Faculty of Pharmacy

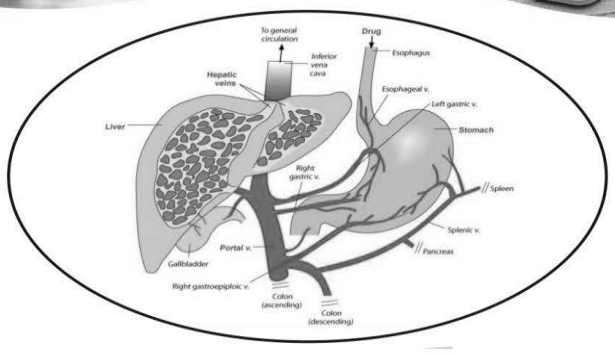
Menoufia University

BIOPHARMACEUTICS

For

Second Year Pharmacy Students

Second Semester



By Staff Members Of

Pharmaceutical Technology Department

Menoufia University, Faculty of Pharmacy
Course Specifications

Biopharmaceutics
Second Year, Second Semester

Professional Information

1. Overall aims of the course

Upon successful completion of this course, the students should be able to:

- Outline the factors affecting oral drug bioavailability.
- Point out the absorption mechanisms and the factors affecting them.
- Review the role of food and formulation design in modifying the drug absorption, distribution and elimination.
- Identify the factors affecting drug distribution, metabolism and elimination.

2. Intended learning outcomes of the course (ILOs)

a- Knowledge and understanding:

On successful completion of the course, the graduate should be able to:

- a1- Describe the mechanisms of gastrointestinal absorption of drugs.
- a2- Discuss the factors affecting gastrointestinal absorption of drugs**.**
- a3- Identify the role of dosage form on drug bioavailability.
- a4-Enumerate the factors affecting drug distribution, metabolism and elimination.
- a5- Define bioavailability and bioequivalance.

b- Intellectual skills

- b1- Suggest the dosage regimen.
- b2-Comprehend the biopharmaceutical considerations in drug product design.
- b3-Recognize the relationship between product design and the drug absorption, distribution and elimination.
- b4- Predict the effect of excipients and food on drug absorption, distribution and elimination.

c- Professional and practical skills

- c1- Handle the results of the *in-vitro* and *in-vivo* studies.
- c2-Assess physicochemical characteristics of drug substances as a factor affecting drug absorption.
- c3- Conduct bioavailability and bioequivalence studies.
- c4- Apply the biopharmaceutical consideration in dosage form design.

d- General and transferable skills

- d1- Work independently and in groups.
- d2- Retrieve and evaluate information from different sources.

3. Teaching and learning methods

a. Lectures
b. Practical training / laboratory
c. Seminar / Workshop
d. Class Activity

BIOPHARMACEUTICS

Definitions

- **Biopharmaceutics**: is the study of the relationship between the physicochemical properties of the drug [active pharmaceutical ingredients, (API)] and the drug product (dosage form in which the drug is fabricated) and the biological performance of the drug

- **Bioavailability**: is the rate and extent of systemic drug absorption

Definitions

- **Pharmacokinetics:** is the study of the time course and fate of drugs in the body.

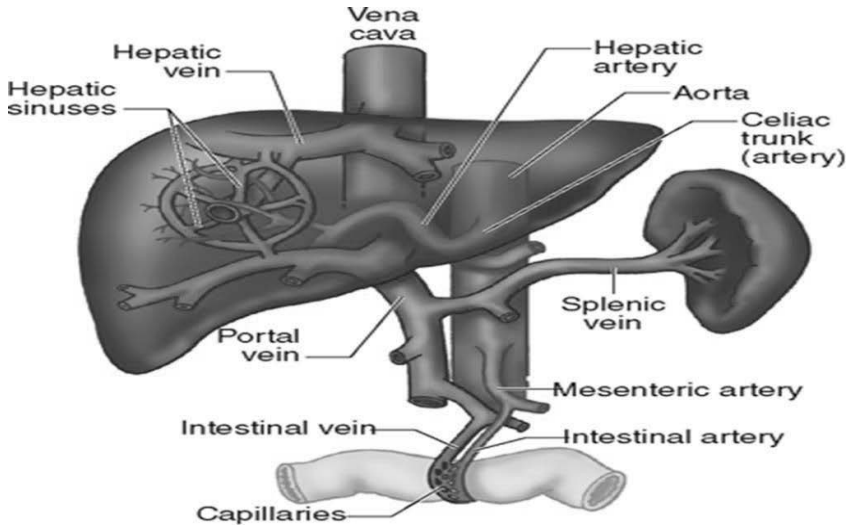
- **Pharmacokinetics** involves the kinetics of drug absorption, distribution, and elimination (metabolism and excretion) (ADME).

- The description of drug distribution and elimination is often termed drug **disposition**

Definitions

- **Pharmacodynamics:** is the study of the relation of the drug concentration at the site of action and its pharmacologic response.
- **Systemic circulation is the venous blood (excluding hepatic portal blood during the absorption phase) and arterial blood.**

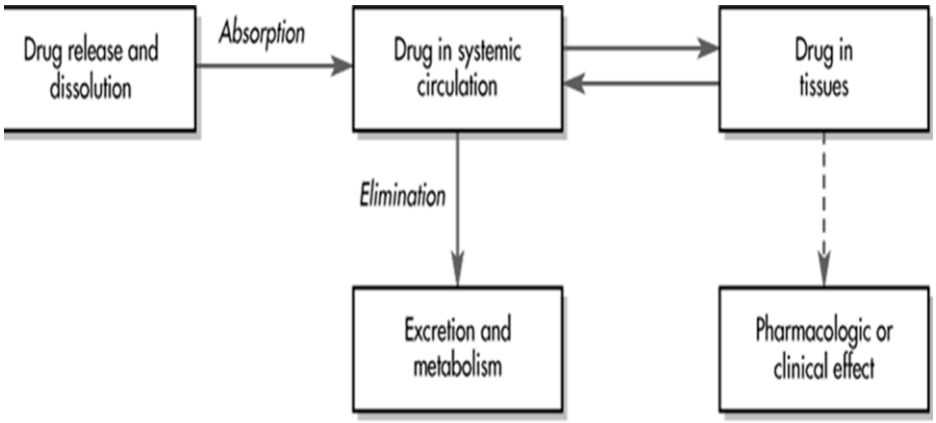
Hepatic portal blood during the absorption phase



LADME System

- It is the factors affecting drug concentration in blood plasma that refer to:
- L (Liberation),
- A (Absorption),
- D (Distribution),
- M (Metabolism)
- E (Excretion)
- Elimination = metabolism and excretion

The dynamic relationships among the drug, the drug product, and the pharmacological effect



LADME

- **Input processes are:**
- **L = Liberation,** the release of the drug from it's dosage form.
- **A = Absorption,** the movement of the drug from the site of administration to the blood circulation. The term commonly used to describe the rate and extent of the drug input is **bioavailability**. Drugs administered by **intravenous** routes exhibit essentially **100%** bioavailability
- **Output processes**, or disposition of the drug are:
- **D = Distribution**, the process by which drug diffuses or is transferred from intravascular space to extravascular space (body tissues).
- **M = Metabolism**, the chemical conversion or transformation of drugs into compounds which are easier to eliminate.
- **E = Excretion**, the elimination of unchanged drug or metabolite from the body via renal, biliary, or pulmonary

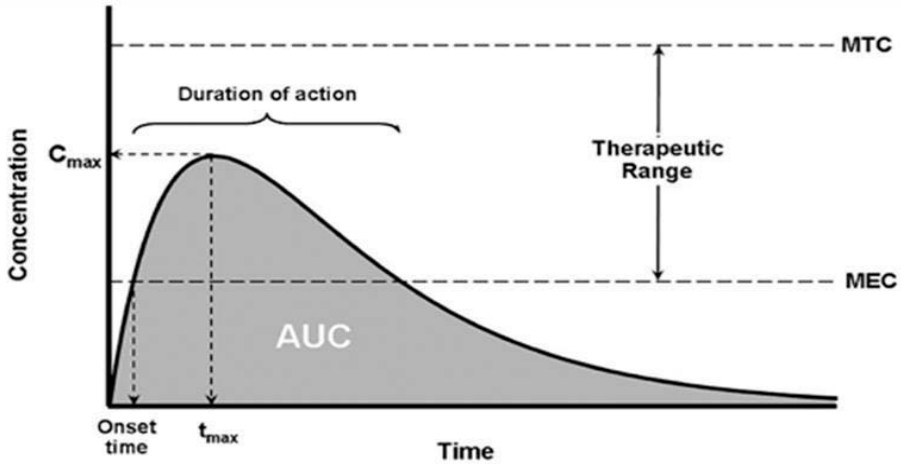
Pharmacokinetics	Pharmacodynamics
Pharmacokinetics describes the time course of drug concentration in one or more biological specimen, normally plasma, serum, or whole blood, which reflects several processes including absorption, distribution, metabolism and elimination	Pharmacodynamics describes the time course and the magnitude of the pharmacological response of the drugs.
	Based on the classic receptor-occupancy theory, after drug molecules reach the target biophase, it binds to the receptors to form the drug-receptor complex to exert pharmacological response
What does the body do to the drug?	What does the drug do to the body?

