PHARMACOKINETICS

3rd year lecture

Department of pharmacology

Dr. Noor A. Abdullah

2022

Pharmacokinetics it is the the movement of a drug over time through the body .

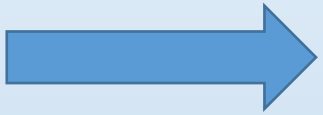
(what the body does to the drug after being taken) -**behavior of drugs inside human body:**

-**Absorption**

-**Distribution**

-**Metabolism**

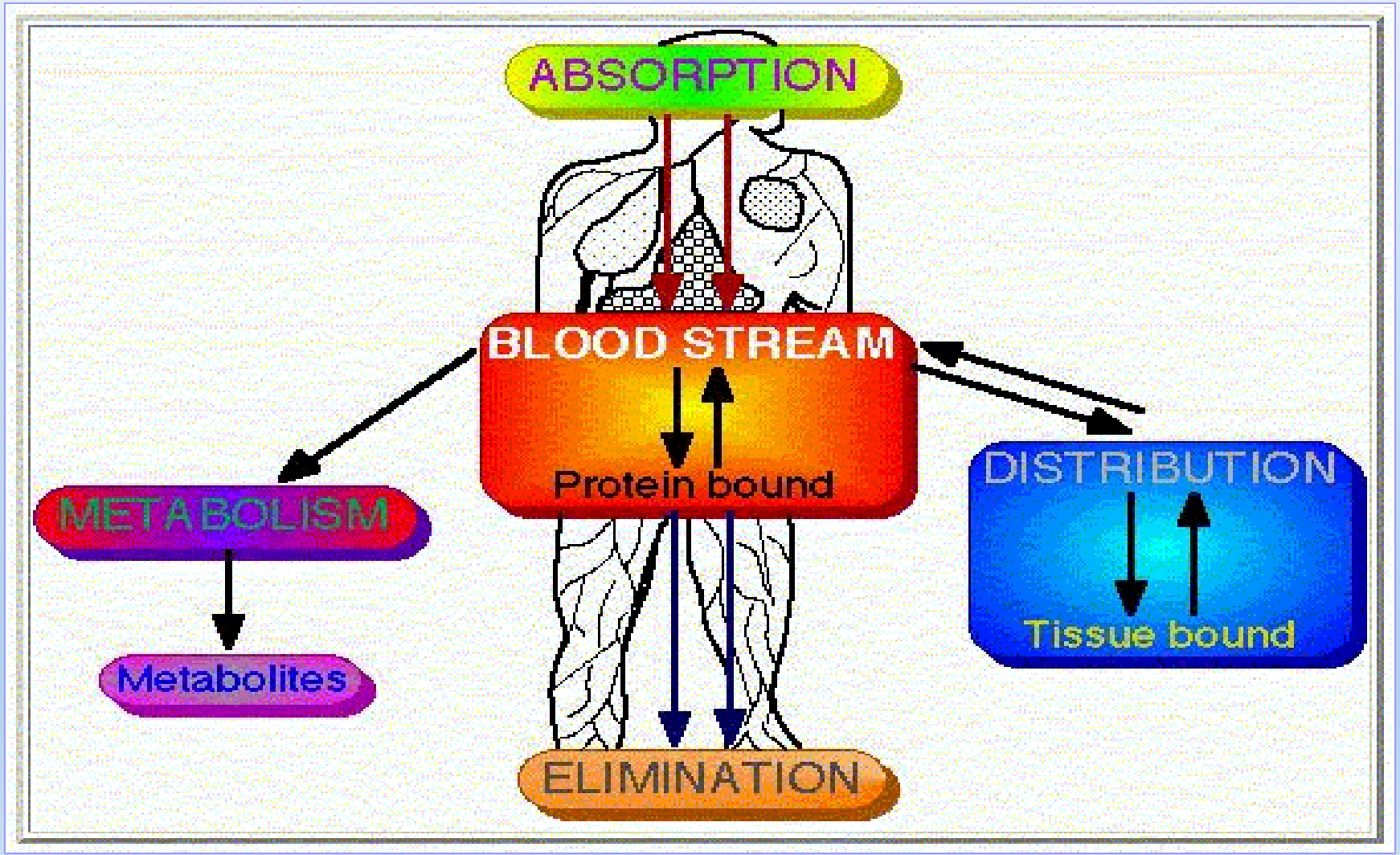
-**Excretion**



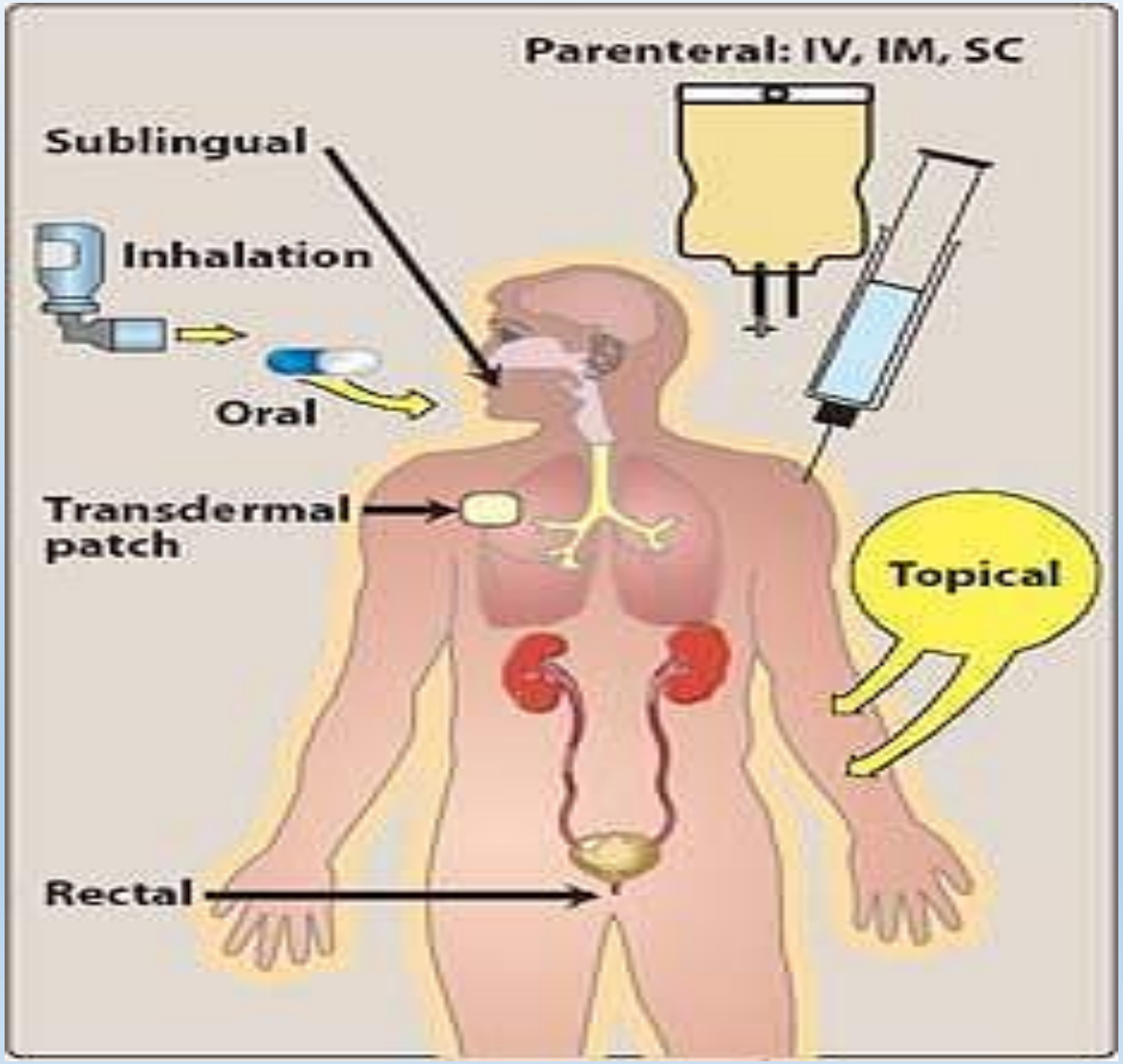
ADME

Therefore, its concerned with the time course **(the rate)** at which drug molecules cross cell membranes to enter the body.
(**absorption**), to **distribute** within it and to leave the body **(excretion)** as well as with the structural changes **(metabolism)** to which they are subjected.

ADME


ABSORPTION
BLOOD STREAM
Protein bound
METABOLISM
Metabolites
DISTRIBUTION
Tissue bound
ELIMINATION

