## MULTICOMPARTMENT MODELS
### (Delayed Distribution Models)

The one-compartment model adequately describes pharmacokinetics of many drugs. Instantaneous distribution equilibrium is assumed in such cases and decline in the amount of drug in the body with time is expressed by an equation with a monoexponential term (i.e. elimination). However, instantaneous distribution is not truly possible for an even larger number of drugs[6] and drug disposition is not monoexponential but bi- or multi-exponential. This is because the body is composed of a heterogeneous group of tissues each with different degree of blood flow and affinity for drug and therefore different rates of equilibration. *Ideally, a true pharmacokinetic model should be the one with a rate constant for each tissue undergoing equilibrium*, which is difficult mathematically. The best approach is therefore to pool together tissues on the basis of similarity in their distribution characteristics. As for one-compartment models, drug disposition in multicompartment systems is also assumed to occur by first-order. Multicompartment characteristics of a drug are best understood by giving it as i.v. bolus and observing the manner in which the plasma concentration declines with time. The number of exponentials required to describe such a plasma level-time profile determines the number of kinetically homogeneous compartments into which a drug will distribute.

## Zero-Order Half-Life

**Half-life** ($t_{1/2}$) or **half-time** *is defined as the time period required for the concentration of drug to decrease by one-half.* When $t = t_{1/2}$, $C = C_0/2$ and the equation 9.7 becomes:

$$\frac{C_0}{2} = C_0 - K_0 t_{1/2} \tag{9.8}$$

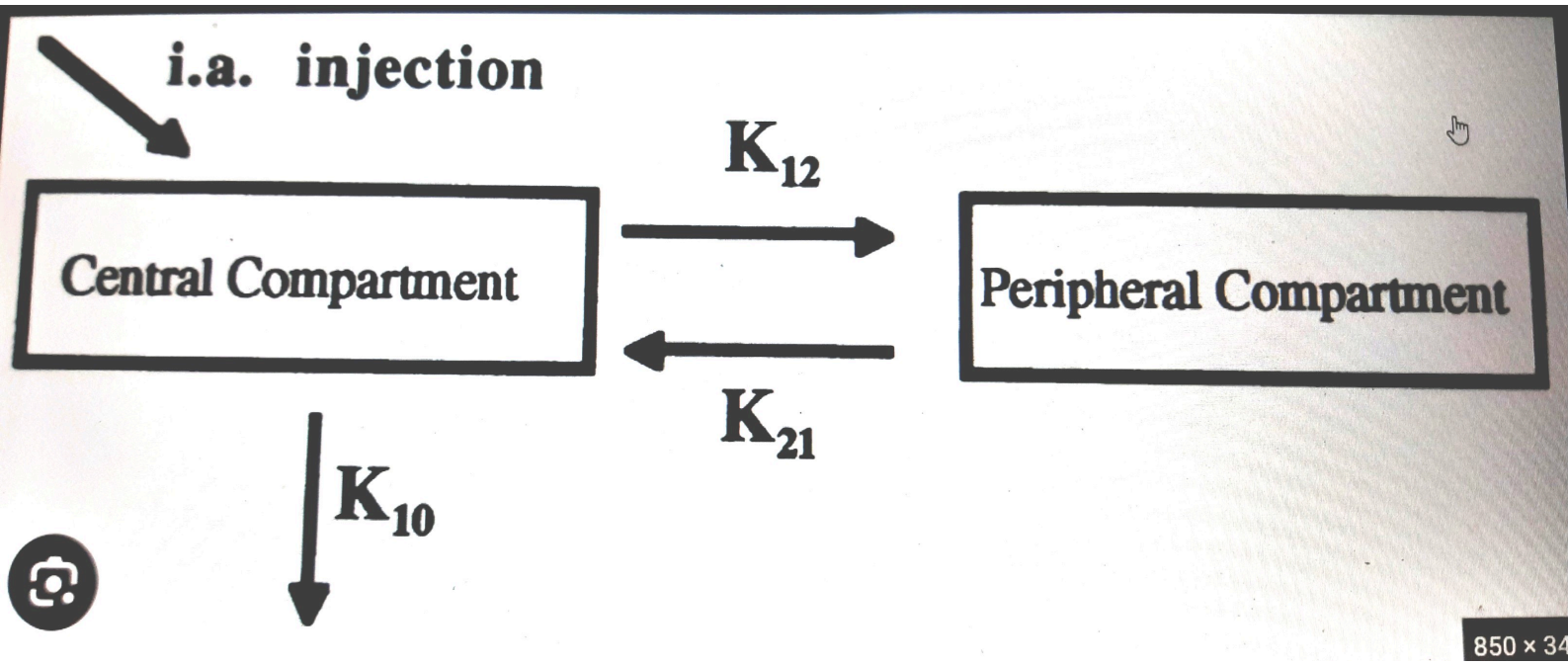
Solving 9.8, we get:

$$t_{1/2} = \frac{C_0}{2\,K_0} = \frac{0.5\,C_0}{K_0} \tag{9.9}$$

Equation 9.9 shows that the $t_{1/2}$ of a zero-order process is not constant but proportional to the initial concentration of drug $C_0$ and inversely proportional to the zero-order rate constant $K_0$. Since the zero-order $t_{1/2}$ changes with the decline in drug concentration, it is of little practical importance. Zero-order equations do not require logarithmic transformations.

Examples of zero-order processes are:

1. Metabolism/protein-drug binding/enzyme or carrier-mediated transport under saturated conditions. The rate of metabolism, binding or transport of drug remains constant as long as its concentration is in excess of saturating concentration.
2. Administration of a drug as a constant rate i.v. infusion.
3. Controlled drug delivery such as that from i.m. implants or osmotic pumps.


i.a. injection
K12
Central Compartment
Peripheral Compartment
K21
K10

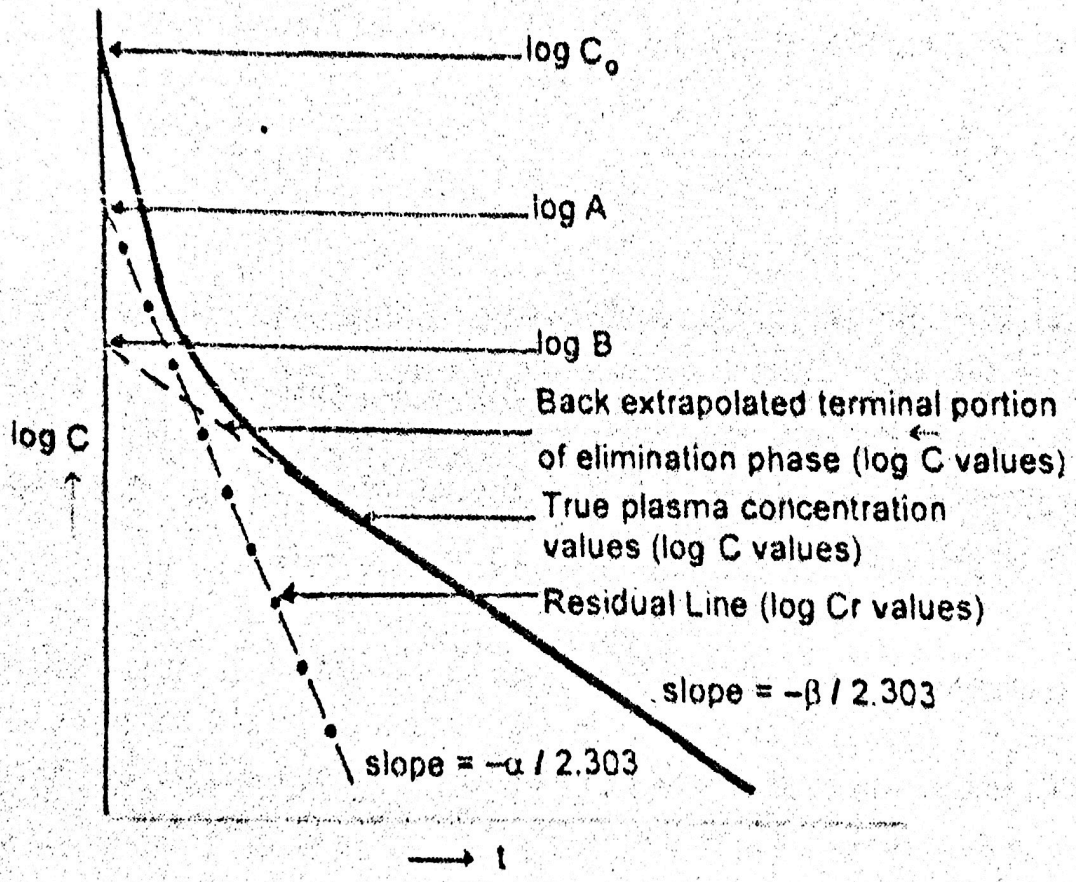



**Fig. 10.13** Resolution of biexponential plasma concentration-time curve by the method of residuals for a drug that follows two-compartment kinetics on i.v. bolus administration.

**Assessment of Pharmacokinetic Parameters :** All the parameters of equation 10.92 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.

$$C_0 = A + B \tag{10.99}$$

$$K_E = \frac{\alpha \beta C_0}{A\beta + B\alpha} \tag{10.100}$$

$$\frac{A B (\beta - \alpha)^2}{}$$

The absolute bioavailability is the dose-corrected area under curve (AUC) non-intravenous divided by AUC intravenous.

For example, the formula for calculating *F* for a drug administered by the oral route (po) is given below.

$$F_{abs} = 100 \cdot \frac{AUC_{po} \cdot D_{iv}}{AUC_{iv} \cdot D_{po}}$$

