Pharmacokinetics

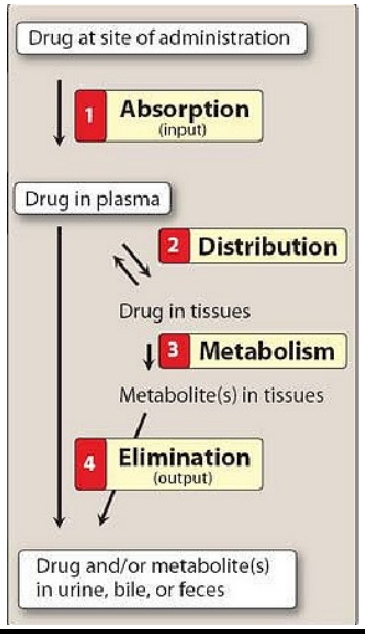
Pharmacokinetics: the action of the body on the drug. (how the body deals with the drug).

There are 4 fundamental pathways of drug movement and modification in the body:

Absorption ***distribution*** ***metabolism*** ***elimination***

Absorption

the transfer of a drug from its site of administration* to the bloodstream.



The drug has to choose one of these mechanism to be transported from the GI tract to the bloodstream

Passive transport	***Active transport***	***Facilitated diffusion***	***endocytosis***
No carrier involved	Carrier mediated	Carrier mediated	engulfment of a drug molecule by the cell membrane and transport into the cell
Energy independent	Energy dependent	Energy independent	
Along concentration gradient	Against concentration gradient	Along concentration gradient	
No saturation	Shows carrier saturation kinetics	Saturated	
No selectivity	Selective & specific	Selective	
		Can be inhibited	Undergo lysosomal digestion or fusion
Lipid soluble or water soluble drugs choose this mechanism			High molecular weight particles e.g. : proteins & lipid soluble vitamins

* see page 3

Factors Affecting Absorption

PH | Blood flow | Total surface area | Contact time at absorptive site | Food | Formulation fators

PH

A drug passes through membranes if it's non ionized.

Weak acids: $HA \longrightarrow H^+ + A^-$

Weak bases: $BH^+ \longrightarrow B + H^+$

Non ionized

Non ionized

PK_a : it's the PH at which half of the drug is ionized and the other half is unionized.

So if the PH

Less than PK_a :

Protonated* form predominate HA and BH^+

More than PK_a:

Nonprotonated form predominate A^- and B

In summary :
1– acidic drugs absorbed in low PH
2– basic drugs absorbed in high PH

blood flow

- ↑blood flow —> ↑absorption.
- Intestine has greater blood flow than stomach.

Total surface area

Intestine is better than stomach in absorption because it has microvilli that increase surface area.

formulation factors

- Solid dosage forms dissolution & sol are essential
- Aqueous solutions are absorbed more quickly than tablets. or suspensions

contact time

- Diarrhea ↓absorption because the drug moves very rapidly.
- But in case of accelerated gastric emptying there will be faster delivery of intestine and this leads to ↑ absorption.

food

- Presence of food ↓absorption (delays).
- But the increased blood flow during eating ↑ absorption.
- Tetracylcline forms insoluble complexes with Ca^+ in food.

* protonated: with proton (H^+)

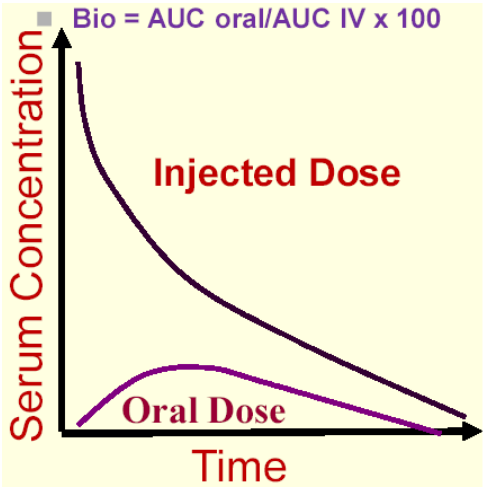
bioavailability

bioavailability

How can I express absorption in numbers ???

