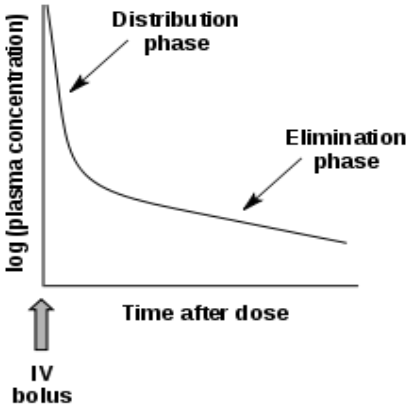
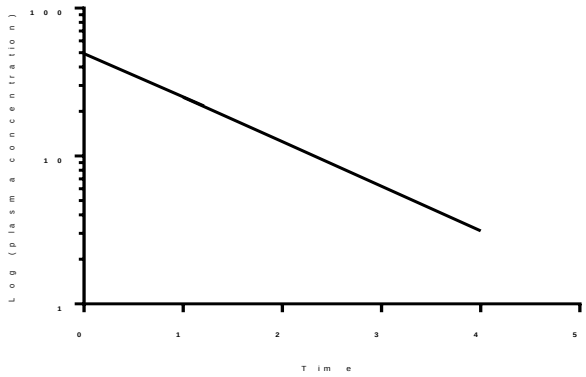
Multicompartments models

Most drugs entering the systemic circulation require a time to distribute fully throughout the available body space (need time for homogenous distribution).
When given by IV bolus dose, drug concentration declines in a ***biphasic fashion or triphasic fashion***, that is, plasma drug concentrations rapidly decline soon after IV bolus injection, and then decline moderately as some of the drug that initially distributes (equilibrates) into the tissue moves back into the plasma.



Biphasic
Biexponentional



Monophasic
Monoexponential

The early decline phase is commonly called the **distribution phase** (changes in the concentration of drug in plasma primarily reflect the movement of drug within the body rather than elimination) and the latter phase is called the terminal or **elimination phase** (the decline of the plasma concentration is associated primarily with elimination of drug from the body).

Unlike the one-compartment model, the multicompartment model assumes that the body composed of more than one-compartment, usually a **central compartment and peripheral compartment(s)**.

- The **central compartment** usually composed of the blood and highly perfused tissues like the kidney and the liver.
- The **tissue** or **peripheral compartments** are composed of groups of tissues with lower blood perfusion and different affinity for the drug like fat, muscle, and cerebrospinal fluid.
- The transfer rate processes for the passage of drug into or out of individual compartments are first-order processes.

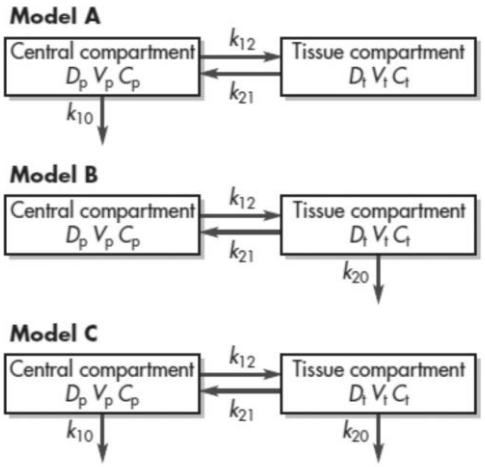
The nonlinear profile of plasma drug concentration–time is the result of many factors interacting together, including

1. Blood flow to the tissues.
2. The permeability of the drug into the tissues (fat solubility).
3. Partitioning.
4. The capacity of the tissues to accumulate drug.
5. The effect of disease factors on these processes.

Two-compartment Open Model

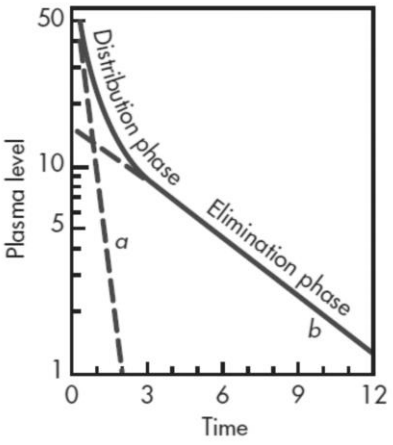
The drug that shows biexponential plasma-concentration time curve is said to follow the two-compartment model. Drug movement to and out of these compartments can be described as first-order processes.

