Name of Unit	Multi compartment Models
Course/Subject Name	Biopharmaceutics and Pharmacokinetics
Course/Subject Code	BP604T
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Learning Outcome of Unit-4

LO	Learning Outcome(LO)	Course Outcome Code
LO1	Students will learn about the calculation of various pharmacokinetic parameters using two compartment modeling	BP604.4
LO2	Students will learn about the significance and calculation of loading and maintenance doses.	BP604.2

CONTENT OF MODULE

Topics
Multi compartment Models • Two compartment open model. IV bolus. • Kinetics of multiple dosing • steady state drug levels • calculation of loading and maintenance doses and their significance in clinical settings

MULTI COMPARTMENT MODELS

Multi compartment models are thus based on following assumptions –

1. Blood/plasma and the highly perfused tissues such as tissues such as brain, heart, lung, liver and kidneys constitute the central compartment.
2. Other tissues with similar distribution characteristics are pooled together to constitute peripheral compartments tissues on the basis of similarity in their distribution characteristics.
3. Intravenously administered medications are introduced directly into the central compartment.
4. Irreversible drug elimination, either by hepatic biotransformation or renal excretion, takes place only from the central compartment.
5. Reversible distribution occurs between central and peripheral compartments, with a finite time required for distribution equilibrium to be attained.
6. After drug equilibration between drug and the peripheral compartments, elimination of drug follows first-order kinetics.
7. All rate processes involving passage of drug in and out of individual compartment are first-order processes and plasma level-time curve is best described by sum of series of exponential terms each corresponding to first-order rate processes associated with a given compartment.
8. The peripheral compartment is usually inaccessible to direct measurement and is not a site of drug elimination or clearance.

TWO-COMPARTMENT OPEN MODEL

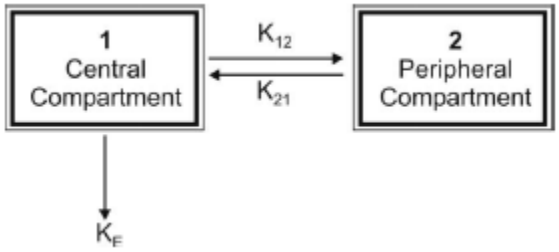
The commonest of all multicompartment models is a two-compartment model. In such a model, the body tissues are broadly classified into 2 categories –

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.

- **Two-Compartment Open Model**
- **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 bi exponential 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 semi log plot of C versus t is made, they can be identified. 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.

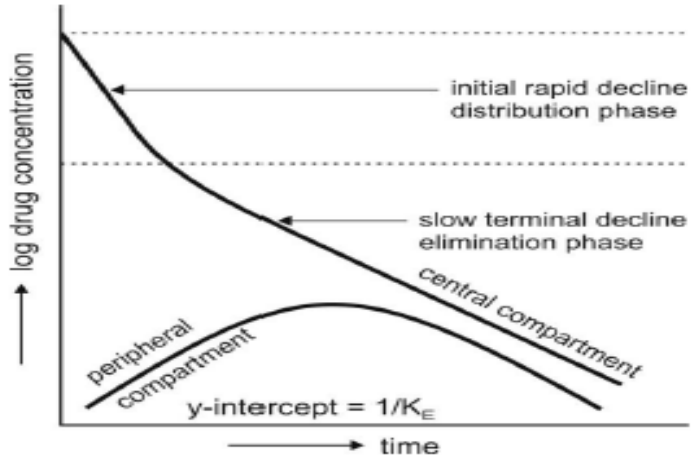


Fig. *Changes in drug concentration in the central (plasma) and the peripheral compartment after i.v. bolus of a drug that fits two-compartment model.*

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:

$$\frac{dC_c}{dt} = K_{21}C_p - K_{12}C_c - K_E C_c$$

Extending the relationship X = Vd.C to the above equation, we have

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

where Xc and Xp are the amounts of drug in the central and peripheral compartments respectively and Vc and Vp 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:

$$\frac{dC_c}{dt} = K_{12}C_c - K_{21}C_p$$
$$= \frac{K_{12}X_c}{V_c} - \frac{K_{21}X_p}{V_p}$$

Integration of above equations yield that the concentration of drug in the central and peripheral compartments at any given time t:

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

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

where Xo = 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 micro constants or transfer constants. The mathematical relationships between hybrid and micro constants are given as:

$$\alpha + \beta = K_{12} + K_{21} + K_E$$

$$\alpha\beta = K_{21}K_E$$

Equation can be written in simplified form as:

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

$$C_c = \text{Distribution exponent} + \text{Elimination exponent}$$

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

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

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

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

Kinetics of Multiple Dosing

For drugs that have a narrow therapeutic range (eg, digoxin and phenytoin), there is a need to define the therapeutic minimum and maximum nontoxic plasma concentrations (MEC and MTC, respectively). In calculating a multiple-dose regimen, the desired or *target* plasma drug concentration must be related to a therapeutic response, and the multiple-dose regimen must be designed to produce plasma concentrations within the therapeutic window.

An **optimal multiple dosage regimen** is the one in which the drug is administered in suitable doses (by a suitable route), with sufficient frequency that ensures maintenance of plasma concentration within the therapeutic window (without excessive fluctuations and drug accumulation) for the entire duration of therapy.

There are two main parameters that can be adjusted in developing a dosage regimen:

(1) The size of the drug dose and

(2) τ, the frequency of drug administration (i.e, the time interval between doses).

Dose Size

The magnitude of both therapeutic and toxic responses depends upon dose size. Dose size calculation also requires the knowledge of amount of drug absorbed after administration of each dose. Greater the dose size, greater the fluctuations between Css,max and Css,min during each

dosing interval and greater the chances of toxicity. For drugs administered chronically, dose size calculation is based on average steady state blood levels and is computed from equation

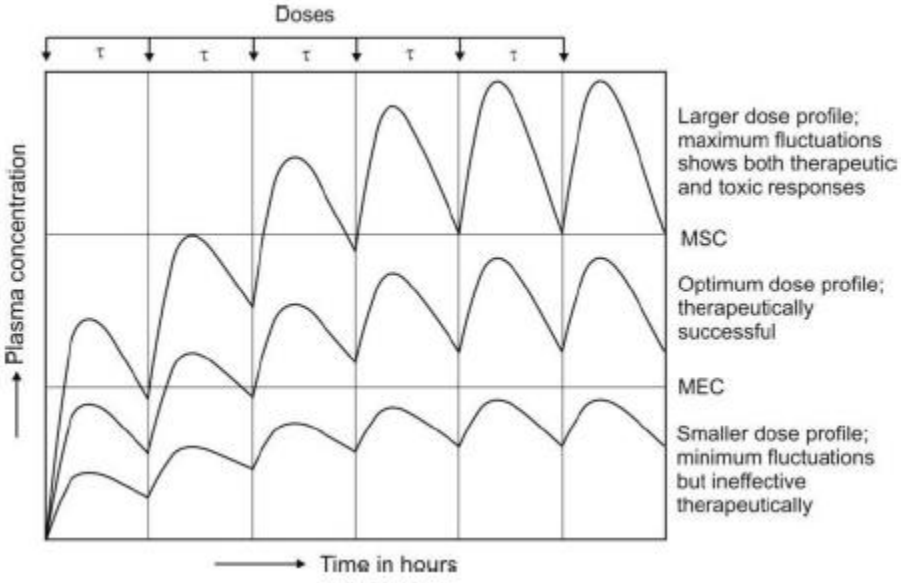


Fig. Schematic representation of influence of dose size on plasma concentration-time profile after oral administration of a drug at fixed intervals of time.

Dosing Frequency

The dose interval is calculated on the basis of half-life of the drug. If the interval is increased and the dose is unchanged, Cmax, Cmin and Cav decrease but the ratio Cmax/Cmin increases. Opposite is observed when dosing interval is reduced or dosing frequency increased. It also results in greater drug accumulation in the body and toxicity.