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



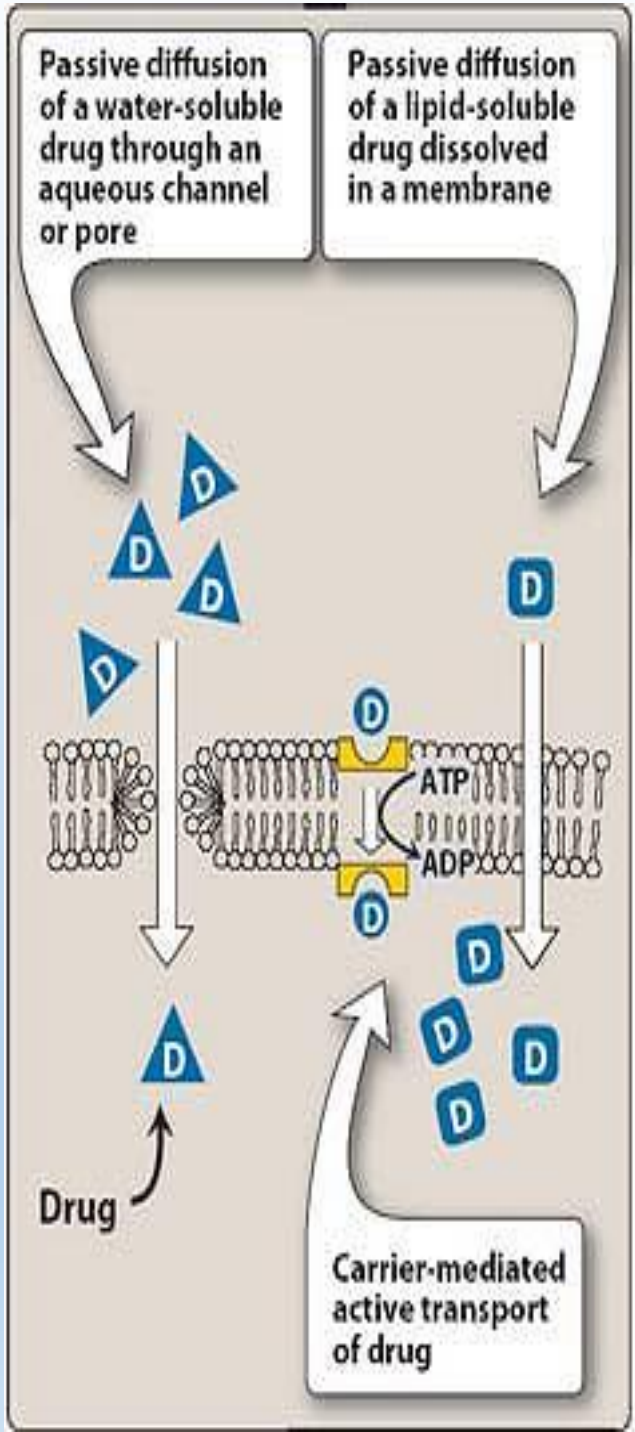
Mechanism of entrance drug inside the body

Drug passage across cell membrane

Cell membranes are essentially **bilayers of lipid** molecules with islands of proteins in between.

its strongly Hydrophobic therefore, lipid-soluble substances can diffuse easily.

Water soluble substances of small molecular size may filter through **water- filled** channels between some epithelial and endothelial cells e.g. jejunum and proximal renal tubules.



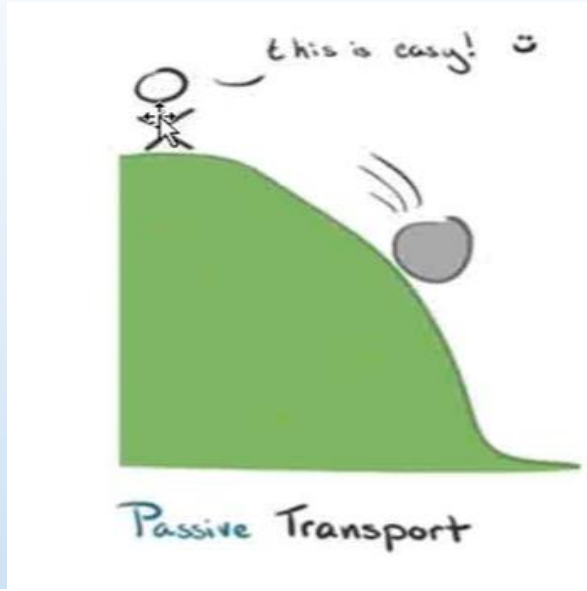
Mechanisms of passage of drugs across cell membrane

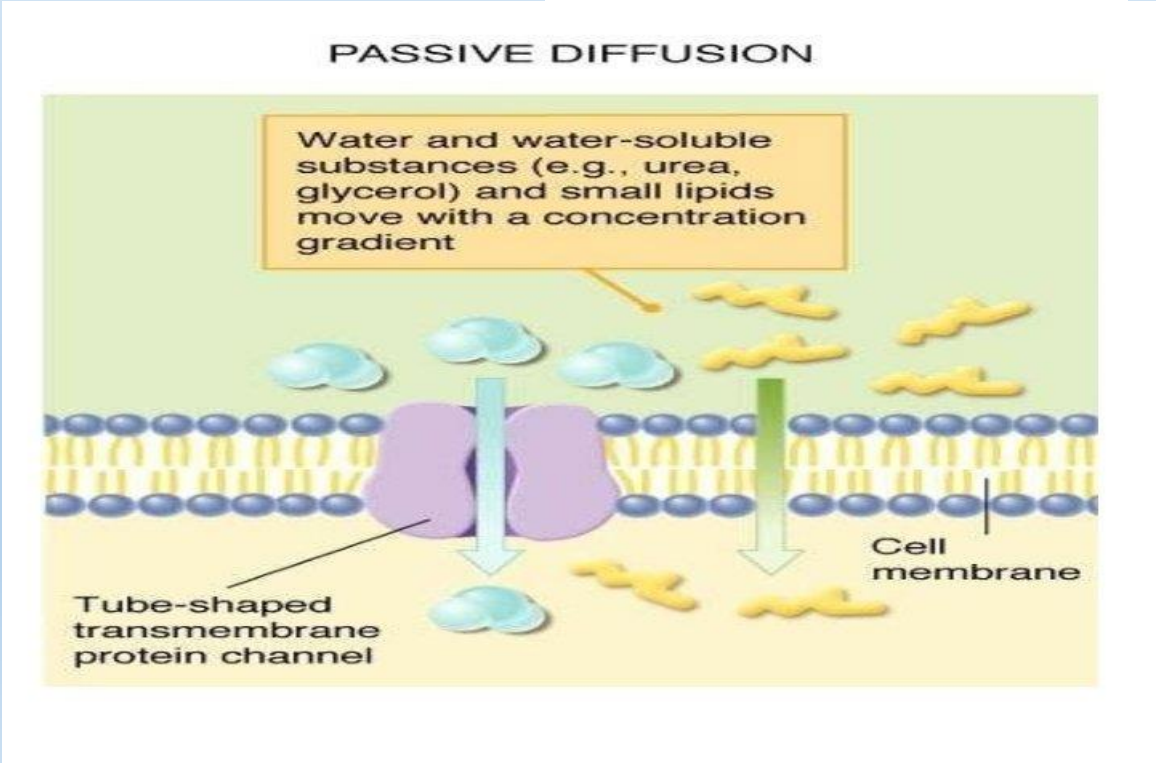
1. Passive diffusion (the most important)

- move passively from an area of high concentration to one of low conc**.**

-The rate is concentration dependent**.**

Cellular energy is **not** required





Factors affect passive diffusion

1-the concentration gradient

2-molecular size

3-lipid solubility

4- degree of ionization of the drug.

Lipid or water solubility is influenced by:

-structural properties of the drug molecules

-environmental pH.

Most drugs are either weak acids or weak bases.

Acidic drugs (HA) release a proton (H+),

causing a charged anion (A−) to form:

(unionized) HA ⟶ H+ + A− (unionised acid

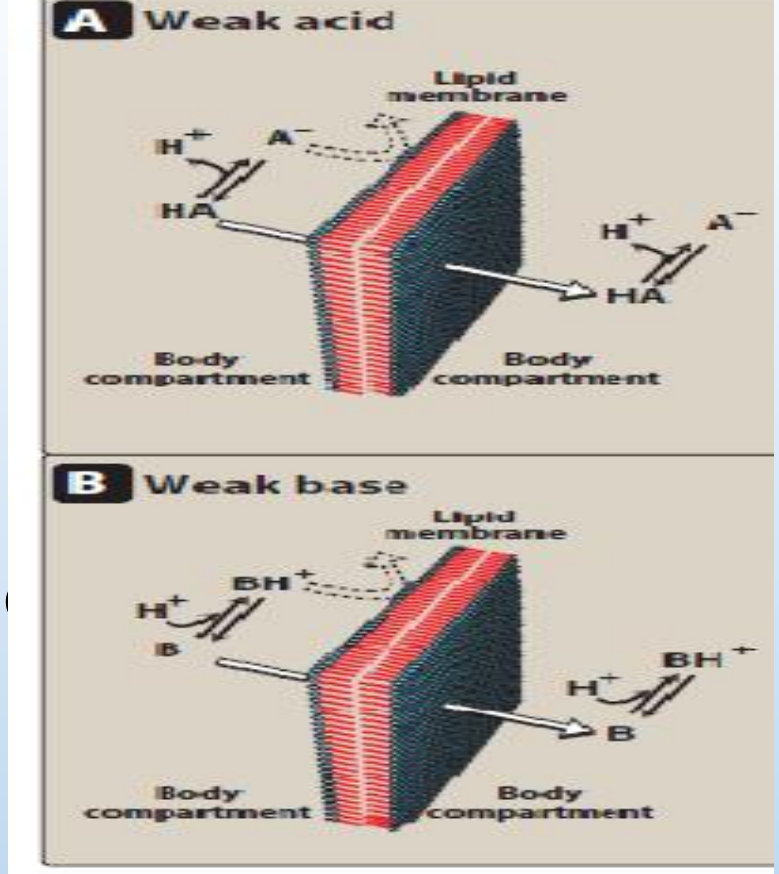
More readily permeates through membranes.

Weak bases (BH+) can also release an H+.

