MULTICOMPARTMENT MODELS

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Subject- BIOPHARMACEUTICS AND PHARMACOKINETICS (BP604T)

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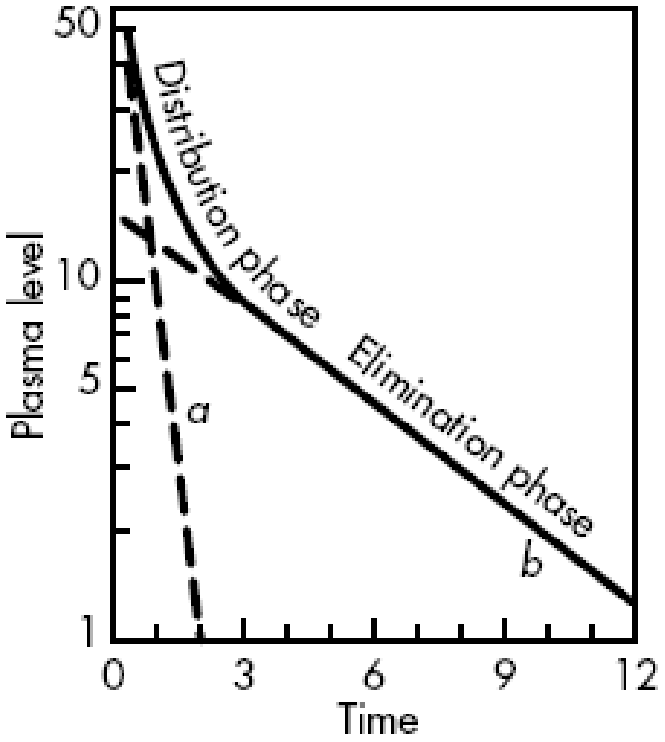
Two-compartment models

- 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 shows that the plasma drug concentration declines *biexponentially* as the sum of two first-order processes – distribution and elimination.

Two-compartment models

- 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.



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

Two-compartment models

- Multicompartment models were developed to explain and predict plasma and tissue concentrations for the behavior of these drugs.

- In this model, the drug distributes into two compartments:

  - ***CENTRAL COMPARTMENT:***
    These highly perfused tissues, extracellular fluid, and blood with rapid and uniform drug distribution.

  - ***PERIPHERAL COMPARTMENTS:***
    composed of groups of tissues with lower blood perfusion and different affinity for the drug with slow drug distribution.

Two-compartment models

- A drug will concentrate in a tissue in accordance with the affinity of the drug for that particular tissue.
  - For example, lipid-soluble drugs tend to accumulate in fat tissues.
  - Drugs that bind plasma proteins may be more concentrated in the plasma, because protein-bound drugs do not diffuse easily into the tissues.
- Tissue sampling is invasive, and the drug concentration in the tissue sample may not represent the drug concentration in the entire organ.

Multicompartment models provide answers

- (1) How much of a dose is eliminated?
- (2) How much drug remains in the plasma compartment at any given time?
- (3) How much drug accumulates in the tissue compartment?
- The latter information is particularly useful for drug safety since the amount of drug in a deep tissue compartment may be harder to eliminate by renal excretion or by dialysis after drug overdose.

Two-compartment models

- a multicompartment model assumes that all transfer rate processes for the passage of drug into or out of individual compartments are first-order processes.

TABLE 5-2 General Grouping of Tissues According to Blood Supply[a]

Blood Supply	Tissue Group	Percent Body Weight
Highly perfused	Heart, brain, hepatic-portal system, kidney, and endocrine glands	9
	Skin and muscle	50
	Adipose (fat) tissue and marrow	19
Slowly perfused	Bone, ligaments, tendons, cartilage, teeth, and hair	22

- Tissue uptake will also depend on such factors as fat solubility, degree of ionization, partitioning, and protein binding of the drug.

