PHARMACOKINETICS

Dr. M.Mothilal
Assistant professor

OVERVIEW

- Basic considerations in pharmacokinetics
- Compartment models
- One compartment model
  - Assumptions
  - Intravenous bolus administration
  - Intravenous infusion
  - Extravascular administration (zero order and first order absorption model)
- References

BASIC CONSIDERATIONS IN PHARMACOKINETICS

- Pharmacokinetic parameters
- Pharmacodynamic parameters
- Zero order kinetic
- First order kinetic
- Mixed order kinetic
- Compartment model
- Non compartment model
- Physiologic model

Pharmacokinetic models

Means of expressing mathematically or quantitatively, time course of drug through out the body and compute meaningful pharmacokinetic parameters.

Useful in :

- Characterize the behavior of drug in patient.
- Predicting conc. of drug in various body fluids with dosage regimen.
- Calculating optimum dosage regimen for individual patient.
- Evaluating bioequivalence between different formulation.
- Explaining drug interaction.

Compartment models

OBJECTIVE

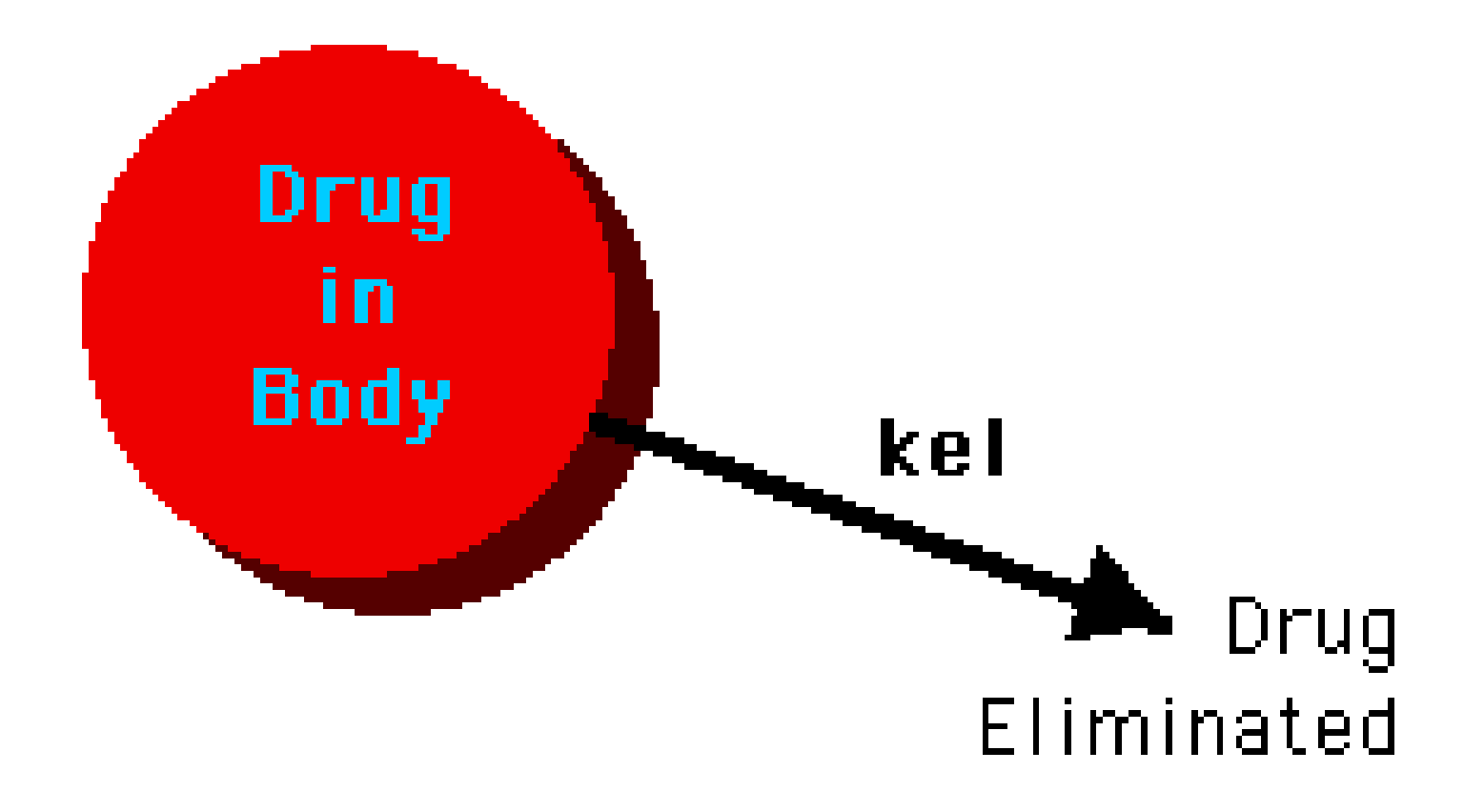
- To understand the assumptions associated with the one compartment model
- To understand the properties of first order kinetics and linear models
- To write the differential equations for a simple pharmacokinetic model
- To derive and use the integrated equations for a one compartment linear model
- To define, use, and calculate the parameters, Kel (elimination rate constant), t1/2 (half-life), Cl (clearance), V (apparent volume of distribution), and AUC (area under the concentration versus time curve) as they apply to a one compartment linear model

“OPEN” and “CLOSED” models:

- The term “open” itself mean that, the administered drug dose is removed from body by an excretory mechanism (for most drugs, organs of excretion of drug is kidney)

- If the drug is not removed from the body then model refers as “closed” model.

