Biopharmaceutics

Two Compartment Open IV bolus Model

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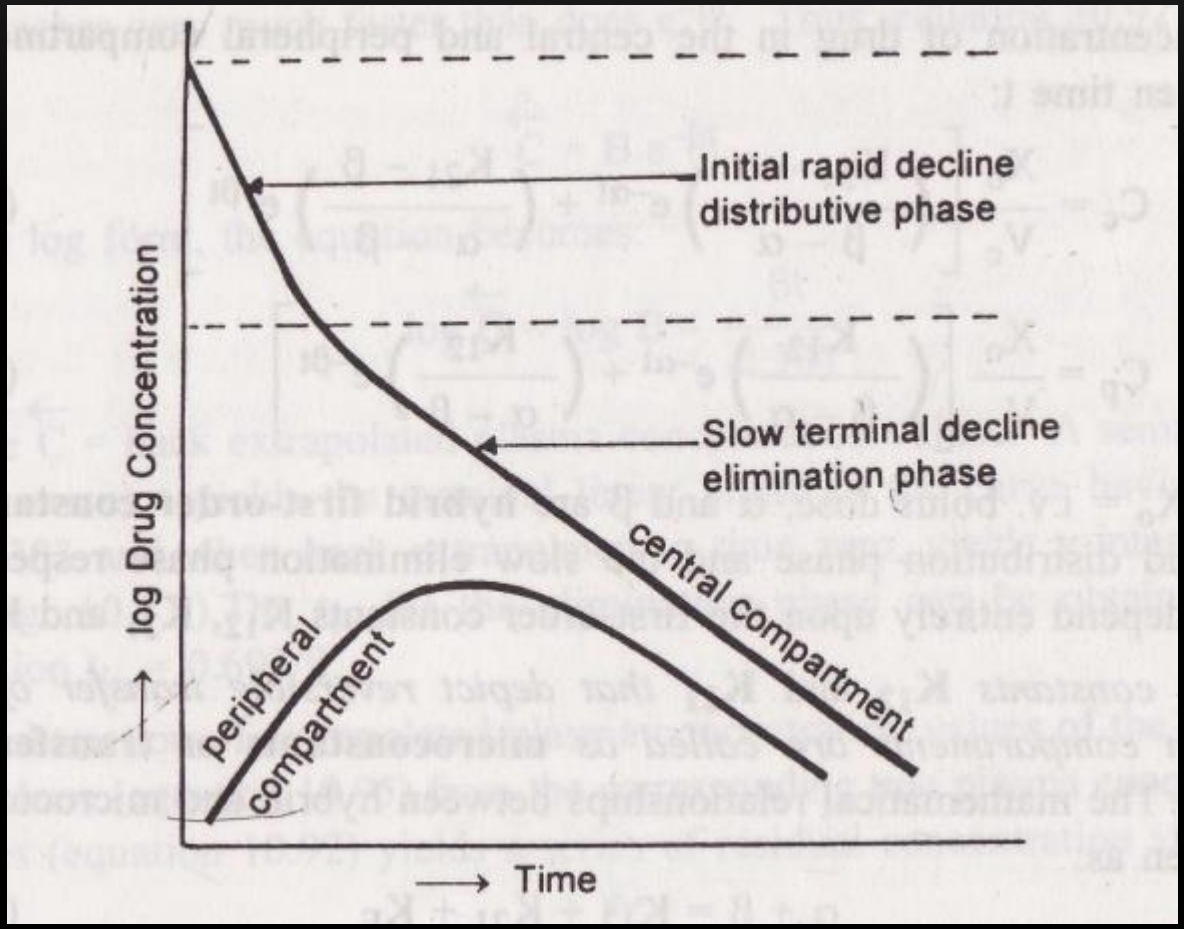
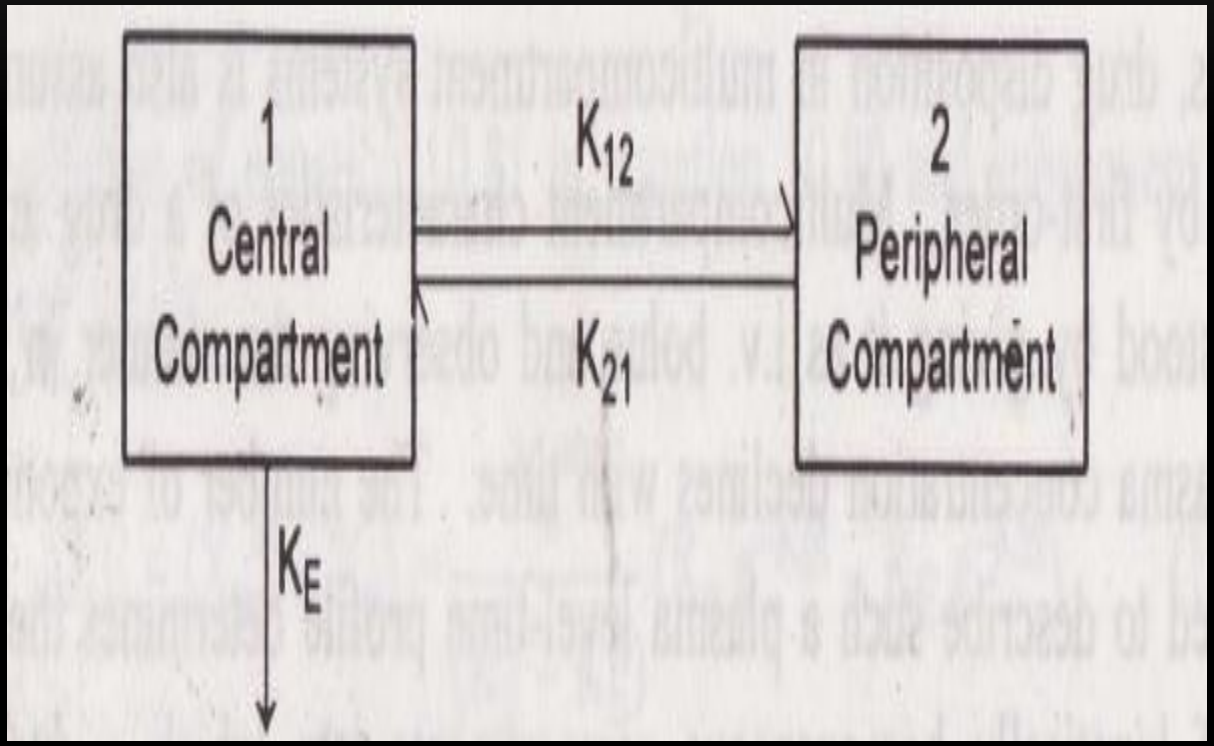
The commonest of multicompartment models is two compartment model. In such a model, the body tissues are broadly classified into 2 categories:

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.

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


Initial rapid decline
distributive phase
Slow terminal decline
elimination phase
central compartment
peripheral
compartment
log Drug Concentration
Time


1
Central
Compartment
K_{12}
K_{21}
2
Peripheral
Compartment
K_E

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:

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

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

where 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:

$$\frac{dC_p}{dt} = K_{12}\, C_c - K_{21}\, C_p$$

$$= \frac{K_{12}\, X_c}{V_c} - \frac{K_{21}\, X_p}{V_p}$$

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 $\mathbf{K_{12}}$ and $\mathbf{K_{21}}$ *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:

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

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

$$C_0 = A + B$$

$$C_c = A\, e^{-\alpha t} + B\, e^{-\beta t}$$

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

where A and B are also hybrid constants for the two exponents

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 $t_{1/2}$ should therefore be calculated from β.

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

$$AUC = \frac{A}{\alpha} + \frac{B}{\beta}$$

The apparent volume of central compartment V_c is given as:

$$V_c = \frac{X_o}{C_o}$$

Apparent volume of peripheral compartment can be obtained from equation:

$$V_p = \frac{V_c\, K_{12}}{K_{21}}$$

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

$$V_{d,ss} = V_c + V_p$$

Total systemic clearance is given as: $Cl_T = \beta V_d$

Renal clearance is given as: $Cl_R = K_e V_c$

Following a 650 mg i.v. bolus dose of a drug to a 65 Kg subject, the plasma drug concentration was found to decline biexponentially. The equation that best described the drug kinetics was:

$$C = 67\ e^{-14t} + 33\ e^{-3t}$$

where t is in hours and C is in mcg/ml. Calculate the following:

The volume of the central compartment.

Answer : $V_c = 6.5$ liters.

The volume of the peripheral compartment.

Answer : $V_p = 3.95$ liters.

The apparent V_d at steady-state.

Answer : $V_{d,ss} = 10.45$ liters.

Volume of distribution by area.

Answer : $V_{d,area} = 13.7$ liters.

The microconstants K_{12} and K_{21}

Answer : $K_{12} = 4.035$/hour and $K_{21} = 6.63$/hour.

The elimination rate constant for the disposal of drug from the central compartment.

Answer : $K_E = 6.33$/hour.

The overall elimination half-life

Answer : $t_{½} = 0.231$ hours.

The total systemic clearance of the drug (use $V_{d,area}$ for calculation).

Answer : $Cl_T = 686.2$ ml/min.

The plasma level of the drug after 30 minutes of i.v. dose.

Answer : 7.42 mcg/ml.

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Bioavailability and Bioequivalence

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A multisource drug product is a drug product that contains the same active drug substance in the same dosage form and is marketed by more than one pharmaceutical manufacturer.

Single-source drug products (brand) are drug products for which the patent has not yet expired so that only one manufacturer can make it.

After the patent for the brand-name drug expires, a pharmaceutical firm may manufacture a generic drug product that can be substituted for the branded drug product. Since the formulation and method of manufacture of the drug product can affect the bioavailability and stability of the drug, the generic drug manufacturer must demonstrate that the generic drug product is bioequivalent and therapeutically equivalent to the brand drug product.