# RENAL EXCRETION OF DRUGS

Almost all drugs and their metabolites are excreted by the kidneys to some extent or the other. Some drugs such as gentamicin are exclusively eliminated by renal route only. Agents that are water-soluble, nonvolatile, small in molecular size (less than 500 daltons) and which are metabolized slowly, are excreted in the urine.

The basic functional unit of the kidney involved in excretion is the **nephron**. Each kidney comprises of one million nephrons. Each nephron is made up of the glomerulus, the proximal tubule, the loop of Henle, the distal tubule and the collecting tubule.

The **principal processes** that determine the urinary excretion of a drug are:

1. Glomerular filtration,
2. Active tubular secretion, and
3. Active or passive tubular reabsorption.

These processes are depicted in Fig.7.1.

Glomerular filtration and active tubular secretion tend to increase the concentration of drugs in lumen and hence facilitate excretion whereas tubular reabsorption decreases it and prevents the movement of drug out of the body. Thus, the rate of excretion can be given by equation:

## NON-RENAL ROUTES OF DRUG EXCRETION

*Drugs and their metabolites may also be excreted by routes other than the renal route, called as the* **extrarenal** or **nonrenal routes of drug excretion**. The various such excretion processes are:

1. Biliary excretion
2. Pulmonary excretion
3. Salivary excretion
4. Mammary excretion
5. Skin/dermal excretion
6. Gastrointestinal excretion
7. Genital excretion

## Zero-order Kinetics (Constant Rate Processes)

If n = 0, equation 9.4 becomes:

$$\frac{dC}{dt} = -K_0 C^0 = -K_0 \qquad (9.5)$$

where $K_0$ = zero-order rate constant (in mg/min)

From equation 9.5, the **zero-order process** *can be defined as the one whose rate is independent of the concentration of drug undergoing reaction i.e. the rate of reaction cannot be increased further by increasing the concentration of reactants.*