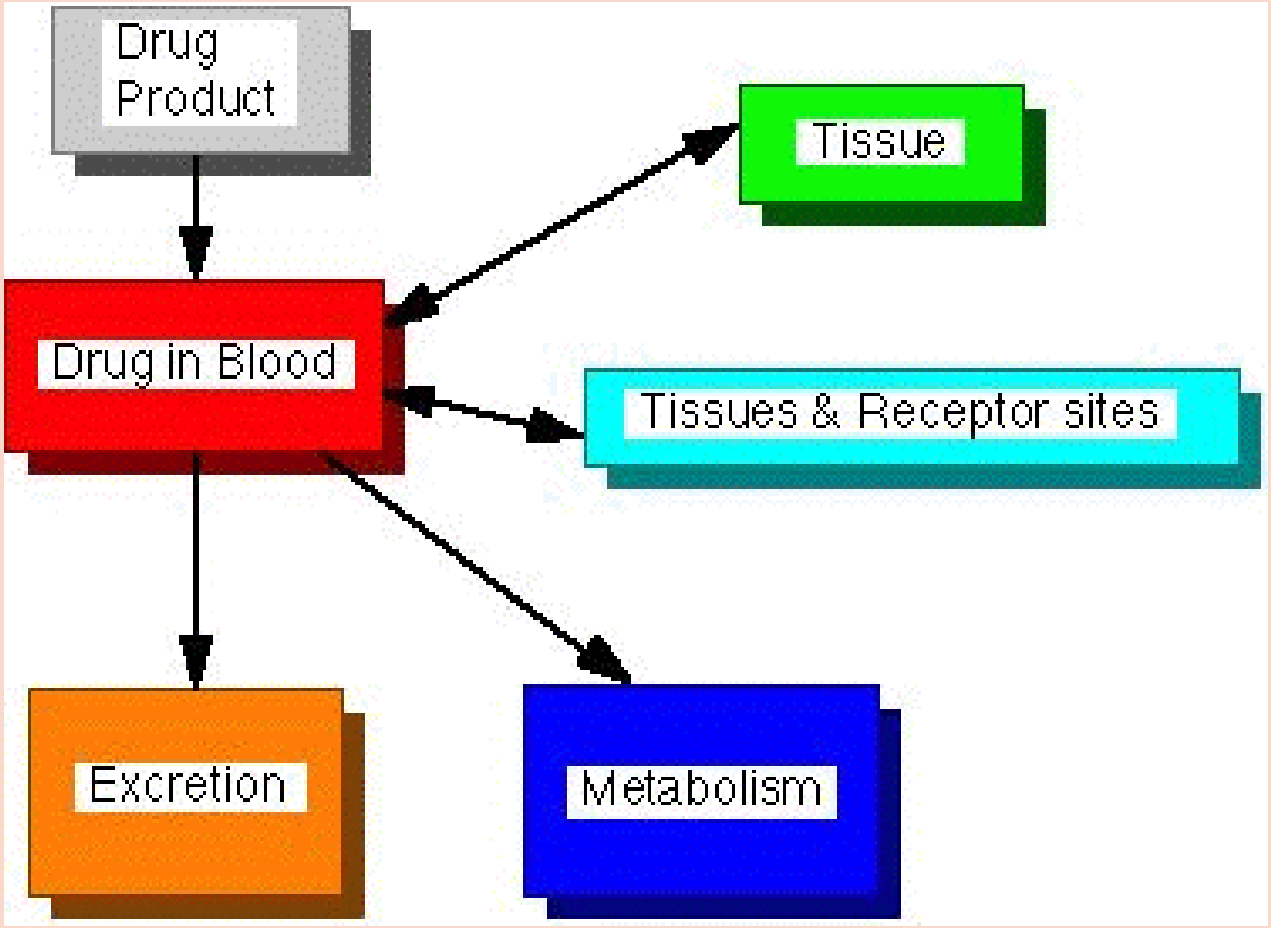
One Compartment



PHARMACOKINETICS

- **Pharmacokinetics** is the study of drug and/or metabolite **kinetics** in the body.

- The body is a very complex system and a drug undergoes many steps as it is being **absorbed**, **distributed** through the body, **metabolized** or **excreted** (**ADME**).


Drug Product
Tissue
Drug in Blood
Tissues & Receptor sites
Excretion
Metabolism

Assumptions

1. One compartment

- The drug in the blood is in rapid equilibrium with drug in the extravascular tissues.

- This is not an exact representation however it is useful for a number of drugs to a reasonable approximation.

2. Rapid Mixing

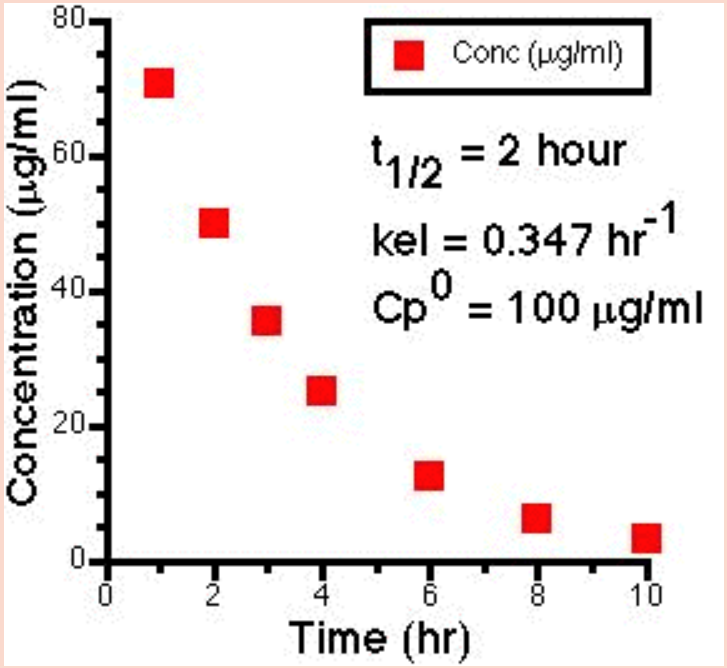
- We also need to assume that the drug is mixed instantaneously in blood or plasma.

