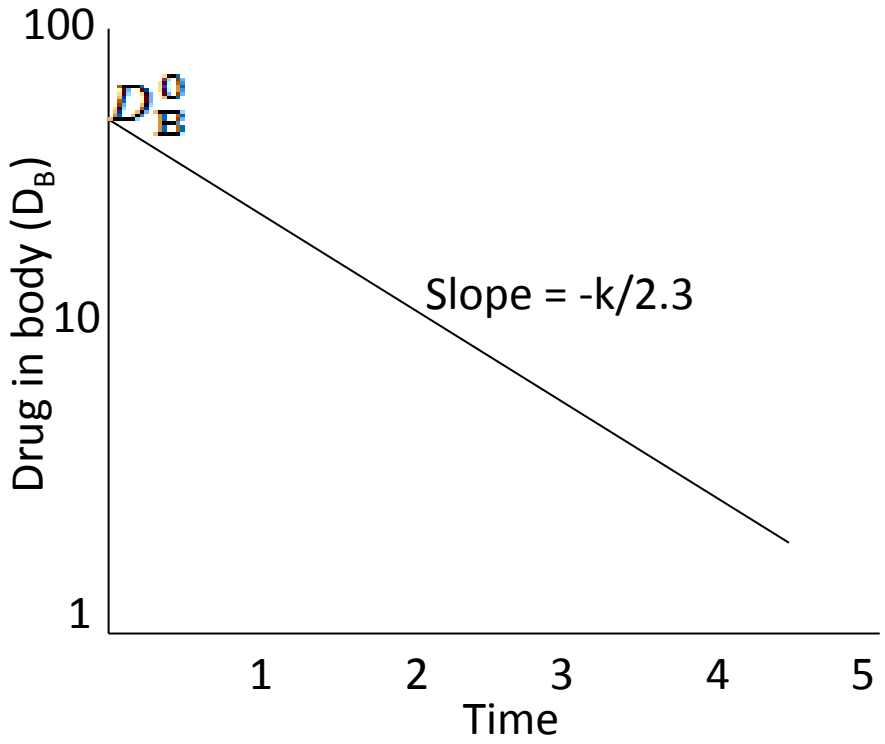
gives the following expression:

$$\ln D_B - ln\, D_B^0 = -k\,t$$

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

- Where D_B = drug in the body at time t and D_B^0 = drug in the body at t = 0.
- When log D_B is plotted against t for this equation, a straight line is obtained(Figure 3-2).
- 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.

Figure 3-2. Semilog graph of rate of drug elimination in a one-compartment model



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

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

- Equation 3.3 can also be expressed as

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

$$\boldsymbol{D_B = V_D C_p} \quad \mathbf{(3.5)}$$

Apparent volume of distribution

- 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 reflect the volume of fluid the drug 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.

- 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:

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

where Cp = 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

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

Example

- Exactly 1 g of drug is dissolved in an unknown volume of water. Upon assay, the concentration of this solution is 1mg/ml. What is the original volume of this solution?
- The original volume of the solution may be obtained by the following proportion, remembering that

  1g = 1000 mg:

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

  x = 1000mL or 1 L
- If, the above example, the volume of 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,

  X mg / 1000 mL = 1 mg / mL

  x = 1000 mg

Therefore, the total amount of drug in the solution is 1000mg, 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:

$$D_B^0 = V_D C_p^0 \ldots\ldots (3.5)$$

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

- 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.

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

Calculation of volume of distribution

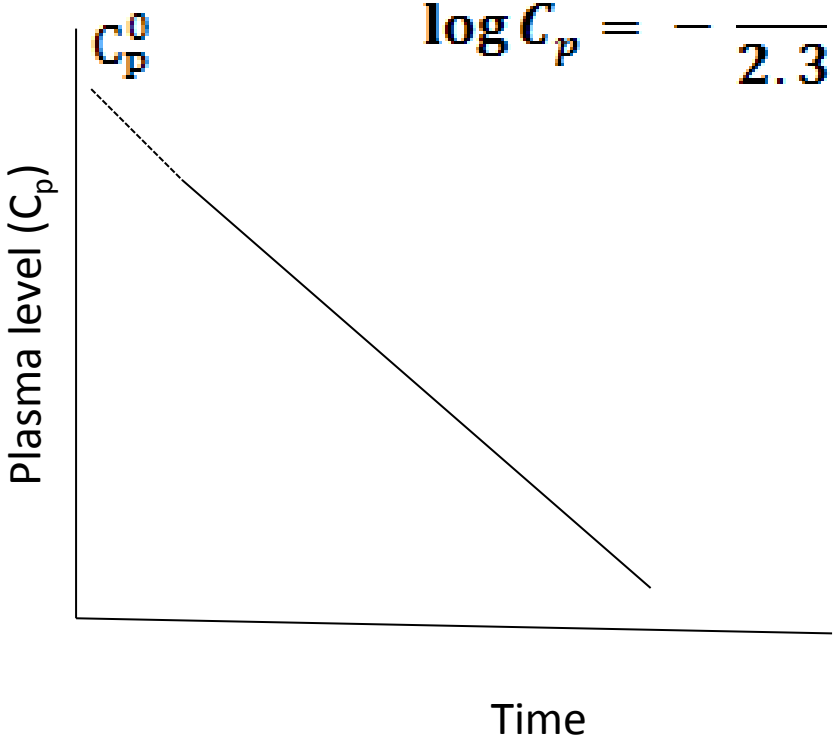
- In a one-compartment model (IV administration), the V_D is calculated with the following equation:

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

- When C_p^0 is determined by extrapolation, it represents the instantaneous drug concentration (concentration of drug at t = 0) after drug equilibration in the body (Fig. 3.3). The dose of drug given by IV bolus (rapid IV injection) represents the amount of drug in the body, D_B^0, at t = 0. Because both D_B^0 and C_p^0 are known at t = 0, then the apparent volume of distribution, V_D, may be calculated from Equation 3.9.

Figure 3.3. semilog graph giving the value of C_p^0 by extrapolation

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



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

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

- By substitution of Equation 3.5, $D_B = V_D C_p$, into equation 3.2, the following expression is obtained:

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

Rearrangement of Equation 3.10 gives

$$dD_B = -k\, V_D C_p \mathrm{dt} \quad (3.11)$$

- As both k and V_D are constants, Equation 3.10 may be integrated as follows:

$$\int_0^{D_B} \mathrm{dD_B} = -k\,V_D \int_0^{\infty} \mathrm{C_p}\; dt \quad (3.12)$$

- 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 $\int_0^{\infty} \mathrm{C_p}\; dt$ 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 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 trapezoidal rule.

- After integration, Equation 3.12 becomes

$$D_0 = k\, V_D\, AUC_0^{\infty}$$

- Which upon rearrangement yields the following equation

$$V_D = \frac{D_0}{k\, AUC_0^{\infty}} \qquad (3.13)$$

The calculation of the apparent V_D by means of Equation 3.13 is a model-independent method, because no pharmacokinetic model is considered and the AUC is determined directly by the trapezoidal rule.