Unit-4

Biopharmaceutics and Pharmacokinetics

B.Pharma 6th Sem Notes

Unit: 4

- **Multicompartment models**
  Two compartment open model. IV bolus Kinetics of multiple dosing, steady state drug levels, calculation of loading and mainetnance doses and their significance in clinical settins.

Multicompartment Models

After administration, a drug does not distribute uniformly throughout the body. Some drugs first distribute rapidly to highly perfused tissues (like blood, liver, kidney), and then slowly to less perfused tissues (like muscle, fat).
To describe this behavior, **multicompartment models** are used.

Types of Compartment Models

1. **One-compartment model** – Drug distributes instantly and uniformly throughout the body.
2. **Two-compartment model** – Drug distributes rapidly in the central compartment and slowly into a peripheral compartment.

Two-Compartment Open Model:

The commonest of all multicompartment models is a two-compartment model. In such a model, the body tissues are broadly classified into 2 categories –

1. Central Compartment or **Compartment 1** comprising of blood and highly perfused tissues like liver, lungs, kidneys, etc. that equilibrate with the drug rapidly. Elimination usually occurs from this compartment.

2. Peripheral or **Tissue Compartment** or **Compartment 2** comprising of poorly perfused and slow equilibrating tissues such as muscles, skin, adipose, etc. and considered as a hybrid of several functional physiologic units.

Classification of a particular tissue, for example brain, into central or peripheral compartment depends upon the physicochemical properties of the drug. A highly lipophilic drug can cross the BBB and brain would then be included in the central compartment. In contrast, a polar drug cannot penetrate the BBB and brain in this case will be a part of peripheral compartment despite the fact that it is a highly perfused organ.

The plasma concentration for a drug that follows a two-compartment model declines biexponentially as the sum of two first-order processes – distribution and elimination.

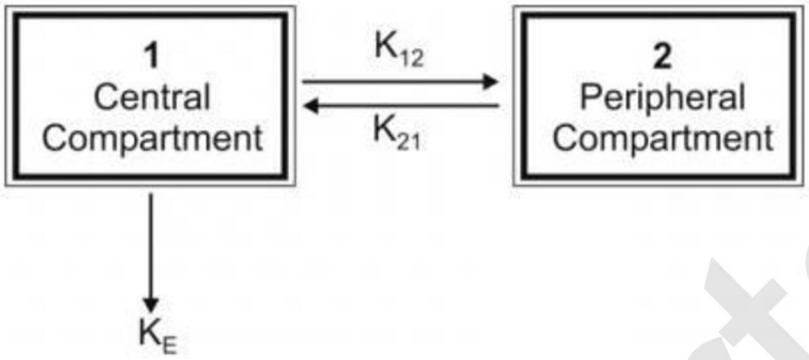
Depending upon the compartment from which the drug is eliminated, the two-compartment model can be categorized into 3 types:

1. Two-compartment model with elimination from central compartment.
2. Two-compartment model with elimination from peripheral compartment.
3. Two-compartment model with elimination from both the compartments.

In the absence of information, elimination is assumed to occur exclusively from central compartment.

Intravenous Bolus Administration:

The model can be depicted as shown below with elimination from the central compartment.



After the i.v. bolus of a drug that follows two-compartment kinetics, the decline in plasma concentration is biexponential indicating the presence of *two disposition processes viz. distribution and elimination*.

These two processes are not evident to the eyes in a regular arithmetic plot but when a semilog plot of C versus t is made, they can be identified (Fig. 9.12). Initially, the concentration of drug in the central compartment *declines rapidly*; this is due to the distribution of drug from the central compartment to the peripheral compartment.

The phase during which this occurs is therefore called as the **distributive phase**. After sometime, a *pseudo-distribution equilibrium* is achieved between the two compartments following which the subsequent loss of drug from the central compartment is slow and mainly due to elimination.

This *second, slower rate process is called as the* **post-distributive** or **elimination phase**. In contrast to the central compartment, the drug concentration in the peripheral compartment first increases and reaches a maximum.

This corresponds with the distribution phase. Following peak, the drug concentration declines which corresponds to the post-distributive phase (Fig.9.12).

