TOPIC: Multicompartment models

Disclaimer

All the content material provided here is only for teaching purpose

CONTENT

- Pharmacokinetic parameters
- Pharmacodynamic parameters
- Zero, first order & mixed order kinetic
- Rates and orders of kinetics
- Plasma drug conc. Time profiles
- Compartmental models – physiological model
- Applications of pharmacokinetics
- Non compartment model

PHARMACOKINETIC PARAMETERS

Three important parameters useful in assessing the bioavailability of a drug from its formulation are:

1. Peak plasma concentration (c_{max})

   the point at which, **maximum concentration** of drug in plasma.

Units : µg/ml

- Peak conc. Related to the intensity of pharmacological response, it should be above MEC but less than MSC.
- The peak level depends on administered dose and rate of absorption and elimination.

2. Time of peak concentration (t_{max})

the time for the drug to reach peak concentration in plasma (after extra vascular administration).

Units : hrs

- Useful in estimating onset of action and rate of absorption.
- Important in assessing the efficacy of single dose drugs used to treat acute conditions (pain, insomnia).

3. Area under curve (AUC)

It represents *the total integrated area under the plasma level-time profile and expresses the* ***total amount of the drug*** *that comes into* ***systemic circulation*** *after its administration.*

Units *: µg/ml x hrs*

- Represents extent of absorption – evaluating the bioavailability of drug from its dosage form.
- Important for drugs administered repetitively for treatment of chronic conditions (asthma or epilepsy).

PHARMACODYNAMIC PARAMETERS

1. Minimum effective concentration (MEC)

Minimum concentration of drug in plasma/receptor site required to produce therapeutic effect.

- Concentration below MEC – **sub therapeutic level**
- Antibiotics - MEC

2. Maximum safe concentration (MSC)

Concentration in plasma above which adverse or unwanted effects are precipitated.

- Concentration above MSC – **toxic level**

3. Onset time

Time required to start producing pharmacological response.

Time for plasma concentration to reach mec after administrating drug

4. Onset of action

The beginning of pharmacologic response.

It occurs when plasma drug concentration just exceeds the required mec.

5. Duration of action

The time period for which the plasma concentration of drug remains above MEC level.

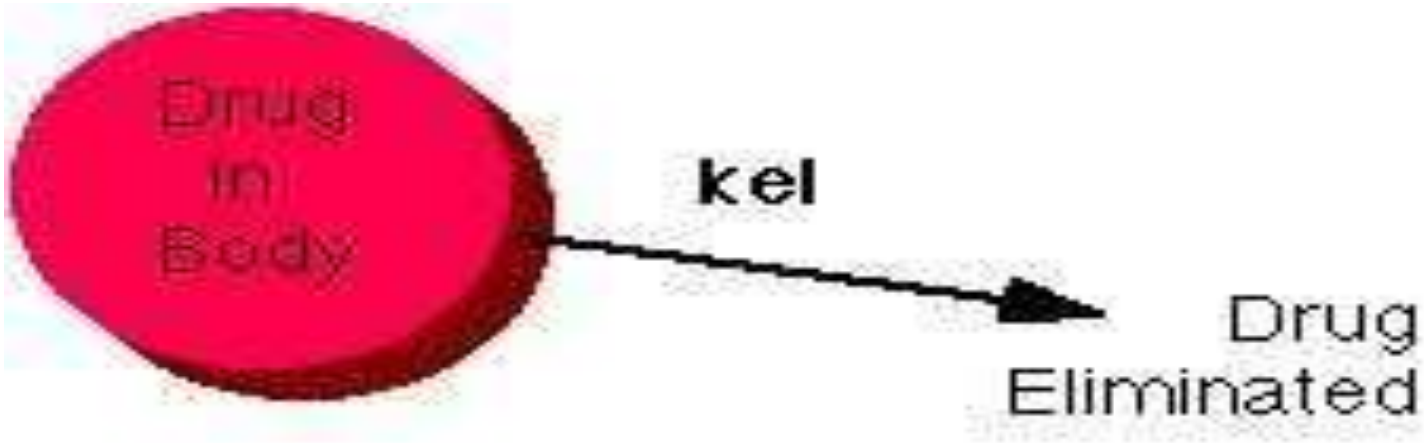
6. Intensity of action

It is the minimum pharmacologic response produced by the peak plasma conc. Of drug.