By using bioavailability.

Fraction of a drug reaching systemic circulation after a particular route



- It's a measure of how much of the drug reach systemic circulation to produce an effect.
- IV provide 100% availability.

Factors affecting bioavailability

Factors in the drug:
1. Molecular weight
2. Drug formulation* : standard or sustained release formulation*.
3. Drug solubility.
4. Drug interaction.

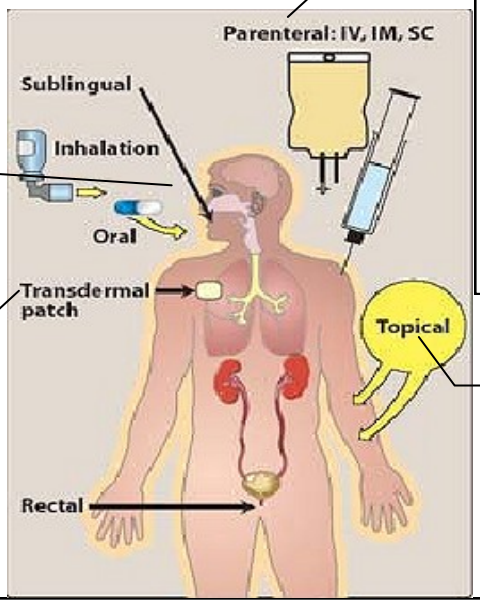
Factors in the patient:
1. First pass metabolism reduced bioavailability.
2. Chemical instability in gastric pH
3. Intestinal motility
4. Lipid/water partition coefficient.

Factors affecting absorption are the same for bioavailability.

administration

administration

Routes of administration:



Intravenous (IV)
Most common

Intramuscular (IM)
Precipitate at site of infection providing sustained dose over extended period of time.

Subcutaneous (SC)
Slower effect than IV

Intranasal (one of the routes)
For systemic administration of drugs as an alternative for parenteral route.

Applied to skin and rate of absorption differ from site to other.

- When local effect is desired.
- Include drops. (eye drops)

*formulation (it's not with us but this for understanding): process in which different chemical substances, including the active drug, are combined to produce a final medicinal product.
*Sustained release : capsule that dissolve slowly and release drug over time.

Route	Advantages	Disadvantages
Enteral	✓ Simple, ✓ self use , ✓ safe , ✓ cheap , ✓ no need for sterilization , ✓ no pain, ✓ convenient, ✓ used in chronic diseases, ✓ common	✓ Labile to 1st pass metabolism (GIT > Liver > GIT) ✓ slow effect, ✓ GIT irritation, ✓ Not suitable for vomitting , unconscious emergencies . ✓ No complete absorption (low bioavailability) ✓ Destruction by GIT enzymes , gastric acids & the pH . ✓ Food – drug interaction ✓ Drug –drug interaction .
Sublingual	reaches the blood stream without 1st pass metabolism (inc. absorption due to inc . blood flow and inc. bioavailability) • Rapid effect (Used in Emergencies) • No 1st pass metabolism • No distruction by GIT • No food drug interactions .	• Limited drugs • Smaller doses than oral • Dosage form (friable tablets) • Not for : irritant drugs , frequent use , Vasoconstriction of buccal blood vessels .
Parenteral	✓ Fast effect, ✓ high bioavailability, ✓ NOT labile to 1st pass metabolism & gastric acid	✓ Infection, ✓ pain, ✓ fear, need for skill, ✓ irreversible, ✓ rapid reactions
Intra muscular injections	✓ Avoid 1st pass metabolism ✓ Onset of action is more rapid than oral ✓ Long duration of action ✓ Solubility of the drug is not important ✓ Used for oily preparation .	✓ pain, ✓ abscess , ✓ tissue necrosis
Intra venous injections	✓ The most rapid absorption ✓ Rapid effect (in ER) ✓ High bioavailability (100 %) ✓ No destruction by GIT . ✓ No gastric irritation ✓ No 1st pass metabolism ✓ No food –drug interaction ✓ Used in Coma , Convulsion ✓ Used in irritant drugs	✓ Only water soluble drugs (clear solution) ✓ Anaphylaxis ✓ Infection (e.g. viral hepatitis) ✓ Thrombophlebitis ✓ Sterilization ✓ Pain at the site of infection ✓ Need skills and training ✓ More expensive.
Topical application (*include : skin , ears , nose , inhalation , eye , vagina)*	✓ Provide local action ✓ Lipid soluble drugs. ✓ Prolonged drug action . ✓ NOT labile to 1st pass metabolism & gastric acid, ✓ minor systemic effect ✓ Simple, ✓ no pain, ✓ Convenient ✓ Fast effect,	✓ Applicable to only few drugs
Inhalation	• Local action in respiratory tract • Rapid effect due to large surface area (inhalation anesthetic & bronchodilators)	
Transdermal	✓ Fast effect, ✓ NOT labile to 1st pass metabolism & gastric acid ✓ Good for prolonged regimen	✓ Only highly lipophilic drugs, ✓ slow effect, ✓ may be irritant
Rectal	✓ Useful for uncooperative patients like children , vomiting , unconsciousness. ✓ Avoid 1st pass metabolism , Rectal route has only ~ 50% first-pass metabolism, so more absorption than oral ✓ For local action e.g. piles	✓ May cause irritation to rectal mucosa. ✓ Irregular absorption and bioavailability ✓ Inconvenience .

