PHARMACOKINETICS (ADME)

www.youtube.com/pharmacologyconceptsbyrajeshchoudhary

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DESCLIMER:

Content of the slide is taken from various books, online contents and google images for the education purpose only

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INTRODUCTION

"What does the body do to the drug?"

"Drug movement throughout the body"

- Pharmacokinetics studies;
  - **Absorption**
  - **Distribution**
  - **Metabolism**
  - **Excretion**

} **Elimination**

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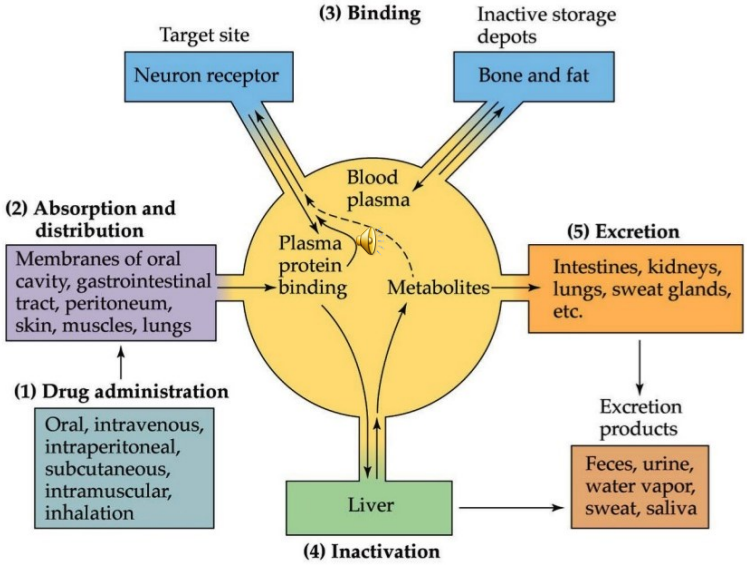
Pharmacokinetics



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ABSORPTION

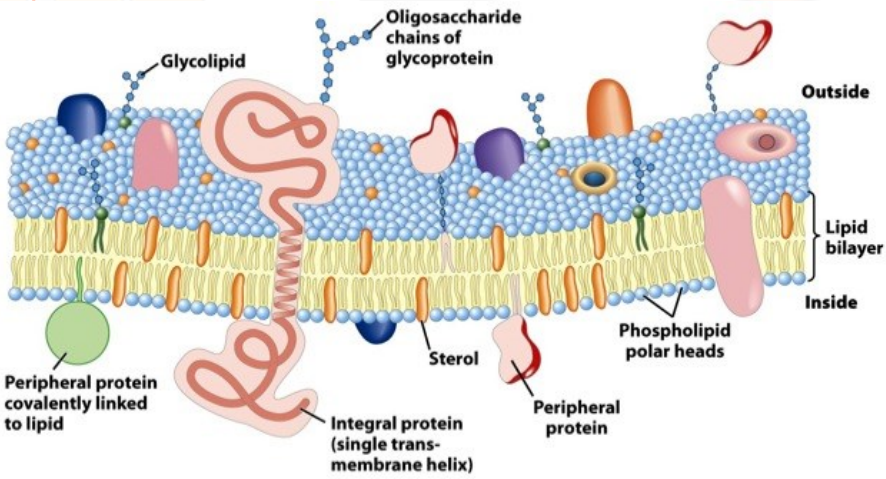

Fig. Plasma membrane

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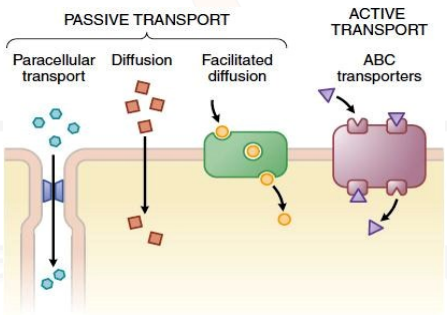
GENERAL INFORMATION

- The absorption is the transportation of the drug across the biological membranes into systemic circulation via portal vein.
- There are different mechanisms for a drug to be transported across a biological membrane:

- ✓ **Passive (simple) diffusion**
- ✓ **Filteration/pore/paracellular**
- ✓ **Facilitated diffusion**
- ✓ **Active transport**
- ✓ **Electrochemical/ionic diffusion**
- ✓ **Ion pair transport.**
- ✓ **Endocytosis/Pinocytosis**



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SIMPLE (PASSIVE) DIFFUSION

- **The major role** for the transportation of the drugs across the cell membrane is simple (passive) diffusion.
- The substances move across a membrane according to a concentration gradient (High to Lower).
- The **concentration gradient** is the factor that determines the **route** and **rate** of the diffusion.
- No energy is required.
- There is no special transport (carrier) protein.
- No saturation.
- **The concentration gradient** and the **lipid solubility** of the drug are the two main factors that determine the diffusion rate (speed) of the drug.
- Molecular weight of the high lipophilic drugs is not important as much as in the drugs that are soluble in water, BUT MW OVER 1000 is generally restrictive!!!

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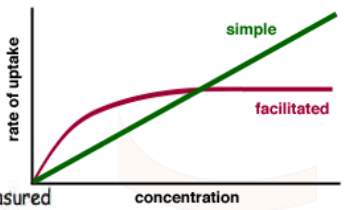
SIMPLE (PASSIVE) DIFFUSION

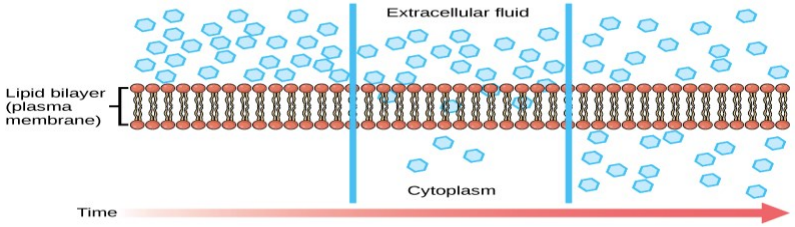
•**Ficks first law of diffusion** (diff. α Conc. Gradient)

Fick's First Law of Diffusion -The rate of diffusion across a plane is proportional to the concentration gradient across the plane and to the area of the plane.

$$J = \frac{DA(C_A - C_B)}{\Delta X}$$



J = flow of solute from region A to region B in the solution
D = diffusion coefficient of the solute in a given solvent
A = cross-sectional area thru which the flow of solute is measured
$C_A - C_B$ or ΔC = the difference in [solute] between regions A & B
ΔX = the distance between regions A and B (membrane thickness)



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FILTERATION/PARACELLULAR TRANSPORT

- **The simple diffusion of the drugs with high solubility in water** occurs via the **aqueous pores (4 Aº)** found on the cell membrane (i.e. caffeine, ascorbic acid, acetylsalicylic acid, nicotinamide, urea, glucose).
- Aqueous pores **do not** play a major role in the simple diffusion of the drugs across the cell membrane.
- Mol. Wt should less then 100 dalton.
- In case of capillaries (except brain), pore size is extent to 40 Aº to filter large molecules. E.g., albumine.
- Capillary absorption/filteration is important on Renal excretion, removal of drug from CSF, and entry of drug into lever.

$$\text{rate of filteraion} = N R^2 A (dC)/\eta h$$

N = no. of pores
R = radius
A = area
dC = conc. Gradient
η = viscosity
h = thicknes

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FIRST ORDER KINETICS

- **Fick's law**: Simple (passive) diffusion of the molecules from the cell membrane depends on Fick's law.
- It represents **the rate of simple diffusion** for non-polar molecules.
- The rate of diffusion (**dn/dt**) is the change in the number of diffusing molecules inside the cell over time.
- Diffusion rate $(dn / dt) = \dfrac{D \times A \times (C_{out} - C_{in})}{d_x}$
- **rate of diffusion = Ka x C_{out}** (or only C)
- Rate of diffusion is proportional to the *concentration of the drug at the administered area.*

ZERO ORDER KINETICS

- If the absorption occurs independently from the concentration of the drug (**rate of diffusion = Ka x C_{out}**, where C: C^0:1), then it fits to the "zero order kinetics".
- Concentration has no effect on the diffusion rate of the drug, ***the absorption occurs in a constant speed***.

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FACILITATED DIFFUSION

- Require a carrier protein/system (PERMIASE) to transport the drug across the membrane.
- Net flux of drug molecules is from the high concentration to low concentration.
- No energy is required.
- Saturable
- **Polar drugs. E.g., trasport of glucose (GLUTs) and amino acids**
- **Trasport of Vit B 12 [intrinsic factor-1 (IF-1)-glycoprotein]**

ACTIVE TRANSPORT

- The transportation of the drug molecules across the cell membrane **against a concentration or an electrochemical gradient**.
- It requires **energy** (ATP) and a special **transporter (carrier) protein**.
- There is «transport maximum» for the substances (the rate of active transport depends on the drug concentration in the enviroment).

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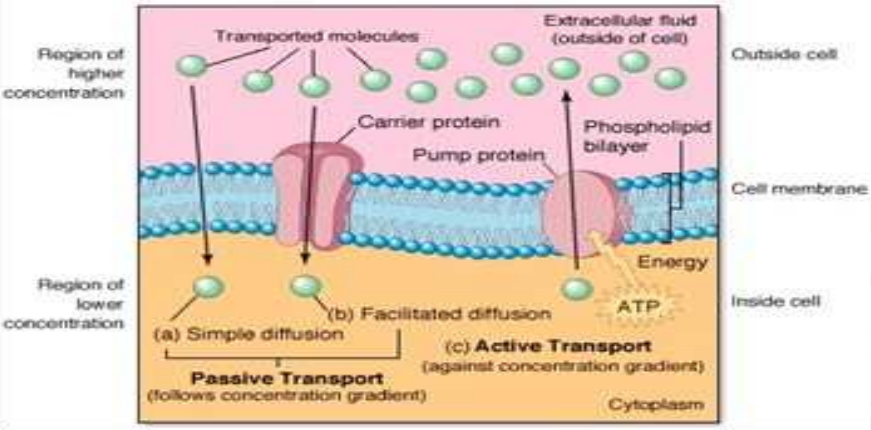
➢Due to energy dependent process, it is inihibited by metabolic poisons like cyanide, fluoride.
➢E.g., L-dopa (alfa-amino acid transport), 5FU (pyrimidine trnasport), ACEIs (peptide transport).