7. Therapeutic range the drug conc. Between MEC and MSC

COMPARTMENTAL MODELS

- A compartment is not a real physiological or anatomic region but an imaginary or hypothetical one consisting of tissue/ group of tissues with similar blood flow & affinity.
- Our body is considered as composed of several compartments connected reversibly with each other.



ADVANTAGES

- Gives visual representation of various rate processes involved in drug disposition.
- Possible to derive equations describing drug concentration changes in each compartment.
- One can estimate the amount of drug in any compartment of the system after drug is introduced into a given compartment.

DISADVANTAGES

- Drug given by IV route may behave according to single compartment model but the same drug given by oral route may show 2 compartment behaviour.
- The type of compartment behaviour i.E. Type of compartment model may change with the route of administration.

MULTI-COMPARTMENT MODELS

- Ideally a true pharmacokinetic model should be the one with a rate constant for each tissue undergoing equilibrium.
- Therefore best approach is to pool together tissues on the basis of similarity in their distribution characteristics.
- The drug disposition occurs by first order.
- Multi-compartment characteristics are best described by administration as i.v bolus and observing the manner in which the plasma concentration declines with time.

  The no. Of exponentials required to describe such a plasma level-time profile determines the no. Of kinetically homogeneous compartments into which a drug will distribute.

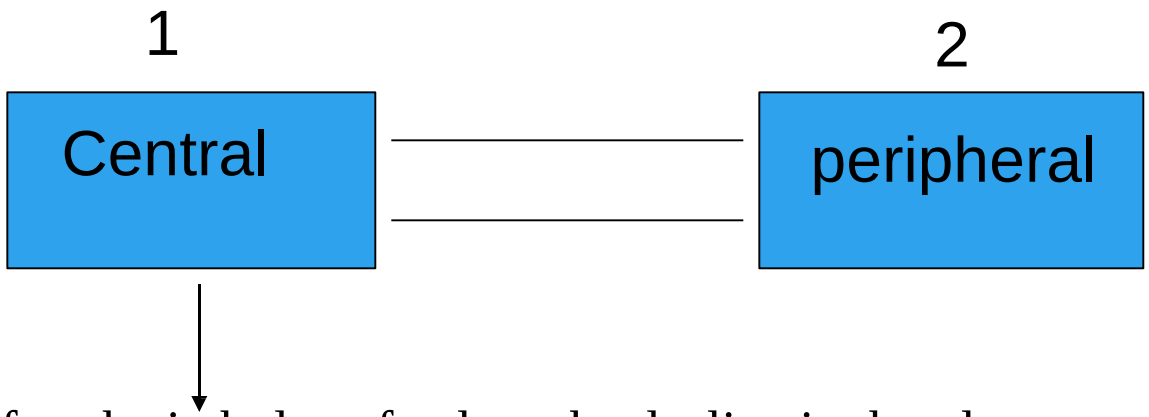
  The simplest and commonest is the two compartment model which classifies the body tissues in two categories :

1. Central compartment or compartment 1
2. Peripheral or tissue compartment or compartment 2.

TWO COMPARTMENT OPEN MODEL-IV BOLUS ADMINISTRATION:

Elimination from central compartment

Fig:



- After the iv bolus of a drug the decline in the plasma conc. Is bi-exponential.
- Two disposition processes- distribution and elimination.
- These two processes are only evident when a semi log plot of C vs. T is made.
- Initially, the conc. Of drug in the central compartment declines rapidly, due to the distribution of drug from the central compartment to the peripheral compartment. This is called distributive phase.

Extending the relationship $X = v_d C$

$$\frac{Dc_c}{Dt} = \frac{K_{21}\, x_p}{v_p} - \frac{K_{12}\, x_c}{v_c} - \frac{K_E\, x_c}{v_c}$$

X= Amt. Of drug in the body at any time t remaining to be eliminated

C=drug conc in plasma

V_d =proportionality const app. Volume of distribution

X_c and x_p=amt of drug in C1 and C2

V_c and v_p=apparent volumes of C1 and C2

$$= \frac{K_{12}\, x_c}{V_c} - \frac{K_{21}\, x_p}{v_p}$$

On integration equation gives conc of drug in central and peripheral compartments at any given time t

$$Cp = \frac{xo}{Vc}\left[\frac{\left(K_{21} - a\right)e^{-at}}{b - a} + \frac{\left(K_{12} - b\right)e^{-bt}}{a - b}\right]$$