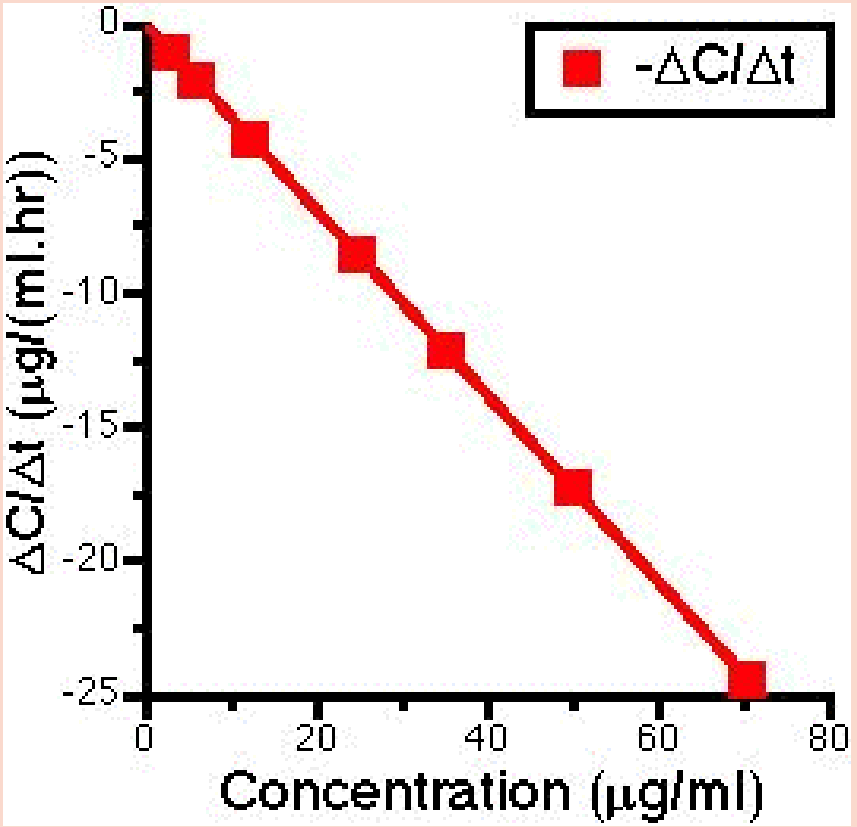
3. Linear Model

- We will assume that drug elimination follows first order kinetics.

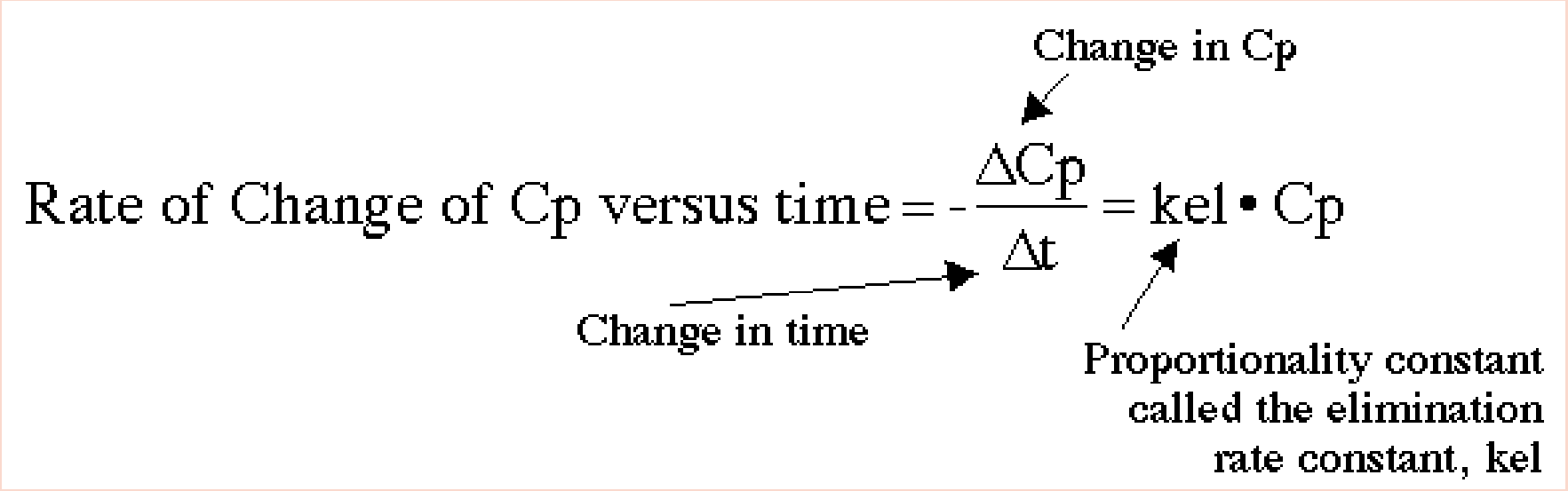
Linear Model - First Order Kinetics

- **First-order kinetics**





- This behavior can be expressed mathematically as :