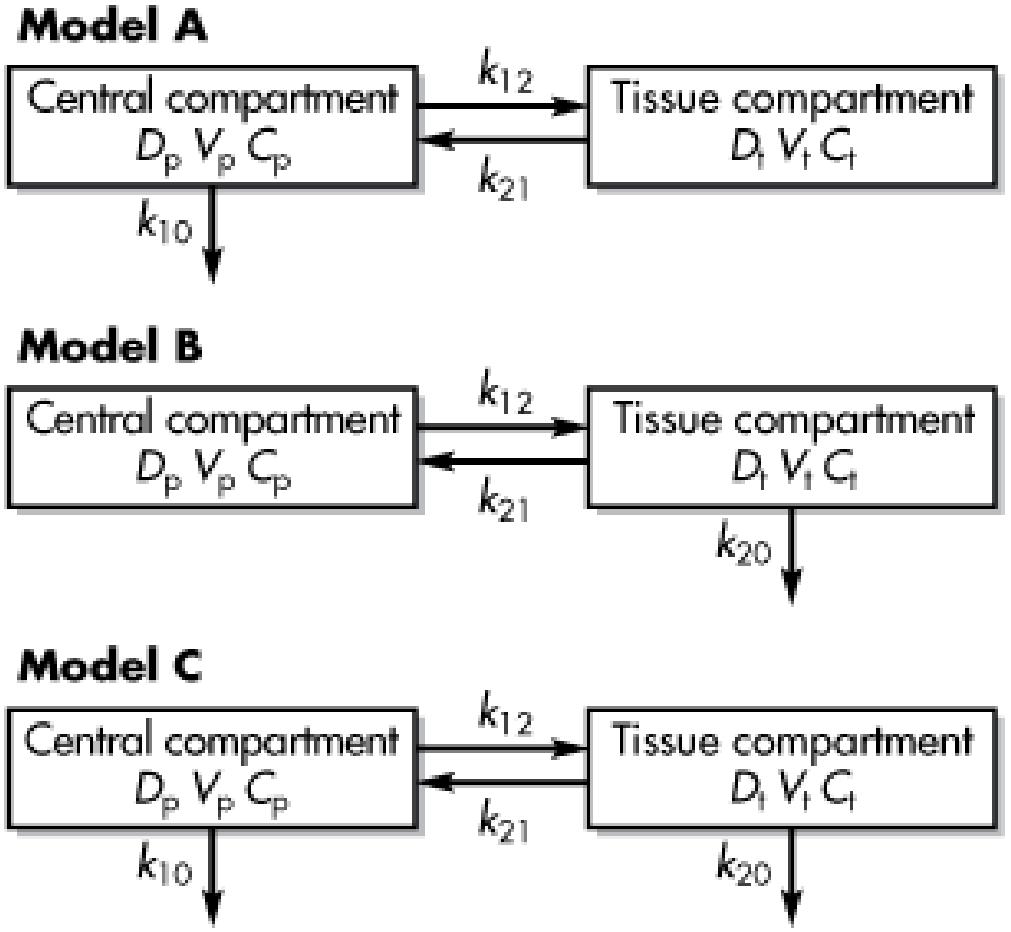
TABLE 5-1 Blood Flow to Human Tissues

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

Two-compartment models

- There are several possible two-compartment models:

Two-compartment open models, intravenous injection.



Two-compartment models

- Model A is used most often and describes the plasma level–time curve.

- By convention, compartment 1 is the central compartment and compartment 2 is the tissue compartment.

Two-compartment models

- 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 (model A), unless other information about the drug is known.

Two-compartment models

- 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.

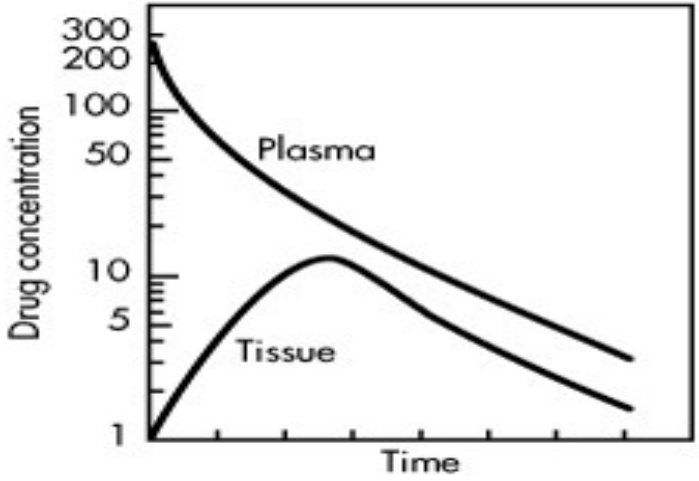
- The plasma level-time curve for a drug that follows a two-compartment model may be divided into two parts, (i) **a distribution phase** and (ii) **an elimination phase.**

Two-compartment models

- 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.

Two-compartment models

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



- The maximum tissue drug concentration may be greater or less than the plasma drug concentration.

Two-compartment models

- The fraction of drug in the tissue compartment is now in equilibrium (*distribution equilibrium*) with the fraction of drug in the central compartment.

- 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 (line *b*).

- 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).

Two-compartment models

- Tissue drug concentrations are theoretical only.
- 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

Two-compartment models

- 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:

$$\frac{dC_t}{dt} = k_{12}C_P - k_{21}C_t$$

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

$$C_P = \frac{D_P}{V_P}$$

$$C_t = \frac{D_t}{V_t}$$

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.
V_t = volume of drug in the tissue compartment.