distribution

is the process by which the drugs leave the blood and enter the interstitium and/or the cells of the tissue

Water Body Compartments

- Extracellular fluid
  - Plasma
  - Interstitial fluid
  - lymph
- Intra cellular fluid
- Transcellular fluid:
  - cerebrospinal , pretoneal ,synovial , pleural , digastive secretions

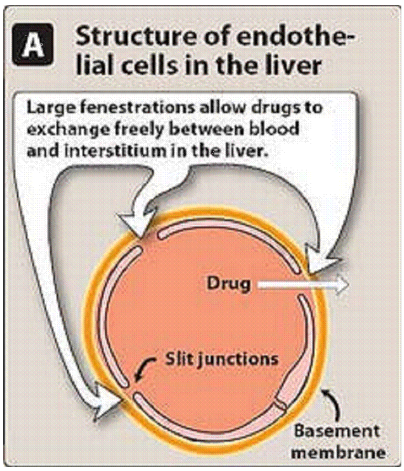
Drug may distribute to

- One compartment (plasma)
  - Also called : intravascular, vascular.
  - The drug has ↑molecular weight .
  - cannot move out of the endothelium of the vessels or capillaries
  - Has low volume of distribution.
- Two compartment :
  - Plasma + interstitial fluid.
  - In the extracellular fluid.
  - The drug has low molecular weight and it's hydrophilic.
  - Low mol weight drugs able to pass the endothelium into interstitial Fluid
  - Hydrophilic so it can't cross the untracellular membrane.
- Multi compartment
  - Extravascular + intravascular.
  - The drugs have low molecular weight and they are hydrophobic.

Factors affecting distribution

- ***Binding of drugs***
- ***Cardiac output and blood flow***
- ***Capillary permeability***
- ***PH***
- ***pK_a***
- ***Tissue binding***
- ***Physiological properties of the drug***

capillary permeability



In liver and spleen there are a lot of slit junctions in capillaries which drugs can pass through

Blood brain barrier (BBB)

- **There are no slit junction only tight junction.**
- **Astrocyte contribute to blood brain barrier**

Drugs that can pass BBB

Type of drug	Pass or not	Method of passing
Lipid soluble	pass	Penetrate the cell membrane
Ionized or polar	No pass	
Actively transported drug	pass	Carrier mediated

Placental barrier is same as BBB :
Only lipophilic drugs cans pass by simple diffusion

caridiac output and blood flow

↑blood flow to an organ result in increase distribution to that organ.

E.g. : blood flow the liver, brain and kidney more than muscles, skin and fat tissue.

binding of drugs

1st : with plasma protein

Drug reversibly bind with plasma proteins.