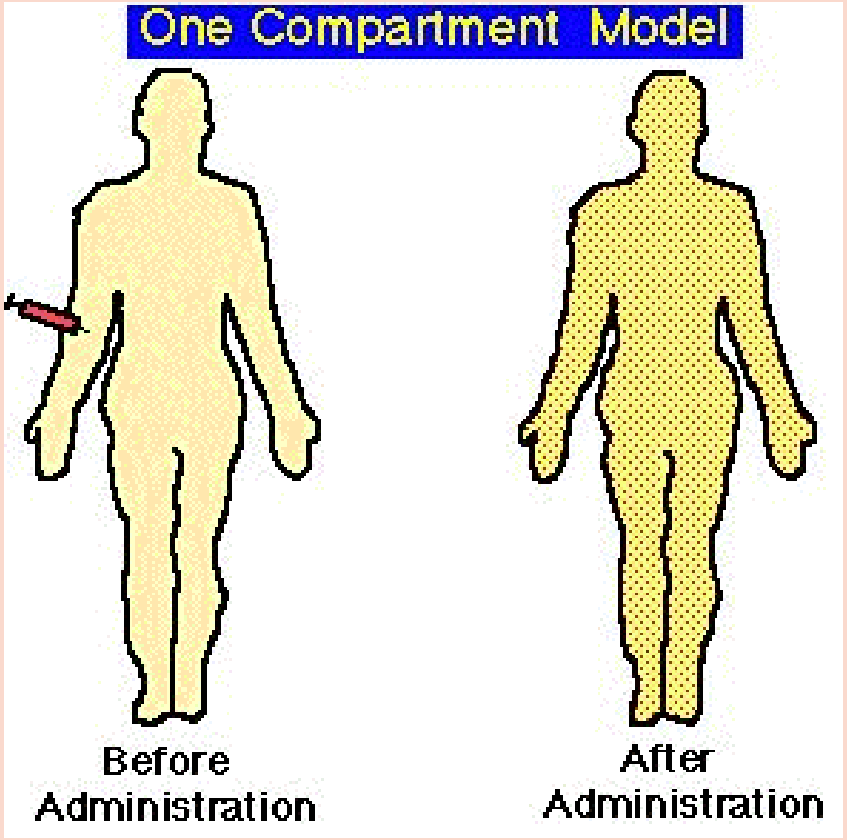


One compartment model

- One compartment model can be defined :

- One com. open model – i.v. bolus.
- One com. open model - cont. intravenous infusion.
- One com. open model - extra vas. administration (zero-order absorption)
- One com. open model - extra vas. Administration (first-order absorption)

One Compartment Model, Intravenous (IV) Bolus Administration



Rate of drug presentation to body is:

- $\frac{dx}{dt}$ = rate in (availability) – rate out (elimination)
- Since rate in or absorption is absent, equation becomes
  $\frac{dx}{dt}$ = - rate out
- If rate out or elimination follows first order kinetic

$$dx/dt = -k_E X \qquad \text{(eq.1)}$$

Elimination phase:

- Elimination phase has three parameters:

- Elimination rate constant
- Elimination half life
- Clearance

Elimination rate constant

- Integration of equation (1)

- $\ln X = \ln Xo - K_E t$ (eq.2)

Xo = amt of drug injected at time t = zero i.e. initial amount of drug injected

$X = Xo\, e^{-KEt}$ (eq.3)

- $\log X = \log Xo - \frac{K_E t}{2.303}$ (eq.4)

- Since it is difficult to directly determine amount of drug in body X, we use relationship that exists between drug conc. in plasma C and X; thus

- $X = V_d C$ (eq. 5)

- So equation-8 becomes

$$\log C = \log Co - \frac{K_E\, t}{2.303} \quad \text{(eq.6)}$$

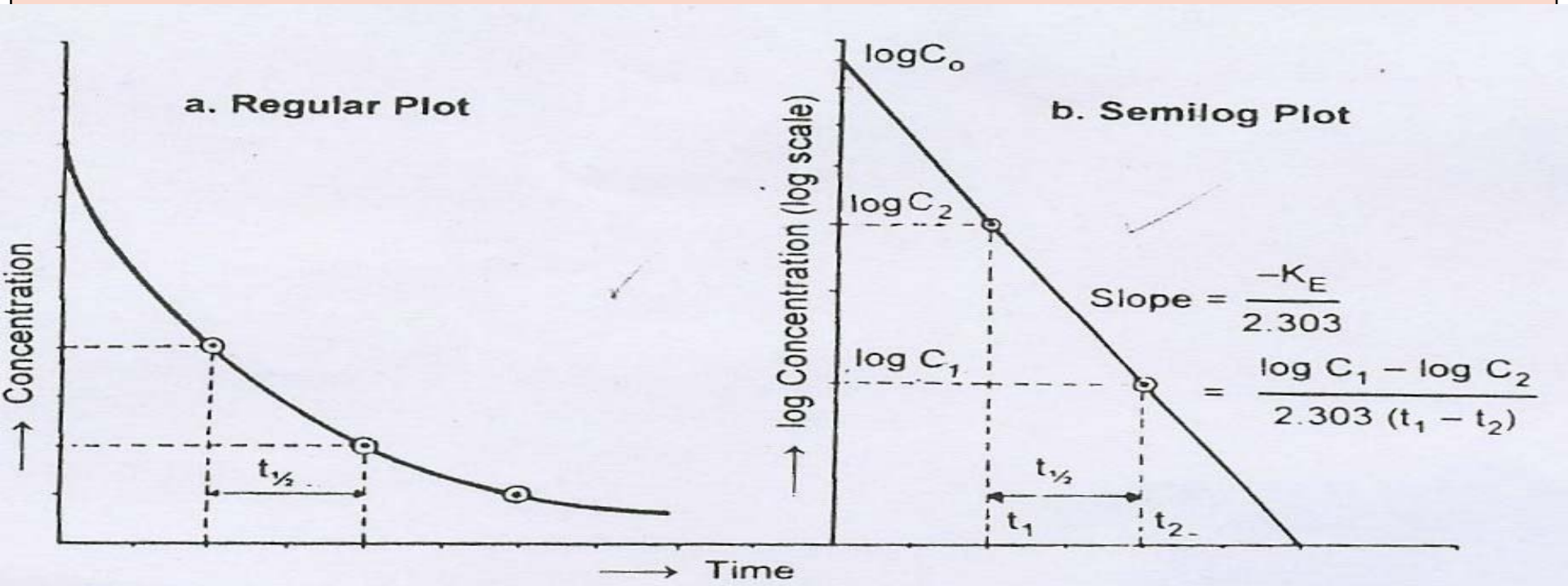


Fig. 10.2 (*a*) Cartesian plot of a drug that follows one-compartment kinetics and given by rapid i.v. injection, and (*b*) Semilogarithmic plot for the rate of elimination in a one-compartment model.