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THE KINETICS OF ACTIVE TRANSPORT

- Active transport occurs according to "**Michaelis-Menten kinetics**"
- **Absorption rate (V) =** $\frac{\text{Vmax x C}}{\text{Km + C}}$
- Active transport of molecules fits to the *"first order kinetics"* until it reaches to transport maximum, but beyond the transport maximum then the transportation across the cell membrane of the active transported drug fits to "*zero order kinetics*".
- The absorption according to the zero order kinetics occurs mainly in 2 situations:

a) Active transport and facilitated diffusion **(**if the transportation of the molecules have reached to a maximum level - transport maximum).

b) Sustained release formulations.

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ELECTROCHEMICAL DIFFUSION

➢Downhill process, depends upon conc. Gradients.

➢Union>Anion>Cation

IONPAIR TRANSPORT

➢Quaternary ammonium compouns and Sulfonic acids drugs are ionized at all pH media. Therefore, they transport via ion-pair system.

➢ Endogeneous mucin (anionic) neutralized the cations and transport across to the membrane.

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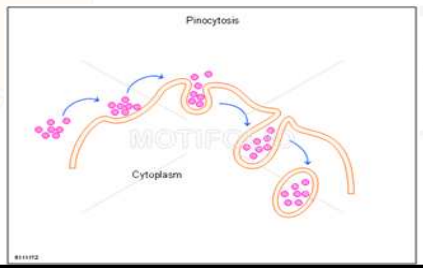
PINOCYTOSIS/CELL ENGULFING

- The drugs which have MW over 900 can be transported by pinocytosis.
- It requires **energy**.
- The drug molecule holds on the cell membrane and then surrounded with plasma membrane and inserted into the cell within small vesicles.
- E.g., Sabin polio vaccin, Fat soluble Vit. (A,D,E,K) and Neurotransmitter uptake.

****Neurotransmitter release/secretion is a exocytosis process.**



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FACTORS THAT AFFECT THE ABSORBTION OF THE DRUGS

A) DRUG-RELATED FACTORS

- Molecular size
- Lipid solubility
- Degree of ionization
- Dosage form
- Chemical nature (Salt/organic forms, crystal forms, solvate form etc.)
- Particle size
- Complex formation
- The pharmacological effect of the drug
- Concentration of the drug

B) SITE of APPLICATION RELATED FACTORS

- Blood flow (at site of application)
- Area of absorption

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DRUG-RELATED FACTORS

- **Molecular size:**
  - ✓ There is a ***negative relationship*** between the molecular size and the absorption rate of the drugs. If the molecular size increases, absorption rate decreases.
  - ✓ **Micronization** (0.1 um) reduces the particle size for better absorption. E.g., Greseofulvin, Aspirin, Spiranolactone, and Chloramphenicol.
- **Lipid solubility:**
  - ✓ A parameter of the lipid solubility is called "***lipid-water partition coefficient (Ko/w)***".
  - ✓ If a lipid-water partition coefficient of a molecule is high, then the lipid solubility of the molecule is high. And Absorption rate is higher in lipid soluble drugs.
  - ✓ E.g., Phenylbutazone, Thiopental
- **Degree of ionization/ pKa:**
  - ✓ The lipid-water partition coefficient of an ionized drug molecule decreases.
  - ✓ The acidic drugs are unionised in acidic media and allow to absorb, and Basic drugs are unionized in basic media and allow to absorb.

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DRUG-RELATED FACTORS

- ✓ Degree of ionization is determined by "***Handersen-Hasselbach equation***"
  - **For weak acids:** pH-pKa = log (ionized drug /unionized drug)
  - **For weak bases**: pH-pKa = log (unionized drug / ionized drug)

*pKa – the value of pH in which drugs have 50 % ionised and 50% unionised.

- According to the equation, for weak acid drugs: if you increase the acidity of the medium (decrease the pH), the unionized form of the drug molecule increases so the absorption rate increases.
- The closer the pKa value to the pH of the body fluids (generally 7.4), the greater is the change in ionization degree

FOR WEAK ACID DRUGS

pH- pKa		Unionized		Ionized	
0		50%		50%	
1	-1	10%	90%	90%	10%
2	-2	1%	99%	99%	1%
3	-3	0.1%	99.9%	99.9%	0.1%

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DRUG-RELATED FACTORS

- **ION TRAPPING:**
  - ➢The distribution of a drug between two compartments separated by a membrane that allows simple diffusion depends on the **pH difference between these compartments**.
  - ➢At steady state, the concentration of unionized form of the drug molecules are the same; however the concentration of ionized form will not be equal at both sides because of the pH difference at both sides.
  - ➢i.e. accumulation of basic drugs in the milk (trapped)

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DRUG-RELATED FACTORS

- **Dosage form:**
  - ✓ **Disintegration:** Breaking up of the drug molecules into smaller pieces after administration (mostly oral) is called disintegration.
  - ✓ **Dissolution:** Entering of the solid drug into a solvent to form a solution is called dissolution.
  - ✓ Solution forms of a drug molecule (liquid dosage forms) are absorbed faster compared to unsolved (solid) forms of the same drug.
  - ✓ High aqueous soluble drugs has high dissoultion rate and have higher absorption rate.
  - ✓ Dissolution rate directly proportion to the Kw/o.
- **Chemical nature (Salt/organic forms, crystal forms, solvate form etc.):**
  - **Salt formations:** Salt forms of weak acids (Na+, K+, Ca2+ compounds) and weak base (HCl, HBr compounds) drugs are more easily absorbed compared to their original (free) forms.
  - **Crystal forms:** Amorphous structure of a drug has a higher dissolution rate compared to its crystalline structure.
  - **Solvate form:** The hydrates are more soluble in water compared to other solvates.

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DRUG-RELATED FACTORS

- **Particle size:**
  - ✓ Decreasing the particle size of the drug fastens its dissolution so increases the absorption rate.
- **Complex formation:**
  - ✓ The solubility of some low-soluble drug molecules can be increased by formation a complex with another drug molecule.
- **The pharmacological effect of the drug:**
  - ✓ Effect on **blood flow** (vasoconstrictors, vasodilators, some cardiac drugs) in the absorption site,
  - ✓ **transition time** of the drug in GI tract (drugs effecting the GI motility).
- **Concentration of the drug:**
  - Higher the concentration of the drug at the administration site, higher the absorption rate of that drug.

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SITE OF APPLICATION RELATED FACTORS

- **Blood flow (at site of application):**
  - ✓ If the blood flow is high at the site of application, it causes an increase in absorption rate.
- **Area of absorption:**
  - ✓ If the surface area that allows the absorption of the drug molecules is wide, then absorption rate from that surface becomes high.
- **Rout of Administration: ….**

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Local Route	• For local action
Systemic route	• For Systemic action

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LOCAL ADMINISTRATION

- If the desired drug action site (target tissue) is placed on the surface of the body or if the site can be reached easily, i.e. by an injector needle, drugs can be applied locally.
  - ✓ Epidermal (percutaneous)
  - ✓ Intracutaneous
  - ✓ Conjunctival
  - ✓ Intranasal
  - ✓ Buccal
  - ✓ Intrathecal
  - ✓ Intrapleural
  - ✓ Intrauterine
  - ✓ Intracardiac
  - ✓ Intravaginal
  - ✓ Intraarticular

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LOCAL ADMINISTRATION

- **Epidermal (percutaneous):**
  - ✓ Application of some drugs over the surface of the skin in some dosage forms like, creams, lotions or solutions.
  - ✓ There are some factors that affect the absorption of an epidermal administered drug:

    a) ***Damage in the stratum corneum*** *layer*

    b) ***Region of the body***

    c) *High* ***lipid-water partition coefficient*** *and small* ***molecular size***

    d) ***Cleansing of the skin*** *and* ***friction***

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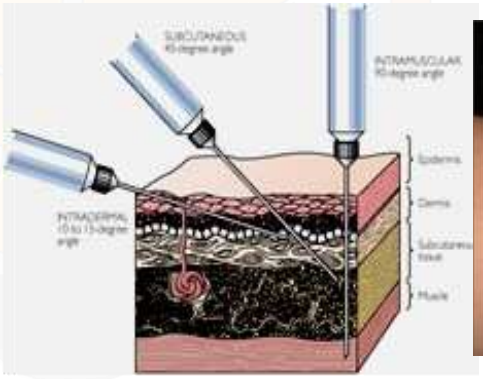
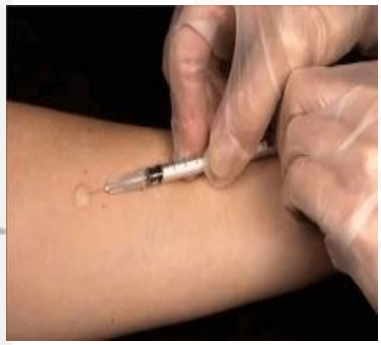
LOCAL ADMINISTRATION

- **Intracutaneous:**
  - ✓ Generally used for allergic or bacteriological tests, BCG vaccine or application of local anesthetics.
  - ✓ The volume over **0.1 ml** is not generally desired in this kind of application.
  - ✓ Injection angle- 10-15°





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LOCAL ADMINISTRATION

- **Conjunctival:**
  - ✓ Ophthalmic solutions or ophthalmic ointments are applied locally for some eye or eyelid diseases.

- **Intranasal:**
  - ✓ Nasal sprays or solutions can be used for nasal mucosa or paranasal sinus diseases (i.e. allergic rhinitis in spring).

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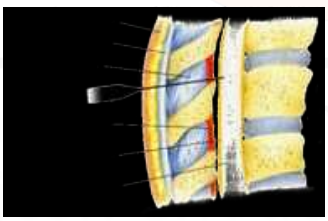
LOCAL ADMINISTRATION

- **Buccal:**
  - ✓ Generally used for the infectious diseases on the surface of the oral/buccal mucosa or some dental problems or throat (i.e. mouthwashes for dental problems).
- **Intrathecal:**
  - ✓ Some local anesthetics, analgesics or antibiotics are given to subarachnoid space between L3 and L4 vertebrate.