Drug + albumin —> drug-albumin + free drug (active)

Free drug can distribute , bind to receptor, metabolized, excreted, and have short duration of action

plasma protein binding divide to

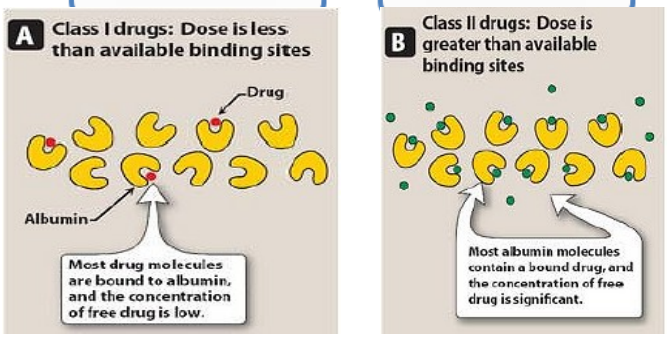
- low capacity: one drug binds to one protein
- high capacity: many drugs bind one protein

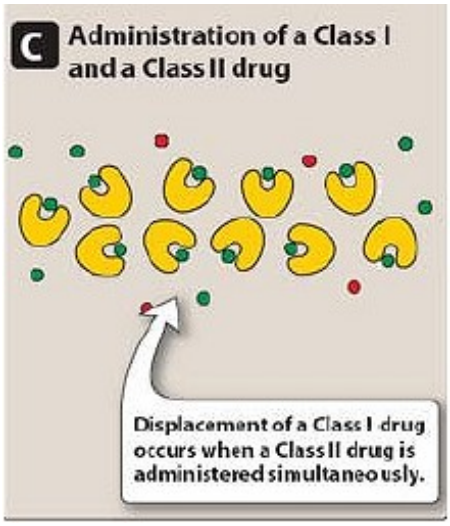
examples of plasma protein

- albumin: major protein, bind to acidic and hydrophobic drugs
- glycoprotein: bind to basic drugs

Clinical Significance of Albumin Binding

- class I: drug dose < albumin binding site
- class II: drug dose > albumin binding site





When class I and II administered together class II will displace I leading to more therapeutic or toxic effect

In case of diseases the binding may be altered. E.g. in uremic patient binding of proteins with acidic drugs will be reduced.

Plasma protein binding ↑duration of action

2nd with tissues

Tissue	*Type of drug the binds to it*
Bone	Tetracycline, lead, and cisplatin
Eye	chlorpromazine (& phenothaizines) & chloroquione
Fat	Highly lipid soluble drugs
Lungs	Basic amine lipophilic drugs with pKa > 8 + herbicides like paraquat
Salivary gland and thyroid gland	Iodide
Hair and skin	Arsenic poison
kidney	Lead, cadmium, and mercury

How can I express distribution in numbers??

By using volume of distribution

volume of distribution

volume of distribution

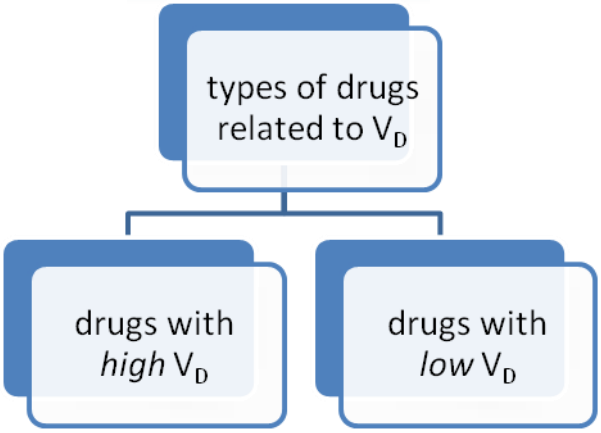
It's the volume necessary to contain the amount of drug homogenously at the concentration found in the blood, plasma, or water.