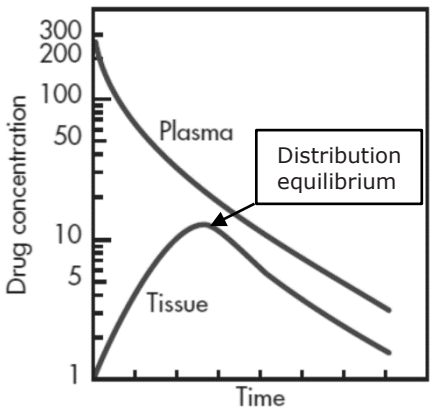
There are several possible two-compartment models based on the compartment from which elimination process occurs. These possibilities are described in the figure below:



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}).
Most two-compartment models assume that elimination occurs from the central compartment model, as shown in the figure, model A. This is 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*) a distribution phase and (*b*) an elimination phase.





At the distribution phase, plasma concentration decreases rapidly as a result of drug distribution to the peripheral (tissue) compartment and drug concentration in the tissues increases until it reaches maximum. At maximum tissue concentrations, 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* (*b*) *phase.*

Method of Residuals for PK analysis of Two-compartments Plasma Curves

This method allows the separation of biexponential plot of plasma concentration against time into its monoexponential constituents.

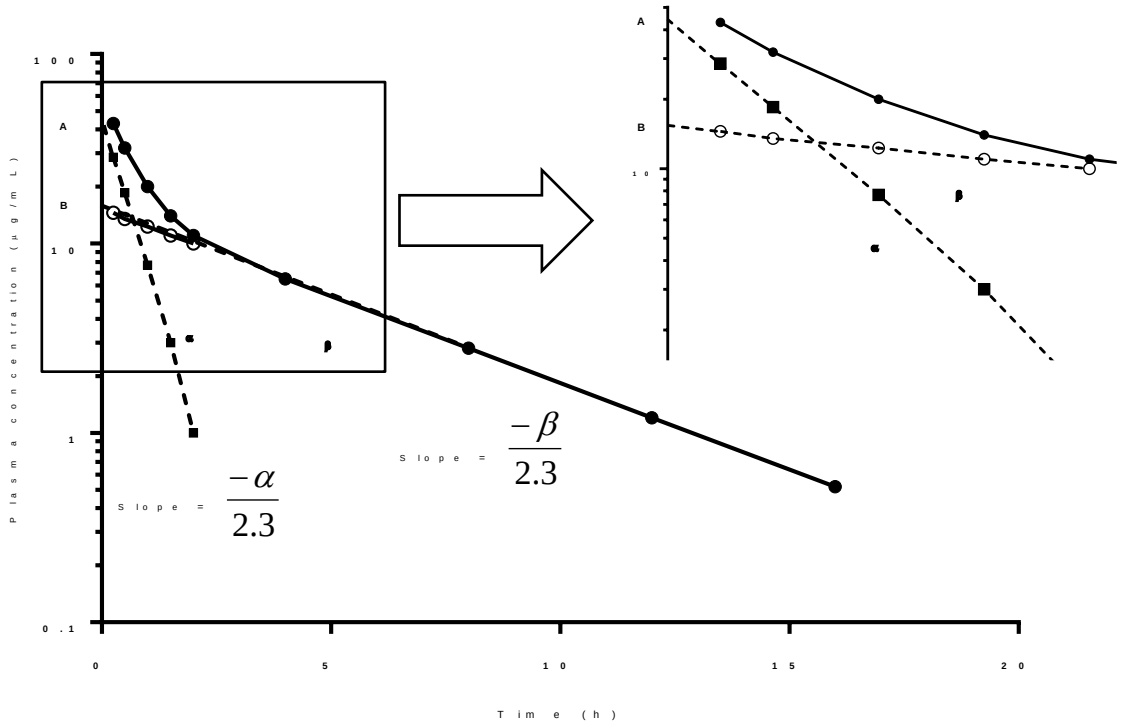
Example:
For example, 100 mg of a drug was administered by rapid IV injection to a healthy 70-kg adult male. Blood samples were taken periodically and assayed for drug. The following data were obtained:

Time (h)	Plasma concentration (µg/mL)
0.25	43
0.5	32
1	20
1.5	14
2	11
4	6.5
8	2.8
12	1.2
16	0.52

When these data are plotted on semilogarithmic graph paper, a curved line is observed which indicates that the drug is distributed in more than one compartment. From these data a biexponential equation can be derived by the method of residuals.

$$C_P = Ae^{-\alpha t} + Be^{-\beta t}$$

The constants ***α*** and **ß** 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. ***A*** and ***B*** can be obtained from the semilogarithmic graph as shown below.