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SYSTEMIC ADMINISTRATION

- If a widespread effect throughout the body is desired or if you can't reach the target tissue to obtain a local effect, then systemic routes are used.
- There are 4 main routes for systemic administration of drugs:
  - Enteral route
  - Parenteral route
  - Inhalation
  - Transdermal route

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ENTERAL ROUTE

- The drug is given to GI tract and absorbed from GI tract.
- There are 3 ways for enteral route:
  - **Oral**
  - **Sublingual**
  - **Rectal**

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ORAL ROUTE

- This is the most often used administration route of the drugs.
- This route is known to be the safest, easiest and the most economic way of administering drugs.
- Drug molecules are mostly absorbed from *duodenum*, *jejunum* and *upper ileum*.
- **Disintegration** and **dissolution** are the two main processes for the oral administered drugs before the absorption process.
- The absorption rate and absorption ratio of the orally administered drugs are closely related with the above two parameters.
- **First pass metabolism is the major disadvantage in oral route. It reduce the bioavailability. E.g.**
- **V = Verapamil**
- **P = Propranolol**
- **Singh = Salbutamol**
- **Not = nitroglycerine**
- **A = Amitryptiline**
- **Popular = Propoxyphen**
- **P = Pethidine**
- **M = Methyl testosterone**
- **Others= Opoids, beta blockers, nitrates, and steroids.**

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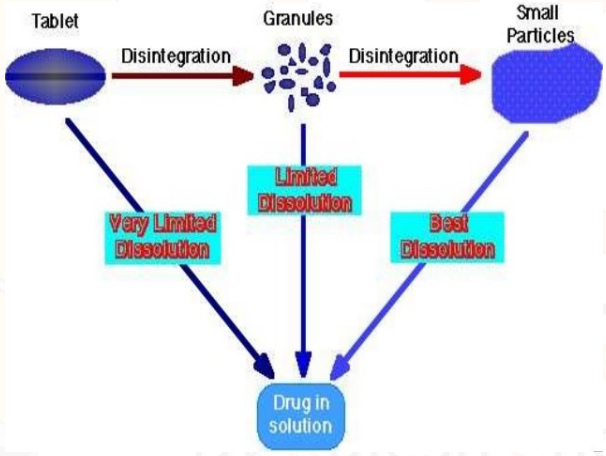
ORAL ROUTE



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ORAL ROUTE

BIOAVAILABILITY:

- **"In which extent (rate) the body benefits from the drug"** is known as bioavailability.
- I.V. dose has 100 % Bioavailability
- For the orally administered drugs, bioavailability (systemic bioavailability) is the "***fraction of unchanged drug that reaches to the systemic circulation from the administration site (after passing through the liver)"***.
- ***Bioequivalence:*** When a preparation/formulation of a drug by different company has similar bioavailability, its called bioequivalent.

$$\text{Relative B. A. (\%)} = [(AUC)o/(AUC)iv] \times 100$$

$$F\ (\%) = (PC_{Oral}/Pc_{iv}) \times 100$$

$$Mass_{(absorbed/iv)} = Mass_{(administeed/oral)} \times (F/100)$$

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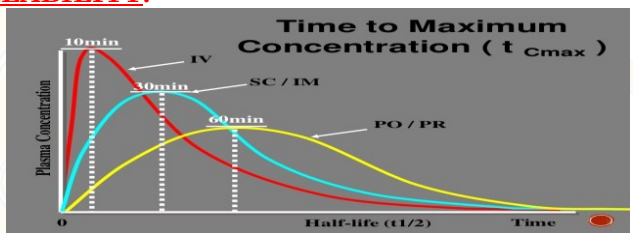
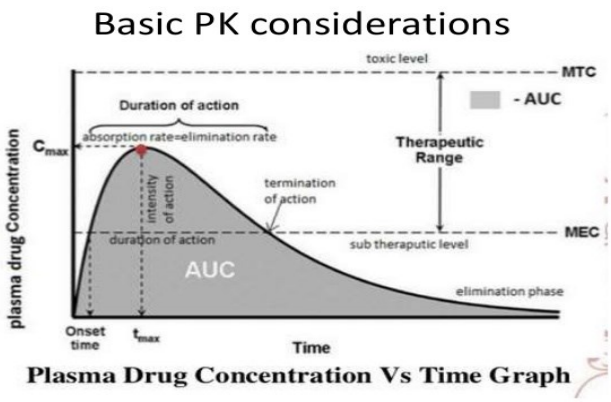
BIOAVAILABILITY:





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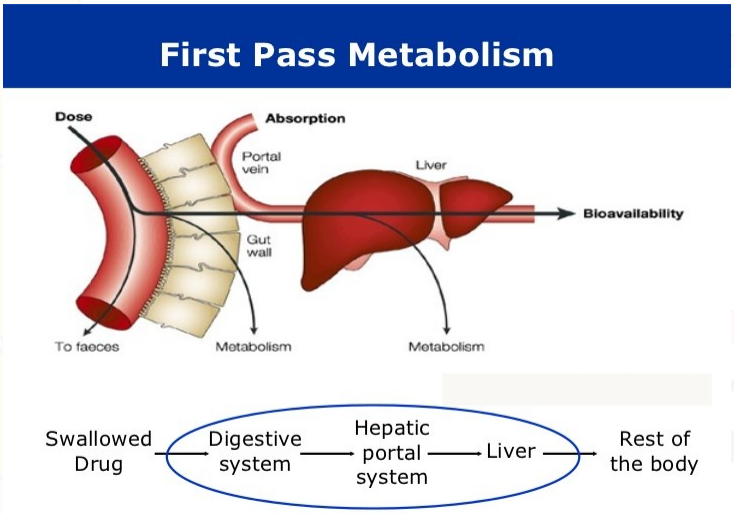
FIRST-PASS METABOLISM (pre-systemic elimination):



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ORAL ROUTE

- **Drug Related Factors That Affect Bioavailability:**
  - Particle size,
  - Crystalloid structure,
  - Salt compound / free,
  - Degree of hydration,
  - Drug formulation affects the dissolution and disintegration.

- **Patient Related Factors That Affect Bioavailability:**
  - **Differences in first-pass metabolism,**
  - drug metabolism differences between individuals (pharmacogenomics),
  - diseases that affect the GI motility,
  - age,
  - gender,
  - body weight,
  - drug-drug or drug-food interactions

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ORAL ROUTE

- **Bioavailibility order in formulations**

Solutions…Suspensions…Capsule…Tablet…Coated tablet…Sustained Release (SR) tablets

- **Physiological Factors That Affect the Absorption from GI Tract:**
  - ***Stomach emptying time***
  - ***Taking pills on a full or empty stomach***
    - Generally doesn't affect the absorption ratio but it affects the absorption rate.
    - Drug-food interactions may be important.
    - Aabsorption of drugs which are taken on an empty stomach starts earlier and it reaches the effective plasma concentration earlier than expected.
    - Some drugs are recommended to be taken with food to minimize the irritant effect of the drug to the gastric mucosa.
  - ***The motility of intestines***
    - diarrhea,
    - constipation

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SUBLINGUAL ROUTE

- Especially high lipophilic drugs are used by this route.
- Cardiac nitrates (Glyceryl trinitrate), Ca+ channel blockers like nifedipine and some steroid sex hormone pills (methyltestosterone) and opoids (Buprenorphine) can be used by this route.
- There are 2 main advantages of this route:
  - ✓ The effect starts very quickly.
  - ✓ Systemic bioavailability of the drug is generally very high.
  - ✓ Bypass first pass metabolism

RACTAL ROUTE

- **Enema:** as a liquid drug formulation
- **Rectal suppositories:** as a solid drug formulation.
- There is no first-pass metabolism in this route and the effect starts immediately.
- E.g., Aminophylline, Indomethacin, Paraldehyde, Ergotamine.

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PARENTERAL ROUTE

- There are 3 ways for parenteral route:
  - Into veins** or arteries
  - Intramuscular
  - Subcutaneous
- Following IV injection, the effect starts immediately and the **bioavailability is 100%**.
- IM injection is applied to generally gluteal (hip) and deltoid (Solder) muscles; upto 5 ml is the maximum injection volume.
- For subcutaneous injections, the injection volume shouldn't exceed 2 ml.
- Sometimes pellet implantation procedure can be performed for subcutaneous injections under the skin.

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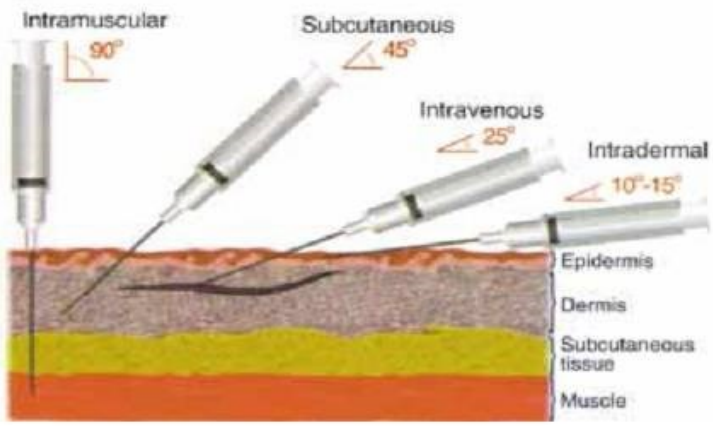
PARENTERAL ROUTE



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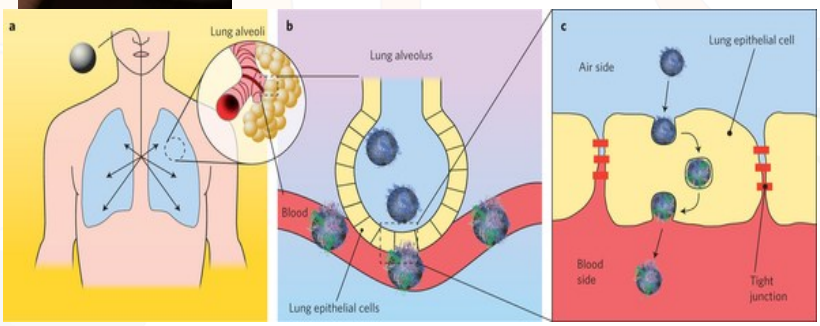
INHALATION

- These drugs should be small particle sized with high lipid-water partition coefficient.
- Volatile liquids and vapour. E.g. Inhaled General Anesthetics



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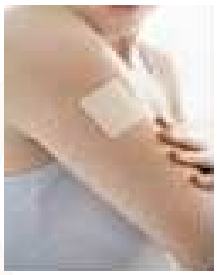
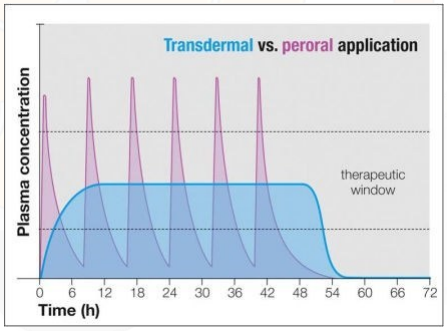
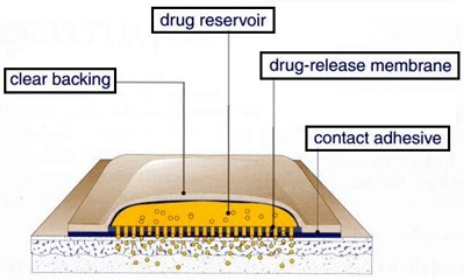
TRANSDERMAL

- Transdermal therapeutic systems **(TTS, patch)** are used generally for transdermal drug application.
- These are absorbed from the skin to circulation to obtain a systemic effect.
- These are generally high lipophilic drugs.