Fate of Drug in the Body

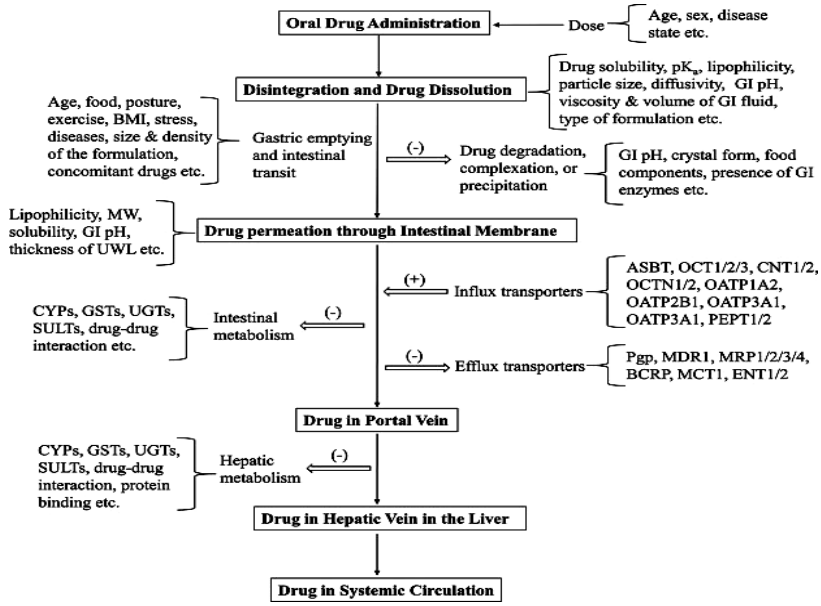
- Once the drug is systemically absorbed, normal physiologic processes for distribution and elimination occur, which usually is not influenced by the specific formulation of the drug.

- The rate of drug release from the product, and the rate of drug absorption, is important in determining the onset, intensity, and duration of drug action.

Generalized plasma level-time curve after oral administration of a drug (pharmacological parameters)



Rate-limiting Steps In Oral Drug Absorption



Rate-limiting Steps In Oral Drug Absorption

- Systemic drug absorption from a drug product consists of succession of the rate processes.
- For solid oral, immediate release drug products (e.g., tablets, capsule), the rate processes include:
  - 1. Disintegration of the drug product and subsequent release of the drug;
  - 2. Dissolution of the drug in an aqueous environment; and
  - 3. Absorption across cell membranes into the systemic circulation

RATE-LIMITING STEPS IN ORAL DRUG ABSORPTION

- In the process of drug disintegration, dissolution, and absorption, the rate at which drug reaches the circulatory system is determined by the slowest step in the sequence
- The slowest step in a kinetic process is the rate limiting step.
- Except for controlled release products, disintegration of a solid oral drug product is usually more rapid than drug dissolution and drug absorption.

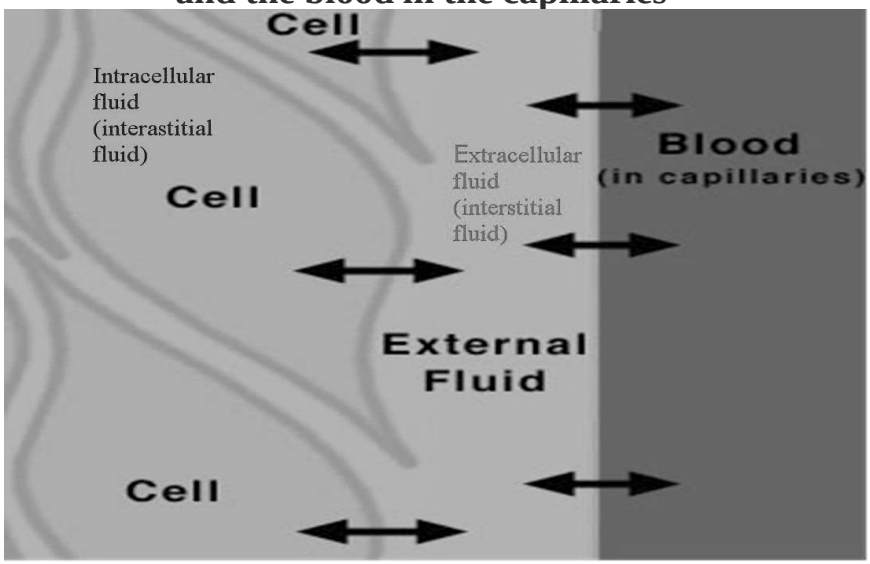
RATE-LIMITING STEPS IN ORAL DRUG ABSORPTION

- For drugs that have very poor aqueous solubility, the rate at which the drug dissolves (dissolution) is often the slowest step, and therefore exerts a rate-limiting effect on drug bioavailability.
- In contrast, for a drug that has a high aqueous solubility, the dissolution rate is rapid and the rate at which the drug crosses or permeates cell membranes is the slowest or rate-limiting step.

Drug Absorption

- For systemic absorption, a drug must pass from the absorption site through or around one or more layers of cells to gain access into the general circulation
- The permeability of a drug at the absorption site into the systemic circulation is intimately related to the molecular structure of the drug and the physical and biochemical properties of the cell membrane
- Membrane is the major structure in the cell, so drug must traverse the cell membrane for absorption into the cell.

Schematic diagram showing the cells, cell membranes, intracellular and extracellular fluids, and the blood in the capillaries



Oral Drug Absorption

- An orally administered drug must pass through a number of membranes in order to be absorbed into the systemic circulation
- Many physiological membranes differ in structure and function
- Despite this, there is general consensus regarding the basic structure of the cell membrane

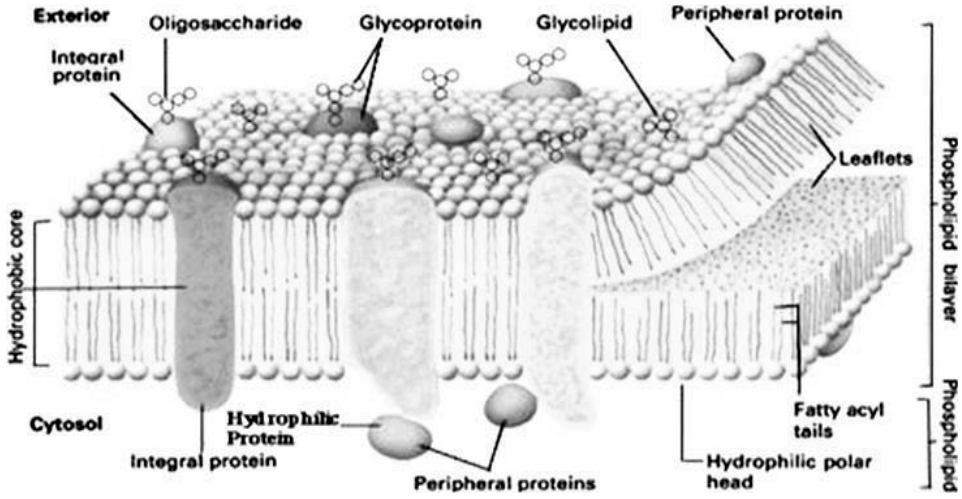
The Cell Membrane

- The primary structure of the cell membrane is a 5-nm thick bimolecular lipid film that separates intracellular and extracellular fluids.
- The lipid is composed mainly of the phospholipids, phosphatidylserine and phosphatidylinositol, and contains saturated and unsaturated fatty acids and sterols
- The bilayer exhibits high permeability to hydrophobic molecules and low permeability to hydrophilic molecules.

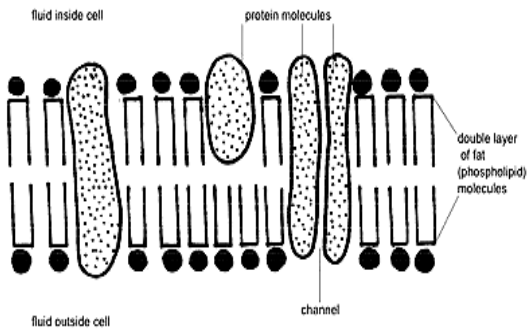
The Cell Membrane

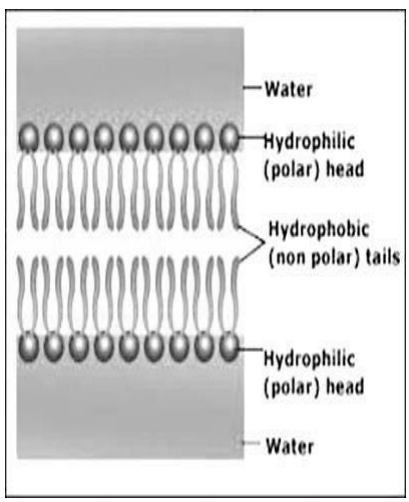
- The cell membrane is associated with intrinsic and extrinsic proteins.
- Intrinsic proteins are globular proteins that generally span the bilayer and are held within the membrane by hydrophobic and electrostatic interactions.
- The proteins can form channels, carriers, or pumps that enable polar molecules to cross the membranes.