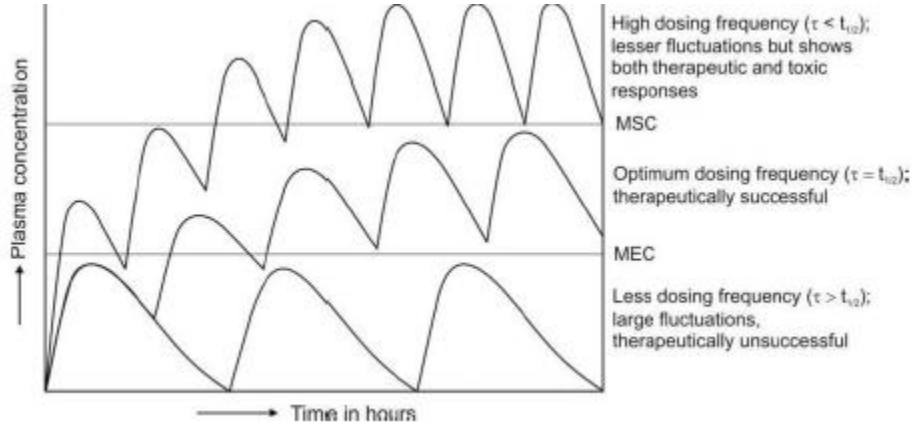


Fig. *Schematic representation of the influence of dosing frequency on plasma concentration-time profile obtained after oral administration of fixed doses of a drug.*

Generally speaking, every subsequent dose should be administered at an interval equal to half-life of the drug. A rule of thumb is that –

(A)For drugs with wide therapeutic index such as penicillin, larger doses may be administered at relatively longer intervals (more than the half-life of drug) without any toxicity problem

(B)For drugs with narrow therapeutic index such as digoxin, small doses at frequent intervals (usually less than the half-life of the drug) is better to obtain a profile with least fluctuations which is similar to that observed with constant rate infusion or controlled-release system.

Principle of superposition:

For calculation of multiple-dose regimens, it is necessary to decide whether successive doses of drug will have any effect on the previous dose. The principle of *superposition* assumes that early doses of drug do not affect the pharmacokinetics of subsequent doses. Therefore, the blood levels after the second, third, or *n*th dose will overlay or superimpose the blood level attained after the (*n*-1)th dose.

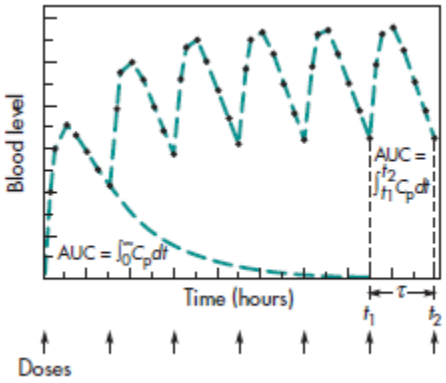


Fig. Simulated data showing blood levels after administration of multiple doses and accumulation of blood levels when equal doses are given at equal time intervals.

The principle of *superposition* allows the pharmacokineticist to project the plasma drug concentration– time curve of a drug after multiple consecutive doses based on the plasma drug concentration–time curve obtained after a single dose. The basic assumptions are

(1) The drug is eliminated by first-order kinetics and

(2) That the pharmacokinetics of the drug after a single dose (first dose) are not altered after taking multiple doses.

Drug Accumulation During Multiple Dosing

If the drug is administered at a fixed dose and a fixed dosage interval, as is the case with many multiple-dose regimens, the amount of drug in the body will increase and then plateau to a mean plasma level higher than the peak *C*p obtained from the initial dose. When the second dose is given after a time interval shorter than the time required to "completely" eliminate the previous dose, *drug accumulation* will occur in the body. In other words, the plasma concentrations following the second dose will be higher than corresponding plasma concentrations immediately following the first dose. However, if the second dose is given after a time interval longer than the time required to eliminate the previous dose, drug will not accumulate.

The extent to which a drug accumulates in the body during multiple dosing is independent of dose size, and is a function of –

(A)Dosing interval, and

(B)Elimination half-life.

The extent to which a drug will accumulate with any dosing interval in a patient can be derived from information obtained with a single dose and is given by **accumulation index Rac** as:

$$R_{ac} = \frac{1}{1 - e^{-K_E \tau}}$$

Steady-State during Multiple Dosing

The time required to reach steady-state depends primarily upon the half-life of the drug. Provided

Ka >> K_E, the plateau is reached in approximately 5 half-lives. This is called as **plateau principle**. It also means that the rate at which the multiple dose steady-state is reached is determined only by K_E. The time taken to reach steady-state is independent of dose size, dosing interval and number of doses.