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ROUTE	ADVANTAGE	DISADVANTAGE/WARNINGS
Sublingual	-The effect starts immediately, -NO first-pass elimination	-The absorption may decrease if emesis happens.
Oral	-Easy, reliable, economic	-First-pass elimination occurs, -Emesis, diarrhea, heavy constipation may cause decrease in absorption
Rectal	-The effect starts immediately, -NO first-pass elimination, -Suitable for patients with heavy emesis or when the oral route is not an appropriate route.	-Unpleasant way of application -Risk of rectal bleeding -Increased bacteremia risk for immunosuppressive patients -Decreased absorption in diarrhea and constipation.
Inhalation	-The effect starts immediately, -suitable for general anesthetics and bronchodilators	-Intubation and special equipment are required
Intramuscular	-The effect starts immediately,	-Edema, local irritation or pain -Risk of infection
Intravenous	-The effect starts immediately, -Bioavailability is 100%	-Irritation or pain -Risk of infection -Solution must be dissolved well -Risk of embolism
Subcutaneous	-Absorption is slower compared to im inj.	-Edema, local irritation or pain -Volume shouldn't exceed 2 ml -Risk of infection
Intranasal	-The effect starts immediately, -NO first-pass elimination.	-Local irritation -Suitable for administration of small doses of drugs
Transdermal	-Enables for slow and long-term drug application	-The effect starts very slowly -Local skin reactions can be seen
Percutaneous	-Suitable for local effect.	-The effect starts very slowly -Local skin reactions can be seen

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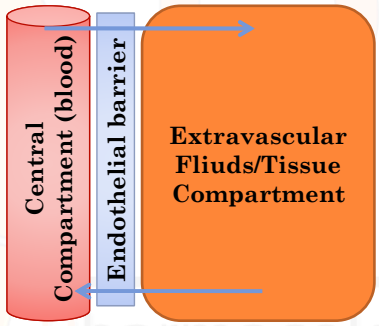
DISTRIBUTION



✓Passive Process
✓Depends upon Conc grad. And oil-water partition coff.
✓Dispersion of the drug throughout the body

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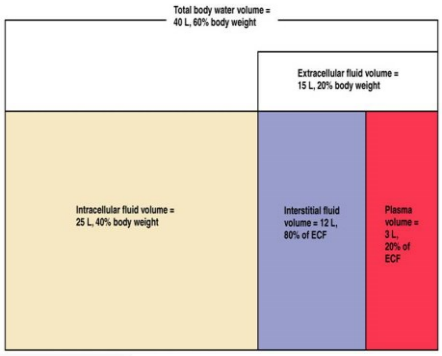
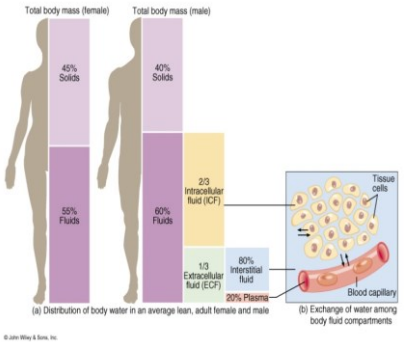
INTRODUCTION

- Distribution is passage of drug molecules to liquid compartments and tissues in the body via transportation across the capillary membrane.
- The body fluid compartments and volumes in which the drugs are distributed:





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DISTRIBUTION

- **The distribution of drugs can occur in 4 patterns throughout the body:**
  - **Distribution only in plasma**: **HMW-Dextran, Evans blue dye, suramin**
  - **Distribution to all body fluids homogenously:** Small and non-ionized few molecules like **alcohol**, **some sulfonamides**.
  - **Concentration in specific tissues**: **iodine** in thyroid; **chloroquine** in liver; **tetracyclines** in bones and teeth**; high lipophilic drugs** in fat tissue
  - **Non-homogenous (non-uniform) distribution pattern**: Most of the drugs are distributed in this pattern according to their abilities to pass through the cell membranes or affinities to the different tissues.

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DISTRIBUTION

Factors Affecting the Distribution of Drugs:

- **Diffusion Rate**
- **The Affinity of the Drug to the Tissue Components**
- **Blood Flow (Perfusion Rate)**
- **Binding to Plasma Proteins**

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FACTORS AFFECTING THE DISTRIBUTION OF DRUGS

- **Diffusion Rate**:
  - ✓ There is a positive correlation between the diffusion rate of the drug and the distribution rate
- **The Affinity of the Drug to the Tissue Components**:
  - ✓ Some drugs tend to be concentrated in particular tissues.
- **Blood Flow (Perfusion Rate):**
  - ✓ There is a positive correlation between the blood flow in the tissue and the distribution of the drugs.
  - ✓ Kidney, liver, brain and heart have a high perfusion rate (ml/100 g tissue/min) in which the drugs distribute higher;
  - ✓ Skin, resting skeletal muscle and bone have a low perfusion rate.
  - ✓ The total concentration of a drug increases faster in well-perfused organs.

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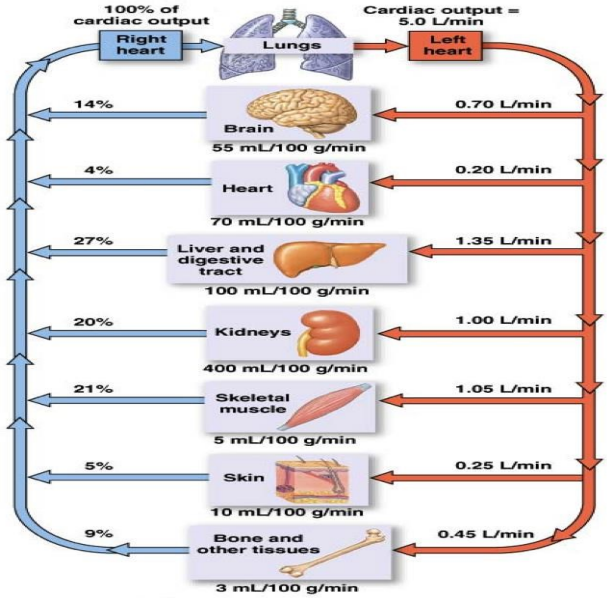
DISTRIBUTION OF BLOOD IN THE BODY AT REST **Blood Flow (Perfusion Rate)**

Blood flow to the major organs is represented in three ways: as a percentage of total flow, as volume per 100 grams of tissue per minute, and as an absolute rate of flow (in L/min).



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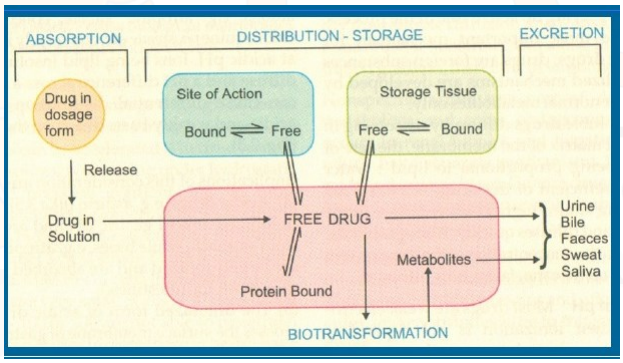
FACTORS AFFECTING THE DISTRIBUTION OF DRUGS

- **Binding to Plasma Proteins**:
  - ✓ Drug that reaches to the blood intract with plasma proteins and bind with them.
  - ✓ Protein bound drugs have not any therapeutic effects.
  - ✓ It allow the temporary drug storage, and reduce the elimintaion.



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Protein Binding

- Plasma Proteins:
  - Albumin
  - Alfa-1 Acid Glycoprotein (AAG/α-AGP)
  - Lipoproteins
  - Globulines

1. Albumin

- The most important protein (59% of total) that binds the drugs in blood is **albumin** for most of the drugs.
- Especially, the **acidic drugs** (salicylates, vitamin C, sulfonamides, barbiturates, penicillin, tetracyclines, warfarin, probenesid etc.) are bound to albumin.
- It has 4 binding site:

I. Warfarin site: NSAIDs, Sulfonamides, Phenytoin, Bilirubin.
II. Diazepam site: BDZs, fatty acid, Tryptophen, Probenecid, Penicilline.
III. Digitoxin site: digitalis alkaloid
IV. Tomoxifen Site: tomoxifen

- If the two drugs have same binding site, thus it can give rise the displacment interaction and further cause drug accumulation, and toxicity.

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Protein Binding

2. Alfa Acid Glycoprotein

- **Basic drugs** (streptomycin, chloramphenicol, LA, TCAs, Prazosin etc.) are bound to alpha-1 and alpha-2 acid glycoproteins.

3. Lipoproteins (chylomicron, LDL, HDL)

- Acidic- Diclofenac
- Neutral- Cyclosporin A
- Basic- Chlorpromazin

4. Globulines

1) **α-1 (Transcortin)**- Corticosteroids, thyroxine, cynocobalamine
2) **α-2 (Ceruloplasmin)-** Vit A, D, E, K
3) **β-1 (Trasferin)-** Fe2+
4) **β-2** – Caritinoids
5) **γ-globulin-** Antigens

- Some drugs like Phenytoin, Phenobarbital are bind with blood hemoglobin. Imipramine and Chlorpromazine are bind with

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PROPERTIES OF PLASMA PROTEIN-DRUG BINDING

- **Saturable:**
  - One plasma protein can bind a limited number of drug molecule
- **Non-selective:**
  - More than one kind of drug which has different chemical structures or pharmacological effects can be bound to the space on plasma protein
- **Reversible:**
  - The bonds between the drug and plasma protein are weak bonds like hydrogen or ionic bonds.

Bound fraction Unbound fraction

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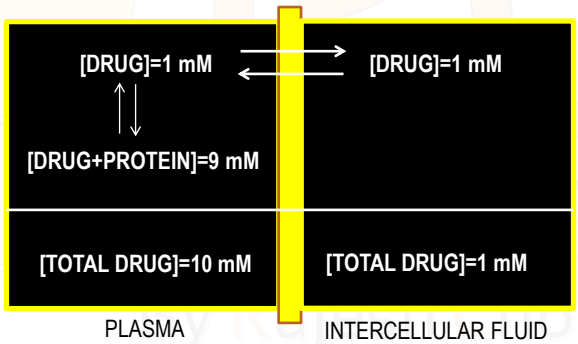
- Only the free (unbound) fraction of the drug circulating in plasma can pass across the capillary membrane .
- Bound fraction serves as **"drug storage"**.