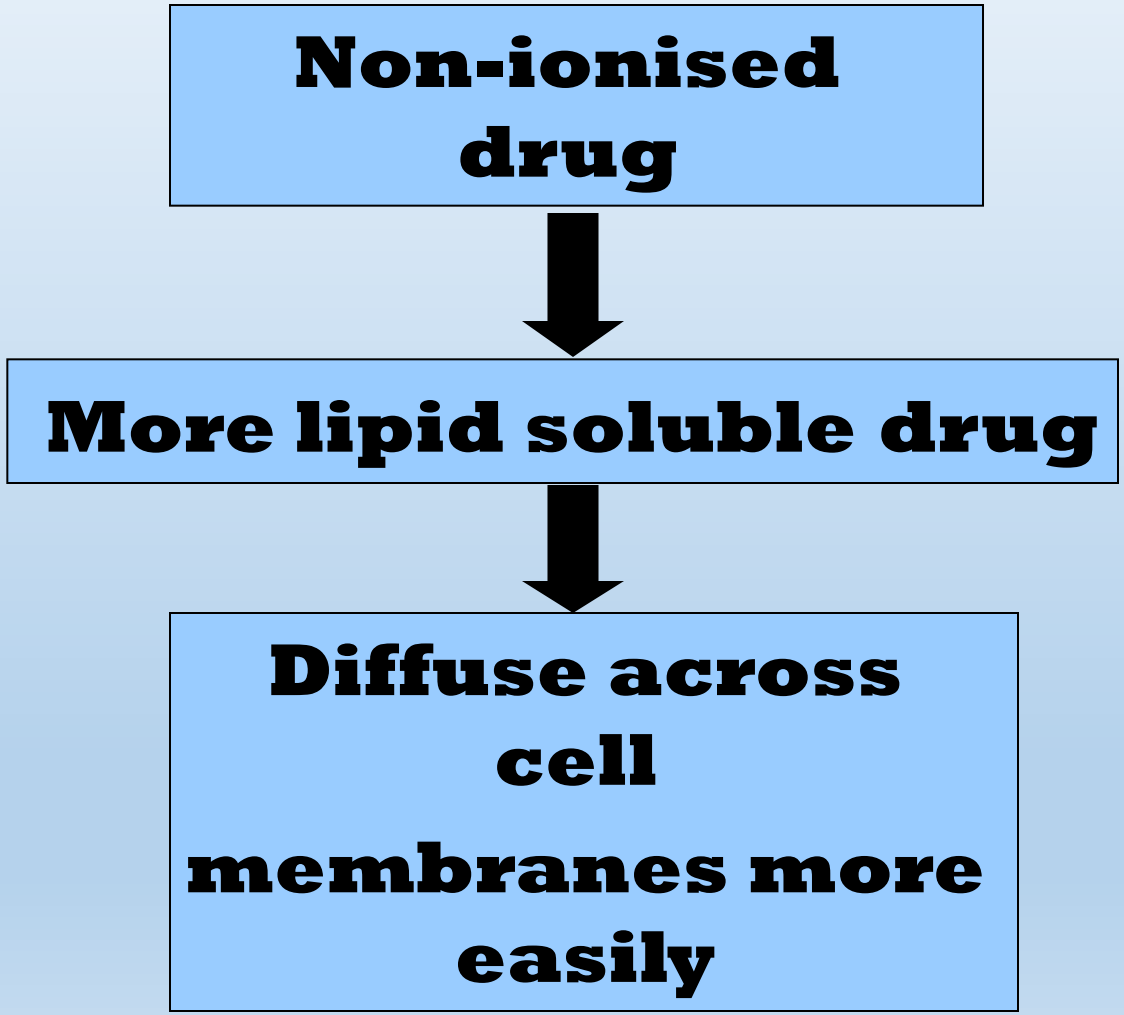
However, the protonated form of basic drugs is

usually charged, and loss of a proton produces the uncharged base (B):

(ionized) BH+ ⟶ B + + H+



Absorption & Ionization



Drugs are classified according to their ionization in response to environmental pH

A. Those that their **ionization is dependent on the environmental pH** (unionized=lipid soluble, ionized=water soluble)

B. Those that are **unionized** whatever the environmental pH (unionized lipid-soluble, non-polar compounds)

C. Those that are **ionized** whatever the environmental pH (ionized, water soluble, polar compounds)

A. Drugs ionized according to environmental pH

The extent to which a molecule has a tendency to ionize is given by the dissociation (ionization) constant, usually expressed as the **pKa** (i.e. negative logarithm of the Ka)

- **Acidic** drugs in an **acidic** environment become: **unionized,**

lipid soluble, easily diffusible.

- **Acidic** drugs in an **alkaline** environment become: **ionized,**

water soluble, non-diffusible.

pKa is the pH at which 50% of the drug is ionized

i.e. when aspirin pKa is 3.5, this means that at pH 3.5, 50% of aspirin is ionized

Gut pH varies: stomach 1.5, upper intestine 6.8, lower intestine 7.6, and pH inside the body 7.4.

Therefore, aspirin in stomach (acid in acid medium):

un-ionized, lipid soluble, diffuse easily into gastric epithelial cells.

Inside epithelial cells, pH is 7.4, aspirin becomes ionized, less diffusible, and localize there **(ion trapping)(this is one mechanism for aspirin-induced gastric injury)**

B. Drugs that are unionized whatever the environmental pH

Example: steroids (e.g. Prednisolone), chloramphenicol

- Unaffected by environmental pH
- Lipid soluble (non-polar compounds)
- Diffuse readily across tissues (good oral absorption)

c-Drugs that are permanently ionized drugs whatever the environmental pH

Water-soluble (polar)

- Limited capacity to cross membranes, poor GIT absorption, usually given parenterally

-Does not cross placenta; useful in pregnancy (heparin compared with warfarin)

They are either**: negatively charged** (acidic, e.g. heparin), or **Positively charged** (basic, e.g. ipratropium, tubocurarine, suxamethonium)

-One of the following characteristics of unionized drugs whatever the environmental pH is true:

a. Its water soluble

b. Its good oral absorption

c. Heparin is an example

d. Its usually given parenterally

e. Its can not cross placenta

2. Carrier- mediated transport

Active transport:

drugs are capable to move against concentration gradient

- require cellular energy.
- rapid diffusion.
- high degree of specificity.
-subjected to saturation and can be inhibited by other compounds, and are important for some drugs with structural similarity for endogenous molecules.

Examples: Levodopa across BBB

secretion of many weak organic acids and bases through renal tubules and biliary ducts e.g. penicillin probenecid and uric acid are actively transported in renal tubules

3-Facilitated diffusion

Occurs by the **carrier proteins.**

Net flux of drug molecules is from the high concentration to low concentration.

No energy is required.

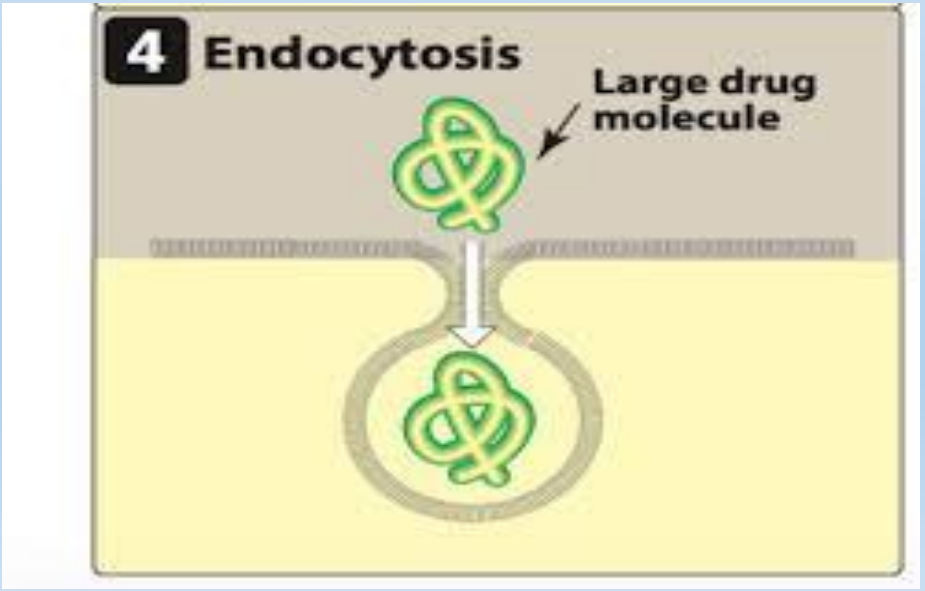
Saturable

Can inhibited by molecules competed for these carriers.

4-**Endocytosis** :The drug molecule holds on the cell membrane and then surrounded with plasma membrane and inserted into the cell within small vesicles

Large polar molecules such as peptides.

- Small polar substances such as vitamin B12 and iron combine with special proteins (intrinsic factor or transferrin) and the complexes enter the cell by this mechanism.



5-Filtration plays a minor role in drug transfer except for glomerular filtration. It occurs through water (aqueous) channels allowing passage of water soluble substances

Q-Active transport is characterized by one of the following:

a. It does not require energy

b. Its slower than passive diffusion

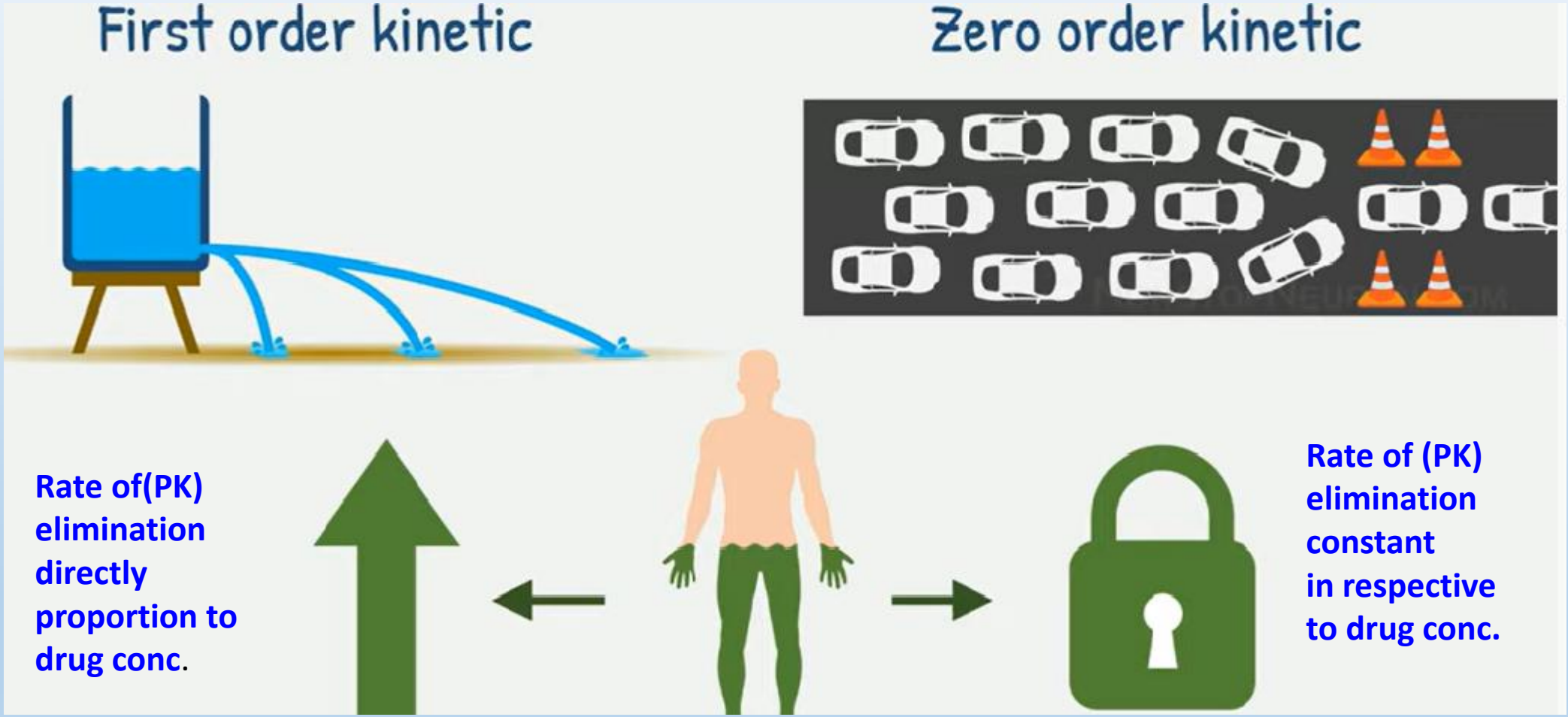
c. The transport occur mainly through water pores