Maximum and Minimum Concentration During Multiple Dosing

If n is the number of doses administered, the Cmax and Cmin obtained on multiple dosing after the nth dose is given as:

$$C_{n,max} = C_0\left[\frac{1-e^{-nK_E\tau}}{1-e^{-K_E\tau}}\right]$$

$$C_{n,min} = C_0\left[\frac{1-e^{-nK_E\tau}}{1-e^{-K_E\tau}}\right]e^{-K_E\tau} = C_{n,max}\,e^{-K_E\tau}$$

The maximum and minimum concentration of drug in plasma at steady-state are found by following equations:

$$C_{ss,max} = \frac{C_0}{1-e^{-K_E\tau}}$$

$$C_{ss,min} = \frac{C_0 e^{-K_E\tau}}{1-e^{-K_E\tau}} = C_{ss,max}\,e^{-K_E\tau}$$

Where Co = concentration that would be attained from instantaneous absorption and distribution (obtained by extrapolation of elimination curve to time zero).

Fluctuation is defined as the ratio Cmax/Cmin. Greater the ratio, greater the fluctuation. Like accumulation, it depends upon dosing frequency and half-life of the drug. It also depends upon the rate of absorption. The greatest fluctuation is observed when the drug is given as i.v. bolus. Fluctuations are small when the drug is given extravascular because of continuous absorption.

Loading and Maintenance Doses:

A drug does not show therapeutic activity unless it reaches the desired steady-state. It takes about 5 half-lives to attain it and therefore the time taken will be too long if the drug has a long half-life. Plateau can be reached immediately by administering a dose that gives the desired steady-state instantaneously before the commencement of maintenance doses Xo. Such an initial or first dose intended to be therapeutic is called as **priming dose** or **loading dose** Xo,L. A simple equation for calculating loading dose is:

$$X_{0,L} = \frac{C_{ss,av}V_d}{F}$$

The characteristics that define an individual medication's PK can help determine the *loading dose*. While a patient is taking a specific drug to achieve the therapeutic benefit, the drug must reach a certain steady-state concentration. Typically, for any medication, five to seven half-lives

are required for this to be achieved. Reaching this concentration is typically not an issue for drugs with short half-lives; however, other medications or conditions may require more rapid therapeutic onset. For instances where a therapeutic steady-state concentration is needed immediately, loading doses can be utilized to more rapidly achieve this therapeutic concentration.

A loading dose is typically calculated through the following formula:

LD= (Volume of Distribution X Concentration Steady State)/Bioavailability

For this formula, concentration steady-state is defined as the therapeutic concentration of medication in the body, while bioavailability is the fraction of an administered dose that reaches systemic circulation. The volume of distribution is typically calculated as follows:

Vd = Dose of medication given/Concentration in the Plasma

The calculation of loading dose should not be confused with maintenance dose, which is the dose required to maintain steady-state concentration. This calculation is:

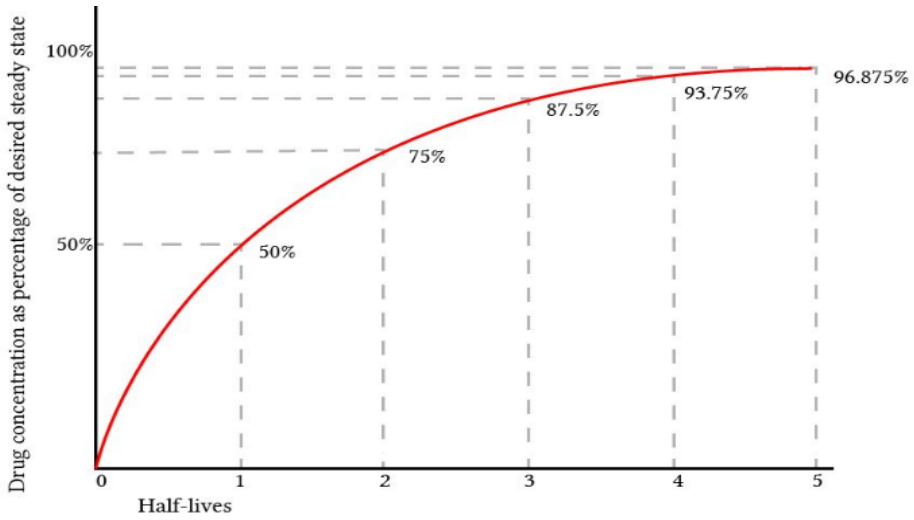
MD = (Concentration Steady State X Clearance X Dosing Interval)/Bioavailability