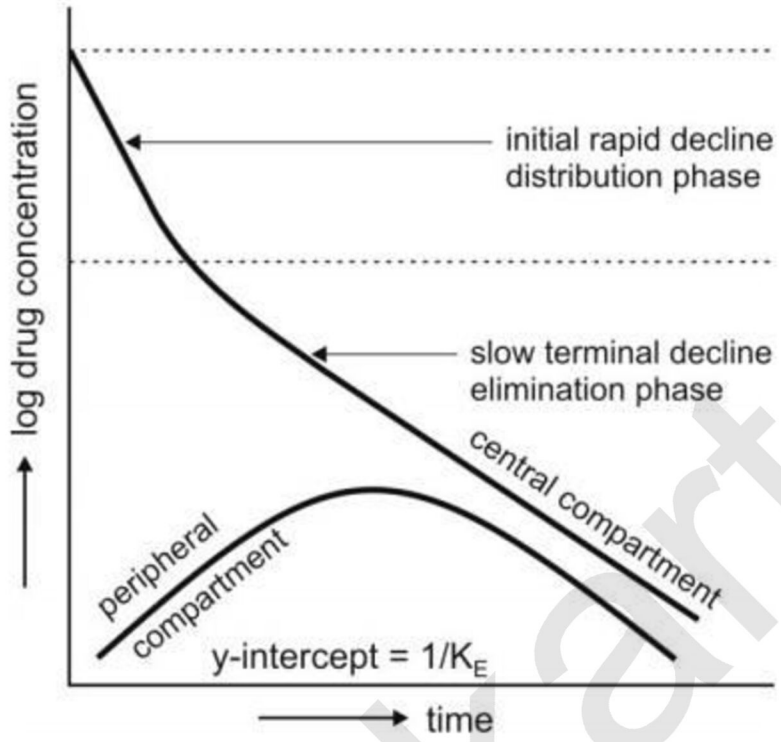


Fig. 9.12. *Changes in drug concentration in the central (plasma) and the peripheral compartment after i.v. bolus of a drug that fits two-compartment model.*

Let K_{12} and K_{21} be the first-order distribution rate constants depicting drug transfer between the central and the peripheral compartments and let subscript c and p define central and peripheral compartment respectively. The rate of change in drug concentration in the central compartment is given by:

$$\frac{dC_c}{dt} = K_{21}C_p - K_{12}C_c - K_E C_c \qquad (9.84)$$

Extending the relationship $X = V_d C$ to the above equation, we have

$$\frac{dC_c}{dt} = \frac{K_{21}X_p}{V_p} - \frac{K_{12}X_c}{V_c} - \frac{K_E X_c}{V_c} \qquad (9.85)$$

where X_c and X_p are the amounts of drug in the central and peripheral compartments respectively and V_c and V_p are the apparent volumes of the central and the peripheral compartment respectively. The rate of change in drug concentration in the peripheral compartment is given by:

$$\frac{dC_c}{dt} = K_{12}C_c - K_{21}C_p \qquad (9.86)$$

$$= \frac{K_{12}X_c}{V_c} - \frac{K_{21}X_p}{V_p} \qquad (9.87)$$

Integration of equations 9.85 and 9.87 yields equations that describe the concentration of drug in the central and peripheral compartments at any given time t:

$$C_c = \frac{X_0}{V_c}\left[\left(\frac{K_{21}-\alpha}{\beta-\alpha}\right)e^{-\alpha t} + \left(\frac{K_{21}-\beta}{\alpha-\beta}\right)e^{-\beta t}\right] \qquad (9.88)$$

$$C_p = \frac{X_0}{V_p}\left[\left(\frac{K_{12}}{\beta-\alpha}\right)e^{-\alpha t} + \left(\frac{K_{12}}{\alpha-\beta}\right)e^{-\beta t}\right] \qquad (9.89)$$

where X_o = i.v. bolus dose, α and β are **hybrid first-order constants** for the rapid distribution phase and the slow elimination phase respectively which depend entirely upon the first-order constants K_{12}, K_{21} and K_E.

The constants **K_{12}** and **K_{21}** *that depict reversible transfer of drug between compartments are called as* **microconstants** or **transfer constants**. The mathematical relationships between hybrid and microconstants are given as:

$$\alpha + \beta = K_{12} + K_{21} + K_E \qquad (9.90)$$

$$\alpha\beta = K_{21}K_E \qquad (9.91)$$

Equation 9.88 can be written in simplified form as:

$$C_c = Ae^{-\alpha\alpha} + Be^{\beta t} \qquad (9.92)$$

C_c = Distribution exponent Elimination exponent

where A and B are also hybrid constants for the two exponents and can be resolved graphically by the method of residuals.

$$A = \frac{X_0}{V_c}\left[\frac{K_{21}-\alpha}{\beta-\alpha}\right] = C_0\left[\frac{K_{21}-\alpha}{\beta-\alpha}\right] \qquad (9.93)$$

$$B = \frac{X_0}{V_c}\left[\frac{K_{21}-\beta}{\alpha-\beta}\right] = C_0\left[\frac{K_{21}-\beta}{\alpha-\beta}\right] \qquad (9.94)$$

where C_o = plasma drug concentration immediately after i.v. injection.