It's the ratio of drug amount in the body to the concentration of the drug in blood or plasma

$$V_D = \frac{\text{Dose of the drug in the body (mg)}}{\text{Concentration of the drug in plasma or blood (mg/L)}}$$

- **It is useful to calculate the amount of drug needed to achieve a desired plasma concentration**

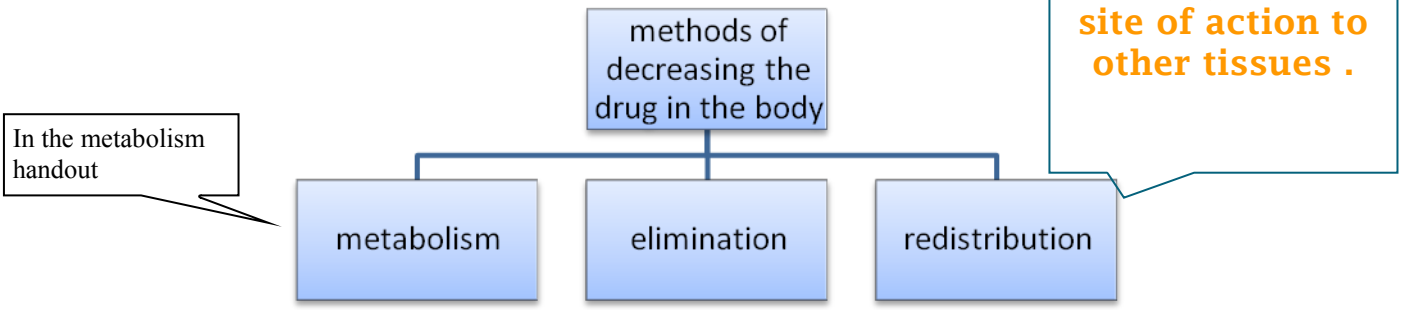
Units are L and L/Kg



high V_D	low V_d
• have low molecular weight. • highly lipid soluble. • not bounded to plasma proteins. • distributed in intracellular compartment. • have long duration of action.	• high molecular weight. • polar or lipid insoluble • bounded to plasma proteins. • retain in intravascular space.

Because the elimination of drug depends on delivery of drug to liver and kidney, and since the high V_D drug is at extravascular compartments it's unavailable to excretory organs

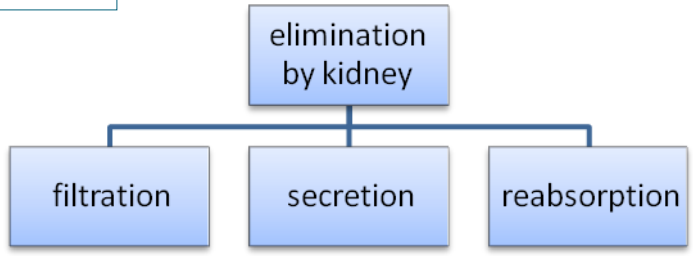
redistribution of the drug from its site of action to other tissues .



In the metabolism handout

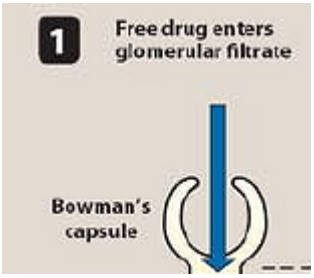
elimination

Removal of the drug from the body via kidney, lung, bile, or milk in nursing mother



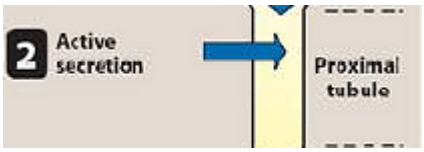
Glomerular Filtration:

- Depends on GFR and renal blood flow . Direct relationship.
- Only free unbound drugs will be filtered.
- Drugs with high molecular weight will not be filtered.



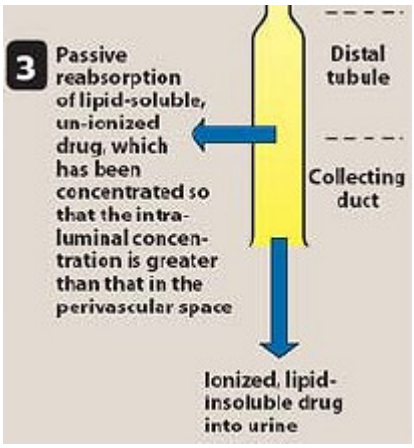
Tubular secretion:

- By 2 active transporters. One for anionic compounds and the other for cationic compounds.
- The transporters have low specificity competition between drugs for these carriers can occur within each transport system.
- For uncharged drugs they use passive diffusion.
- Charged and uncharged drugs use facilitated diffusion.
- Plasma protein binding has ONLY slight effect because of the fast removal of unbound drug from peritubular



Tubular reabsorption:

- Lipophilic drugs will be reabsorbed by passive diffusion because water reabsorption will increase the concentration of drug inside the tubule.