Clearance can be determined using the known half-life of a medication, which is the length of time required for a dose to reach 50% of its initial plasma concentration. Clearance can ultimately be determined through:

CL = (0.693 X Vd)/ Half-life

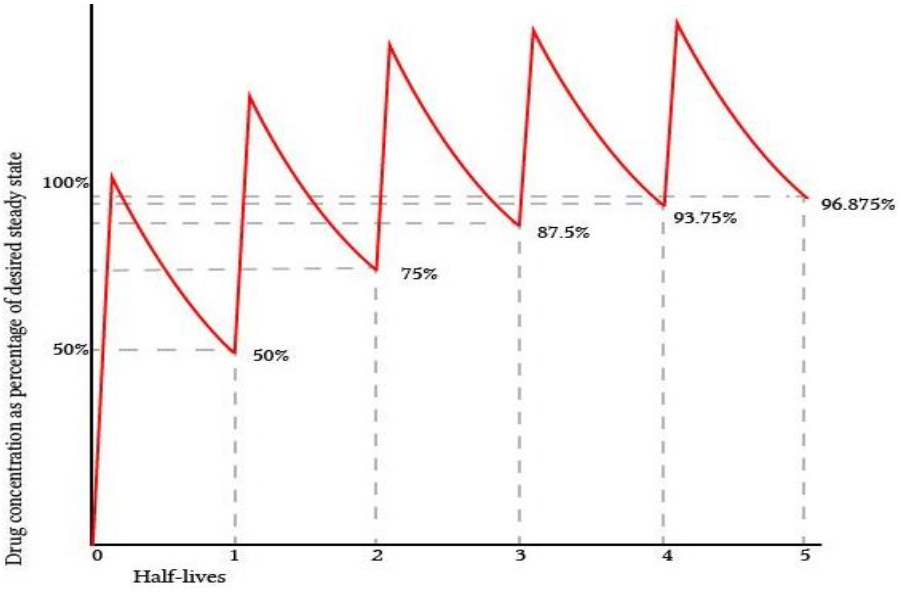
Maintenance dose in continuous infusion

This is pretty much the simplest model of maintenance dosing. When it is given by continuous infusion the drug accumulates gradually. The steady state concentration is determined only by two major factors, the dose rate and the clearance rate. Steady state is achieved when clearance rate and dose rate are equal, and the time taken to achieve this steady state in continuous infusion is 3-5 half lives.



Maintenance dose in regular dosing

In regular doses, drug concentration achieves a steady state in steps, but the end result is the same - the plasma drug concentration reaches a point at which the dose rate and the clearance rate are equal after about five half-lives.



Maintenance of Drug within the Therapeutic Range

The ease or difficulty in maintaining drug concentration within the therapeutic window depends upon —

1. The therapeutic index of the drug
2. The half-life of the drug
3. Convenience of dosing.

It is extremely difficult to maintain such a level for a drug with short half-life (less than 3 hours) and narrow therapeutic index e.g. heparin, since the dosing frequency has to be essentially less than t½. However, drugs such as penicillin (t½ = 0.9 hours) with high therapeutic index may be given less frequently (every 4 to 6 hours) but the maintenance dose has to be larger so that the plasma concentration persists above the minimum inhibitory level. A drug with intermediate t½ (3 to 8 hours) may be given at intervals t½ if therapeutic index is low and those with high indices can be given at intervals between 1 to 3 half-lives. Drugs with half-lives greater than 8 hours are more convenient to dose. Such drugs are usually administered once every half-life. Steady-state in such cases can be attained rapidly by administering a loading dose. For drugs with very long half-lives (above 24 hours) e.g. amlodipine, once daily dose is very convenient.

IMPORTANT QUESTIONS

1 .Define loading and maintenance dose. Give the formula for the same.

2. Give the equations to calculate the steady state maximum, minimum and average drug concentrations.

3. Give the plasma concentration time – plot for multiple dosing of an IV bolus.

4. What do you understand by accumulation index and give the formula.

5. Explain principle of plateau or steady state.

6. What are the factors which influence dosage regimen?

7. Name two parameters used in adjusting dosage regimen.

8. Define dosing frequency.

9. Give relation between loading dose and maintenance dose.

10. Give the plasma concentration time – plot for multiple oral administration.