Xo = iv bolus dose

- The relation between hybrid and microconstants is given as :

$a + b = K12 + K21 + KE$

$A\ b = K21\ KE$

$Cc = a\ e^{-at} + be^{-bt}$

Cc=distribution exponent + elimination exponent

A and B are hybrid constants for two exponents and can be resolved by graph by method of residuals.

$$A = \frac{X_0}{V_C} \quad \frac{[K_{21} - A]}{B - A} = \frac{C_O\,[K_{21} - A]}{B - A}$$

$$B = \frac{X_0}{V_C} \quad \frac{[K_{21} - B]}{A - B} = \frac{C_O\,[K_{21} - B]}{A - B}$$

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.

$$C = a\,e^{-at} + b\,e^{-bt}$$

From graph the initial decline due to distribution is more rapid than the terminal decline due to elimination i.E. The rate constant a >> b and hence the term e^{-at} approaches zero much faster than e^{-bt}

$$C = B\,e^{-bt}$$

$$\text{Log } C = \log B - \overleftarrow{bt/2.303}$$ C = back extrapolated pl. Conc.

- A semilog plot of C vs t yields the terminal linear phase of the curve having slope –b/2.303 and when back extrapolated to time zero, yields y-intercept log B. The $t^{1/2}$ for the elimination phase can be obtained from equation
- $t^{1/2} = 0.693/b$.
- Residual conc values can be found as-

$$C_r = C - \overleftarrow{C} = ae^{-at}$$

$$\text{Log cr} = \frac{\log A - at}{2.303}$$

A semilog plot cr vs t gives a straight line.

$$K_e = \frac{a\ b\ c}{A\ b + B\ a}$$

$$K_{12} = \frac{a\ b\ (b - a)^2}{C_0\ (A\ b + B\ a)}$$

$$K_{21} = \frac{A\ b + B\ a}{C_0}$$

- For two compartment model, K_E is the rate constant for elimination of drug from the central compartment and b is the rate constant for elimination from the entire body. Overall elimination t1/2 can be calculated from b.

$$\text{Area under (auc)} = \frac{a}{\text{The curve}} + \frac{b}{}$$

$$\text{App. Volume of central compartment} = \frac{X_0}{C_0} = \frac{X_0}{K_E\ (AUC)}$$

App. Volume of = $V_P = \frac{V_C K_{12}}{}$

Peripheral compartment K_{21}

Apparent volume of distribution at steady state or equilibrium

$$V_{d,ss} = V_C + V_P$$

$$V_{d,area} = \frac{X_0}{B\,AUC}$$

Total systemic clearence= $cl_t = b\ v_d$

Renal clearence= $cl_r = \frac{dx_u}{dt} = \frac{K_E V_C}{}$

The rate of excretion of unchanged drug in urine can be represented by :

$$\frac{dx_u}{dt} = K_E A e^{-at} + K_E B e^{-bt}$$

The above equation can be resolved into individual exponents by the **method of residuals**.

TWO – COMPARTMENT OPEN MODEL- I.V. INFUSION

The plasma or central compartment conc of a drug when administered as constant rate (0 order) i.V. Infusion is given as:

$$C = \frac{R0}{VC\,KE}\left[1+\left(\frac{KE - b}{b - a}\right)e^{-at} + \left(\frac{KE - a}{a - b}\right)e^{-bt}\right]$$

At steady state (i.E.At time infinity) the second and the third term in the bracket becomes zero and the equation reduces to:

$$Css = \frac{R0}{Vc\,ke}$$

Now VC KE =

vd b Css = $\frac{r0}{}$ =

$\frac{r0}{}$

Vdb clt

The loading dose X0,L = css vc = $\frac{R0}{Ke}$

TWO-COMPARTMENT OPEN MODEL- EXTRAVASCULAR ADMINISTRATION

- First - order absorption :
- For a drug that enters the body by a first-order absorption process and distributed according to two compartment model, the rate of change in drug conc in the central compartment is described by three exponents :
- An absorption exponent, and the two usual exponents that describe drug disposition.