Two-compartment models

$$\frac{dC_P}{dt} = k_{21}\frac{D_t}{V_t} - k_{12}\frac{D_P}{V_P} - k\frac{D_P}{V_p}$$

$$\frac{dC_t}{dt} = k_{12}\frac{D_P}{V_P} - k_{21}\frac{D_t}{V_t}$$

Two-compartment models

- Equations describe the change in drug concentration in the blood and in the tissue with respect to time:

$$C_P = \frac{D_P^0}{V_P}\left(\frac{k_{21} - a}{b - a}e^{-at} + \frac{k_{21} - b}{a - b}e^{-bt}\right)$$

$$C_t = \frac{D_P^0}{V_t}\left(\frac{k_{12}}{b - a}e^{-at} + \frac{k_{12}}{a - b}e^{-bt}\right)$$

$$D_P = D_P^0\left(\frac{k_{21} - a}{b - a}e^{-at} + \frac{k_{21} - b}{a - b}e^{-bt}\right)$$

$$D_t = D_P^0\left(\frac{k_{12}}{b - a}e^{-at} + \frac{k_{12}}{a - b}e^{-bt}\right)$$

Where:
D^0_p = dose given intravenously.
t = time after administration of dose.
a and b are constants that depend on k_{12}, k_{21}, and k.

Two-compartment models

- 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.

$$a + b = k_{12} + k_{21} + k$$

$$ab = k_{21}k$$

Where:
a and ***b*** are rate constants for the distribution phase and elimination phase, respectively.

Two-compartment models

$$C_P = Ae^{-at} + Be^{-bt}$$

- 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.
- These values may be obtained graphically by the method of residuals or by computer.

Method of Residuals

- 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:

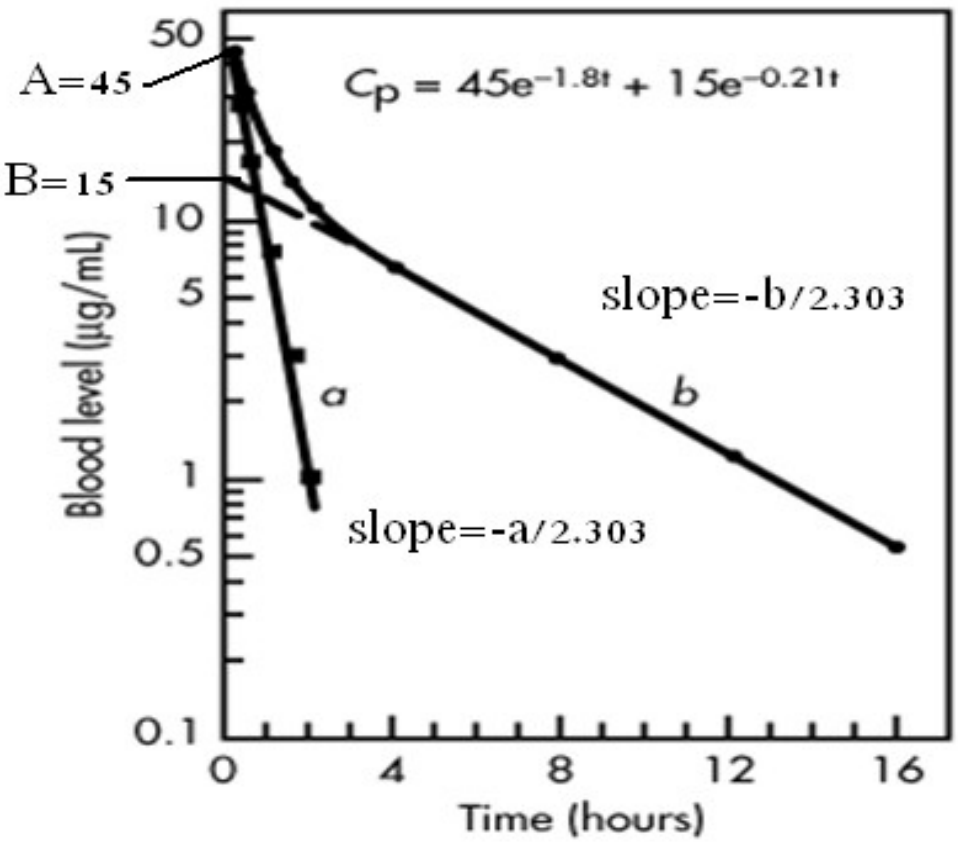
Time (hr)	Plasma Concentration (mcg/mL)
0.25	43.00
0.5	32.00
1.0	20.00
1.5	14.00
2.0	11.00
4.0	6.50
8.0	2.80
12.0	1.20
16.0	0.52

Method of Residuals

- 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.