- From the graph, the elimination phase (**ß** phase) is extrapolated and the y intercept is found to be **15 µg/mL = B.**
- Values from the extrapolated **ß** phase (Shown as empty circles in the graph) are subtracted from the original experimental data points to get a straight line that represents the **α** phase (distribution phase). These values are shown in the table below:

Application of the Method of Residuals			
Time (h)	**C_P Observed plasma level**	**C'_p Extrapolated plasma conc. (Empty circles in the graph)**	**$C_P - C'_p$ Residual plasma concentration**
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
4	6.5		

At time = 0,

$$C_P^0 = Ae^{-\alpha t} + Be^{-\beta t}$$

Since $e^0 = 1$, therefore

$$C_P^0 = A + B$$

- The rapid distribution phase is confirmed with the constant **α** being larger than the rate constant **ß.** At a time following the **distribution equilibrium,** the term $\boldsymbol{Ae^{-\alpha t}}$

will approach **0**. Therefore, plasma concentration after this time will be obtained by the following equation:

$$C_P = Be^{-\beta t}$$

$$K = \frac{\alpha ß(A+B)}{Aß+B\alpha}$$

Apparent Volumes of Distribution (V_D)

In the two-compartment model the term apparent volume of distribution does not consider individual volumes of different compartments. Other terms are more representative to the situation in the two-compartment model like:

- **Volume of the Central Compartment (V_p)**

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

$$V_p = \frac{D_0}{C_P^0} \quad , \quad C_P^0 = \frac{D_0}{V_p}$$

- **Apparent Volume of Distribution at Steady State $(V_D)_{ss}$**

This constant relates the plasma concentration and the amount of drug remaining in the body at the time following practical steady state.

At steady-state conditions, the rate of drug entry into the tissue compartment from the central compartment is equal to the rate of drug exit from the tissue compartment into the central compartment.

$$(V_D)_{ss} = \frac{D_p + D_t}{C_p}$$

Where D_p is the amount of the drug in the plasma and D_t is the amount of the drug in the tissue compartment.

- **Volume of Distribution by Area $(V_D)_{area}$ or $(V_D)_ß$**

$$(V_D)_ß = \frac{K V_p}{ß}$$

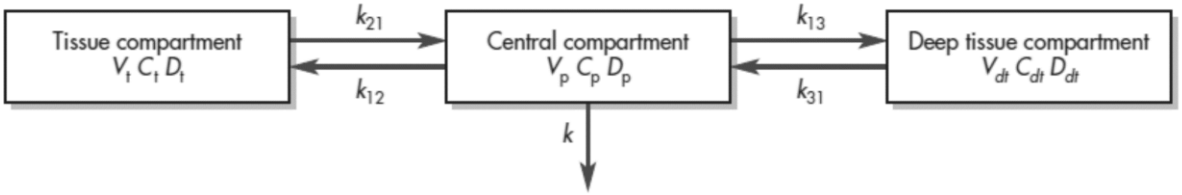
The value of $(V_D)_ß$ might decrease as a result of the reduction in the clearance of the drug as in the case of renal problems.

Clearance

The definition of clearance of a drug that follows a two-compartment model is similar to that of the one-compartment model.

Three-compartment Open Model

The three-compartment model is an extension of the two-compartment model, with an additional deep tissue compartment.