The plasma conc at any time t is

$$C = n\, e^{-kat} + l\, e^{-at} + m\, e^{-bt}$$

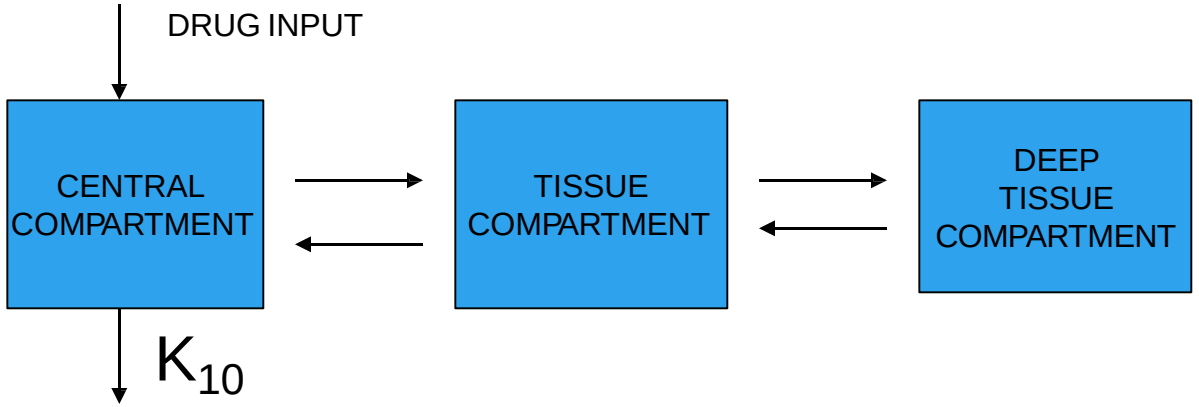
C = absorption + distribution + elimination

Exponent exponent exponent

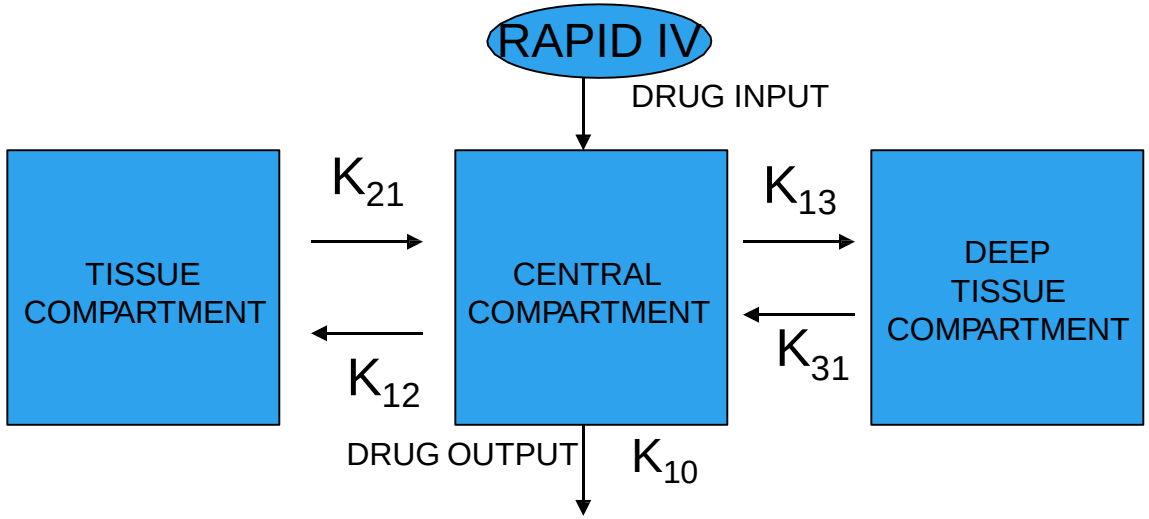
- Besides the method of residuals, ka can also be found by loo-riegelman method for drug that follows two-compartment characteristics.
- Despite its complexity, the method can be applied to drugs that distribute in any number of compartments.

THREE COMPARTMENT MODEL

- Gibaldi & feldman described a three compartment open model to explain the influence of route of administration .I.E. Intravenous vs. Oral, on the area under the plasma concentration vs. Time curve.
- Portman utilized a three compartment model which included metabolism & excretion of hydroxy nalidixic acid.



THREE COMPARTMENT CATENARY MODEL



THREE COMPARTMENT MAMMILLARY MODEL

- Three compartment model consist of the following compartments .
- ✓ Central compartment.
- ✓ Tissue compartment.
- ✓ Deep tissue compartment.