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DISTRIBUTION

- **Storage (Concentration-Sequestration) of the Drugs in Tissues**
  - Stored drug molecules in tissues serve as **drug reservoir**.
  - The duration of the drug effect may get longer.
  - May cause a late start in the therapeutic effect or a decrease in the amount of the drug effect.
- **Redistribution:**
  - Some drugs (especially general anesthetics) which are very lipophilic, following the injection, firstly (initially) distributes to the well-perfused organs like central nervous system..
  - Later, the distribution occurs to less perfused organs like muscles.
  - At last, distribution of these drugs shifts to the very low-perfused tissues like adipose (fat) tissue.
  - Redistribution results with the running away of the drugs from their target tissue and last their effect.

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DISTRIBUTION

- **Passage of the drugs to CNS:**
  - A **blood-brain barrier** exists (except some areas in the brain) which limits the passage of substances.
  - **Non-ionized, highly lipophilic, small molecules** can pass into the CNS and show their effects.
  - Some antibiotics like penicillin can pass through the inflamed blood-brain barrier while it can't pass through the healthy one.
- **Passage of the drugs to fetus:**
  - Placenta doesn't form a limiting barrier for the drugs to pass to fetus.
  - The factors that play role in simple passive diffusion, effect the passage of drug molecules to the fetus.
    - Placental blood flow
    - Molecular size
    - Drug solubility in lipids
    - Fetal pH (ion trapping): fetal plasma pH: 7.0 to 7.2; pH of maternal plasma: 7.4, so according to the ion trapping rules, **weak basic drugs** tend to accumulate in **fetal plasma** compared to maternal plasma.

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VOLUME OF DISRIBUTION

Volume of Distribution = Amount of drug administered (dose) (mg) / concentration of drug in plasma (mg/ml)

Vd (L)= X (mg) / PC (mg/L)

- Most of the times, volume of distribution calculated in this way is not equal to the real total volume of physiological liquid compartments in which the drug is distributed.
- So it may be called as "**apparent volume of distribution (V_d)**".
- Following a single-dose intravenous administration of a drug, log plasma concentration-time graph is plotted according to the values of plasma concentration taken at particular time points.
- Then the formula is:

Volume of Distribution (V_d) = Dose $_{(iv)}$ / C_0'

- Also, you can calculate the volume of distribution from the same graph by using AUC (area under curve) and K_e (rate constant for elimination) like:

Volume of Distribution (V_d) = Dose $_{(iv)}$ / (AUC x K_e)

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VOLUME OF DISRIBUTION

To know the volume of distribution (V_d) value of a drug helps us to calculate:

- **The amount of drug found in the body at a particular time** from the analyzed plasma drug concentration.
- The drug dose **(loading dose)** that has to be given (required) to obtain a desired plasma drug concentration.
- To find the **rate constant for elimination** from the formula:

K_e = Clearence / V_d

- Case: IV dose 10 mg, plasma vol. 2.5L and 7.5L tissue volume then calculate Vd (Vd = X/PC)
- At 0 time, PC_0 = 10/2.5 = 4mg/L then Vd_0 = 10/4 = 2.5L
- At time t, PC_t = 10/10 = 1mg/L then Vd_t = 10/1 = 1

- High Vd (>20L) means Tissue Accumulation and causes toxicity (highly lipid soluble drugs).
- Low Vd (<10L) means drug drugs are present in intracellular fluid (blood).

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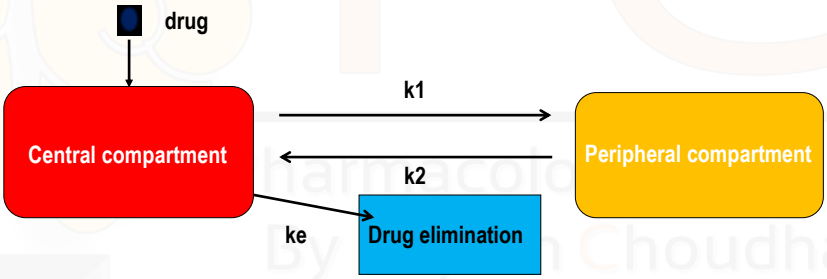
KINETICS OF DISTRIBUTION

- **One compartment model:** In this model, the whole body is considered to be the compartment (the volume) in which the drugs and/or the metabolites are distributed homogenously.
- **Two compartment model:** In this model, whole body is divided into two compartments regarding the distribution of drugs.



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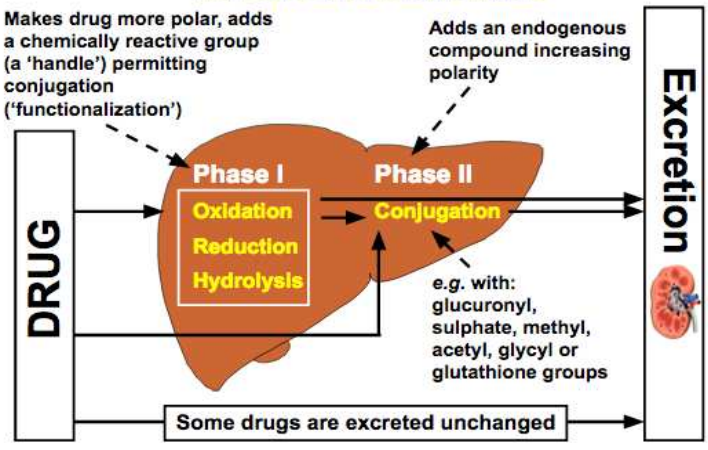
BIOTRANSFORMATION



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INTRODUCTION

- The process of alterations in the drug structure by the enzymes in the body is called **"biotransformation (drug metabolism)"** and the products form after these reactions are called **"drug metabolites"**.
- Some drugs which don't have any activity in vitro, may gain activity after their biotransformation in the body. These types of drugs are called "**pro-drug**" or "**inactive precursor**".
- **Drug examples that gain activity after biotransformation (pro-drugs):**

PRO-DRUG	EFFECTIVE METABOLITE
Chloral hydrate	Trichloroethanol
Cortisone	Hydrocortisone
Enalapril	Enalaprilate
Lovastatin	Lovastatin acid
Clofibrate	Clofibric acid
L-DOPA	Dopamine

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INTRODUCTION

- **Drug examples that is transformed to more active compounds after biotransformation:**

DRUG	MORE ACTIVE METABOLITE
Imipramine	Desmethylimipramine
Codeine	Morphine
Nitroglycerin	Nitric oxide
Losartan	EXP 3174 (5-carboxylic acid metabolite)
Thioridazine	Mesoridazine

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INTRODUCTION

- **Drug examples that is transformed to less active compounds after biotransformation:**

DRUG	LESS ACTIVE METABOLITE
Aspirin	Salicylic acid
Meperidine	Normeperidine
Lidocaine	De-ethyl lidocaine (dealkylated)

- **Drug examples that is transformed to inactive metabolites after biotransformation**

DRUG	INACTIVE METABOLITE
Most of the drugs	Conjugated compounds
Ester drugs	Hydrolytic products
Barbiturates	Oxidation products

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INTRODUCTION

- The metabolites that are formed after biotransformation are generally *more polar*, more easily ionized compounds compared to the main (original) drug. So, these metabolites can be excreted from the body easily.

Organs that biotransformation occurs:

- **Liver**** (the most important organ, the number and variability of the biotransformation enzymes are the highest)
- Lungs
- Kidney (tubular epithelium, sulphate conjugation)
- Gastrointestinal system (duodenal mucosa, MAO)
- Placenta
- Adrenal glands
- Skin
- Central nervous system
- Blood

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ENZYMATIC REACTIONS

The enzymatic reactions which the drugs are exposed to:

1. Oxidation
2. Reduction
3. Hydrolysis

} PHASE I (responsible for metabolic alteration)

4. Conjugation → PHASE II (responsible for detoxification and excretion)

- ✓ Highly water soluble drug excrete unchanged.
- ✓ Lipid soluble drugs go to P I and P II
- ✓ The drugs having –NH2, -SH, or –OH groups are directly go to Phase II.

DRUG → **X** (inactive or less active**, same activity, higher activity) → **Y** (generally inactive)

PHASE I **PHASE II**

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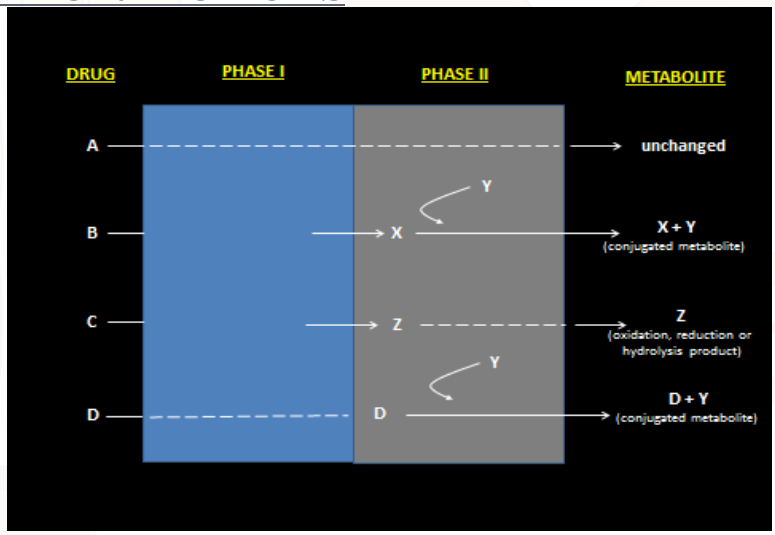
ENZYMATIC REACTIONS



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OXIDATION REACTIONS

- Oxidation reactions are performed **mostly***** by the enzymes in liver (hepatocytes) which are localized in the *endoplasmic reticulum* in microsomal fractions.
- These enzymes are **cytochrome P450 mixed-functional oxidases**. P= pink, 450 = absorbance wavelength λ (450 nm)
- For the oxidation reactions, also **molecular oxygen (O_2)** and **NADPH** (generate from pentose phosphate shunt) are required.
- Some special characteristics of microsomal P450 enzyme system:
  - ✓ They are located in hepatic microsomes.
  - ✓ The substrate specificity is low.
  - ✓ Shows high affinity to high lipophilic molecules.
  - ✓ NADPH and molecular oxygen (O_2) is required for its activity.
  - ✓ Metabolic poison inhibit the CyP 450 dependent metabolism