Structure of Cell Membrane

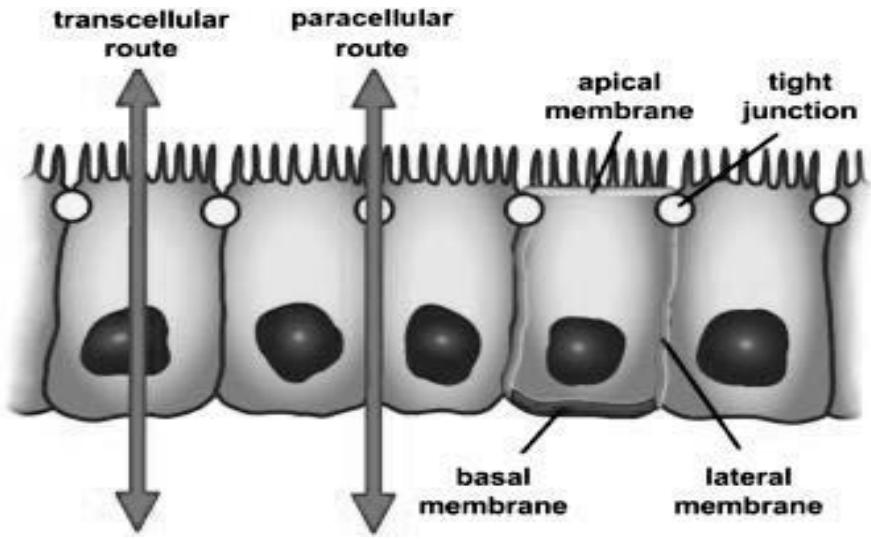


Structure of Cell Membrane





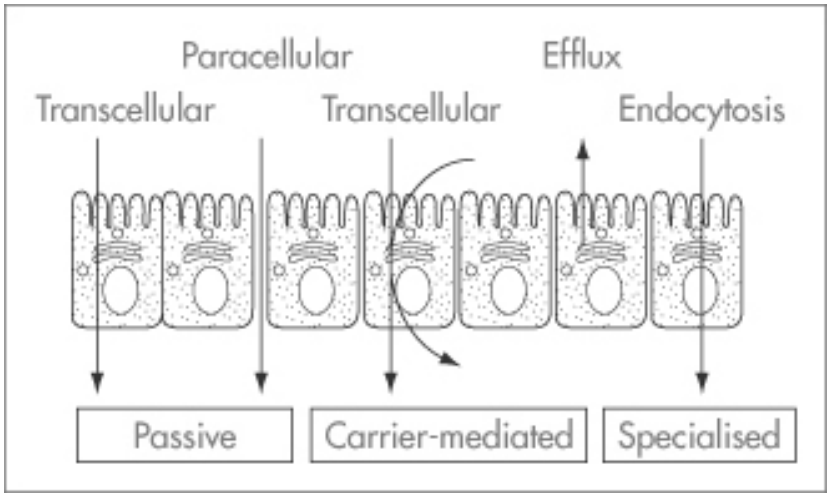
Intestinal Membrane



Passage of Drugs across Cell Membranes

- For absorption into the cell, a drug must traverse the cell membrane.
- **Transcellular** absorption is the process of a drug movement across the cell.
- Some polar molecules may not be able to traverse the cell membrane, but instead, go through gaps or "tight junctions" between cells, a process known as **paracellular** drug adsorption
- Some drugs are probably absorbed by a mixed mechanism involving one or more processes

Drug transport and site of action



Types of Intestinal Membrane Transport

- Intestinal membrane transport include paracellular and transcellular transport.
- Transcellular transport can be further divided into passive diffusion, endocytosis, and carrier-mediated transport
- Paracellular transport refers to the passage of solute without passage through the epithelium cells

1- Passive Diffusion

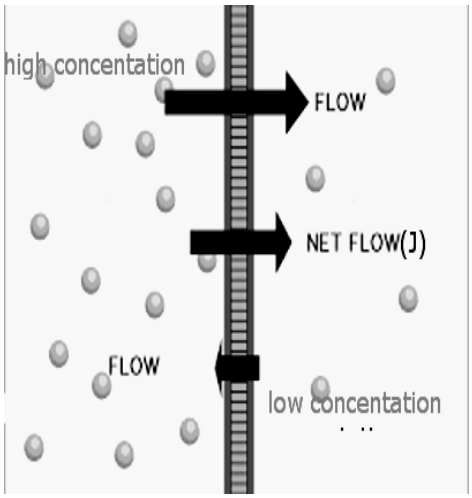
- This mechanism is based primarily on liquid solubility and concentration gradient.
- It is responsible for membrane transport of the great majority of drugs.
- Passive diffusion is the process by which molecules spontaneously diffuse from a region of higher concentration to a region of lower concentration

Follow; 1- Passive Diffusion

- This process is passive because no external energy is expended
- The direction of mass transfer of molecules or substances by passive diffusion depends on the concentration gradient on the two sides of the membrane (the driving force for passive diffusion)

Passive Diffusion of molecules

- Molecules **<u>in solution</u>** diffuse randomly in all directions
- As molecules diffuse from left to right and vice versa (small arrows), a net diffusion from the high-concentration side to the low-concentration side results.
- This results in a net flux (J) to the right side.



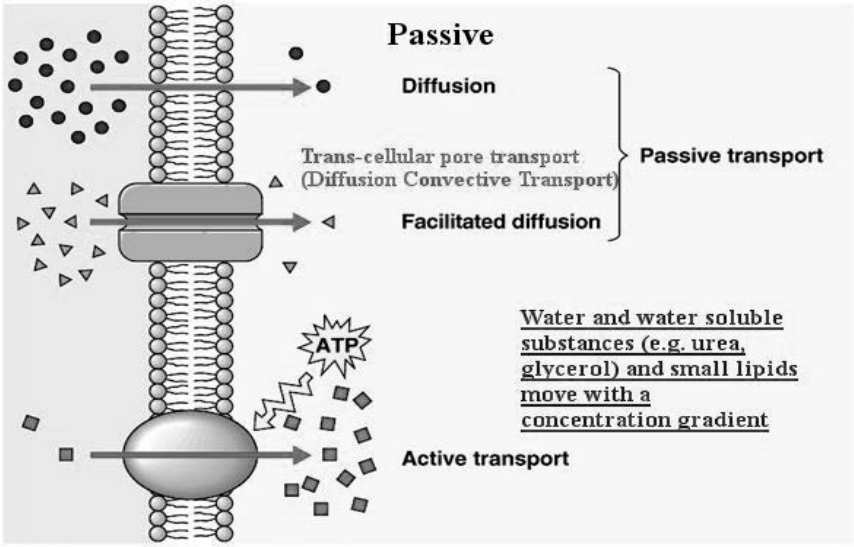
Follow; 1- Passive Diffusion

- The transport of drug molecules occurs until equilibrium.
- This equilibrium is not attained *in vivo* and the drug quantitatively absorbed.
- This is because drug distributes rapidly into a large volume after entering the blood resulting in a very low plasma drug concentration with respect to the concentration at the site of drug administration.

Follow; 1- Passive Diffusion

- Drug is usually given in milligram doses, whereas plasma drug concentrations are often in the microgram per milliliter or nanogram per milliliter range.
- For drugs given orally, $C_{GI} > C_P$.
- A large concentration gradient is maintained driving drug molecules into the plasma from the GI tract

Passive Diffusion



Follow; 1- Passive Diffusion

- According to Fick's Law of Diffusion, drug molecules diffuse from a region of high drug concentration to a region of low drug concentration

Fick's Law

- $dQ/dt = \{DAK/h\}(C_{GI} - C_p)$

- Where dQ/dt = rate of diffusion; D = diffusion coefficient; K = partition coefficient; A = surface area of the membrane; h = membrane thickness; and $C_{GI} - C_p$ = difference between the concentrations of drug in the GI tract and in the plasma.

Factors affecting passive diffusion

1- partition coefficient of the drug

- The partition coefficient, K, represents the lipid-water partitioning of a drug
- Typically, hydrophobic molecules have high partition coefficients, while hydrophilic molecules have low partition coefficients.
- More lipid soluble drugs have larger K values that theoretically increase the rate of systemic drug absorption
- In practice, drug absorption is influenced by other physical factors of the drug, limiting its practical application of K.