$K_E = Ke + Km + Kb + KI + \ldots$ (eq.7)

K_E is overall elimination rate constant

Elimination half life

$$t_{1/2} = \frac{0.693}{K_E} \qquad \text{(eq.8)}$$

- Elimination half life can be readily obtained from the graph of log C versus t

- Half life is a secondary parameter that depends upon the primary parameters such as clearance and volume of distribution.

- $t_{1/2} = \frac{0.693\ V_d}{Cl_T}$ (eq.9)

Apparent volume of distribution

- Defined as volume of fluid in which drug appears to be distributed.
- $Vd = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}} = \frac{X}{C}$ (eq.10)

$$Vd = Xo/Co$$
$$= \text{i.v.bolus dose}/Co \quad \text{(eq.11)}$$

- E.g. 30 mg i.v. bolus, plasma conc.= 0.732 mcg/ml.
- Vol. of dist. = 30mg/0.732mcg/ml
  =30000mcg/0.732mcg/ml
  = 41 liter.

- For drugs given as i.v.bolus,

$$V_d \text{ (area)} = Xo/K_E.AUC$$

…….12.a

- For drugs admins. Extra. Vas.

$$V_d \text{ (area)} = F\ Xo/K_E.AUC$$

……..12.b

Clearance

$$\text{Clearance} = \frac{\text{rate of elimination}}{\text{plasma drug conc..}}$$

- Or $Cl = \frac{dx/dt}{C}$ (eq.13)

Thus

$$\text{Renal clearance} = \frac{\text{rate of elimination by kidney}}{C}$$

$$\text{Hepatic clearance} = \frac{\text{rate of elimination by liver}}{C}$$

$$\text{Other organ clearance} = \frac{\text{rate of elimination by organ}}{C}$$

- Total body clearance:

$$Cl_T = Cl_R + Cl_H + Cl_{other} \quad \text{(eq.14)}$$

- According to earlier definition

$$Cl = \frac{dx/dt}{C}$$

- Submitting eq.1 $dx/dt = K_E X$, above eq. becomes

$$Cl_T = K_E X / C \qquad \text{(eq 15)}$$

- By incorporating equation 1 and equation for vol. of dist. ($Vd = X/C$) We can get

$$Cl_T = K_E \ Vd \qquad \text{(eq.16)}$$

- Parallel equations can be written for renal and hepatic clearance.

$$Cl_H = Km \; Vd \qquad \text{(eq.17)}$$

$$Cl_R = Ke \; Vd \qquad \text{(eq.18)}$$

- but $K_E = 0.693/t_{1/2}$
- so,

$$Cl_T = \frac{0.693 \; Vd}{t_{1/2}} \qquad \text{(eq.19)}$$

- For non compartmental method which follows one compartmental kinetic is :
- For drug given by i.v. bolus

$$Cl_T = \frac{Xo}{AUC} \quad \text{.....20.a}$$

- For drug administered by e.v.

$$Cl_T = \frac{F\ Xo}{AUC} \quad \text{.....20.b}$$

- For drug given by i.v. bolus

$$\text{renal clearance} = \frac{Xu\infty}{AUC} \quad \text{(eq. 21)}$$

Organ clearance

- Rate of elimination by organ= rate of presentation to the organ – rate of exit from the organ.

- Rate of elimination $= Q.C_{in} - Q.C_{out}$
  (rate of extraction) $= Q(C_{in} - C_{out})$
  Cl_{organ} = rate of extraction/C_{in}
  $= Q(C_{in} - C_{out})/C_{in}$
  $= Q.ER$ …….(eq 22)
- Extraction ratio:
  $ER = (C_{in} - C_{out})/ C_{in}$
- ER is an index of how efficiently the eliminating organ clear the blood flowing through it of drug.

- According to ER, drugs can be classified as-
- Drugs with high ER (above 0.7)
- Drugs with intermediate ER (between 0.7-0.3)
- Drugs with low ER (below 0.3)
- The fraction of drug that escapes removal by organ is expressed as

$$F = 1 - ER$$

- where F= systemic availability when the eliminating organ is liver.

Hepatic clearance

$$Cl_H = Cl_T - Cl_R$$

- Can also be written down from eq 22
- $Cl_H = Q_H\ ER_H$
- Q_H= hepatic blood flow. ER_H = hepatic extraction ratio.
- Hepatic clearance of drug can be divided into two groups :

1. Drugs with hepatic blood flow rate-limited clearance
2. Drugs with intrinsic capacity- limited clearance

Hepatic blood flow

- $F = 1 - ER_H$

  $= \frac{AUC_{oral}}{AUC_{i.v}}$

Influence of Blood Flow Rate and Protein Binding on Total Clearance of Drugs with High and with Low ER Values.

Drugs with	*Changes in Total Clearance due to*			
	↑ Blood Flow	*↓ Blood Flow*	*↑ Binding*	*↓ Binding*
High ER (above 0.7)	↑	↓	No Change	No Change
Low ER (below 0.3)	No Change	No Change	↓	↑

where, ↑ = increase, and ↓ = decrease.