d. It cannot move against concentration gradient

e. Its occurs in renal tubules only


STOP
Adobe Stock | #162946456

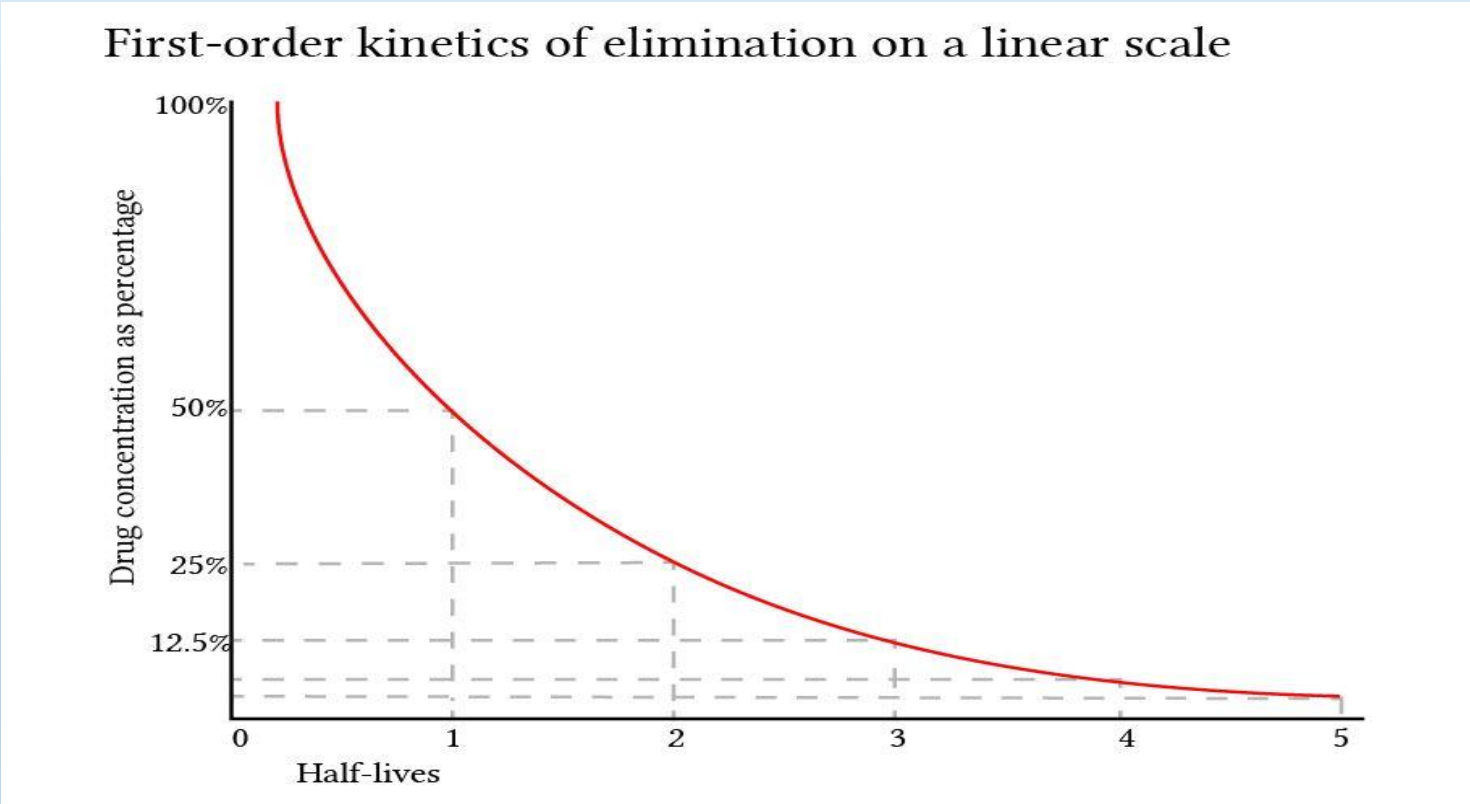
The order of the pharmacokinetic processes :Rate of processes



The order of the pharmacokinetic processes :

First order processes

A constant **fraction** (**proportion**, **percentage)** of the drug is processed per unit time e.g. 50% of the dose is metabolized per hour



In first order kinetics:

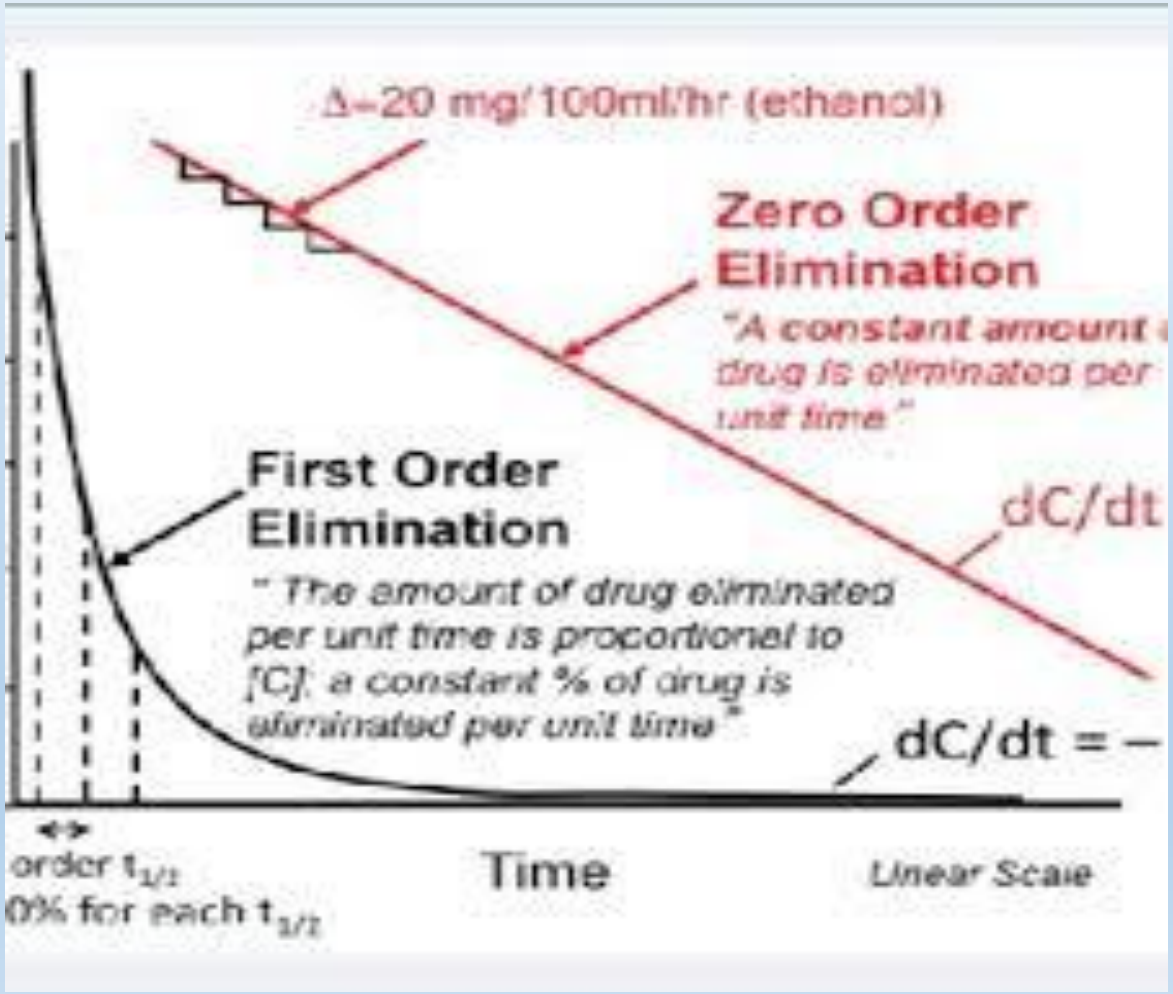
The rate of the pharmacokinetic process of a drug (A D M E) is **directly proportional** to the amount of the drug administered or to its concentration in the blood (high at high concentration, low at low concentration).

The plasma half-life (t1/2) (which is the time for any plasma concentration to fall by 50%) is **always the same** (**constant**) When different therapeutic doses are given.

The majority of drugs in doses used clinically follow first order kinetics but in overdose, their kinetic processes may get saturated.

Zero-order processes

A constant **amount** of the drug is processed per unit time e.g. 10 **mg** of the dose is metabolized per hour.



In zero-order (saturation) kinetics, the process may become easily saturated e.g. limited amount of metabolizing enzymes

A **small** increase in the dose can result in a **steep** and disproportionate increase in plasma concentration.