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OXIDATION REACTIONS

- Cytochrome P450 is a "**hem**" containing protein.
- The active site of the protein is the **Fe ion**. This active site can bind the drug only if the Fe is oxidized in the form of **Fe^{+3}**.
- After the formation of enzyme-drug complex, **an electron (e^-)** released from NADPH by the enzyme *NADPH-cytochrome P450 reductase* is transferred to this complex.
- Reducted enzyme-drug complex binds molecular O_2.
- Following this binding, enzyme-drug-O_2 complex breaks down into oxidized enzyme (oxidized free cytochrome P 450), water (H_2O) and oxidized drug.
- RH + O2 + NADPH2 → ROH + H2O + $NADP^+$

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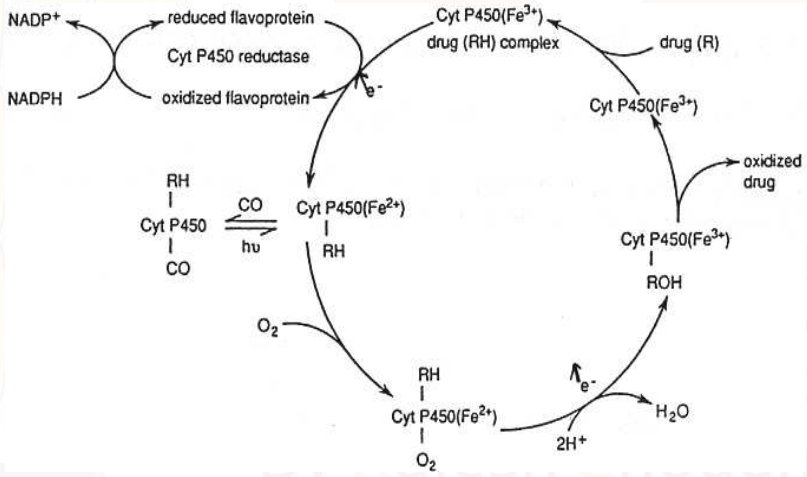
OXIDATION REACTIONS



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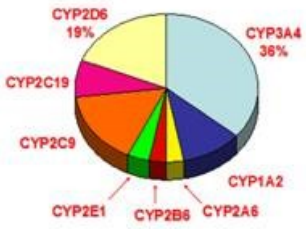
OXIDATION REACTIONS

- Cytochrome P450 enzyme is not an enzyme with only one type.
- P450 1, 2 and 3 (CYP1, CYP2 and CYP3) genes are involved in coding the enzymes which are responsible for the drug metabolism.
- Especially **CYP3** type codes the enzymes that are responsible for the pre-systemic elimination of orally administered drugs.

Drug metabolism by different CYP450 enzymes



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OXIDATION REACTIONS

Some main cytochrome P450 enzymes which play important role in drug metabolism

Enzyme	Drug examples
CYP3A4	Most of the drugs
CYP1A2	Caffeine, theophylline, paracetamol, propranolol… **Activation of Prooncogens
CYP2C9	Phenytoin, oral antidiabetics, NSAIDs…
CYP2C19	Diazepam, propranolol, omeprazole…
CYP2D6	Beta-blockers, some antidepressants, nicotine, opioid analgesics…
CYP2E1	Chronic alcohalism induces this enzyme

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OXIDATION REACTIONS

Hydroxylation reactions	Aromatic, aliphatic and other hydroxylation	Cytochrome P450 enzymes
N-, O-, and S-dealkylation		Cytochrome P450 enzymes
Desulphurization	-thio group is transformed to ketone, -sulfhydryl group turns into hydroxyl group	Cytochrome P450 enzymes
Oxidative deamination (amines with α-methyl)		Cytochrome P450 enzymes
S- and N-oxidation		Cytochrome P450 enzymes
N-hydroxylation		Cytochrome P450 enzymes
Oxidation reactions ***	Alcohol dehydrogenase, Aldehyde dehydrogenase, Monoamine oxidase, tyrosine hydroxylase	Performed by oxidases other than cytochrome P450 enzymes (cytoplasmic)
Dehalogenation		Dehalogenation enzymes

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REDUCTION REACTIONS:

- These reactions are seen in fewer amounts compared to oxidation reactions.
- FAD is required additional to NADPH for these reactions.

REDUCTION REACTIONS

Aldehyde reduction	Transformation to alcohol	Cytoplasmic flavin containing enzymes
Azo (N=N) reduction	Transformation to amines	Microsomal flavin containing enzymes
Nitro reduction	Transformation to amine or hydroxilamine	Microsomal and cytoplasmic flavin containing enzymes

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HYDROLYSIS REACTIONS

- A group is separated from the drug molecule, or drug molecule is broken down into two smaller molecules.

HYDROLYSIS REACTIONS

Esterase (hydrolysis) reactions	Acetylcholine esterase, pseudo choline esterase, amidase
Decarboxylation	Decarboxylases
Glycoside hydrolysis	ß-glycosidases
O-dealkylation	
N-dealkylation	
S-dealkylation	

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CONJUGATION REACTIONS:

1. **Glucuronidation**
   - ✓ **UDP-glucuronosyltransferases** catalyze the reaction.
   - ✓ This is a microsomal enzyme located in the endoplasmic reticulum of liver cell.
   - ✓ Glucuronidation is the only conjugation reaction performed by microsomal enzymes. All the other conjugation reactions are performed by non-microsomal enzymes.
   - ✓ Drugs like chloramphenicol, salicylic acid, morphine and endogenous compounds like steroids and bilirubin are conjugated with glucuronic acid.
   - ✓ Glucuronic acid is a highly hydrophilic compound, so it decreases the lipid solubility of the drug after conjugation. Thus, excretion of the drug becomes easier.

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CONJUGATION REACTIONS

2. N-methylation
3. O-methylation
4. N-acetylation
5. Sulfate conjugation (sulfation)
6. Glutathione conjugation
7. Conjugation with amino acids
8. Conjugation with ribose or ribose phosphates

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Type of Conjugation	Endogenous Reactant	Transferase (Location)	Types of Substrates	Examples
Glucuronidation	UDP glucuronic acid	UDP glucuronosyl-transferase (microsomes)	Phenols, alcohols, carboxylic acids, hydroxylamines, sulfonamides	Nitrophenol, morphine, acetaminophen, diazepam, N-hydroxydapsone, sulfathiazole, meprobamate, digitoxin, digoxin
Acetylation	Acetyl-CoA	N-Acetyltransferase (cytosol)	Amines	Sulfonamides, isoniazid, clonazepam, dapsone, mescaline
Glutathione conjugation	Glutathione (GSH)	GSH-S-transferase (cytosol, microsomes)	Epoxides, arene oxides, nitro groups, hydroxylamines	Acetminphen, ethacrynic acid, bromobenzene
Glycine conjugation	Glycine	Acyl-CoA glycinetransferase (mitochondria)	Acyl-CoA derivatives of carboxylic acids	Salicylic acid, benzoic acid, nicotinic acid, cinnamic acid, cholic acid, deoxycholic acid
Sulfation	Phosphoadenosyl phosphosulfate	Sulfotransferase (cytosol)	Phenols, alcohols, aromatic amines	Estrone, aniline, phenol, 3-hydroxy-coumarin, acetaminophen, methyldopa
Methylation	S-Adenosyl-methionine	Transmethylases (cytosol)	Catecholamines, phenols, amines	Dopamine, epinephrine, pyridine, histamine, thiouracil
Water conjugation	Water	Epoxide hydrolase (microsomes)	Arene oxides, cis-disubstituted and monosubstituted oxiranes	Benzopyrene 7,8-epoxide, styrene 1,2-oxide, carbamazepine epoxide
		(cytosol)	Alkene oxides, fatty acid epoxides	Leukotriene A_4

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Factors That Affect The Biotransformation of Drugs

1. Induction or inhibition of microsomal enzymes
2. Genetic differences
3. Age
4. Gender
5. Liver diseases
6. Environmental factors

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INDUCTION OR INHIBITION OF MICROSOMAL ENZYMES

- Various drugs or environmental factors lead to increases in the activity of these enzymes by increasing the synthesis of microsomal enzymes.
- The importance of the enzyme induction is the increasing metabolism rate of the drugs and the reduction in their activities.
- On the other hand, some drugs stimulate the enzymes that inhibit themselves **(biochemical tolerance).**
- **E.g., INDUCER (P C BAR PG)=** Phenytoin, Carbamezapine, Barbiturates, Alcohal, Rifampicin, Phenylbutazone, Griseofulvin.
- Unlike the enzyme induction, some drugs can inhibit the microsomal enzymes.
- INHIBITOR (COKE PI) = Cemitidine, Omeperazole, Ketakonazole, Erythromycin, Protease Inhibitor (Saquinavir), INH.
- **Enz. Inducers enhance the elimination and reduce the therapeutic efficacy.
- *** Enz inhibitors decrease the elimination and increase the toxic effects.

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INDUCERS

ENZYME	DRUG or SUBSTANCE THAT INDUCES THE ENZYME
CYP1A2	Cigarette smoke, grilled meat (barbecue), aromatic polycyclic hydrocarbons, phenytoin
CYP2C9	Barbiturates, phenytoin, carbamazepine, rifampin
CYP2C19	NOT INDUCIBLE
CYP2D6	NOT INDUCIBLE
CYP3A4	Barbiturates, phenytoin, rifampin, carbamazepine, glucocorticoids, griseofulvin,

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INHIBITORS

ENZYME	DRUG or SUBSTANCE THAT INHIBITS THE ENZYME
CYP1A2	Cimetidine, ethinyl estradiol, ciprofloxacin
CYP2C9	Amiodarone, isoniazid, co-trimoxazole, cimetidine, ketoconazole
CYP2C19	Fluoxetine, omeprazole
CYP2D6	Amiodarone, cimetidine, fluoxetine, paroxetine, haloperidol, diphenhydramine
CYP3A4	Ketoconazole, erythromycin, , isoniazid, Ca channel blockers, red wine, grapefruit juice

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GENETIC DIFFERENCES

- Genetic polymorphism in some of the enzymes that play role in biotransformation of drugs can cause changes in the activity of the drugs which are metabolized by these enzymes.
- **Hydrolysis of succinylcholine:** *Cholinesterase enzyme (BuChE) in plasma* play important role in the hydrolysis of succinylcholine which is generally used for its muscle relaxant activity.
  - ✓ The metabolism of succinylcholine slows down in the individuals who have **atypical cholinesterase Enz.** And futher activity of succinylcholine can rise up to hours in individuals who have atypical cholinesterase enzyme **(long duration (prolonged) succinylcholine apnea).**
- **Acetylation of isoniazid:**
  - ✓ Some individuals can metabolize this drug slowly (*slow acetylators*) and some faster (*rapid acetylators*).
- **CYP2D6 polymorphism:**
  - ✓ CYP2D6 enzyme plays important role in the metabolism of many widely used drugs.
  - ✓ this polymorphism can be also named as "**debrisoquine type polymorphism**".
  - ✓ The metabolism rate of some beta-blockers (metoprolol, timolol), some neuroleptics (thioridazine, perphenazine), and antitussives like dextromethorphan or codeine decrease significantly in the slow metabolizers.