Intrinsic capacity clearance

- Denoted as Cl_{int}, it is defined as the inherent ability of an organ to irreversibly remove a drug in the absence of any flow limitation.

TABLE 10.2
Hepatic and Renal Extraction Ratio of Some Drugs and Metabolites

	Extraction Ratio		
	High	*Intermediate*	*Low*
Hepatic Extraction	Propranolol Lidocaine Nitroglycerine Morphine Isoprenaline	Aspirin Codeine Nortriptyline Quinidine	Diazepam Phenobarbital Phenytoin Procainamide Theophylline
Renal Extraction	Some Penicillins Hippuric acid Several Sulfates Several Glucuronides	Some Penicillins Procainamide Cimetidine	Digoxin Furosemide Atenolol Tetracycline

One compartment open model: Intravenous infusion

- Model can be represent as : (i.v infusion)

Drug $\xrightarrow[\text{Zero order Infusion rate}]{R_0}$ Blood & other Body tissues $\xrightarrow{K_E}$

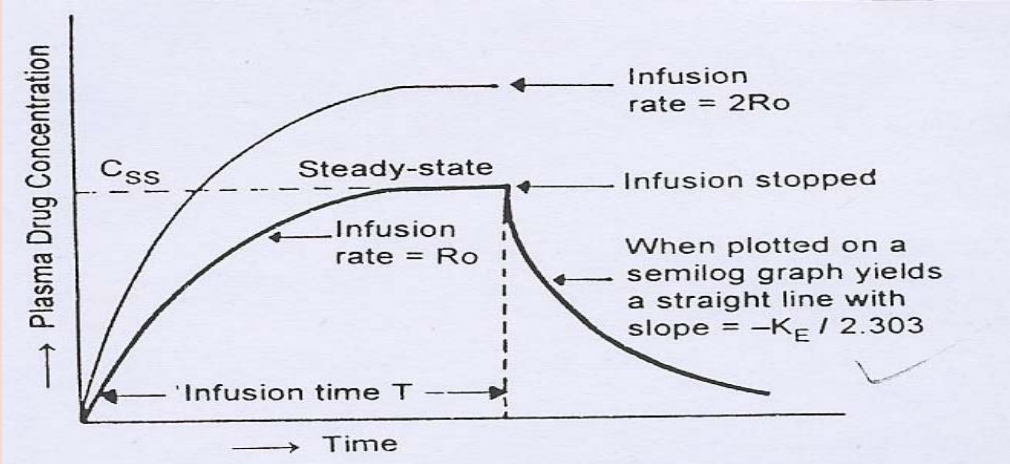
$$dX/dt = R_o - K_E X \quad \ldots \text{eq } 23$$

$$X = R_o/K_E(1-e^{-KEt}) \quad \ldots \text{eq } 24$$

Since $X = V_d C$

$$C = R_o/K_E V_d(1-e^{-KEt}) \quad \ldots \text{eq } 25$$

$$= R_o/Cl_T(1-e^{-KEt}) \quad \ldots \text{eq } 26$$



ig. 10.3 Plasma concentration-time profile for a drug given by constant rate i.v. infusion (the two curves indicate different infusion rates R_o and $2R_o$ for the same drug)

- At steady state. The rate of change of amount of drug in the body is zero ,eq 23 becomes

$Zero = R_o - K_E X_{SS}$ …27

$K_E X_{SS} = R_o$ …28

$C_{SS} = R_o / K_E V_d$ …29

$= R_o / Cl_T$ i.e infusion rate 30
clearance

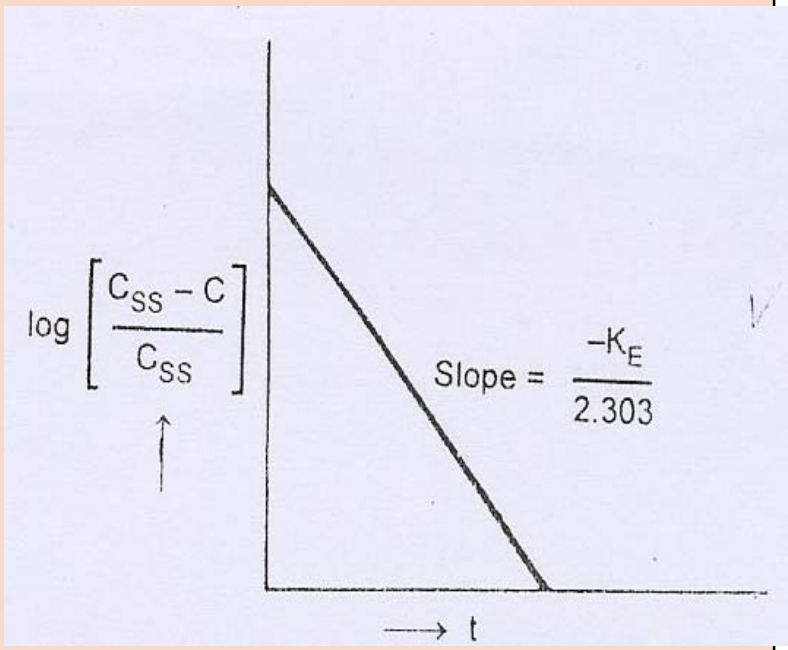
Substituting eq. 30 in eq. 26

- $C = C_{SS}(1 - e^{-KEt})$ …31

Rearrangement yields:

- $\left[\frac{C_{SS} - C}{C_{SS}}\right] = e^{-KEt}$ ...32

- $\log \frac{C_{SS} - C}{C_{SS}} = \frac{-K_E t}{2.303}$ …33

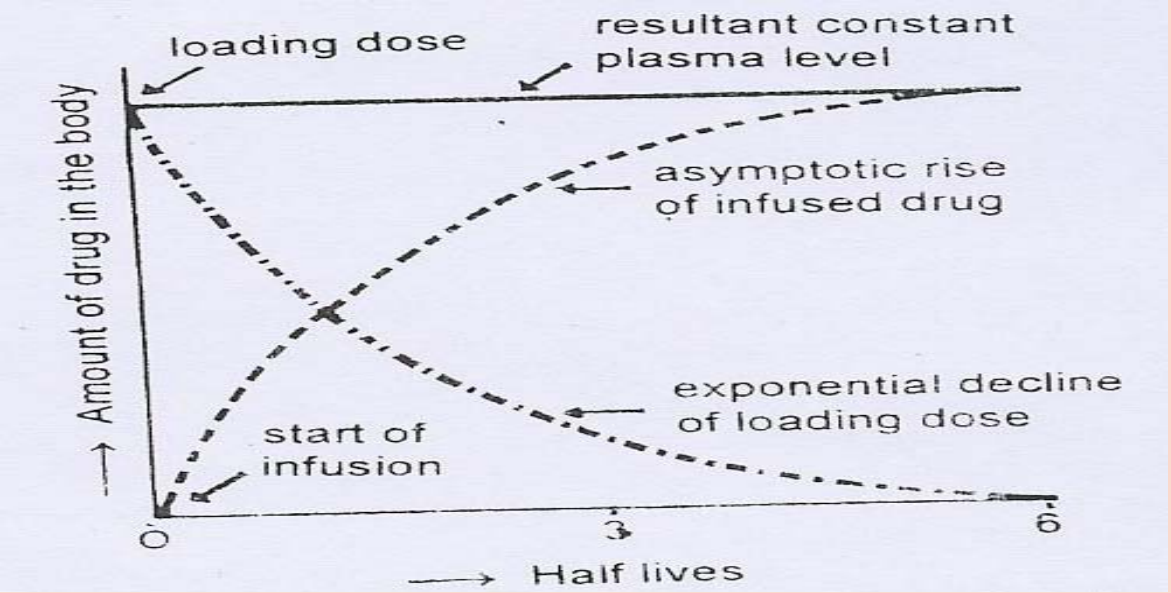


- If n is the no. of half lives passed since the start of infusion($t/t_{1/2}$)
- Eq. can be written as
- $C=C_{SS}\,[1-(1/2)^n]$ …34

Percent of C_{ss} attained at the end of a given $t_{1/2}$

Half-life	*% Remaining*	*% C_{ss} Achieved*
1	50	50
2	25	50 + 25 = 75
3	12.5	75 + 12.5 = 87.5
4	6.25	87.5 + 6.25 = 93.75
5	3.125	93.75 + 3.125 = 96.875
6	1.562	96.875 + 1.562 = 98.437
7	0.781	98.437 + 0.781 = 99.218

Infusion plus loading dose



- $Xo,L=C_{SS}V_d$ …35
- Substitution of $C_{SS}=R_o/K_EV_d$
- $Xo,L=R_o/K_E$ …36
- $C=Xo,L/V_d\ e^{-KEt}+ R_o/K_EV_d(1-e^{-KEt})$ …37

Assessment of pharmacokinetic parameter

- AUC=R_o T/K_E V_d
  =R_o T/Cl_T
  =C_{SS} T
- Where T=infusion time

One compartment open model : extra vascular administration

- When drug administered by extra vascular route (e.g. oral, i.m, rectal), absorption is prerequisite for its therapeutic activity.

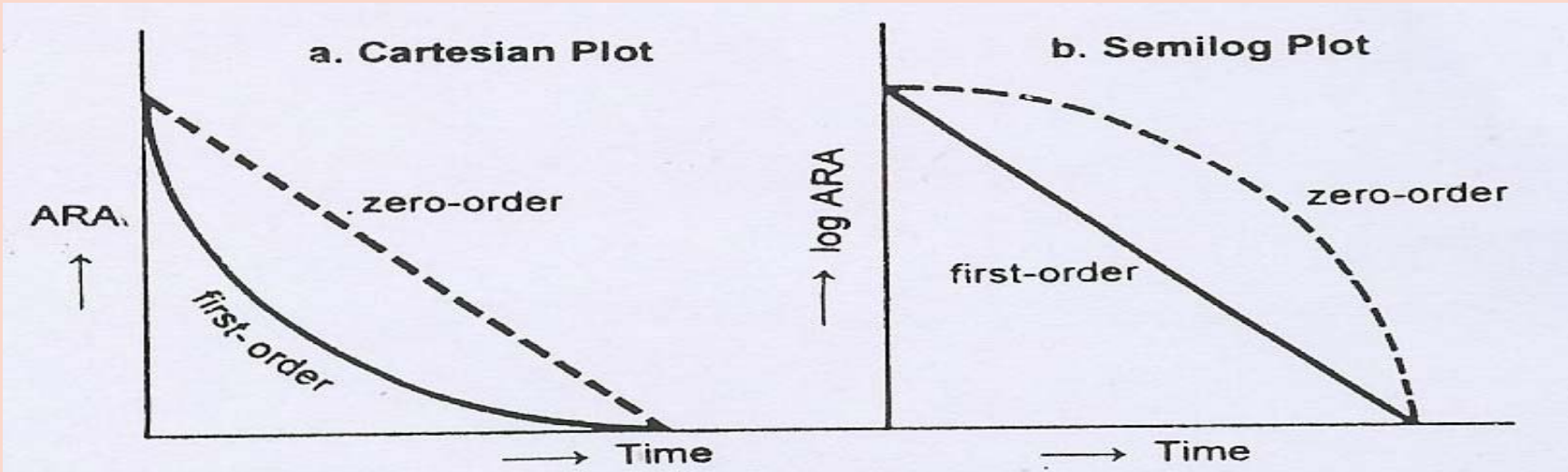


Fig. 10.6 Distinction between zero-order and first-order absorption processes. *Figure a* is regular plot, and *Figure b* a semilog plot of amount of drug remaining to be absorbed (ARA) versus time t.