Method of Residuals: The biexponential disposition curve obtained after i.v. bolus of a drug that fits two compartment model can be resolved into its individual exponents by the method of residuals. Rewriting the equation 9.92:

$$C_c = Ae^{-\alpha\alpha} + Be^{-\beta t} \qquad (9.92)$$

As apparent from the biexponential curve given in Fig. 9.12., the initial decline due to distribution is more rapid than the terminal decline due to elimination i.e. the rate constant α >> ß and hence the term $e^{-\alpha t}$ approaches zero much faster than does $e^{-\beta t}$. Thus, equation 9.92 reduces to:

$$\bar{C} = Be^{-\beta t} \qquad (9.95)$$

In log form, the equation

$$\log \bar{C} = \log B - \frac{\beta t}{2.303} \qquad (9.96)$$

where C = back extrapolated plasma concentration values. A semilog plot of C versus t yields the terminal linear phase of the curve having slope –β/2.303 and when back extrapolated to time zero, yields y-intercept log B (Fig. 9.13.).The $t_{½}$ for the elimination phase can be obtained from equation $t_{½} = 0.693/\beta$.

Subtraction of extrapolated plasma concentration values of the elimination phase (equation 9.95) from the corresponding true plasma concentration values (equation 9.92) yields a series of residual concentration values C_r.

$$C_r = C - \bar{C} = Ae^{-\alpha t} \qquad (9.97)$$

In log form, the equation becomes:

$$\log C_r = \log A - \frac{\alpha t}{2.303} \qquad (9.98)$$

A semilog plot of C_r versus t yields a straight line with slope –α/2.303 and *Y*-intercept log A (Fig. 9.13).

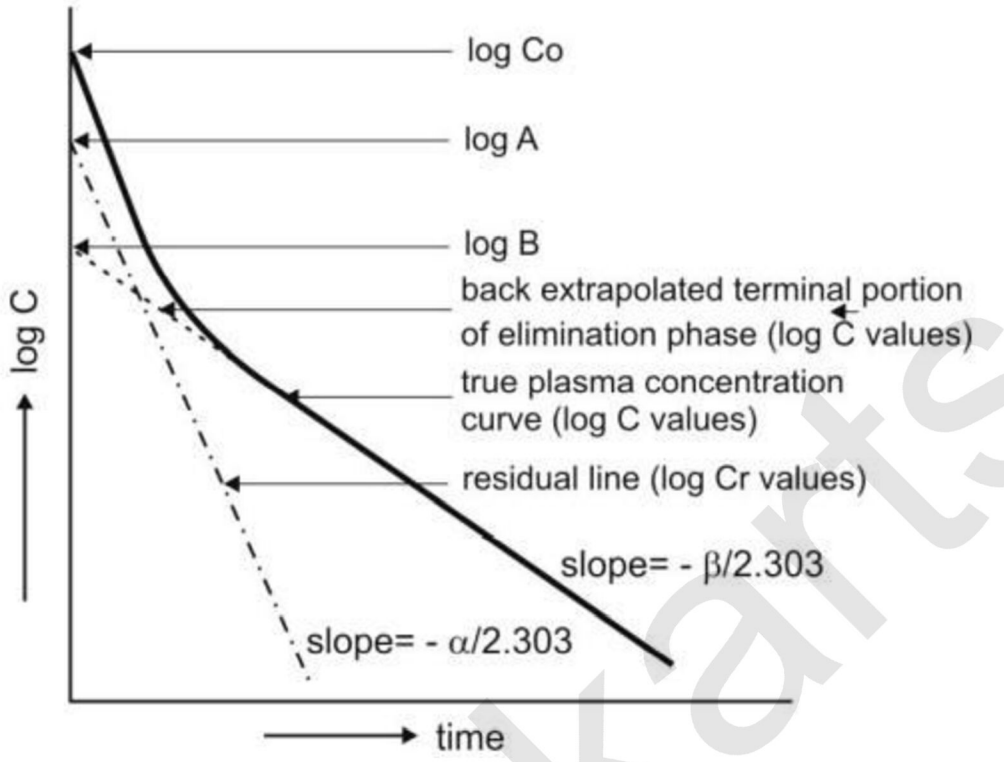


Fig. 9.13. *Resolution of biexponential plasma concentration-time curve by the method of residuals for a drug that follows two-compartment kinetics on i.v. bolus administration.*

Assessment of Pharmacokinetic Parameters: All the parameters of equation 9.92 can be resolved by the method of residuals as described above. Other parameters of the model viz. K_{12}, K_{21}, K_E, etc. can now be derived by proper substitution of these values.