Drug product selection and generic drug product substitution are major responsibilities for physicians, and pharmacists. To facilitate such decisions, the FDA publishes annually, Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the Orange Book.

The Orange Book identifies drug products approved on the basis of safety and effectiveness by the FDA and contains therapeutic equivalence evaluations for approved multisource prescription drug products.

Bioavailability means the rate and extent to which the active ingredient is absorbed from a drug product and becomes available at the site of action.

Bioequivalent drug products. This term describes pharmaceutical equivalent or pharmaceutical alternative products that display comparable bioavailability when studied under similar experimental conditions.

For systemically absorbed drugs, the test (generic) and reference drug (brand) shall be considered bioequivalent if: the rate and extent of absorption of the test drug do not show a significant difference from the rate and extent of absorption of the reference drug when administered at the same dose of the therapeutic ingredient under similar experimental conditions.

Two drug formulations are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations.

Two drug formulations are therapeutically equivalent if they are pharmaceutically equivalent (that is, they have the same dosage form, contain the same active ingredient at the same strength, and use the same route of administration) with similar clinical and safety profiles. Thus, therapeutic equivalence requires that drug products are bioequivalent and pharmaceutically equivalent.

RELATIVE AND ABSOLUTE AVAILABILITY

The area under the drug concentration time curve (AUC) is used as a measure of the total amount of unaltered drug that reaches the systemic circulation.

The AUC is dependent on the total quantity of available drug, FD0, the elimination rate constant, and the apparent volume of distribution.

F is the fraction of the dose absorbed. After IV administration, F is equal to unity, because the entire dose enters the systemic circulation. Therefore, the drug is considered to be completely available after IV administration. After oral administration of a drug, F may vary from a value of 0 (no drug absorption) to 1 (complete drug absorption).

$$[\mathrm{AUC}]_0^\infty = \int_0^\infty C_\mathrm{p}\,dt \qquad (15.6)$$

$$[\mathrm{AUC}]_0^\infty = \frac{FD_0}{\mathrm{clearance}} = \frac{FD_0}{kV_\mathrm{D}} \qquad (15.7)$$

Relative Availability

Relative (apparent) availability is the availability of the drug from a drug product as compared to a recognized standard.

$$\text{Relative availability} = \frac{[\text{AUC}]_A / \text{dose A}}{[\text{AUC}]_B / \text{dose B}} \qquad (15.2)$$

Relative availability may be expressed as a fraction or as a percent by multiplying F x100.

Absolute Availability

The absolute availability of drug is the systemic availability of a drug after extravascular administration (eg, oral, rectal, transdermal, subcutaneous) compared to IV dosing. The absolute availability of a drug is generally measured by comparing the respective AUCs after extravascular and IV administration.

$$\text{Absolute availability} = F = \frac{[\text{AUC}]_{\text{PO}}/\text{dose}_{\text{PO}}}{[\text{AUC}]_{\text{IV}}/\text{dose}_{\text{IV}}} \qquad (15.4)$$

Absolute availability may be expressed as a fraction or as a percent by multiplying F x100.

Table 15.1 Methods for Assessing Bioavailability and Bioequivalence

Plasma drug concentration
Time for peak plasma (blood) concentration (t_{max})
Peak plasma drug concentration (C_{max})
Area under the plasma drug concentrationâ€"time curve (AUC)
Urinary drug excretion
Cumulative amount of drug excreted in the urine (D_u)
Rate of drug excretion in the urine (dD_u/dt)
Time for maximum urinary excretion (t)
Acute pharmacodynamic effect
Maximum pharmacodynamic effect (E_{max})
Time for maximum pharmacodynamic effect
Area under the pharmacodynamic effectâ€"time curve
Onset time for pharmacodynamic effect
Clinical observations
Well-controlled clinical trials

Drug dissolution

METHODS FOR ENHANCEMENT OF BIOAVAILABILITY

As far as the definition of bioavailability is concerned, a drug with poor bioavailability is the one with -

1. Poor aqueous solubility and/or slow dissolution rate in the biologic fluids.
2. Poor stability of the dissolved drug at the physiologic pH.
3. Inadequate partition coefficient and thus poor permeation through the biomembrane.
4. Extensive presystemic metabolism.

The three major approaches in overcoming the bioavailability problems due to such causes are:

1. **The Pharmaceutic Approach** which involves modification of formulation, manufacturing process or the physicochemical properties of the drug without changing the chemical structure.
2. **The Pharmacokinetic Approach** in which the pharmacokinetics of the drug is altered by modifying its chemical structure.
3. **The Biologic Approach** whereby the route of drug administration may be changed such as changing from oral to parenteral route.

The attempts, whether optimizing the formulation, manufacturing process or physicochemical properties of the drug, are mainly aimed at enhancement of dissolution rate as it is the major rate-limiting step in the absorption of most drugs. There are several ways in which the dissolution rate of a drug can be enhanced. Some of the widely used methods, most of which are aimed at increasing the effective surface area of the drugs,