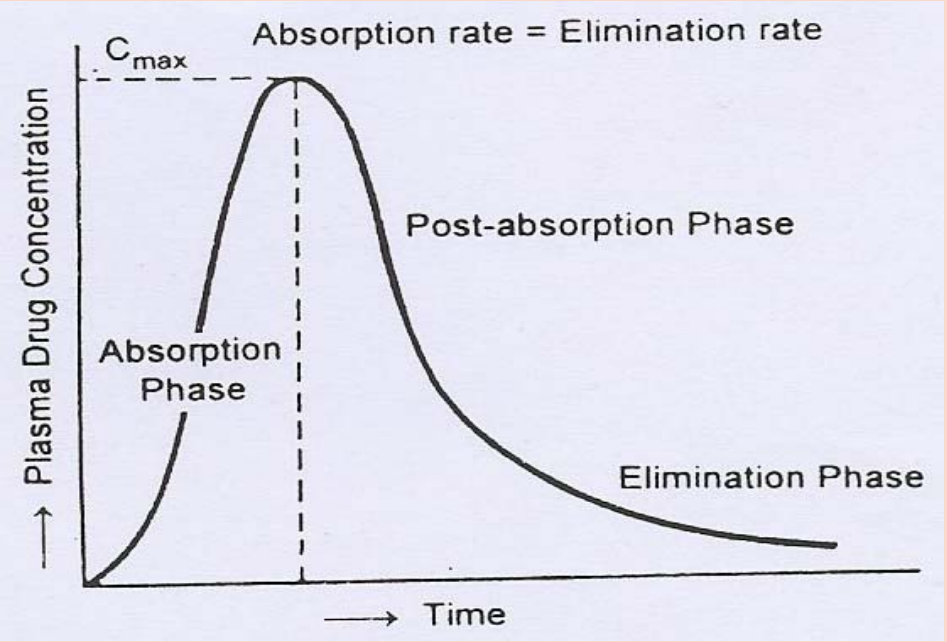
- dX/dt=rate of absorption-rate of elimination

$$dX/dt = dX_{ev}/dt - dX_E/dt \quad \ldots 38$$

$dX_{ev}/dt > dX_E/dt$

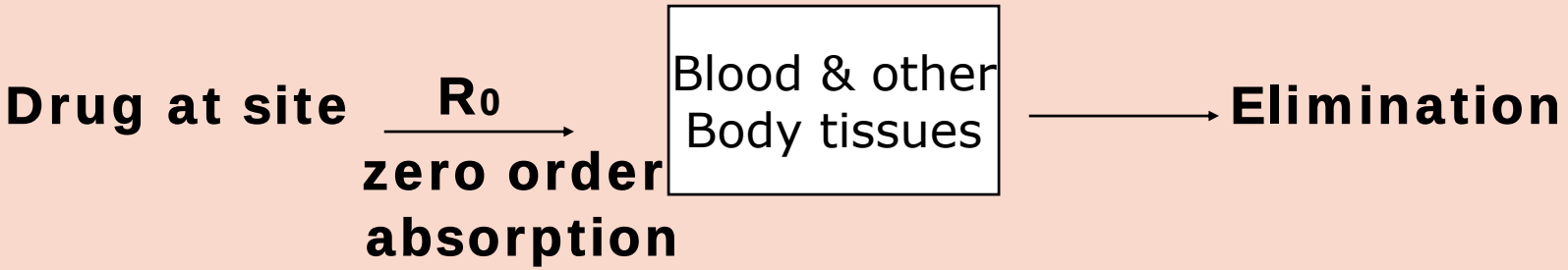
$dX_{ev}/dt = dX_E/dt$

$dX_{ev}/dt < dX_E/dt$



One compartment model: extra vascular admin (zero order absorption)

- This model is similar to that for constant rate infusion.

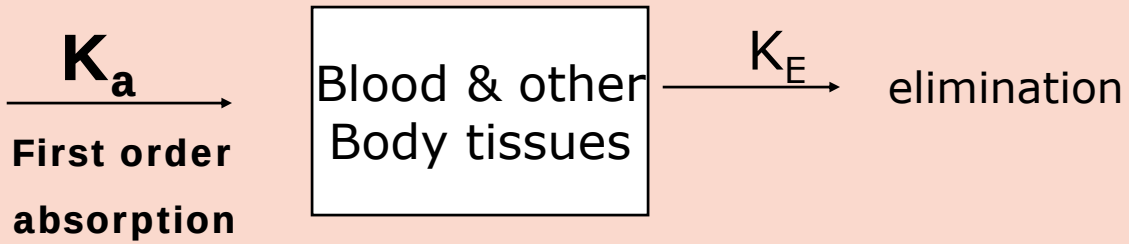


- Rate of drug absorption as in case of CDDS , is constant and continues until the amount of drug at the absorption site (e.g. GIT) is depleted.
- All equations for plasma drug conc. profile for constant rate i.v. infusion are also applicable to this model.

One compartment model: extra vascular admin (first order absorption)

- Drug that enters the body by first order absorption process gets distributed in the body according to one compartment kinetic and is eliminated by first order process.
- The model can be depicted as follows:

- **Drug at site**



- The differential form if eq. 38 is
- $dX/dt = k_a X_a - K_E X$ …39
- $X = K_a F X_o / K_a - K_E [e^{-KEt} - e^{-Kat}]$ …40
- $C = K_a F X_o / V_d (K_a - K_E) [e^{-KEt} - e^{-Kat}]$ …41

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