$C_0 = A + B$ (9.99)

$$C_0 = A + B \qquad (9.99)$$

$$K_E = \frac{\alpha\beta C_0}{A\beta + B\alpha} \qquad (9.100)$$

$$K_{12} = \frac{A\,B\,(\beta - \alpha)^2}{C_0\,(A\,\beta + B\,\alpha)} \qquad (9.101)$$

$$K_{21} = \frac{A\beta + B\alpha}{C_0} \qquad (9.102)$$

It must be noted that for two-compartment model, K_E is the rate constant for elimination of drug from the central compartment and β *is the rate constant for elimination from the entire body*. Overall elimination $t_{½}$ should therefore be calculated from β.

Area under the plasma concentration-time curve can be obtained by the following equation:

$$AUC = \frac{A}{\alpha} + \frac{B}{\beta} \qquad (9.103)$$

The apparent volume of central compartment V_c is given as:

$$V_d = \frac{X_0}{C_0} = \frac{X_0}{K_E\ AUC} \qquad (9.104)$$

Apparent volume of peripheral compartment can be obtained from equation:

$$V_p = \frac{V_c K_{12}}{K_{21}} \qquad (9.105)$$

The apparent volume of distribution at steady-state or equilibrium can now be defined as:

$$V_{d,ss} = V_c + V_p \qquad (9.106)$$

It is also given as:

$$V_{d,area} = \frac{X_0}{\beta\ AUC} \qquad (9.107)$$

Total systemic clearance is given as:

$$Cl_T = \beta V_d \qquad (9.108)$$

The pharmacokinetic parameters can also be calculated by using urinary excretion data:

$$\frac{dX_u}{dt} = K_e\ V_c \qquad (9.109)$$

An equation identical to equation 9.92 can be derived for rate of excretion of unchanged drug in urine:

$$\frac{dX_u}{dt} = K_e A e^{-\alpha t} + K_e B e^{-\beta t} \qquad (9.110)$$

The above equation can be resolved into individual exponents by the method of residuals as described for plasma concentration-time data.

Renal clearance is given as:

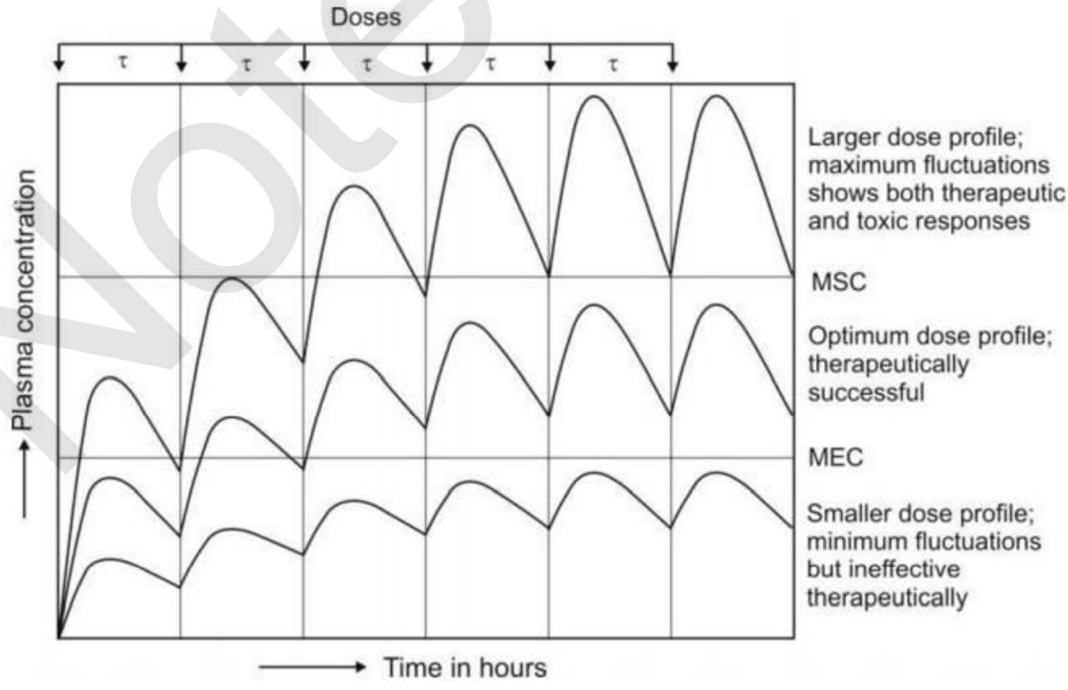
Cl_R K_e V_c (9.111)

Dosage Regimen:

It is defined as the manner in which a drug is taken. For certain analgesics, hypnotics, anti-emetics etc. a single dose may provide an effective treatment.