Examples of drugs following zero-order kinetics in **metabolism**:

Phenytoin, theophylline, ethanol and also aspirin in high therapeutic doses, Zero-order **absorption** applies to iron, also to depot formulation and to drug implants e.g. antipsychotics and sex hormones.

	First order kinetics	Zero order kinetics
Other names	**Linear** kinetics	**Non-linear,** saturation
Definition	Fixed **fraction** (proportion), a change of 10% per hour 1000 →900 →810 → 730 ..	Fixed **amount**, a change of 10 mg per hour 1000 →990 →980→970, ..
Half life	**Constant**; does not change with changing dose	**Varies**; increase with increasing the dose
Drug example	Paracetamol, ampicillin,….	Phenytoin, theophylline, ethanol
Predictability	Plasma concentration of the drug can be **predicted**	Plasma concentration **cannot be predicted** and TDM is necessary
Practical example	300mg dose produces 12mg/l concentration in plasma, an increase of dose to 400mg results in 16mg/l (proportional)	The same increase from 300mg to 400mg may increase plasma concentration from 12mg/l to more than 30mg/l

Plasma half-life and steady state concentration

Plasma elimination half life

Is the time taken for any plasma concentration to fall by half of its original value. It is **constant** if elimination follows first order kinetics

Half-life can be used:

1-to determine the dosing frequency if drug effect is directly related to plasma concentration.

2- calculate the time taken to reach a steady state.

3- calculate the time for the decline in plasma concentration after dosing ceases.

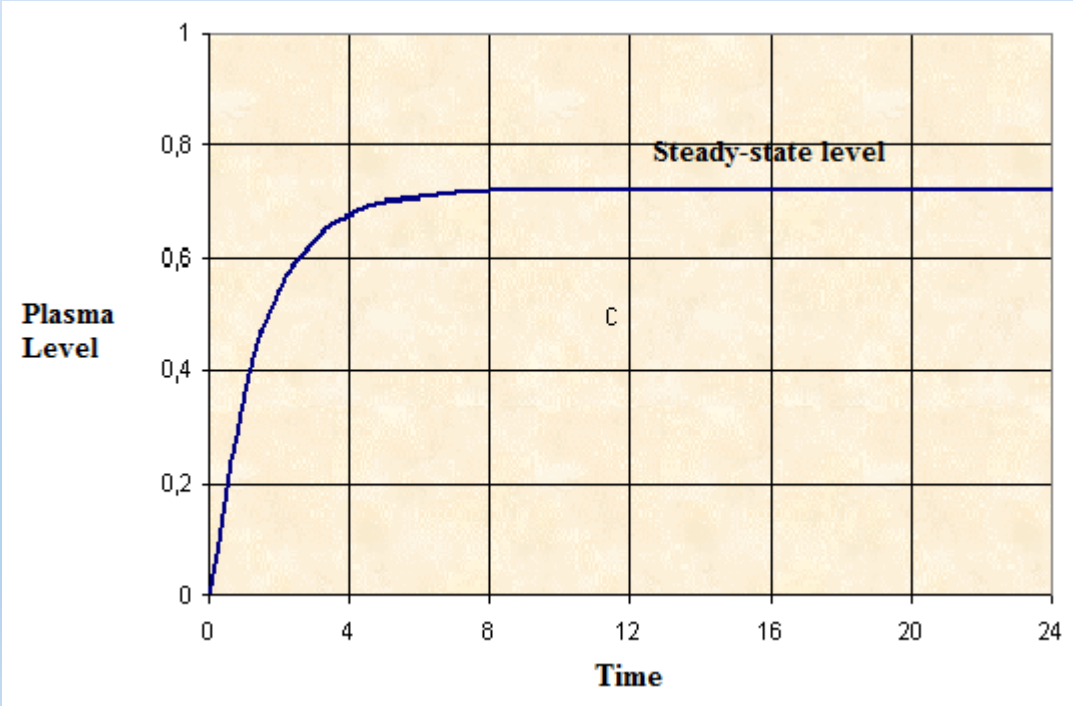
4- calculate the clearance and volume of distribution.

The steady state concentration

When a drug is given at a constant rate, the time to reach a steady state depends on the drug half-life and is practically reached after **five half-lives.**

In a steady state: The rate of administration is equal to the rate of elimination and the plasma concentration will be at a plateau

Any increase or decrease in drug dosing, the new steady state is reached after **five** half-lives.



example; the time required to reach a steady state concentration for dobutamine (t1/2 is 2 minutes) is 10 minutes, and for digoxin (half life is 36 hours) is 7.5 days (here, a loading dose is required to reach SS state quickly).

Half-life **varies** in the population over a range of values but a single average half life is given for clarity, **examples**:

Adenosine	< 2 seconds	Paracetamol	2hours
Dobutamine	2 minutes	Diazepam	41 hour
Benzylpenicillin	31 minutes	Piroxicam	45 hours

Plasma concentration can be measured for therapeutic purposes **(Therapeutic Drug Monitoring, TDM)** if the drug effect is related to drug concentration at receptors in the tissues (drugs that can be easily under- or overdose)

A drug with a half-life of 10 hours is administered by continuous intravenous infusion. Which of the following best approximates the time for the drug to reach steady state?

A. 10 hours.

B. 20 hours.

C. 33 hours.

D. 70 hours.

E. 50 hours

Individual Pharmacokinetic processes

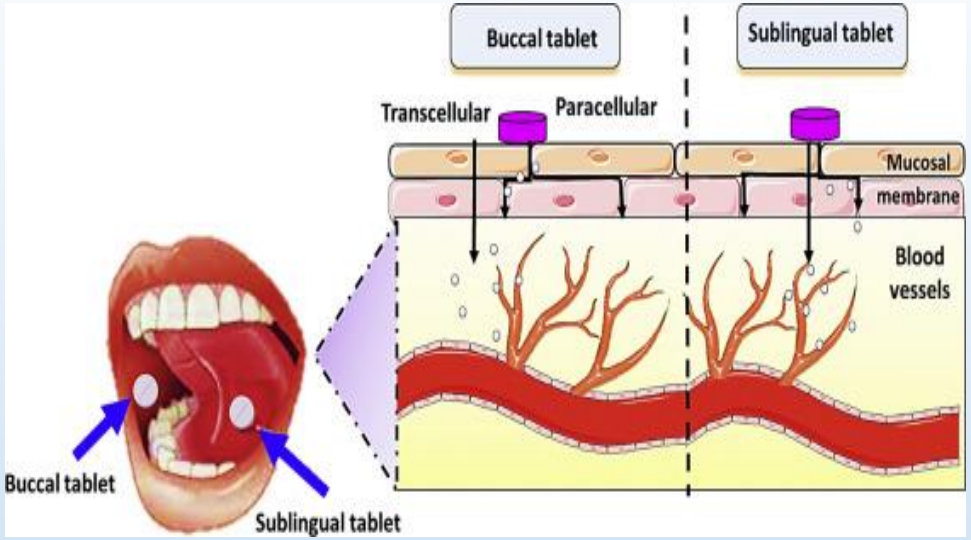
1-Absorption

Absorption from GIT

*Small intestine is the **main site** of absorption of drugs**.**

*Stomach does not play a major role in absorbing drugs **(small surface area, rapid gastric emptying),** even with acidic drugs; the **onset** of absorption occurs in stomach, but the main part of the dose is absorbed in the small intestine.

*The colon is also capable of absorbing drugs particularly slow-release formulations (SR)



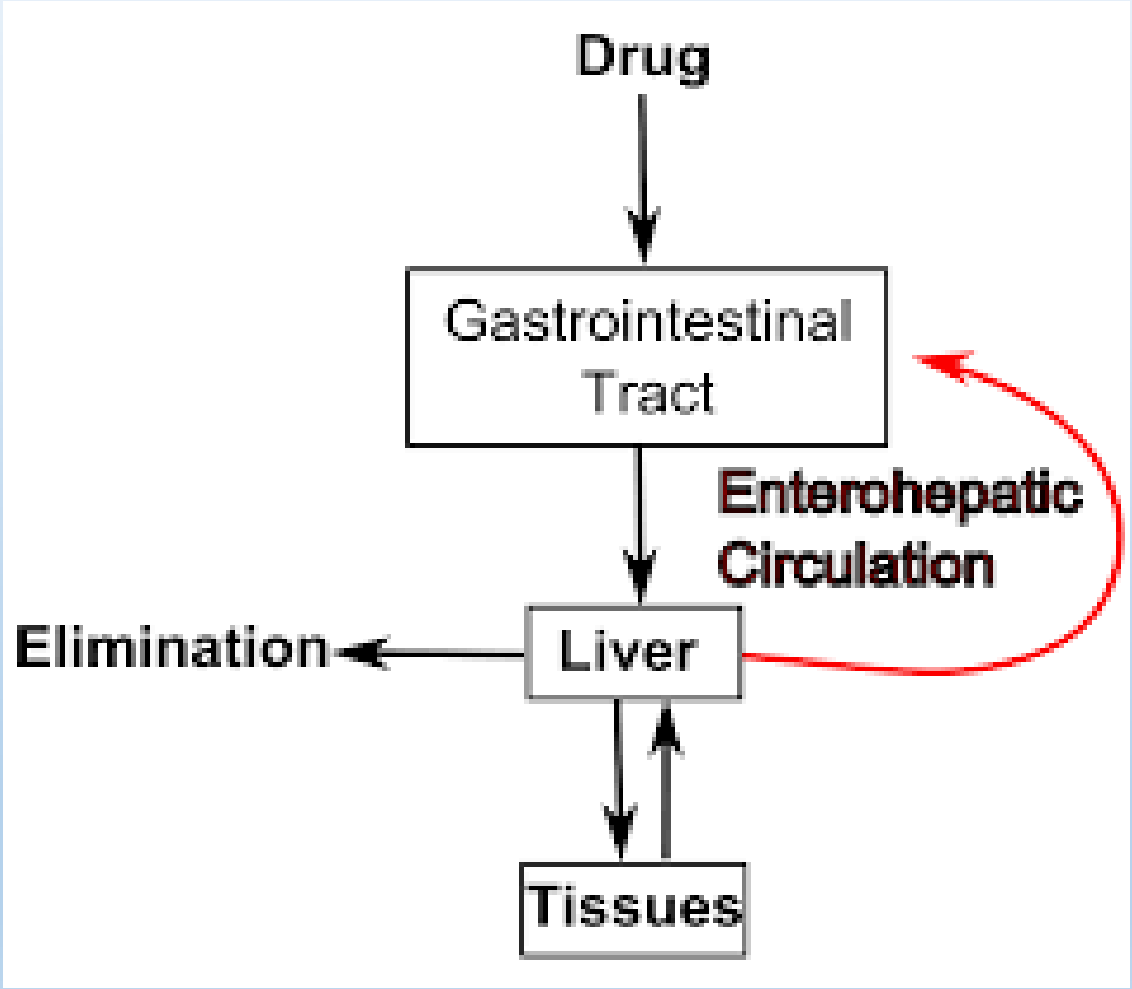
Buccal absorption is rapid for lipid-soluble drugs; blood flow is abundant, entry into systemic circulation avoiding first pass Metabolism.