Non-compartmental Analysis

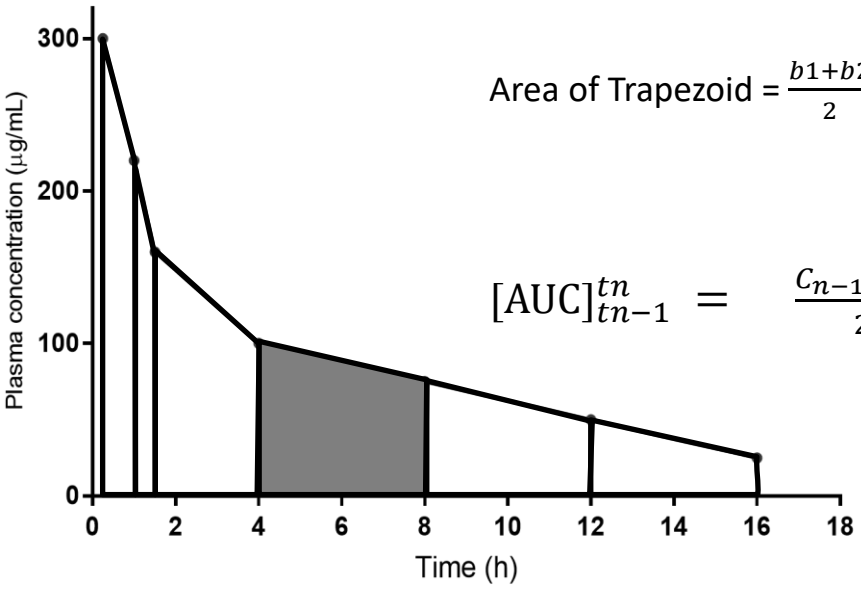
Non-compartmental analysis (NCA) is the most commonly used technique of pharmacokinetic data analysis directly from plasma-concentration data without the need to assume that drug disposition follows compartmental model.

Application of NCA include:

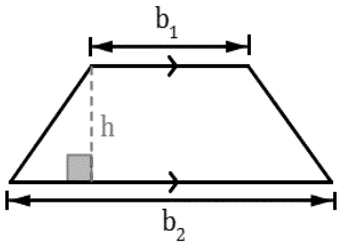
1. The area under the concentration time curve (e.g., in plasma or serum) describes the extent of systemic drug exposure; the peak concentration and its timing indicate the rate of drug input (absorption).
2. Provides estimates for clearance, volume of distribution, terminal half-life, and mean residence time.

The area under the concentration time curve (AUC)

Area under the concentration time curve (AUC) is the pharmacokinetic parameter reflecting the exposure of the drug. It can be calculated by **trapezoidal rule** by assuming the area under the curve is the sum of several small trapezoids as illustrated in the figure below:



Area of Trapezoid = $\frac{b1+b2}{2}\ h$



$$[\mathrm{AUC}]_{tn-1}^{tn} = \frac{C_{n-1}+C_n}{2}\ (t_n - t_{n-1})$$

$$[\mathrm{AUC}]_{tn-1}^{tn} = \frac{C_{n-1}+C_n}{2}(t_n - t_{n-1})$$

Where [AUC] = area under the curve, t_n = time of observation of drug concentration C_n, and t_{n-1} = time of prior observation of drug concentration corresponding to C_{n-1}.

- To calculate AUC from t =0 to the last observed point t = n, we sum all the calculated trapezoid areas.

$$[\mathrm{AUC}]_{t0}^{tn} = \sum [\mathrm{AUC}]_{tn-1}^{tn}$$

- The calculation of AUC from t = 0 to t = ∞, we have to calculate the residual area from last time point to t = ∞. This can be done by calculating the slope of the last plasma-time curve (the curve has to be plotted on a semilogarhithm paper for proper calculations).

$$[\mathrm{AUC}]_{tn}^{t\infty} = \frac{C_{pn}}{k}$$

where C_{pn} = last observed plasma concentration at t_n and **k = - slope x 2.3** obtained from the terminal portion of the curve.