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AGE & GENDER

- In newborns cytochrome P450 enzymes and glucuronosyltransferases are not sufficient.
- So, biotransformation of some drugs (diazepam, digoxin, acetaminophen, theophylline etc…) is very slow in newborns.
- Oxidation reactions performed by cytochrome P450 enzyme system are slower than normal metabolizing rates in elderly.
- The effect of aging on these enzymes can differ according to gender (reduction in enzyme activity is higher in old males) and between individuals.
- First-pass elimination shows a reduction with age as well.
- Metabolism rates of some drugs may change with gender. For example, succinylcholine and other choline esters and procaine are inactivated faster in **men**.

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LIVER DISEASES

- Especially, the metabolism of drugs with a **"high hepatic clearance"** decreases in liver diseases.
- This leads to accumulation of drugs in the body which are metabolized in liver, and eventually causes an increase in the effect and adverse effects as well.
- On the other hand, transformation of pro-drugs into their active forms occurs less in liver diseases.
- **Induction of microsomal enzymes can occur with;**
  - ✓ Biphenylles with polychlor
  - ✓ DDT and some insecticides
  - ✓ Benzopyrenes and other polycyclic aromatic hydrocarbons (products of burned coal and petroleum products)
  - ✓ Polycyclic hydrocarbons in the cigarette smoke can induce some enzymes like CYP1A2 and CYP1A1 (For this reason, the metabolism rate of chlorpromazine, theophylline and imipramine is significantly high in heavy smokers).
  - ✓ Diet (Cabbage and cauliflower can induce CYP1A1 and CYP1A2)

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ENVIRONMENTAL FACTORS

- Especially **pollutants** can affect the microsomal enzymes.
- **Induction of microsomal enzymes can occur with;**
  - ✓ Biphenylles with polychlor
  - ✓ DDT and some insecticides
  - ✓ Benzopyrenes and other polycyclic aromatic hydrocarbons (products of burned coal and petroleum products)
  - ✓ Polycyclic hydrocarbons in the cigarette smoke can induce some enzymes like CYP1A2 and CYP1A1 (For this reason, the metabolism rate of chlorpromazine, theophylline and imipramine is significantly high in heavy smokers).
  - ✓ Diet (Cabbage and cauliflower can induce CYP1A1 and CYP1A2)

- **Inhibition of microsomal enzymes can occur with**;
  - ✓ Carbon monoxide inhibits the microsomal enzymes.
  - ✓ Grapefruit juice (some flavonoids in grapefruit juice can inhibit CYP3A4)

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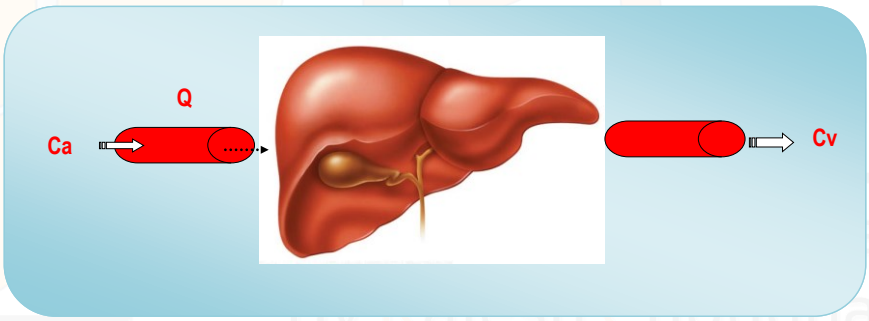
HEPATIC CLEARANCE

- It can be described as "**the volume of plasma** cleared from the drug **via metabolism in liver** per unit time (ml/min)"
- It is an indicator of the *metabolism rate* of the drugs.



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Q= Total hepatic blood flow
C_a= Portal venous drug concentration + hepatic arterial drug concentration
C_V= Hepatic venous drug concentration

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HEPATIC CLEARANCE

$\frac{C_a - C_v}{C_a}$ = HEPATIC EXTRACTION RATIO (E)

Hepatic Clearance (CL_H) = Q x $\frac{C_a - C_v}{C_a}$

OR

$(CL_H) = Q \times E$

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HEPATIC CLEARANCE

- Drugs can be divided into 3 groups according to their hepatic clearances:
  - Drugs with **high** hepatic clearance (Drugs with **high extraction ratio**)
  - Drugs with **low** hepatic clearance (Drugs with **low extraction ratio**)
  - Other drugs

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HEPATIC CLEARANCE

- Drugs with **high** hepatic clearance (Drugs with **high extraction ratio**):
  - Generally these are high-lipophilic drugs
  - Absorption ratios from the gastrointestinal tract is 100% or very close to 100%.
  - The pre-systemic elimination of these drugs is very high; so because of this reason systemic bioavailability of these drugs are low.
  - The ratio between the oral and parenteral dose of the drug is high (high difference in dose between oral and parenteral route)
  - The bioavailability of these types of drugs shows considerable differences between the individuals.
  - Hepatic blood flow has high influence on the metabolism rate of these drugs.

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HEPATIC CLEARANCE

- Drugs with **low** hepatic clearance (Drugs with **low extraction ratio**):
  - Metabolic rates of these drugs in liver are low.
  - Elimination rate of these drugs **are not affected** considerably with the changes in hepatic blood flow.
  - However, the induction/inhibition of metabolizing enzymes affects the metabolism rate.

- Other drugs:
  - These drugs are the ones between the above two groups.
  - Hepatic clearances of these drugs are affected in high amounts by both hepatic blood flow and metabolizing capacity of the biotransformation enzymes.

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EXCRETION

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OVERVIEW

- **RENAL EXCRETION**
- **BILIARY EXCRETION**
- **EXCRETION from the LUNGS**
- **EXCRETION into BREAST MILK**
- **ARTIFICIAL EXCRETION WAYS**

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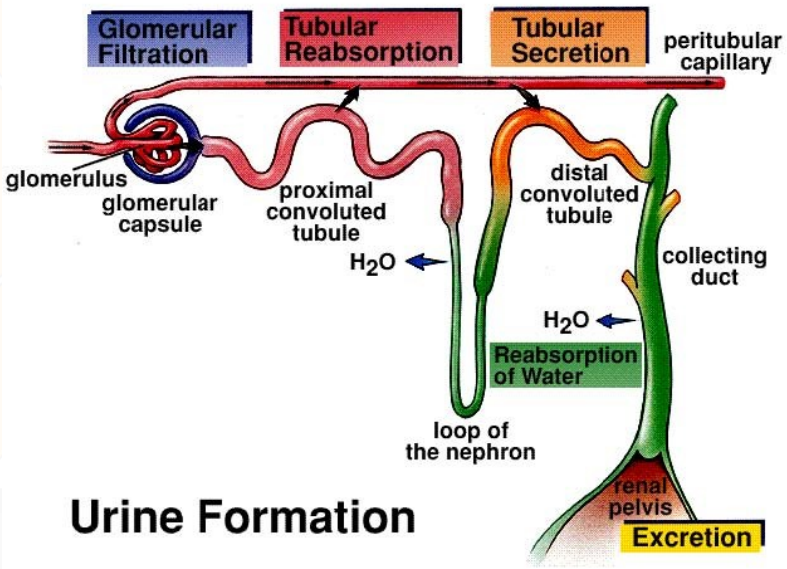
RENAL EXCRETION



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RENAL EXCRETION

- Drugs and metabolites are excreted from the kidneys by 2 ways.
  - **a) Glomerular filtration**
  - **b) Tubular secretion**
- Tubular reabsorption is not an excretion way; however there is no doubt that it effects the excretion of drugs from the body by the kidney.

a) Glomerular filtration:

- ***Simple passive diffusion*** play role in glomerular filtration.
- The filtration rate is 110-130 ml/min.
- Standard GFR = 120 ml/min = Creatinine Clearance
- They are filtered free drug from the glomerulus into proximal tubules except the bound fraction of drug molecules to the plasma proteins. Because albumin cannot be filtered from the glomerulus, the drugs cannot pass through into the proximal tubules.
- GFR can monitored by Creatinine or inulin.
- GFR decreases with aging (>50 y) or renal failure. It can cause the reduction of elimination and may pracipitate toxicity.

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RENAL EXCRETION

b) Tubular secretion:

- There are important points about the tubular secretion mechanism of the drugs:
- ✓ Tubular secretion occurs mainly in the **proximal tubules**.
- ✓ **Active transport** is the main mechanism for tubular secretion.
- ✓ Anionic trasnport (OAT)- for acidic drug (Pencilline, probenecid, salicylate, MTX). And Cationic transport (OCT)- for basic drug (Thiazides, quinidine, procainamide, cemitidine).
- ✓ Due to specific active transport system displacement interaction is occurs. E.g. probenecid decrease the T. secretion of penicillin thus reduce the elimination and increase the duration of action.
- ✓ The **efficiency (performance) of the excretion by tubular secretion is higher** than glomerular filtration route. Clearance maximum in glomerular filtration is approximately 120 ml/min, whereas the clearance maximum of tubular secretion is about 600 ml/min.
- ✓ Protein bound drugs are dissociate in PCT and excrete via T. secretion.

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RENAL EXCRETION

- **Tubular reabsorption:**
- ✓ This mechanism works in an opposite (counter) way by reducing the drug or metabolite excretion.
- ✓ Tubular reabsorption occurs **mainly in distal tubules** and partially in proximal tubules.
- ✓ It occurs by **simple passive diffusion** generally
- ✓ **Changing the pH value of the urine** (making the urine acidic or basic) is going to change the ionization degree and the simple passive diffusion of the drug or the metabolite and lastly affect the excretion from the kidney.
- ✓ If we make the urine acidic (NH4Cl), the reabsorption of the weak acid drug from the renal tubules into the blood will increase, thus the excretion will decrease. But clinically, urine acidifying increase the risk Cardiotoxocity and Rhabdomyolysis.
- ✓ In the opposite way, making the urine basic (Na2CO3) will cause an increase in the excretion of weak acid drugs.