Factors affecting passive diffusion

2- The surface area of the membrane

- The surface area of the membrane through which the drug is absorbed directly influences the rate of drug absorption.
- Drugs may be absorbed from most areas of the GI tract
- However, the duodenal area of the small intestine shows the most rapid drug absorption due to such anatomic features as villi and microvilli, which provide a large surface area.
- These villi are not found in such numbers in other areas of the GI tract.

Factors affecting passive diffusion

3- The membrane thickness

- The membrane thickness, h, is a constant at the absorption site but may be altered by disease.
- Drugs usually diffuse very rapidly into tissues through capillary cell membranes in the vascular compartments.
- In the brain, the capillaries are densely lined with glial cells creating a thicker lipid barrier (blood-brain barrier) causing a drug to diffuse more slowly into brain
- In certain disease states (e.g., meningitis) the cell membranes may be disrupted or become more permeable to drug diffusion.

Factors affecting passive diffusion

4- Diffusion coefficient (D)

- The value of D depends on the size of the molecule and the viscosity of the dissolution medium.
- Increasing the viscosity will decrease the diffusion coefficient and thus the dissolution rate.
- This could be used to produce a sustained release effect by including a larger proportion of something like sucrose or acacia in a tablet formulation.

Factors affecting passive diffusion

5- The degree of ionization

- Drugs may be classified into three categories:

1-Strong electrolytes: ex. K^+, Cl^- or NH_4^+

2-Non- electrolyte: ex. Sugars and steroids

3-Weak electrolytes: weak acids and weak bases

- For weak electrolyte drugs (i.e., weak acids, bases), the extent of ionization influences drug solubility and the rate of drug transport.

Factors affecting passive diffusion

Follow; 5- The degree of ionization

- Molecules that are weak acids or bases cross membranes more rapidly when they are in the non-ionized form.
- However, aqueous solubility is favored for the ionized form.
- In order to be available to cross any membrane, a drug must be in solution.
- This paradoxical requirement of both aqueous and lipid solubility is of particular concern in the area of drug absorption and presents a constant challenge in pharmaceutical formulation.

Factors affecting passive diffusion

Follow; 5- The degree of ionization

- Ionized drugs are more water soluble than non-ionized drugs which are more lipid soluble.
- The extent of ionization of a weak electrolyte depends on the pKa of the drug and the (pH) of the medium in which the drug is dissolved.
- The **Henderson and Hasselbalch** equation describes the ratio of ionized (charged) to unionized form of the drug and is dependent on the pH of the medium and the pKa of the drug:

Factors affecting passive diffusion

Follow; 5- The degree of ionization

For weak acids:

- $HA + H_2O \Longleftrightarrow H_3O^+ + A^-$
- $K_a = (A^-)\ (H_3O^+) / (HA)$
- $pH = pK_a + Log\ (A^-) / (HA)$

For weak bases:

- $BH^+ + H_2O \Longleftrightarrow H_3O^+ + B$
- $K_a = (B)\ (H_3O^+) / (BH^+)$
- $pH = pK_a + Log\ (B) / (BH^+)$

Follow; 5- The degree of ionization

- For an acid:

$$HA \rightleftharpoons H^+ + A^- \quad (K_a)$$

$$K_a = \frac{[H^+][A^-]}{[AH]} \qquad \% \text{ ionised} = \frac{100}{1 + 10^{(pK_a - pH)}}$$

- For a base:

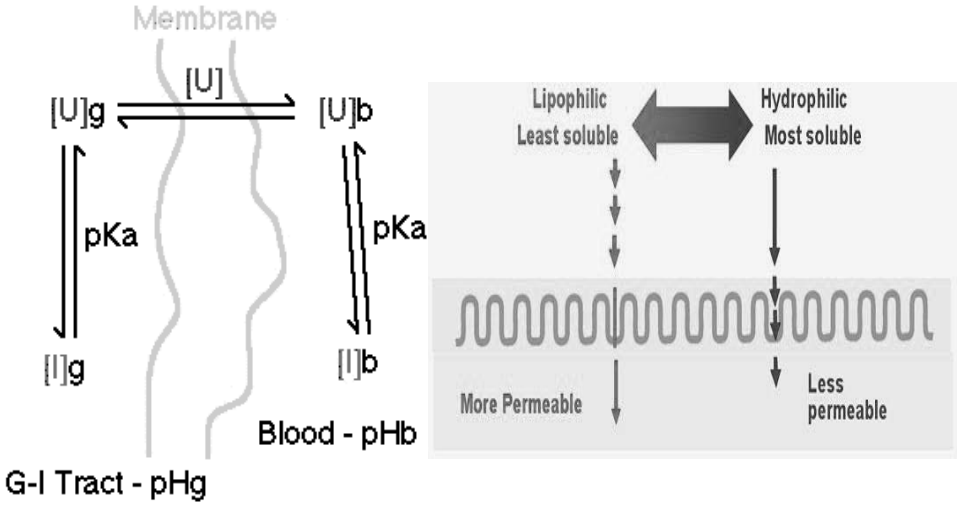
$$BH^+ \rightleftharpoons H^+ + B \quad (K_a)$$

$$K_a = \frac{[H^+][B]}{[BH^+]} \qquad \% \text{ ionised} = \frac{100}{1 + 10^{(pH - pK_a)}}$$

When an acid or base is 50% ionised:

$$pH = pK_a$$

pH – Partition Hypothesis



pH – Partition Hypothesis

- Describe the influence of **GI pH** and **drug pKa** (the degree of ionization) on the **extent of drug transfer** or drug absorption

- The non-ionized form is the absorbable form due to higher lipid solubility.

- The ionized form is not able to get through the lipid membrane.

Factors affecting passive diffusion

6- The drug affinity for tissue component

- The drug concentration on either side of a membrane is also influenced by the affinity of the drug for a tissue component, which prevents the drug from freely moving back across the cell membrane
- For example, drug that binds plasma or tissue proteins causes the drug to concentrate in that region
- Dicumarol and sulfonamides strongly bind plasma proteins; whereas, chlordane, a lipid-soluble insecticide, partitions and concentrates into adipose (fat) tissue.

Factors affecting passive diffusion

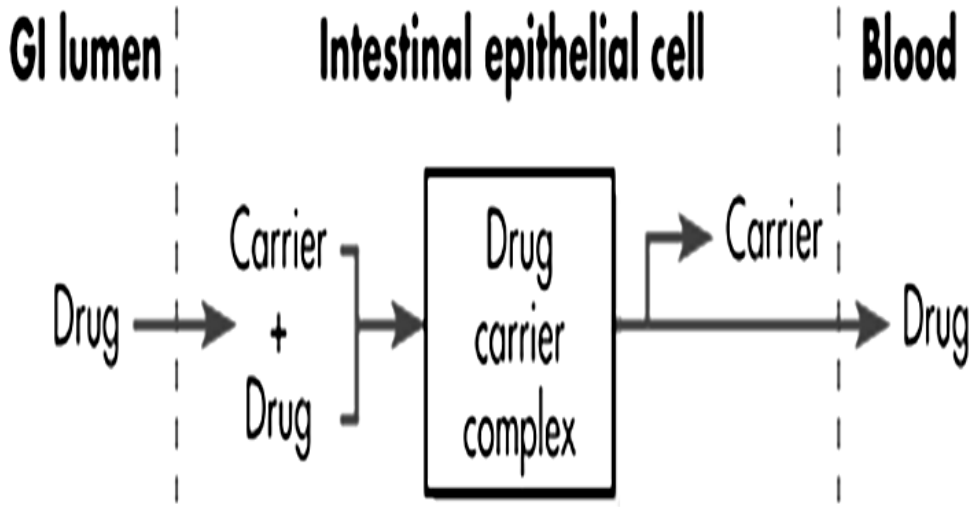
Follow; 6- The drug affinity for tissue component

- Tetracycline forms a complex with calcium and concentrates in the bones and teeth.
- Drugs may concentrate in a tissue due to a specific uptake or active transport process.
- Such processes have been demonstrated for iodide in thyroid tissue, potassium in the intracellular water, and certain catecholamines in adrenergic storage sites.

Carrier-mediated transport

- **2.1- Active transport**
- **2.2- Facilitated diffusion**
- **2.3- Carrier-Mediated Intestinal transport**

Hypothetical carrier – mediated transport process.



2.1- Active transport

- Active transport is a carrier mediated trans-membrane process that is important for GI absorption of some drugs and also involved in the renal and biliary secretion of many drugs and metabolites.
- A carrier binds the drug to form a carrier-drug complex that shuttles the drug across the membrane and then dissociates the drug on the other side of the membrane.