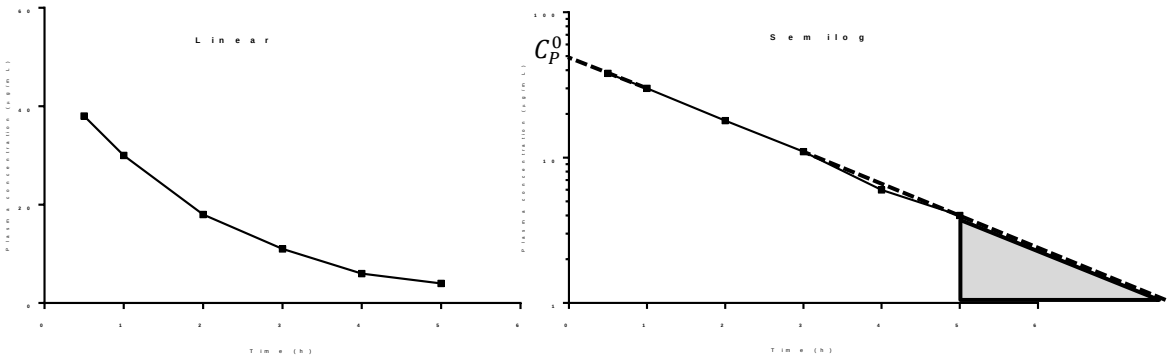
- The trapezoidal rule written in its full form to calculate the AUC from t = 0 to t = ∞ is as follows:

$$[\mathrm{AUC}]_0^{\infty} = \sum [\mathrm{AUC}]_{tn-1}^{tn} + \frac{C_{pn}}{k}$$

The unit of AUC is concentration x time (such as ng/mL . h)

Example: Drug A has the following concentration time profile. Calculate $[\mathrm{AUC}]_0^{t\ terminal}$ and $[\mathrm{AUC}]_0^{\infty}$.

Time (h)	Concentration (ng/mL)
0.5	38
1	30
2	18
3	11
4	6
5	4



Solution:

By extrapolating the plasma-concentration time curve to time = 0, the y intercept = C_P^0 = 50 ng/mL

$$[\text{AUC}]_0^{t\ terminal} = \sum [\text{AUC}]_{tn-1}^{tn}$$

$$[\text{AUC}]_0^{t\ terminal} = [(\frac{50+38}{2})\ x\ (0.5-0) + (\frac{38+30}{2})\ x\ (1-0.5) + (\frac{30+18}{2})\ x\ (2-1) + (\frac{18+11}{2})\ x\ (3-2) + (\frac{11+6}{2})\ x\ (4-3) + (\frac{6+4}{2})\ x\ (5-4)] = 91 \text{ ng/mL*h}$$

For the calculation of $[\text{AUC}]_0^{\infty}$, we have to calculate the residual area t= 5 to t = ∞ by calculating the slope.

Slope = $\frac{\log 4 - \log 6}{5-3} = -0.219$, ***k* = - slope x 2.3**

K = 0.5

$$[\text{AUC}]_0^{\infty} = [\text{AUC}]_0^{t\ terminal} + \frac{C_{p\ last\ observed}}{k}$$

$[\text{AUC}]_0^{\infty} = 91 + \frac{4}{0.5}$ = 99 ng/mL*h

Calculation of Volume of Distribution

The apparent V_D can be calculated from knowledge of the dose, elimination rate constant, and the area under the curve (AUC) from *t* = 0 to *t* = ∞.

$V_D = \frac{D_0}{k[AUC]_0^{\infty}}$

Note that the V_D calculated from this equation is equivalent to V_p (volume of the central compartment) if the drug follows multicompartment model.

$V_P = \frac{D_0}{k[AUC]_0^{\infty}}$

Using $[AUC]_0^{\infty}$ we ca also calculate $\boldsymbol{(V_D)_{ß}}$. In this case the elimination constant to be used is ***ß*** as follows:

$(V_D)_{ß} = \frac{D_0}{ß[AUC]_0^{\infty}}$

Calculation of Clearance

Clearance can be determined directly from the plasma drug concentration–time curve by

$Cl_T = \frac{D_0}{[AUC]_0^{\infty}}$

Clearance can be calculation based on AUC without the need for the assumption of compartmental models.

Half-life ($t_{1/2}$)

The time required to reduce the plasma concentration to one half its initial value. The t½ provides an index of:

1. The time-course of drug elimination.
2. The time-course of drug accumulation.
3. Choice of dose interval.

The half-life of elimination ($t_{½}$) can be determined directly by plotting actual concentrations on semilog graph paper. Other method for the calculation of t1/2 is through the estimation of the slope in the plasma-concentration time curve using the following equations:

K = - slope x 2.3

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

The selection of the time points from the plasma-concentration time curve for the calculation of the slope is crucial in the determination of elimination $t_{1/2}$. The last few points of the curve represent the elimination phase. Therefore, the slope should be determined from the elimination phase by using at least the last three points of the curve.