- In this compartment model drug distributes most rapidly in to first or central compartment.
- Less rapidly in to second or tissue compartment .
- Very slowly to the third or deep tissue compartment. The third compartment is poor in tissue such as bone & fat.

- Each compartment independently connected to the central compartment.
- Notari reported the tri exponential equation

  $c = a\, e^{-\alpha t} + b\, e^{-\beta t} + c\, e^{-\gamma t}$

- A,B,C are the y-intercept of extrapolated lines.
- A,β,γ are the rate constants

RAPID I.V BOLUS ADMINISTRATIONS

- When the drug is administered by i.V the drug will rapidly distributed in c.C ,less rapidly in to t.C. Very slowly in to deep tissue compartment.

  Plasma profile

- When the drug is administered by i.V the plasma conc. Will increased in c.C this is first order release.
- The conc. Of drug in c.C. Exhibits an initial distribution this is very rapid.
- Drug in central compartment exhibits an initial distribution this is very rapid .

Pharmacokinetic parameters

Bioloigical half-life ::

- It is defined as the time taken for the amount of drug in the body as well as plasma to decline by one half or 50% its initial value.
- Concentration of drug in plasma as a function of time is

$c=a\ e^{-\alpha t}+ b\ e^{-\beta t}+ c\ e^{-\gamma t}$

- In this equation $\alpha>\beta>\gamma$ some time after the distributive phase (i.e. When time become large) the two right hand side terms values are equal to zero.
- The eq.. Is converted in to

$c=a\ e^{-\alpha t}$

Taking the natural logarithm on both sides
the rate constant of this straight line is ‘α’ and biological half life is

$t_{1/2} =0.693/\alpha$

VOLUME OF CENTRAL COMPARTMENT

- At time=0

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

This equation becomes

$$C_O = A+B+C \quad \text{-----1}$$

C_O =conc. Of plasma immediately after the i.V administration

- When administered the dose is not distributed in tissue compartment.
- Therefore the drug is present in c.C only .
- If D is dose administered then $C_O = D / V_C$---------2

  V_c=volume of drug in c.C

Combining the 1&2 eq.. We get $\mathbf{V_c = d/c_o}$ **(**c_o----- conc. Of drug in plasma)

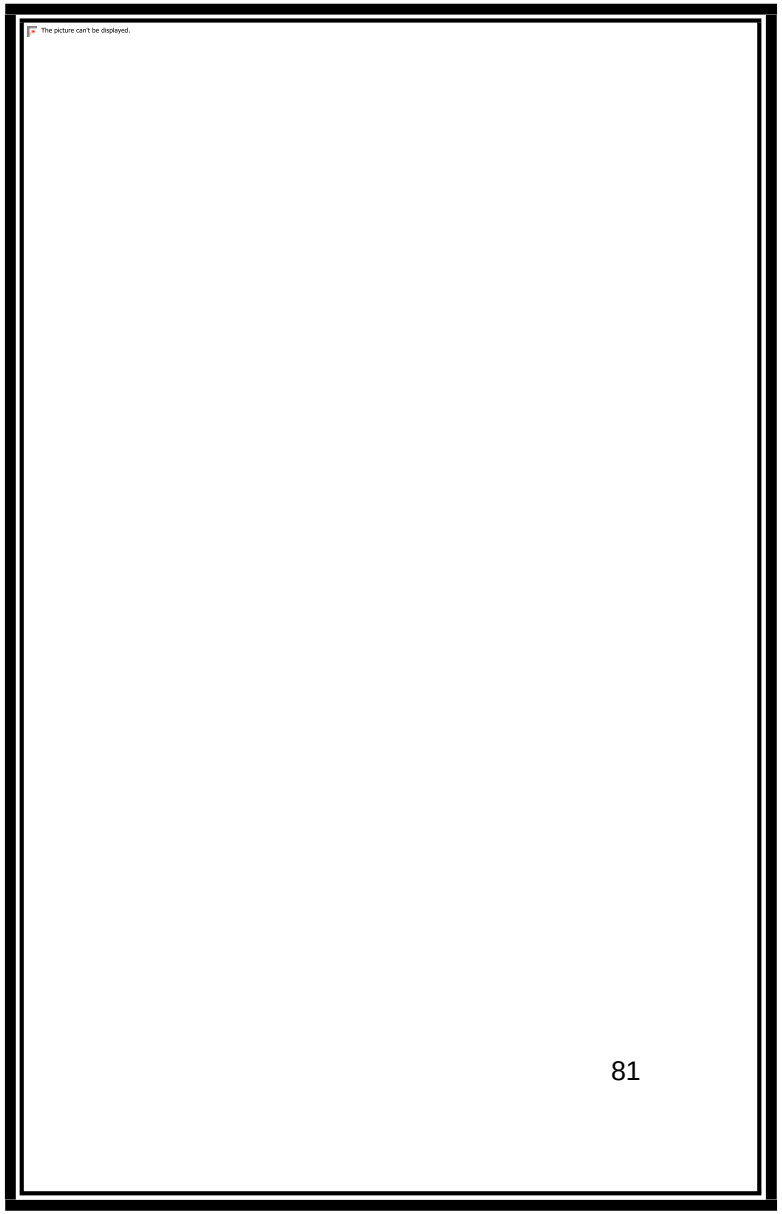
ELIMINATION RATE CONSTANT:

- Drug that follows three compartment kinetics and administered by i.V injection the decline in the plasma drug conc. Is due to elimination of drug from the three compartments.

$$K_e=(a+b+c)\,\alpha\,\beta\,\gamma/a\,\beta\,\gamma+b\,\alpha\,\gamma+c\alpha\,\beta$$

PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELS

- Blood flow rate limited or perfusion rate limited model.
- Drawn on the basis of **anatomic** and **physiologic data**.(More realistic)
- Organs or tissues having no perfusion are excluded.
- **Drug movement** to a particular region is much **more rapid than** its **rate of delivery** to that region by blood - perfusion rate limited model.
- Thus, applicable to **highly membrane permeable** drugs, i.e. Low molecular weight, poorly ionized and highly lipophilic drugs.
- For highly polar, ionized and charged drugs, the model is referred to as **membrane permeation rate limited**.



Development of a PBPK Model

A PBPK model envisages the body as being comprised of physiologically similar compartments. Each compartment represents an organ or tissue group, and linked to the central blood compartment by arterial and venous blood flow. The model is characterized by physiologic parameters such as tissue volumes and blood flow rates, biochemical parameters such as the partition coefficients, and kinetic parameters for metabolism and removal. These parameters are used to provide a mathematical description of the model using mass–balance equations for individual compartments.

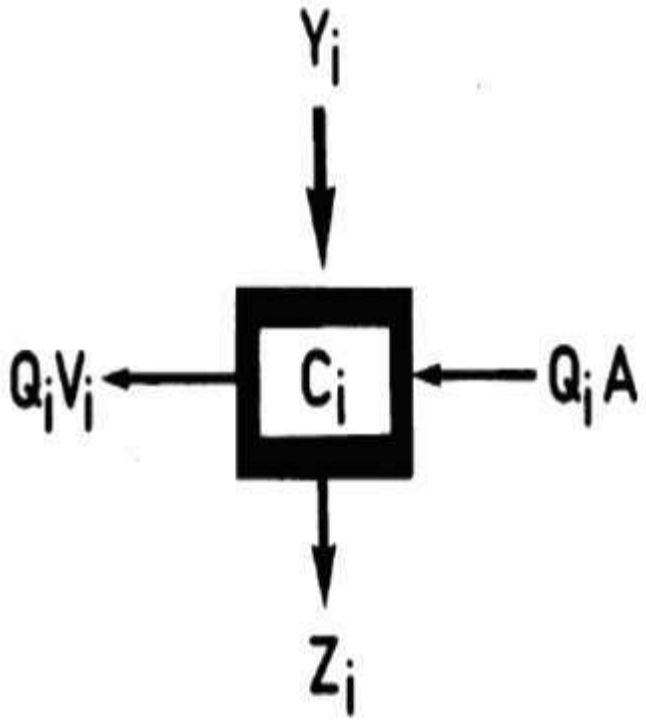


Figure 1. Schematic diagram of a general organ compartment: $C_i(t)$ = concentration of xenobiotic in tissue *i* at time *t*; Q_i = blood flow rate; U_i = tissue volume; $A(t)$ = concentration of xenobiotic in arterial blood; $V_i(t)$ = concentration of xenobiotic in venous blood; $Y_i(t)$ = amount of xenobiotic directly entering compartment; $Z_i(t)$ = amount of xenobiotic directly removed from compartment.

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