Enterohepatic circulation

Bile salts are conserved about 8 times a day. A number of drugs form conjugates with glucuronic acid and are excreted in bile.

Glucuronides are polar (ionized) and are not absorbed, but the parent drugs are released by being hydrolyzed by intestinal enzymes and bacteria.

Recycling helps to sustain plasma concentration and increase duration of action. **Examples**: sulindac, ethinylestradiol


Drug
Gastrointestinal Tract
Enterohepatic Circulation
Elimination
Liver
Tissues

Bioavailability (Systemic availability)

Systemic availability is the percentage of the administered dose that reaches the systemic circulation intact. In simple terms, bioavailability Is how much of the drug dose is available to produce a biological effect.

Bioavailability is useful to:

1. Determine the dose and route of administration e.g. propranolol i.v. 1-10mg, oral 10-320mg (because of FPM); a drug with oral bioavailability of 5% should not be given orally.

2. Compare between different formulations of a drug e.g. sublingual GTN >90%, oral GTN <10%.

3. To know the large number of factors that might increase or decrease the systemic availability of a drug and lead to failure or to toxicity.

bioavailability is calculated from the equation:

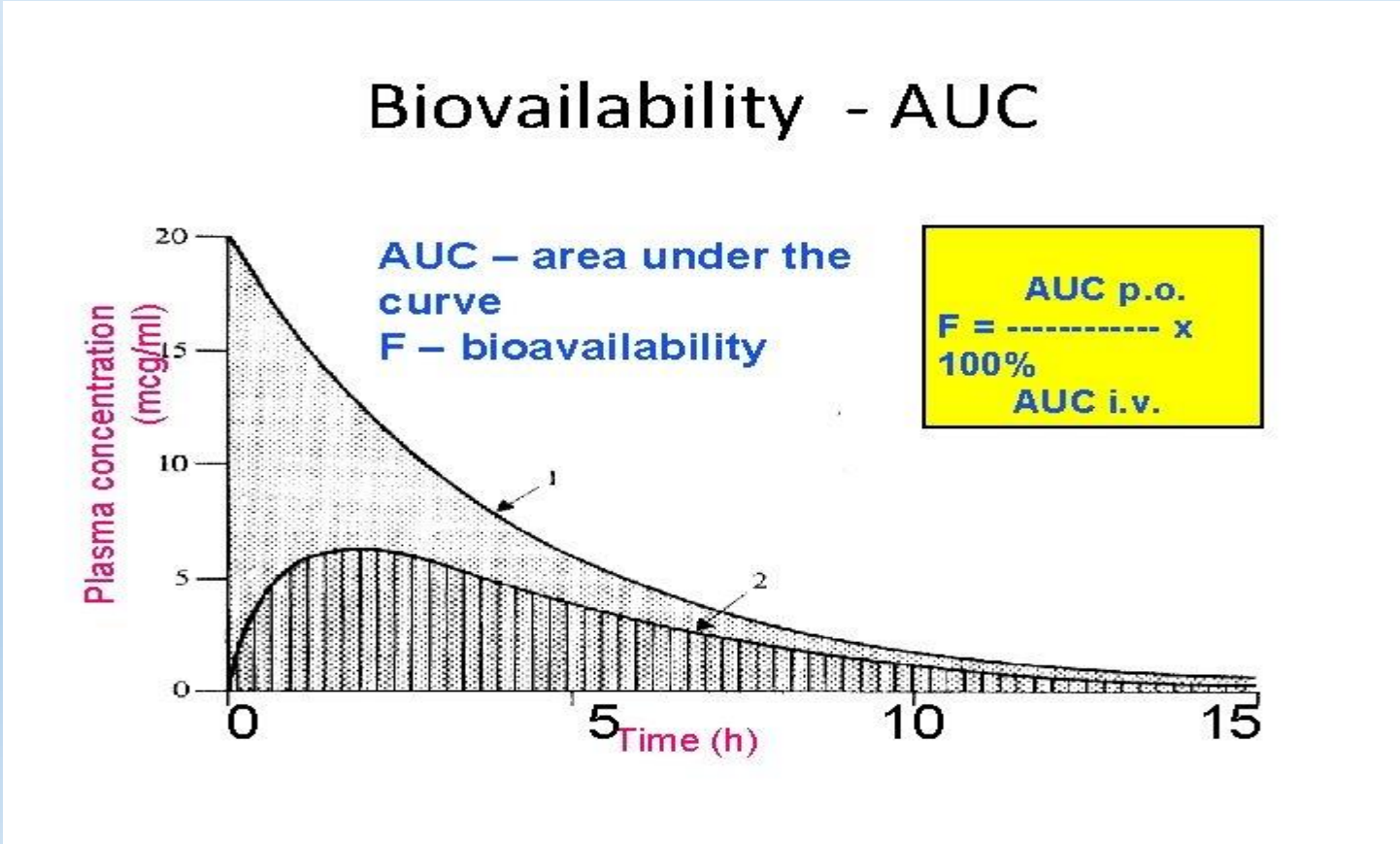
AUC oral .

---------- X 100

AUC i.v

AUC = Area under plasma concentration-time curve

A drug injected i.v. is 100% available to exert its biological effect.



Factors affecting systemic availability

1. Pharmacological factors

a. Drug properties: e.g. instability in gastric acid such as benzylpenicillin in gastric acid.

b. Pharmaceutical factors: type of ingredients, compression force,….affecting disintegration and dissolution of the tablets e.g. tablets containing same amount of digoxin made by different companies may produce different plasma concentrations and therefore different effects.

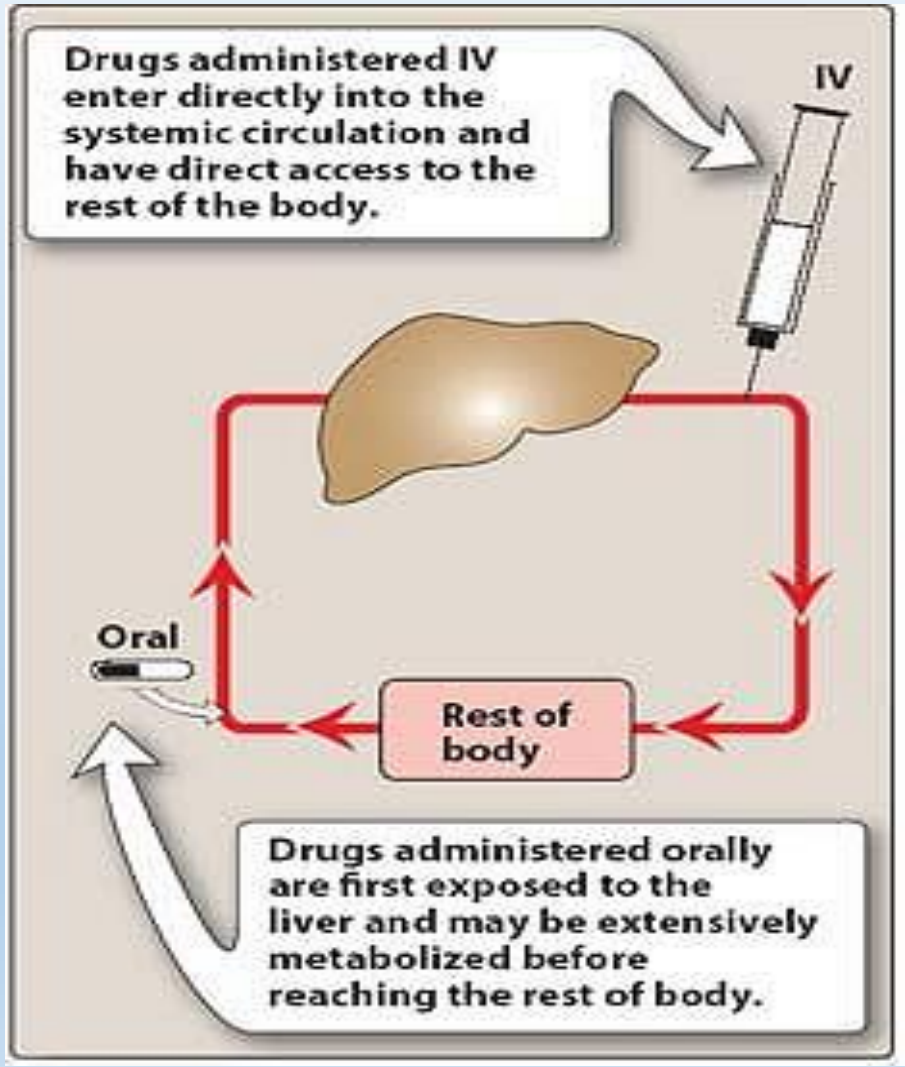
c. Interaction with other substances in the gut e.g. food and drugs (such as tetracycline binding to calcium and iron)

2. Patient characteristics

- disease e.g. (malabsorption, hepatic dysfunction)
- GI factors e.g. motility, pH, and blood flow
- genetic factors e.g. acetylator status: fast and slow

3. Pre-systemic (first-pass) elimination (FPM)

It is the extent of drug metabolism which takes place after oral administration during **first passage** of the drug through the gut wall and mainly through the liver **before reaching** the systemic circulation.