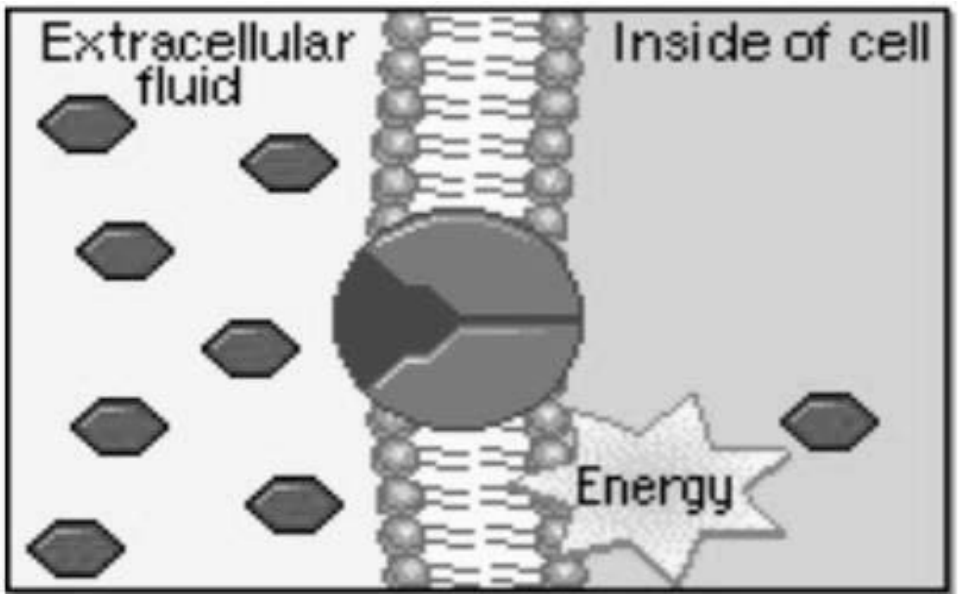
Follow 2.1- Active transport

- Active transport is an energy-consuming system characterized by the transport of drug against a concentration gradient, that is, from regions of low drug concentrations to regions of high concentrations.
- A drug may be actively transported, if the drug molecule structurally resembles a natural substrate that is actively transported.

Follow 2.1- Active transport

- A few lipid-insoluble drugs that resemble natural physiologic metabolites (e.g., 5-fluorouracil) are absorbed from the GI tract by this process.
- Drugs of similar structure may compete for adsorption sites on the carrier.
- Because only a certain amount of carrier is available, the binding sites on the carrier may become saturated at high drug concentrations.
- In contrast, passive diffusion is not saturable.

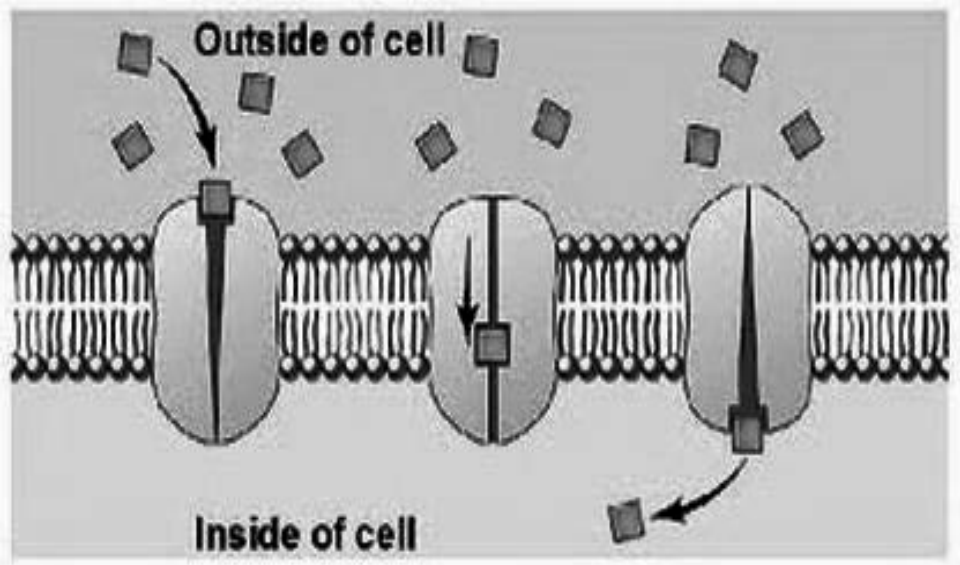
Active Transport



2.2- Facilitated Diffusion

- Facilitated diffusion is a non-energy requiring, carrier-mediated transport system in which the drug moves along a concentration gradient (i.e., moves from a region of high drug concentration to a region of low drug concentration).
- Facilitated diffusion is saturable, structurally selective for the drug and shows competition kinetics for drugs of similar structure.
- Facilitated diffusion seems to play a very minor role in drug absorption (**Vit.B_{12}**)

Facilitated Diffusion

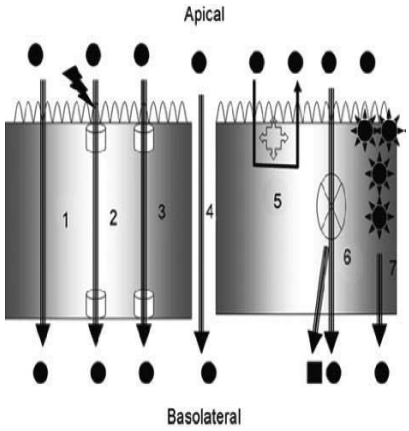


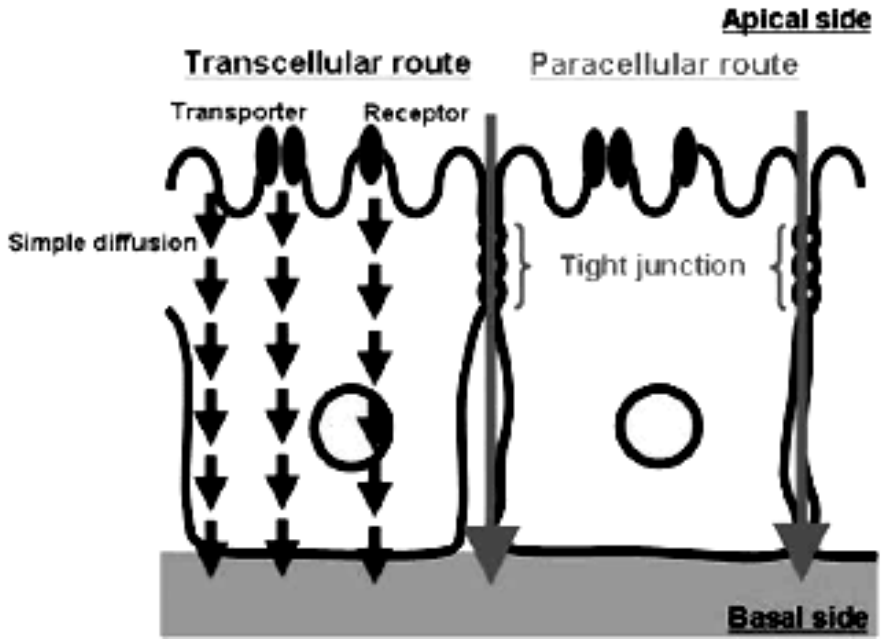
Carrier – Mediated Intestinal Transport

- Various carrier mediated systems (transporters) are present at the intestinal brush border and basolateral membrane for the absorption of specific ions and nutrients essential for the body.
- Many drugs are absorbed by these carriers because of the structural similarity to natural substrates.
- An intestinal trans-membrane protein, p-Glycoprotein (p-Gp) appears to reduce apparent intestinal epithelial cell permeability from lumen to blood for various lipophilic or cytotoxic drugs.

Multiple pathways for intestinal absorption of a compound

1) **Passive transcellular**
2) **Active transcellular**
3) **Facilitated diffusion**
4) **Passive paracellular**
5) **Absorption limited by** P-gp and/or other efflux transporters
6) **Intestinal first-pass metabolism** followed by absorption of parent and metabolite
7) **Receptor-mediated influx transport.**





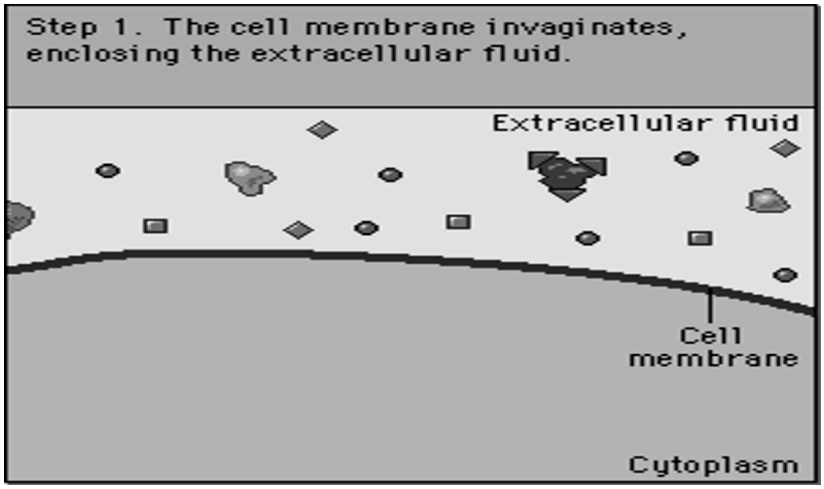
3- Vesicular transport

- Vesicular transport is the process of engulfing particles or dissolved materials by the cell.
- **Pinocytosis** (cell drinking) refers to the engulfment of small solutes or fluid.
- **Phagocytosis** (cell eating) refers to the engulfment of larger particles or macromolecules generally by macrophages.
- **Endocytosis and exocytosis** are the processes of moving macromolecules into and out of a cell, respectively.