Urine PH trapping

Chemical adjustment of urinary pH can inhibit or enhance tubular drug reabsorption

Acidic drugs:

- If we want to decrease the reabsorption of acidic drugs we make the urine more basic.
- Basic PH will make the acidic drugs ionized and thus cannot be reabsorped.
- We alkalize the urine by using sodium bicarbonate (NH_4Cl)

Basic drugs:

- Same mechanism is used here we will make the urine more acidic.
- We acidify the urine by using ammonium chloride ($NaHCO_3$)

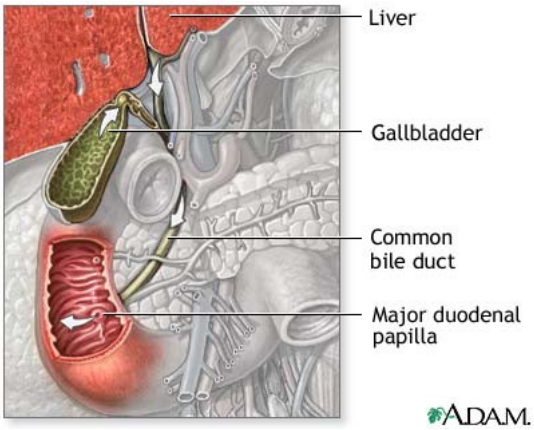
Pulmonary excretion:

- **For gases and volatile substances.**
- **By simple diffusion.**
- **Depends on:**

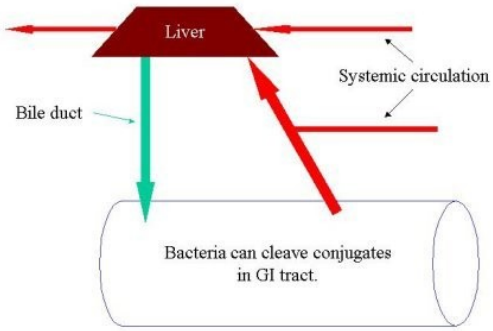
1. **Drug solubility: highly soluble drugs have slow excretion.**
2. **Cardiac output enhance the excretion.**
3. **Respiratory rate is important for gases of high blood solubility**

Bile excretion:

- Drugs secreted from the liver into the bile by active transporters.
- Some drugs undergo enterohepatic circulation back into systemic circulation



Enterohepatic circulation



- Drug excreted in bile conjugated with glucoirindes will be hydrolyzed by flora in the intestine producing free drugs.
- Free drugs can go back to circulation if lipid soluble.

Clearance

the volume **of blood/fluid cleared of drug per unit time**

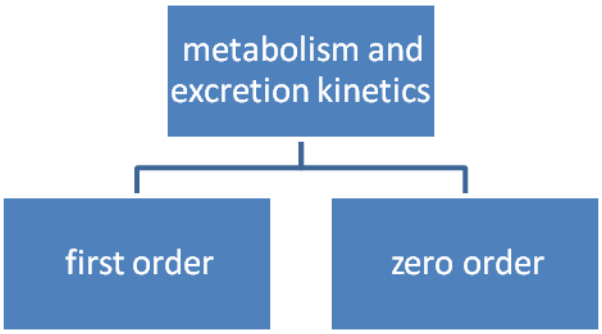
Clearance = rate of elimination / concentration in plasma

Or

Clearance= kV.
K*= elimination rate constant

Clearance unit = L/hr or L/hr/Kg

- Used in determination of maintenance dose (see below.
- Elimination + metabolism = clearance.
- Total clearance = renal clearance + hepatic clearance + others.
- Damage to heart, liver, or kidney result in ↓clearance and ↑duration.