But the duration of most illness is longer than the therapeutic effect produced by a single dose. In such cases drugs are required to be taken on a repetitive basis over a period of time.

The overall objective of dosage regimen design is to achieve a target drug concentration at the receptor site.



Design of dose regimen

Therapeutic Drug Monitoring:

Therapeutic Drug Monitoring (TDM) is the measurement of specific drug concentrations in a patient's blood (plasma or serum) at designated intervals to ensure a constant therapeutic level and avoid toxicity or treatment failure.

Therapeutic Range:

The range of drug concentration between:

- **MEC (Minimum Effective Concentration)** → lowest level for desired effect.
- **MTC (Minimum Toxic Concentration)** → lowest level that causes toxicity.

$$\text{Therapeutic Range} = \text{MTC} - \text{MEC}$$

Steps Involved in TDM

1. **Selection of Drug:**
   Only drugs with narrow therapeutic index or unpredictable kinetics need monitoring.
2. **Proper Sampling Time:**
   Blood sample should be collected at correct time (usually **trough level** – just before next dose).
3. **Measurement (Assay):**
   Drug concentration in plasma is measured using techniques like:
   - Immunoassay
   - High-Performance Liquid Chromatography (HPLC)
   - Spectrophotometry
4. **Interpretation of Results:**
   Compare measured value with therapeutic range.
5. **Dose Adjustment:**
   Modify dose or dosing interval to achieve desired concentration.

Factors Influencing TDM Results

1. **Patient factors:** Age, weight, disease condition, genetic variations.
2. **Drug interactions:** Enzyme inducers or inhibitors.
3. **Sampling errors:** Wrong timing of sample collection.
4. **Analytical errors:** Inaccurate measurement techniques.

Function of Therapeutic Drug Monitoring

- Selection of Drug
- Dosage Regimen Design
- Evaluation of Patient Response

- To Determine need for measuring serum drug cone.
- Monitoring serum drug concentration
- Assay of drug concentration in biological fluid
- Pharmacokinetic evaluation of drug concentration
- Recommend special requirement.

Steady-State Drug Levels

Definition:

When a drug is administered repeatedly at fixed intervals, the amount of drug administered equals the amount of drug eliminated after a few doses.
At this point, the **average plasma concentration remains constant**, called the **steady-state**.

Rate of Drug Administration=Rate of Drug Elimination

The plasma drug concentration fluctuates between a **peak (Cmax)** and **trough (Cmin)** value, but the **average concentration (Css)** remains constant.

Time to Reach Steady State:

- Steady state is usually achieved after **4–5 half-lives ($t_{½}$)** of the drug.
- It is **independent of the dose** but **depends on half-life**.

Example:
If $t_{½}$ = 6 hours → Steady state is achieved in about **24–30 hours**.

Equation for Steady-State Concentration (Css):

$$Css = \frac{F \times Dose}{Cl \times \tau}$$

Where:

- **F** = Bioavailability
- **Dose** = Amount of drug given each time
- **Cl** = Clearance
- **τ (tau)** = Dosing interval

Loading Dose (LD)

Definition:

A **loading dose** is a large **initial dose** given to quickly achieve the desired **therapeutic plasma concentration** of a drug.

It helps to reach the **steady-state level faster**, especially for drugs with long half-lives.

$$LD = C_{target} \times V_d$$

Where:

- **Ctarget** = desired plasma concentration
- **Vd** = apparent volume of distribution

If given by a non-IV route (with incomplete bioavailability),

$$LD = \frac{\text{Ctarget} \times \text{Vd}}{F}$$

Example:

Digoxin has a long half-life (~36 hours).
To achieve a therapeutic level quickly, a **loading dose** is given, followed by smaller maintenance doses.

Maintenance Dose (MD):

Definition:

A **maintenance dose** is the dose required to **replace the amount of drug eliminated** during each dosing interval to maintain the steady-state concentration.

$$MD = C_{ss} \times Cl \times \tau$$

If bioavailability (F) < 1, then:

$$MD = \frac{Css \times Cl \times \tau}{F}$$

Where:

- **Css** = steady-state concentration
- **Cl** = clearance
- **τ** = dosing interval

Examples of Clinical Use:

- **Digoxin, Phenytoin, Theophylline:** require both loading and maintenance doses.
- **Antibiotics, Antihypertensives:** use steady-state dosing for long-term therapy.
- **Emergency Drugs (e.g., Lidocaine):** loading dose ensures rapid onset.