Examples of drugs undergoing extensive (>50%) first pass metabolism (FPM)

Hepatic:

Beta blockers (e.g. propranolol, metoprolol)

Opioids (e.g. morphine, pethidine)

Antiarrhythmics (e.g. lignocaine, verapamil)

Others (e.g. glyceryl tri-nitrate GTN, imipramine)

Gut wall: Estrogens, levodopa, isoprenaline

The importance of extensive FPM

1. It is a major **source of variations** between individuals in response to drugs. A small change in first pass metabolism will have a relatively large effect on systemic availability if the drug is extensively metabolized.
2. If the FPM is over 95% e.g. lignocaine, then the **oral route is not** suitable.
3. In severe **hepatic disease** e.g. cirrhosis with both impaired liver cell function and shunting of blood into systemic circulation; FPM is reduced and systemic availability is increased (i.e. exaggerated response to normal doses).

The effect of food on drug kinetics

1. Changes in gastric emptying (slower absorption of most drugs)

2. Drug chelation (tetracycline and dietary calcium; iron and tannic acid in tea and coffee).

3. Changes in drug metabolizing enzymes (induction by alcohol, charcoal grilled beef, brussel sprout).

4. Changes in splanchnic blood flow (increased after food), FPM is reduced.

Food can decrease bioavailability of certain drugs: Examples

Ampicillin **(markedly reduced)**

Erythromycins **(except erythromycin estolate)**

Rifampicin and INH (anti-Tb)

Atenolol and captopril

Food can increase bioavailability of certain drugs: Examples

- propranolol, metoprolol, hydralazine
- griseofulvin, nitrofurantoin, mebendazole (particularly by fatty food)
- Erythromycin estolate

II. Distribution

Drug distribution is the process by which a drug leaves the bloodstream and enters the interstitium (extracellular fluid) and/or the cells of the tissues.

The extent of distribution depends on:

-water/lipid solubility

-protein and tissue binding

- ability to cross cell membrane passively or actively

The volume of distribution (Vd)

It is a theoretical **(apparent)** volume of fluid in which the drug dose appears to distribute with a concentration equal to that in plasma .

$$Vd = \frac{\text{Dose}}{Co}$$

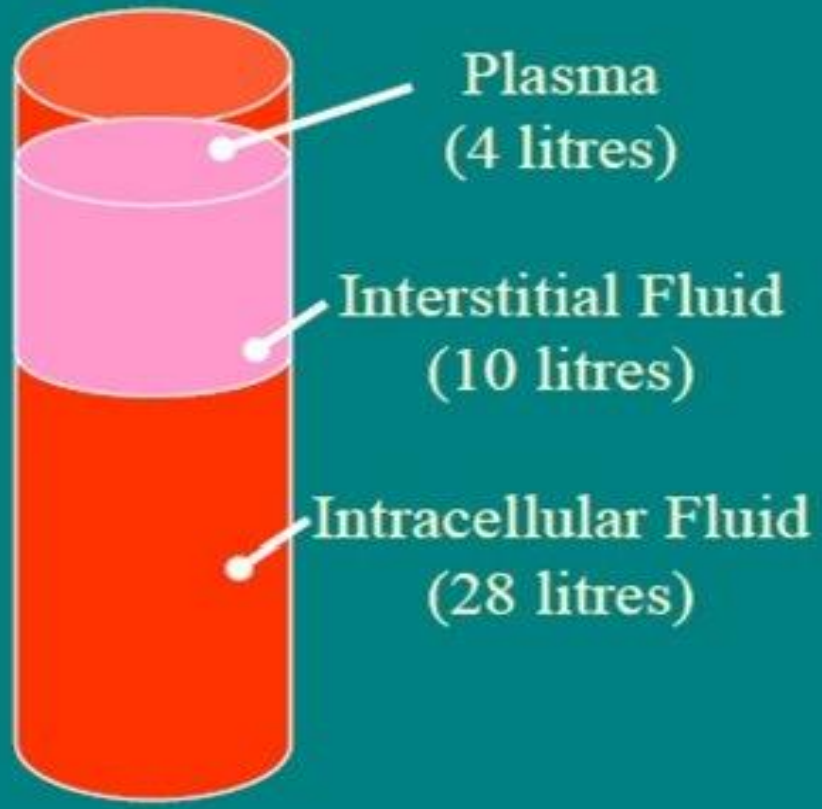
Co is the initial plasma concentration,

Volume of Distribution (V)

Drugs may distribute into any or all of the following compartments:

- **Plasma**
- **Interstitial Fluid**
- **Intracellular Fluid**

Total Body Fluid = 42 L (approx.)



- If 500 mg of drug reaches circulation...(total amount of drug)
- And if plasma concentration is 0.5 mg/ml
- Vd will be 500/0.5 = 1000 ml.
- Which means you require 1000 ml of fluid to accommodate total 500 mg of drug at concentration of 0.5 mg/ml.
- At times it can be larger than total blood volume. (when drug has been **stored in peripheral tissues** so lower blood concentration).
- At times it can be smaller than or equal to total blood volume(when drug **remains in vascular compartment**).

Vd is small: if the drug remains mostly in plasma e.g. warfarin which is highly protein bound (also tolbutamide, salicylates)

Vd is large: if the drug is present mainly in the tissues e.g. digoxin, pethidine, nortriptyline, and chloroquine.

- Plasma compartment:
  - Drugs having high molecular weight or extensively plasma protein bound like heparin Vd= 4L
- Extracellular fluid:
  - Low molecular weight but hydrophilic drugs
  - Aminoglycosides Vd=14L
- Total body water:
  - low molecular weight and lipophilic,
  - E.g *Ethanol* Vd=42 L

A 40-year-old male patient (70 kg) was recently diagnosed with infection involving methicillin-resistant *S. aureus*. He received 2000 mg of vancomycin as an IV loading dose. The peak plasma concentration of vancomycin was reported to be 28.5 mg/L. The apparent volume of distribution is:

a. 1 L/kg.

b. 10 L/kg. =

c. 7 L/kg

d. 70 L/kg.

e. 14 L/kg.

Answer????

The significance of the Vd

In drug overdose; removal of a drug by hemodialysis is appropriate for drugs with small Vd i.e. a major proportion of the dose is present in plasma.

Drug interaction is likely to occur between those with small Vd e.g. displacement from protein binding.

Examples

Drugs	**Vd (in L/70kg)**
Aspirin	5
Atenolol	75
Diazepam	140
Chloroquine	1300

The significance of protein binding

1. It is a source of drug interaction. Displacement may be important for drugs which are highly protein bound and at the same time having small Vd e.g. warfarin and NSAIDs; the free fraction of warfarin is increased leading to bleeding.

2. In renal and liver failure

The free fraction of drugs may increase and therefore, increase in response or toxicity because of hypo-albuminemia and accumulation of endogenous substances that may cause displacement from protein binding sites.

Examples of protein binding of drugs

Drugs	~ % protein bound
Isoniazid, lithium, ethosuximide	0%
Atenolol	5%
Ampicillin	15%
Digoxin	25%
Phenobarbitone	50%
Propranolol	95%
Diazepam	98%
Tolbutamide	98%
Warfarin	99%
Ibuprofen	>99%

III. Metabolism

Only few drugs excreted unchanged

Metabolism changes drugs in two major ways:

1. **by reducing lipid solubility (increased elimination)**
2. **by altering biological activity which occurs in 3 possible ways:**

2. altering biological activity of drug:

a. Conversion of pharmacological active to an inactive substances (most drugs)

b. Conversion of active to another active substance. This prolongs the duration of action

diazepam → oxazepam

Codeine → morphine

Amitriptyline → nortriptyline

3-Conversion of inactive (a pro-drug) to active

levodopa → dopamine

cyclophosphamide → 4-ketocyclophosphamide

Sulfasalazine → 5-aminosalicylic acid

Sites of metabolism

Organs: liver (most important)

Kidney (vitamin D, insulin)

Gut mucosa (isoprenaline, levodopa, estrogen and progesterone

Gut flora (sulfasalazine, hepatic conjugates)

Lung (serotonin, noradrenaline, prostaglandins,testosterone, isoprenaline)

Skin (vitamin D activation, minoxidil, and capsaicin)

Intracellular sites

microsomal (mostly), mitochondria, cytoplasm, plasma

Drug metabolism can occur in two phases:

1: The most important reaction is oxidation by **mixed-function**

Oxidases in the microsomes (the final component of these oxidases is cytochrome P450; mixed means for aliphatic and aromatic

Phase 1 metabolism may occur in:

a) **the endoplasmic reticulum** (microsomal)
b) **cytoplasm**: xanthine oxidase, ethanol metabolism
c) **mitochondria**: monoamine oxidase
d) **plasma**: pseudocholinesterase, histaminase

N.B. Not all drugs broken down by enzymes e.g. melphalan which undergoes spontaneous hydroxylation to inactive metabolites.

Phase II metabolism

Drugs +water soluble molecule=water soluble conjugate
eliminated by kidney or bile e.g. glucuronides, sulfate and others.

Phase II metabolism almost invariably terminates biological activity

Examples

Glucuronide conjugation: salicylates, paracetamol, morphine
Sulfate conjugation: paracetamol, estrogen, steroids.
Acetylation e.g. INH, hydralazine (N-acetyltransferase)
Glutathione conjugation e.g. halothane, paracetamol overdose.
Most drugs undergo both phase I and II reaction; few have no major conjugates e.g. warfarin

Enzyme induction

Enzyme induction refers to the increase in enzyme amount and activity as a result of exposure to certain chemicals

It is accompanied by hypertrophy of liver cell endoplasmic reticulum which contains most drug metabolizing enzymes.