Two-compartment models



Plasma level–time curve for a two-compartment open model.

The rate constants and intercepts were calculated by the method of residuals.

Two-compartment models

- 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*.
- At later time:

$Ae^{-at} approach zero$

$$C_P = Be^{-bt}$$

$$\log C_P = \frac{-bt}{2.3} + \log B$$

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

Two-compartment models

- 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 µg/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 α phase.

Two-compartment models

Application of the Method of Residuals			
TIME (hr)	C_p Observed Plasma Level	C'_p Extrapolated Plasma Concentration	$C_p - C'_p$ Residual Plasma Concentration
0.25	43.0	14.5	28.5
0.5	32.0	13.5	18.5
1.0	20.0	12.3	7.7
1.5	14.0	11.0	3.0
2.0	11.0	10.0	1.0
4.0	6.5		
8.0	2.8		
12.0	1.2		
16.0	0.52		

Two-compartment models

- 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 µg/mL.
- The elimination $t_{1/2b}$ is computed from *b* by use of equation and has the value of 3.3 hr.

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

Two-compartment models

- A number of pharmacokinetic parameters may be derived by proper substitution of rate constants *a* and *b* and *y* intercepts *A* and *B* into the following equations:

$$k = \frac{ab\,(A + B)}{Ab + Ba}$$

$$k_{12} = \frac{AB\,(b - a)^2}{(A + B)(Ab + Ba)}$$

$$k_{21} = \frac{Ab + Ba}{A + B}$$

Apparent Volumes of Distribution

- the apparent V_D is a useful parameter that relates plasma concentration to the amount of drug in the body.

- In the two-compartment model, several volumes of distribution can be calculated.
  - The apparent volume of the Central Compartment (V_P).
  - The apparent volume of the tissue compartment (V_t).

The apparent 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.

- 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.

The apparent volume of the Central Compartment (V_p)

- 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 3L, which is the volume of the plasma fluid for an average adult.
- For many polar drugs, an initial volume of 7-10L may be interpreted as rapid drug distribution within the plasma and some extracellular fluids.

The apparent volume of the Central Compartment (V_P)

$$V_P = \frac{D_0}{C_P^0}$$

$$C_P = Ae^{-at} + Be^{-bt}$$

$$\text{at } t = 0 \Rightarrow C_P^0 = A + B$$

$$V_P = \frac{D_0}{A + B}$$

The apparent Volume of the Tissue Compartment (V_t)

- The apparent volume of the tissue compartment (V_t) is a conceptual volume only and does not represent true anatomic volumes. The V_t may be calculated from knowledge of the transfer rate constants and V_p:

$$V_t = \frac{V_P k_{12}}{k_{21}}$$

- Tissue compartment drug concentration is an average estimate of the tissue pool and does not mean that all tissues have this concentration.

The apparent Volume of the Tissue Compartment (V_t)

- The pharmacodynamic activity may correlate better with the tissue drug concentration–time curve.

- To calculate the amount of drug in the tissue compartment D_t, the following expression is used:

$$D_t = \frac{k_{12} D_P^0}{a-b}\left(e^{-bt} - e^{-at}\right)$$

Elimination Rate Constant

- In the two-compartment model (IV administration), the elimination rate constant, *k*, represents the elimination of drug from the central compartment.

- whereas *b* represents drug elimination during the beta or elimination phase, when distribution is mostly complete.

- Because of redistribution of drug out of the tissue compartment, the plasma-drug level curve declines more slowly in the *b* phase.

Elimination Rate Constant

- Hence *b* is smaller than *k*; thus *k* is a true elimination constant, whereas *b* is a hybrid elimination rate constant that is influenced by the rate of transfer of drug in and out of the tissue compartment.
- When it is impractical to determine *k*, *b* is calculated from the *b* slope.
- The $t_{1/2\beta}$ is often used to calculate the drug dose.

TABLE 5-8 Comparison of Beta Half-Life and Distributional Half-Life of Selected Drugs

Drug	Beta Half-Life	Distributional Half-Life
Lidocaine	1.8 hours	8 minutes
Cocaine	1 hours	18 minutes
Theophylline	4.33 hours	7.2 minutes
Ergometrine	2 hours	11 minutes
Hydromorphone	3 hours	14.7 minutes
Milrinone	3.6 hours	4.6 minutes
Procainamide	2.5–4.7 hours	6 minutes
Quinidine	6–8 hours	7 minutes
Lithium	21.39 hours	5 hours
Digoxin	1.6 days	35 minutes
Human FSH	1 day	60 minutes
IgG1 kappa MAB	9.6 days (monkey)	6.7 hours