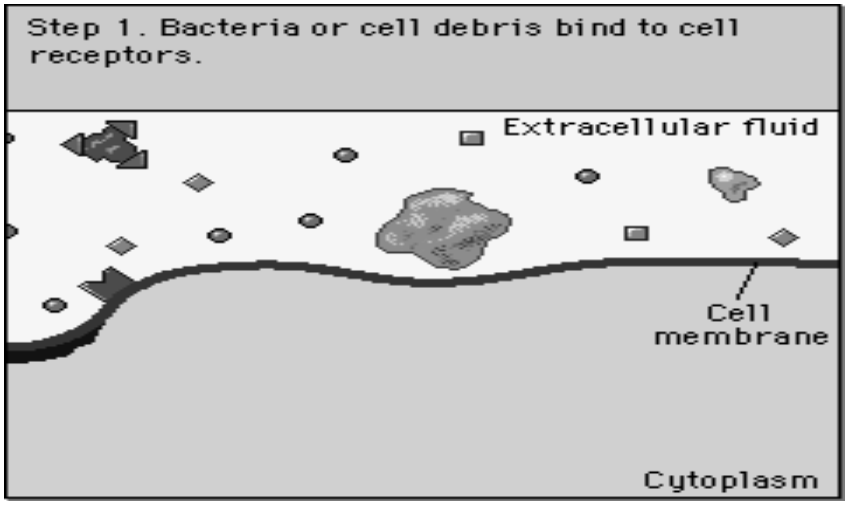
Follow; 3- Vesicular transport

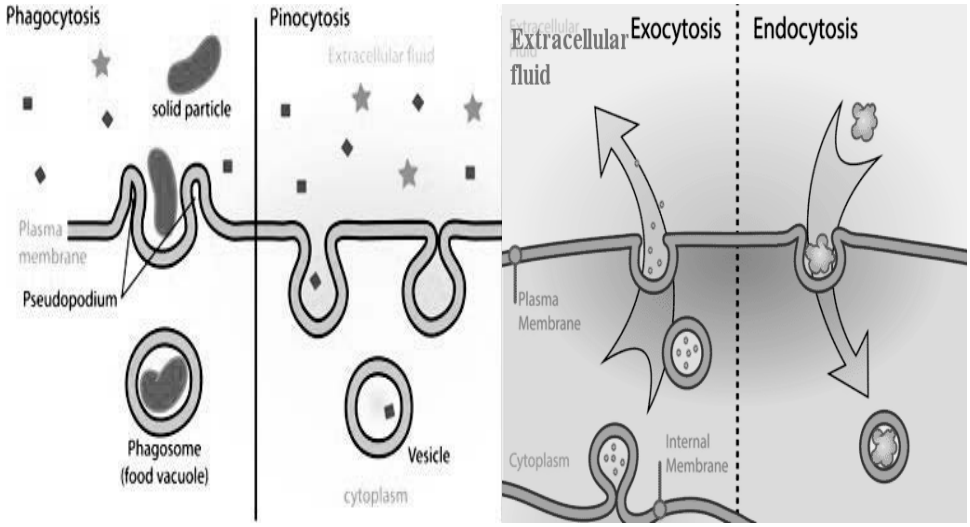
- During pinocytosis or phagocytosis, the cell membrane invaginates to surround the material, and then engulfs the material into cell.
- Subsequently, the cell membrane containing the material forms a vesicle or vacuole within the cell.
- Vesicular transport is the proposed process for the absorption of orally administered sabin polio vaccine and various large proteins

Pinocytosis



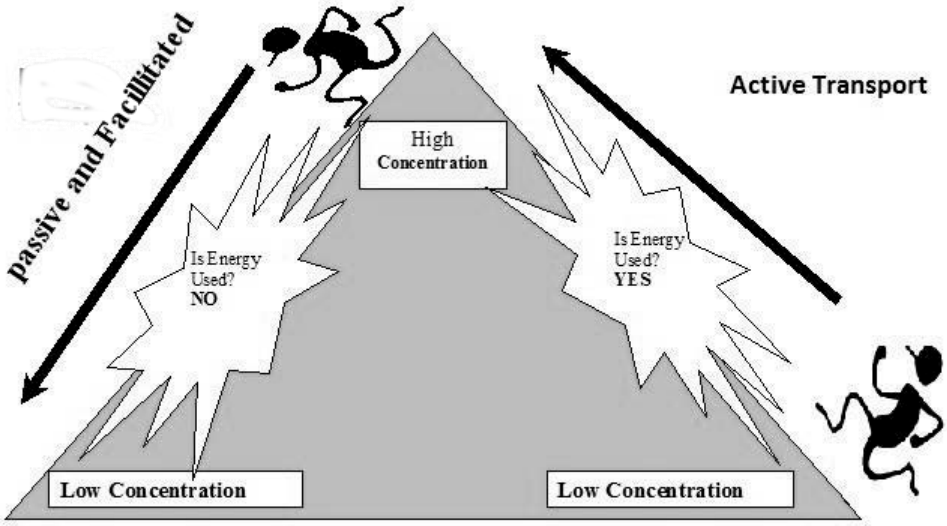
Phagocytosis





4- Paracellular transport

- Paracellular transport refers to transport solutes in between cells, without passage through the epithelial cells themselves.
- It is now well recognized that the intercellular junctions between epithelial cells of capillaries are "leaky," allowing paracellular transport of small molecules.
- Paracellular transport is passive transport, follows drug concentration gradients, and does not require energy.
- In the intestine, molecules smaller than 500 MW may be absorbed by paracellular drug absorption.



Factors Affecting Oral Drug Absorption

1- physicochemical factors:

1.1- Lipophilicity

1.2- Degree of Ionization

1.3- Size

1.4- Charge

1.5- Solubility and Dissolution

1.6- Complexation

1.7- Adsorption

1.8- Stability

2- physiological Factors:

2.1- pH of GIT fluids

2.2- Surface area of GIT absorption sites

2.3- Gastric emptying rate.

2.4- Intestinal motility

2.5- Drug stability in the GIT

2.6- Hepatic metabolism

2.7- Malabsorption

2.8- Food

3- Dosage form Factors

1.1- Lipophilicity

- The lipid solubility or lipophilicity of drugs is a prerequisite for transcellular diffusion across the intestinal membrane.
- The lipophilicity of drug substances is expressed as the apparent partition coefficient or distribution coefficient (log P) between n-octanol and an aqueous buffer (pH 7.4), which is pH-dependent in the case of ionizable compounds.

Follow; 1.1- Lipophilicity

- In general, compounds with low log P are poorly absorbed, whereas compounds with log P > 1 offer satisfactory absorption.
- It is important, however, that the drug possess an optimum lipophilicity, as too low or too high lipophilicity may result in less than optimum oral bioavailability.

Follow; 1.1- Lipophilicity

- The high lipophilicity (log P > 3.5) decreases drug transport across the intestinal epithelial cells and could be accounted for loss of *in vivo* biological activity.
- The "cut-off" point of P value, that is, the P value corresponding to an optimal trans-epithelial passage of drugs, was found to be around 3000 (log P= 3.5).

Barbiturates	PC o/w	% Absorbed
Barbitone	0.7	12
Phenobarbitone	4.8	20
Cyclobarbitone	14	24
Hexobarbitone	100	44
Thiopentone	500	100

1.2- Degree of ionization

- The interrelationship between the degree of ionization of a weak electrolyte drug (determined by its pka and pH of the absorption site) and the extent of drug absorption is embodied in **pH-partition hypothesis.**
- According to **Henderson – Hasselbach** equation and **pH- partition hypothesis**, weak acids are mainly absorbed from the stomach and weak bases are mainly absorbed from the small intestine.
- However, this is not the actual situation and there are limitations of pH – Partition Hypothesis.