Non- microsomal enzymes are not inducible

Examples of enzyme inducers: barbiturates, rifampicin, phenytoin, carbamazepine, griseofulvin, smoking, chronic (not acute) alcohol ingestion

The importance of enzyme induction

1. It can be responsible for clinically important interactions

Examples

a. contraceptive failure if potent inducers are taken at the same time

b. increased breakdown of vitamin D resulting in osteomalacia and hypocalcemia; and also in megaloblastic anemia due to folate deficiency.

c. failure of anticoagulant therapy due to reduction of warfarin level.

Enzyme induction =decrease of drugs concentration
=failure of drug action

2.Tolerance to certain drugs may occur e.g. with antiepileptic drugs which can induce their own metabolism.

3. Drug toxicity may be more likely e.g. in paracetamol overdose and in patients on rifampicin or INH (hepatotoxicity).

4. Enzyme inducers can alter liver function tests The level of serum bilirubin helps to distinguish the effect of enzyme induction from that of liver disease.

5. Enzyme induction can be used as a therapeutic mean e.g. phenobarbitone can reduce severe hyperbilirubinemia in neonates by stimulation of fetal hepatic glucuronyl transferase.

Enzyme inhibition

Enzyme inhibition is an important mechanism for drug-drug interaction

and can lead to drug accumulation and toxicity particularly with drugs

Of low therapeutic index.

A. General non-specific inhibition of microsomal enzymes e.g.

cimetidine (inhibits metabolism of warfarin, diazepam, propranolol)

Other examples: sodium valproate, chloramphenicol, INH, single large dose of ethanol

Enzyme inhibition =drugs accumulation =increased side effects + toxicity of drugs

30-year old epileptic female patient has been well controlled on carbamazepine tablets; 200mg twice daily. She developed dizziness, diplopia and ataxia following prescription of erythromycin for tonsillitis. Explain.

Erythromycin Enzyme Inhibitors so inhibit metabolism of carbamazepine lead to increased side effect of this anti-epileptic drug **which is : dizziness, diplopia and ataxia**

B. Inhibition of specific enzymes could be a mechanism for therapeutic action of drugs

e.g. captopril inhibits ACE
aspirin inhibits cyclooxygenase

selegiline inhibits MAO(B)

allopurinol inhibits xanthine oxidase

4-Elimination

Drugs can be eliminated by the following mechanisms:

1. **Metabolism**
2. **Storage** e.g. highly lipid soluble drugs in fat, heavy metals in bone, phenothiazines and chloroquine in melanin-containing tissues
3. **Excretion**

Renal excretion: is the most important route of excretion if the drug is water-soluble and of low molecular weight

Three mechanisms for excretion

a. Glomerular filtration

- remove small molecules less than the size of albumin, therefore drugs binding to plasma proteins slows the filtration rate of drugs.

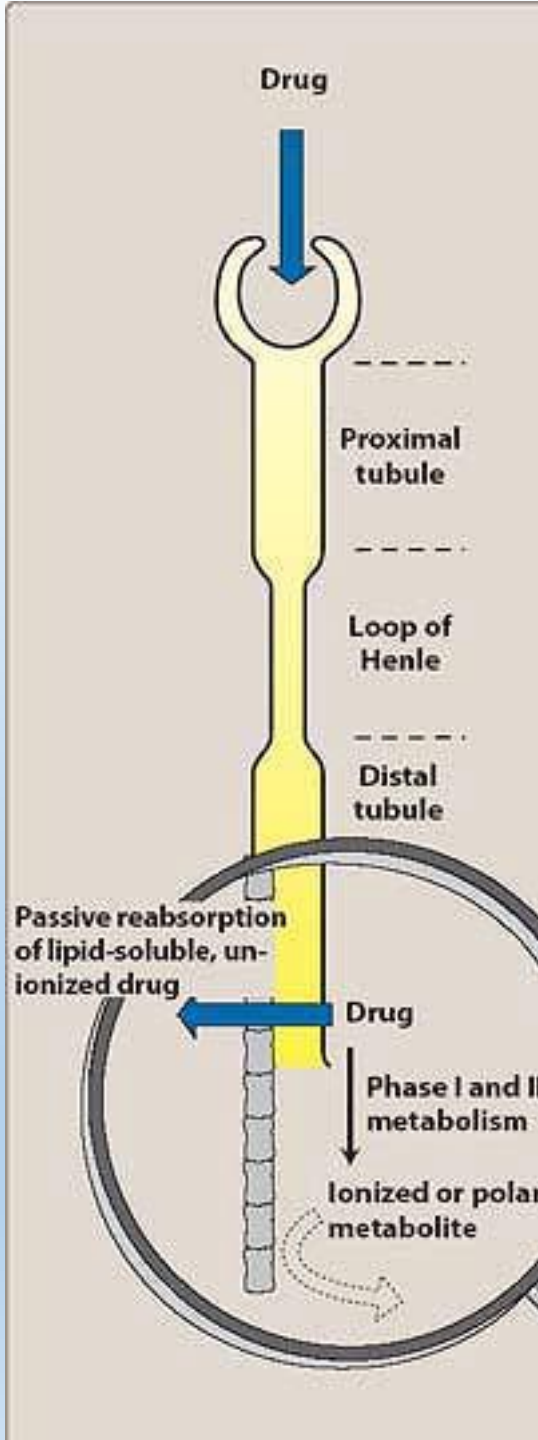
b. Active tubular secretion

- requires energy
- shows competition and saturation
- occurs in the proximal tubules

There are two active transport systems

For **weak acids** e.g. penicillin, probenecid, phenobarbitone, aspirin

For **weak bases** e.g. amphetamine, imipramine, chloroquine

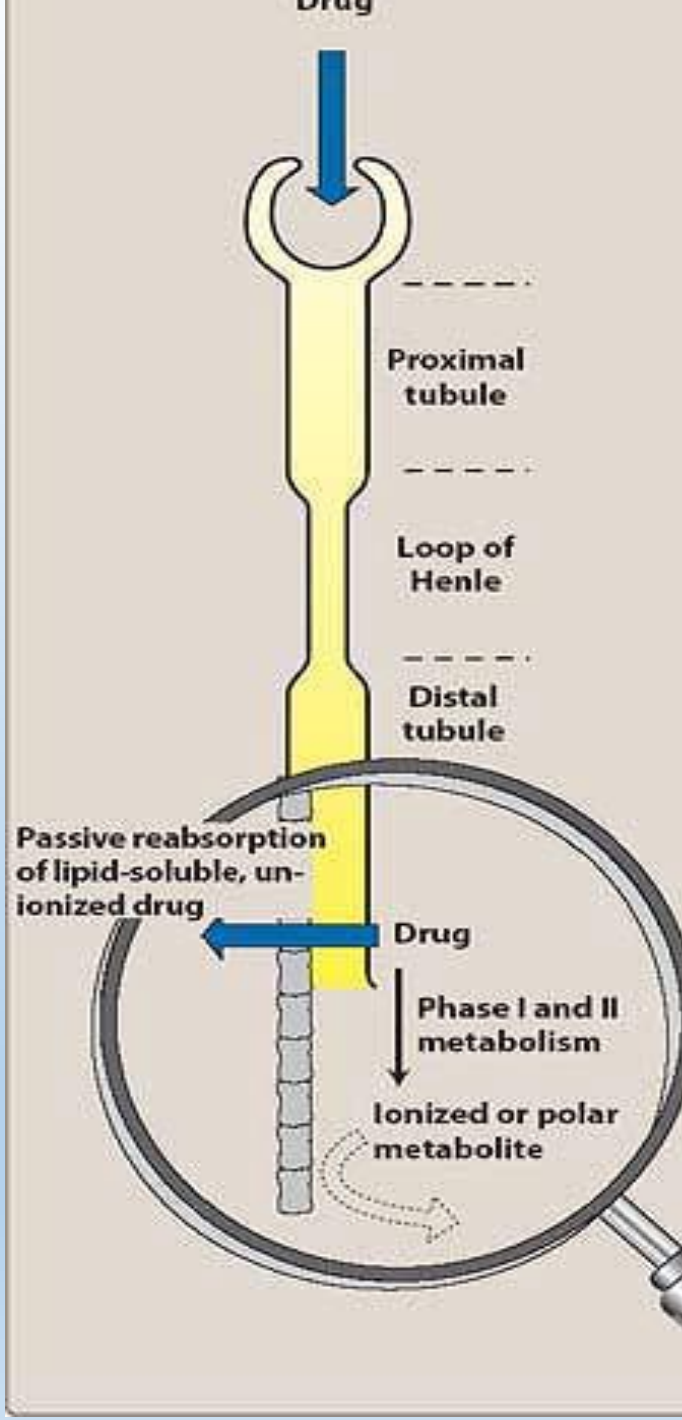


c. Tubular reabsorption

- may be active or passive
- the passive is controlled by the pH of the tubular fluid and pKa of the drug.
- acids are best eliminated in alkaline urine and bases best in acid urine.

Drug clearance: is the volume of the body compartments from which the drug is removed in unit time.

Total body clearance of the drug is the sum of the clearances by all routes of elimination (usually hepatic and renal).



Elimination in milk

Only free (unbound) drug can be excreted in milk according to pH, pKa, and lipid-solubility

Milk pH is toward **acidic side** and, therefore, basic drugs ionize and may accumulate in milk. Examples of drugs contraindicated during breast feeding: chloramphenicol, anticancer drugs, and repeated doses of ergot alkaloids

Pulmonary elimination

Important for volatile anesthetics and for alcohol (from medico legal aspect)from blood .

Fecal elimination

Either the drug is not absorbed Passive diffusion

Biliary elimination

A patient with severe renal impairment, his doctor prescribed for him gentamicin 40 mg three times daily for treatment of urinary tract infection. The nurse, **by mistake, gave him an ampoule of 80 mg three times daily.** He developed deafness. What is the possible explanation?

PK:-polar ,given parenterally IV,IM

More than 90% of the parenteral gentamicin are excreted unchanged in the urine

accumulation occurs in patients with renal dysfunction, and dose adjustments is required.

Which of the following phase II metabolic reactions makes phase I metabolites readily excretable in urine?

A. Oxidation.

B. Reduction.

C. Glucuronidation.

D. Hydrolysis.

E. Alcohol dehydrogenation