MECHAILS MENTIN EQUATION

$$v = \text{rate of drug metabolism} = \frac{V_{max}[C]}{K_m + [C]}$$

Maximum rate metabolism

Drug concentration

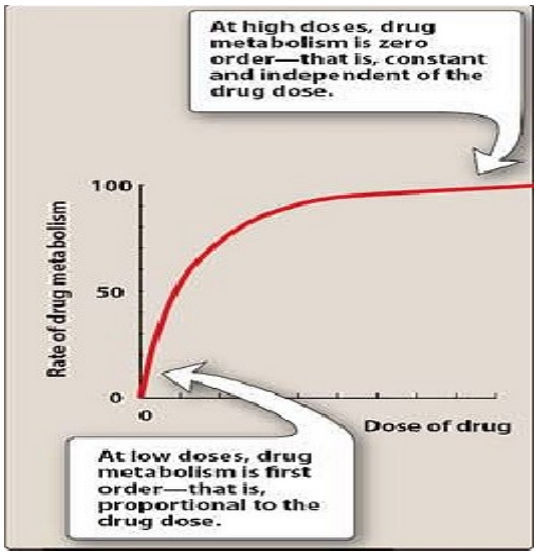
Drug concentration at 50% of maximum rate metabolism

* K : fraction of drug removed per unit time

first order	zero order
• drug concentration is less than K_m • rate of drug metabolism is directly proporional to concentration. • constant fraction of drug is metabolized per unit time. • no saturation. • $t_{1/2}$ is constant , dose independent	• drug concentration is more than K_m • rate of metabolism is constant. • constant amount of drug is metabolized per unit time. • shows saturation • $t_{1/2}$ is variable , dose dependent. • may lead to toxic effects

$$v = \text{rate of drug metabolism} = \frac{V_{max}[C]}{K_m}$$

$$v = \text{rate of drug metabolism} = \frac{V_{max}[C]}{[C]} = V_{max}$$



loading dose

Dose given to reach the target concentration

TARGET CONCENTRATION : CONCENTRATION OF DRUG IN PLASMA THAT GIVES THE THERAPEUTIC EFFECT.

Loading dose = target plasma concentration × V_D

- What is the is the loading dose required for drug A if:
  - target concentration is 10 mg/L
  - VD is 0.75 L/kg, patients weight is 75 kg

Ans: VD = 0.75 L/kg x 75 kg = 56.25 L
Target Conc. = 10 mg/L
Dose = 10 mg/L x 56.25 L = 565 mg

Maintenance dose

dose given to maintain steady state concentration.

Maintenance dose = dosing rate × interval between doses
Dosing rate (SS)= clearance x target concentration

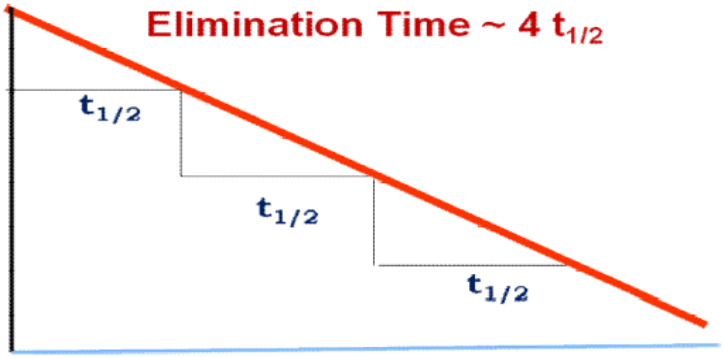
Unit will be ***mg/hr***

Total daily maintenance dose = multiply by 24

Half life

the time taken for the drug concentration to fall to half its original value

Half- life is equal to 50% of steady state concentration



Steady state

A state at which the plasma concentration of a drug remains constant .

- Achieved after 4 or 5 $t_{1/2}$.
- At steady state : the rate of drug administration equal the rate of the drug elimination.
- It is important for drug concentrations interpretation in:

1. Therapeutic Drug Monitoring (TDM)
2. Evaluation of clinical response