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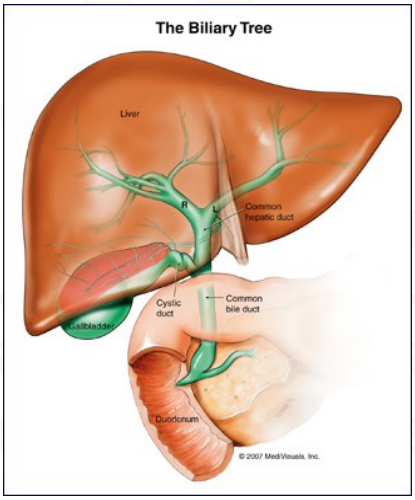
BILIARY EXCRETION

- These substances are generally secreted into the biliary ducts from the hepatocytes by **active transport** and finally they are drained into the intestines.
- Especially, highly ionized polar compounds (conjugation products) can be secreted into the bile in remarkable amounts.
- The most suitable molecular weight for the drugs to be secreted into the bile is approximately 500 KD.
- E.g., Steroids, Purgative, Heavy metal,



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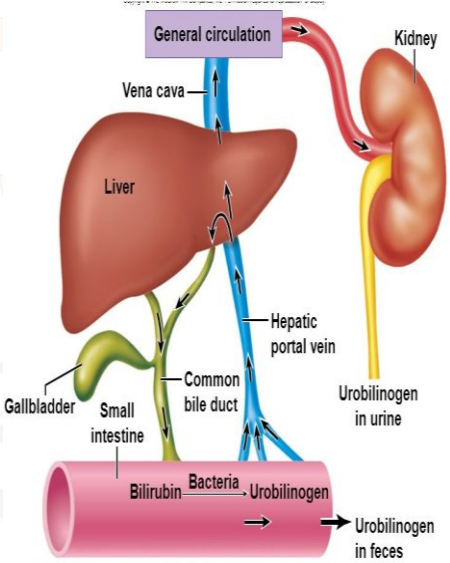
ENTEROHEPATIC CYCLE

- After biotransformation, metabolites are drained into the small intestine by biliary duct.
- Drug metabolites in the small intestine are broken down again in the small intestine and **reabsorbed back** reaching the liver by portal vein again.
- This cycle between the liver and small intestine is called the *enterohepatic cycle*.
- Especially the drugs which are metabolized by the **conjugation reactions** go under enterohepatic cycle.
- This is important, because enterohepatic cycle ***prolongs the duration of stay of the drugs*** in our body which leads an ***increase in the duration of their effect***.
- Drug examples that go under the enterohepatic cycle in remarkable amounts.
  - Chlorpromazine
  - Digitoxin
  - Indomethasin
  - Chloramphenicol



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EXCRETION from the LUNGS

- **Gaseous or the volatile substances** can pass from the blood circulation into the alveoli by passing across the endothelium and epithelium of the alveolar membrane.
- **Simple passive diffusion** is the main mechanism for this transport.
- After passing into the alveoli, these substances can be excreted by expiration.

EXCRETION into BREAST MILK

- Passage of the drugs into breast milk occurs generally by **simple passive diffusion** in breast feeding women.
- Drugs can be concentrated in milk according to the ion trapping phenomenon.
- Because the breast milk is more acidic than plasma, especially basic drugs tend to concentrate in breast milk.
- **Milk / plasma ratios** of a drug can be used as an indicator of the passage of some drugs into the breast milk.
- Milk / plasma ratios for some drugs:
  - ✓ Iodide: 65
  - ✓ Propyltiouracil: 12
  - ✓ Aspirin: 0.6-1.0
  - ✓ Penicillin: 0.1-0.25

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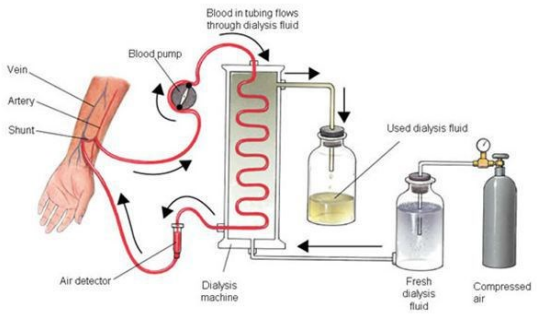
ARTIFICIAL EXCRETION WAYS

- **Hemodialysis** is one of the options among the artificial excretion way for the drugs.
- It is used especially for the treatment of ***acute drug intoxications*** to eliminate the drug from the body.



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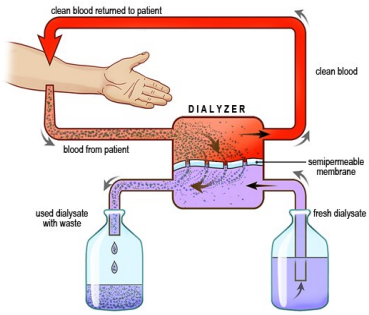
ARTIFICIAL EXCRETION WAYS

- **For the achievement of this system, there are some requirements:**
  - **Plasma protein binding** of the drug should be low (bound fraction should be low).
  - Drug **should not be stored in tissues** (apparent volume of the drug should be low)
  - The main elimination route of the drug should be from kidneys in unchanged (**without biotransformation**) form.



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IMPORTANT PARAMETERS IN DRUG ELIMINATION (CLEARANCE & HALF LIFE)

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CLEARANCE

- It can be described as **the volume of plasma** cleared from the drug per unit time (ml/min).
- **Total Body Clearance**: It is the plasma volume cleared from the drug per unit time via the elimination of the drug **from all biotransformation and excretion mechanisms** in the body.
- **Renal Clearance**: It can be described as **the rate of the excretion of a drug from kidneys**. So in other words, renal clearance is the volume of plasma cleared from the non-metabolized (unchanged) drug via the excretion by kidneys per minute.
- There are four important factors that affect the renal clearance of the drugs:
  - ✓ Plasma protein binding of the drug.--- -------decrease
  - ✓ Tubular reabsorption ratio of the drug.------decrease
  - ✓ Tubular secretion ratio of the drug. ----------increase
  - ✓ Glomerular filtration ratio of the drug.-------increase

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$$\text{Renal Clearence } (CL_R) = \frac{V \times C_U}{t \times C_P}$$

V= collected urine volume
t= duration to collect the urine
C_P= plasma concentration of the drug
C_U= urine concentration of the drug

CL_{renal} = [(Glomerular filtration rate + Tubular secretion rate) – Tubular reabsorption rate] / Cp

If the renal clearance of the drug is higher than the physiological creatinine clearance (120-130 ml/min), that time we can say that the *tubular secretion* helps and contributes the elimination of the drug additionally to filtration.

In early newborns and newborns, *glomerular filtration and tubular secretion mechanisms are immature* and not sufficient.

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ELIMINATION HALF-LIFE ($T_{1/2}$):

- It is the time it takes for the plasma concentration or the amount of drug in the body to be reduced by **50%** via different elimination mechanisms.

$$t_{1/2} = 0{,}693 \times \frac{V_d}{\text{Clearance}}$$

According to the above formulation,

1. Elimination half-life is inversely (negatively) proportional with the clearance.
2. How high the apparent volume of distribution of a drug, that high is the duration of stay of that drug in the body (Positive correlation between the half-life and the volume of distribution).
3. If the apparent volume of distribution of the two different drugs is not the same; having the same clearance does not mean that the rate of elimination of these two drugs is equal to each other.

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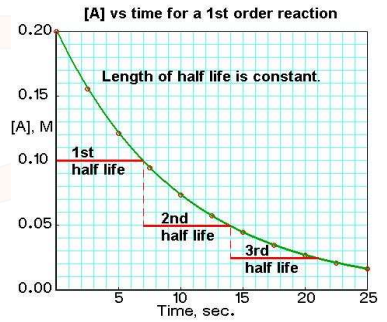
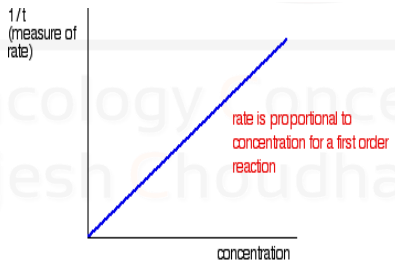
FIRST AND ZERO ORDER KINETICS:

- **First Order kinetic:**
  - ✓ Constant proportion (50%) of drug eliminated per unit time.
  - ✓ Rate α Conc.
  - ✓ Rate= Cl x Conc.
  - ✓ T1/2 = 0.693/k
  - ✓ T1/2= constant
  - ✓ E.g. Most of the drug.





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TIME	DRUG LEFT %	RATIO OF THE DRUG LEFT
0 x $t_{1/2}$	100	1
1 x $t_{1/2}$	50	1/2
2 x $t_{1/2}$	25	1/4
3 x $t_{1/2}$	12,5	1/8
4 x $t_{1/2}$	6,25	1/16
5 x $t_{1/2}$	3,125	1/32

In Fierst Order kinetic: reqire 4-6 t1/2 for complete eliminatio of drugs.

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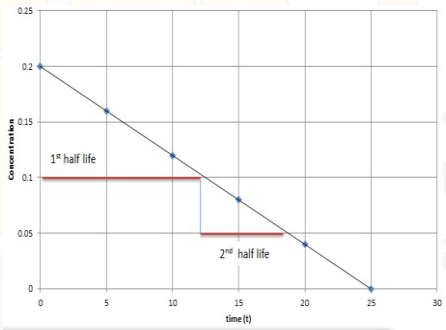
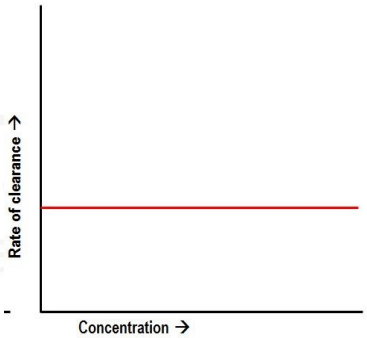
FIRST AND ZERO ORDER KINETICS:

- **Zero order kinetic**
- **Constant amount of drug eliminate per unit time**
- **R α C°**
- **Rate = constant**
- **T1/2 = 0.5 Conc. / k**
- **T1 > T2 > T3**
- **E.g. : (Zero WATT Power)- Warfarin, Alcohal, Theophyllin, Tolbutamide, Phenytoin, and Salicylate.**





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FIRST AND ZERO ORDER KINETICS:

Order	Rate Law	Concentration - Time Equation	Half Life	Graphical Plot
0	Rate = k_0	$[A]_0 - [A] = k_0 t$	$\frac{[A]_0}{2k_0}$	[A] vs t
1	Rate = k_1 [A]	$\log \frac{[A]_0}{[A]} = \frac{k t}{2.303}$	$\frac{0.693}{k}$	log A vs t
2	Rate = k_2 $[A]^2$	$\frac{1}{[A]} = kt + \frac{1}{[A]_0}$	$\frac{1}{(k_2 [A]_0)}$	$\frac{1}{[A]}$ vs t

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