Limitations of pH partition hypothesis

1. The rate of intestinal absorption of weak acids is often higher than its rate of gastric absorption due to:

- **Larger mucosal surface area** available for drug absorption due to presence of villi and microvilli
- Presence of an affective pH at the surface of intestinal mucosa (**virtual membrane pH**) of about 5.3 which is lower than the bulk lumen pH (6.8- 7.5)

Follow; Limitations of pH partition hypothesis

2. A number of drugs are poorly absorbed from certain areas of the gastrointestinal tract despite the fact that their unionized forms predominate in such area:

- Barbitone (pka= 7.8) which is totally unionized at gastric pH (1.5- 3), is only poorly absorbed from the stomach. However, Thiopentone which has a similar pka (7.6) is much better absorbed from the stomach than barbitone.
- This is because the **lipid solubility** of unionized form of thiopentone is more than that of barbitone.

Follow; Limitations of pH partition hypothesis

3. A number of drugs are absorbed readily despite being ionized over the entire pH range (1.5 – 8) of the GIT.

- This could be explained by the fact that these drugs are absorbed by other transport mechanisms (e.g. carrier mediated transport)

1.3- Size

- Passive absorption in the gastrointestinal tract is severely limited by the size of the penetrating drug molecule.
- This is probably due to the well-organized and packed structure of the cell membrane lipid bilayer.
- When a molecule is too large, the potential energy resulting from its concentration difference is not large enough to generate the high energy required to greatly disturb the bilayer

Follow; 1.3- Size

- Therefore, size and perhaps the surface area of a molecule are major factors that limit absorption via passive diffusion.
- The optimal molecular weight is less than 500 and may extend to 550.

1.4- Charge

- Effects of charge on passive absorption of drugs are well recognized.
- In general, charged molecules are not as permeable as the corresponding uncharged species when the compound is absorbed via passive diffusion.
- However, the effect of charge on the absorption of drugs via a carrier-mediated transport process is not simple.
- Some transporters favor neutral substrates, some positively charged, and others negatively charged.

1.5- Solubility and Dissolution

- Solubility is the maximum amount of solute that dissolves in a given quantity of solvent at a specific temperature to form a saturated state (equilibrium solubility).
- Solubility affects the absorption of drugs because it affect the driving force of drug absorption (the concentration of drug molecules at the site of absorption).
- The drug dissolution rate is the amount of drug substance that goes in solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition.
- In biologic systems, drug dissolution in an aqueous medium is an important prior condition of systemic absorption.

Dissolution

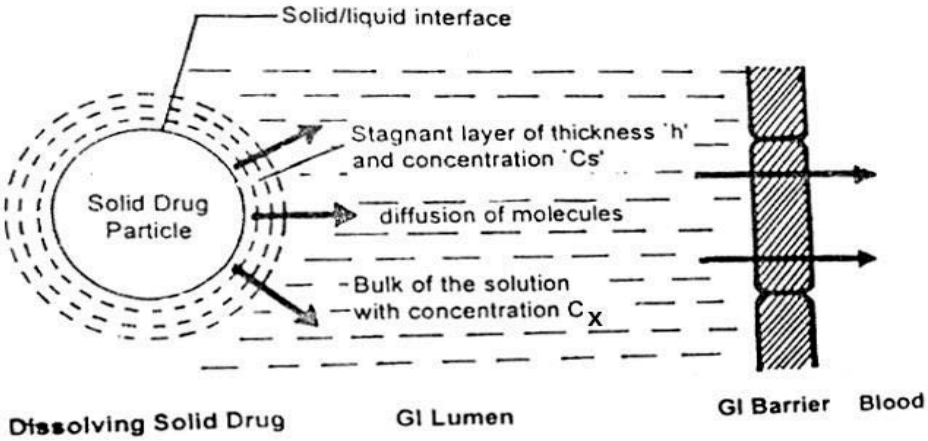
- The overall rate of drug dissolution may be described by the **Noyes-Whitney equation** which models dissolution of spherical drug particles, when dissolution is diffusion controlled and involves no chemical reaction.

$$\frac{\mathrm{d}c}{\mathrm{d}t} = D \times A\left(\frac{c_{\mathrm{S}} - c_{\mathrm{x}}}{h}\right)$$

$$\frac{\mathrm{d}c}{\mathrm{d}t} = D \times A\left(\frac{c_{\mathrm{S}} - c_{\mathrm{x}}}{h}\right)$$

- Where, dC/dt = rate of drug dissolution,
- D = diffusion rate constant,
- A = surface area of the particle,
- Cs = drug concentration in the stagnant layer,
- Cx = drug concentration in the bulk solvent, and
- h = thickness of the stagnant layer.

$$\frac{dc}{dt} = D \times A\left(\frac{c_S - c_x}{h}\right)$$



Follow; 1.5- Solubility and Dissolution

- As the drug particle dissolves, a saturated solution (stagnant layer) is formed at the immediate surface around the particle.
- The dissolved drug in the saturated solution gradually diffuses to the surrounding regions.

1- Physiological factors affecting drug dissolution

1.1 Viscosity of GIT fluids

- The value of ***D*** depends on the size of the molecule and the viscosity of the dissolution medium.
- Increasing the viscosity will decrease the diffusion coefficient and thus the dissolution rate.
- This could be used to produce a sustained release effect by including a larger proportion of something like sucrose or acacia in a tablet formulation.
- The presence of food may decrease the rate of drug dissolution by reducing the rate of diffusion of drug molecules away from the diffusion layer.

1- Physiological factors affecting drug dissolution

1.2- Degree of agitation

- Affect the thickness of the diffusion layer (***h***) exhibited by each drug particles.
- Hence, an increase in gastric and/or intestinal motility may increase the dissolution rate of a sparingly soluble drug by decreasing ***h***

1- Physiological factors affecting drug dissolution

1.3- Rate of absorption

- Affect the concentration (C_x) of drug in the bulk of the gastrointestinal fluids.
- The increased rate of removal of dissolved drug from bulk solution by absorption through GIT resulted in decreased C_x and enhanced dissolution.
- If C_x is much smaller than Cs then we have the so-called "sink condition" and the equation is reduced to:

  Rate of Solution = *D*A*Cs/h*

1- Physiological factors affecting drug dissolution

1.4- Volume of GIT fluids

- Affect the concentration (C_x) of drug in the bulk of the gastrointestinal fluids.
- In the stomach, the volume of fluids will be influenced by the intake of fluid in the diet.
- Low value of C_x will produce sink condition and favor rapid dissolution.

2- Physico-chemical factors affecting drug dissolution

2.1- Particle Size

- The effective surface area (A) of the drug is increased enormously by a reduction in the particle size.
- Particle size reduction to a micronized form increased the absorption of **low aqueous solubility** drugs such as griseofulvin, nitrofurantoin, and many steroids.
- Improved bioavailability has been observed with griseofulvin, digoxin (the drug absorption is dissolution rate- limited)

2- Physico-chemical factors affecting drug dissolution

Follow; 2.1- Particle Size

- Smaller particle size results in an increase in the total surface area of the particles, enhances water penetration into the particles, and increases the dissolution rates.
- With poorly soluble drugs, a disintegrant may be added to the formulation to ensure rapid disintegration of the tablet and release of the particles.

Follow; 2.1- Particle Size

Limitation of particle size reduction:

1. No effect on bioavailability of drugs whose absorption was not dissolution rate- limited.
2. In case of poorly soluble, hydrophobic drug, extensive particle size reduction can increase the tendency of particles to aggregate in the aqueous GIT fluids with consequent reduction in the effective surface area, dissolution rate and bioavailability
3. Certain drug such as penicillin G and erythromycin are unstable in gastric fluids. Hence, increased rate of dissolution will result in increased drug degradation.

2.2 Salt form

- Salts of weak acids and weak bases generally have much higher aqueous solubility than the free acid or base.
- According to Noyes Whitney equation, the dissolution rate is influenced by the solubility (Cs) that the drug exhibits in the diffusion layer surrounding each dissolving drug particle.

Follow; 2.2 Salt form

- For weak electrolytes, the solubilities in the diffusion layer (Cs) are pH –dependent.
- The pH in the diffusion layer could be changed by the salt form even though the bulk pH of the GIT fluids remained at the same value.
- Therefore if the drug can be given as a salt the solubility can be increased and dissolution improved.

Follow; 2.2 Salt form

A- Dissolution of weak acids in gastric fluids by a strong base salt like sodium and potassium salts (ex. Barbiturates, penicillin V and sulfonamides)

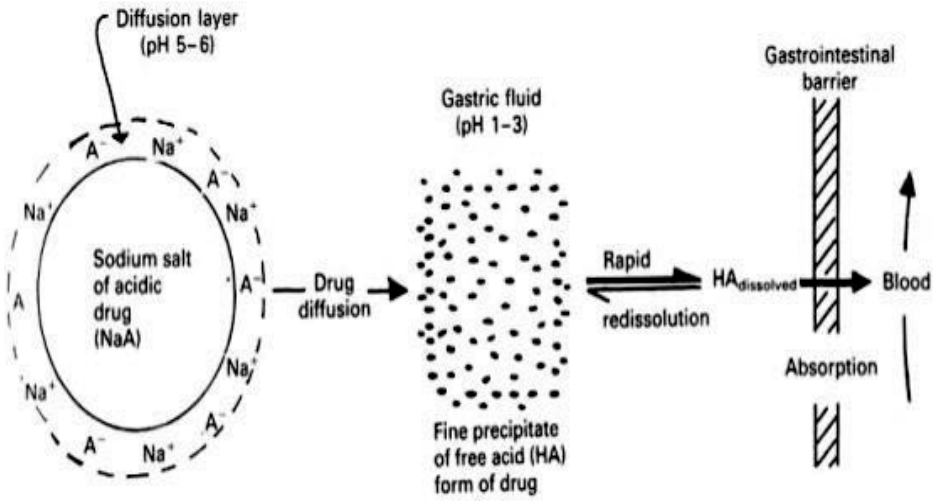
- The potassium salt of penicillin V yields higher peak plasma concentrations of the antibiotic than dose the free acid.

Follow; 2.2 Salt form

- The pH of the diffusion layer surrounding each particle of the salt form would be higher (5-6) than the low bulk pH (1-3) of the gastric fluids due to neutralizing action of the strong alkali cations (K^+ or Na^+) present in the diffusion layer.
- Since the weak acidic drug has a relatively high solubility at elevated pH in the diffusion layer, dissolution of the drug particles will be faster.

Follow; 2.2 Salt form

- When dissolved drug diffuses out of the diffusion layer into the bulk of gastric fluid with lower pH, precipitation of the free acid form occurs.
- The precipitated form will be very fine, non-ionized, wetted drug particles with a very large effective surface area.
- This condition facilitate re-dissolution of the precipitated particles.



schematic representation of the dissolution process of a salt form of a weak acidic drug in gastric fluid

Follow; 2.2 Salt form

- Not all water soluble salts have the desirable therapeutic advantages, e.g., the sulfonylurea oral hypoglycemic drug: tolbutamide and tolbutamide sodium.
- Oral administration of the sodium salt results in a very rapid and dramatic reduction in blood glucose to about 65% to 70 % of control levels. The response resulted in an undesirable degree of hypoglycemia
- The more slowly dissolving free acid produces a gradual decrease in blood sugar to about 80% of control levels, which is observed about 5 hours after administration. The free acid is more useful form of the drug for treatment of diabetes.

Follow; 2.2 Salt form

- B- An alternative method of increasing the dissolution rate of a weak acidic drug in gastric fluid is the inclusion of non-toxic basic substances in a solid dosage form of the free acid.
- The inclusion of aluminum dihydroxy aminoacetate and magnesium carbonate in aspirin tablets to increase gastric dissolution and oral bioavailability.

Follow; 2.2 Salt form

- C- With weakly basic drugs, a strong acid salt is prepared like the hydrochloride salt of chlorpromazine
- The presence of strongly acidic anions (Cl^-) in the diffusion layer will increase the solubility of the drug (Cs)

2.3- Crystal form
2.3.1- Polymorphism

- Polymorphism refers to the arrangement of a drug in various crystal forms (polymorphs)
- Polymorphs have the same chemical structure but different physical properties, such as solubility, stability, melting point, density, hardness, and compression characteristics.

Follow; 2.3- Crystal form
2.3.1- Polymorphism

- Chloramphenicol palmitate, for example, has several crystal forms (stable (A), meta-stable (B) and un-stable (C)) and when given orally as a suspension, the drug concentration in the body depend on the percentage of B- polymorph in the suspension
- Stable polymorph (A) has higher stability and least aqueous solubility
- The B-form is sufficiently stable and more soluble and better absorbed than A- form

Follow; 2.3- Crystal form
2.3.2- Amorphous solid

- A drug may exist in different crystalline forms and in an amorphous form.
- The amorphous form is usually more soluble and rapidly dissolving than the corresponding crystalline forms of a poorly soluble drug.
- The amorphous form of the antibiotic novobiocin is more soluble, more rapidly dissolving and more readily absorbed after oral administration of its aqueous suspension than the crystalline form.
- The crystalline form is therapeutically ineffective

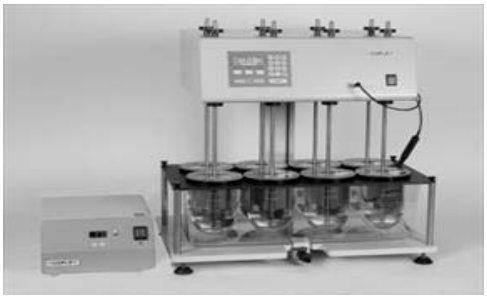
Follow; 2.3- Crystal form
2.3.3- Solvates

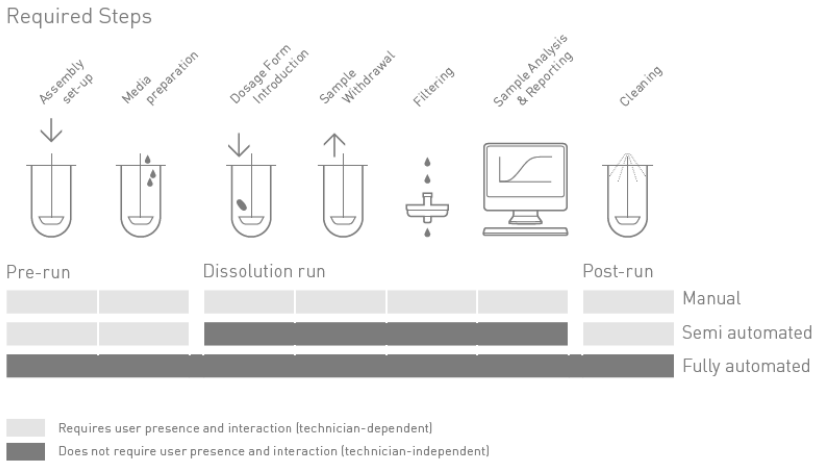
- Some drugs interact with solvent during preparation to form a crystal called solvate.
- Water may form a special crystal with drugs called hydrates.
- For example, erythromycin forms different hydrates which may have quite different solubility compared to the anhydrous form of the drug

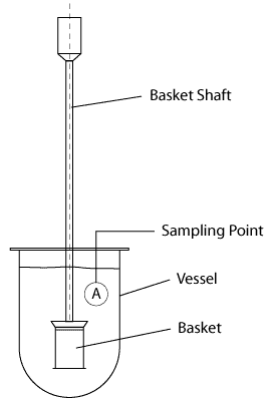
Follow; 2.3- Crystal form
2.3.3- Solvates

- Generally, the greater the solvation in the crystal, the lower is the solubility and dissolution rate in the solvent identical to the solvation molecules
- Ampicillin trihydrate, for example, was reported to be less absorbed from hard gelatin capsule or aqueous suspension than the anhydrous form of ampicillin due to faster dissolution of the later

Dissolution testing




Required Steps
Assembly set-up
Media preparation
Dosage Form Introduction
Sample Withdrawal
Filtering
Sample Analysis & Reporting
Cleaning
Pre-run
Dissolution run
Post-run
Manual
Semi automated
Fully automated
Requires user presence and interaction (technician-dependent)
Does not require user presence and interaction (technician-independent)


Basket Shaft
Sampling Point
Vessel
A
Basket

Dissolution Apparatus (USP Apparatus I and II)

- The apparatus consists of a motor, a metallic drive shaft, a cylindrical basket, and a covered vessel made of glass or other inert transparent material.
- The contents are held at 37^{o} C ± 0.5^{o} C.
- The agitation is achieved by the smoothly rotating stirring element (basket or paddle)
- The vessel is cylindrical with hemispherical bottom and sides that are flanged at the top. It is 160- 175 mm high and has an inside diameter of 98- 106 mm, and a nominal capacity of 1000 ml.

Dissolution Apparatus (USP Apparatus I and II)

- A fitted cover may be used to retard evaporation but should provide sufficient openings to allow ready insertion of a thermometer and allow withdrawal of samples for analysis.
- The shaft rotation speed should be maintained within a range of 25- 150 rpm.
- To the shaft a basket or paddle is fitted into position.
- The distance between the inside bottom of the vessel and basket is 25 mm.

In vitro simulation of *in vivo* dissolution

- Some of the basic aspects of the dissolution test have their origins in general condition in the human body.
- The test is conducted at 37^{o} C.
- The use of a 900- ml volume was determined in order to be enough to establish sink conditions (at least three times saturation) for most active pharmaceutical ingredients.
- Dissolution media were developed to mimic the pH of the gastrointestinal tract (water, simulated gastric fluid, simulated intestinal fluid, buffers,…..)

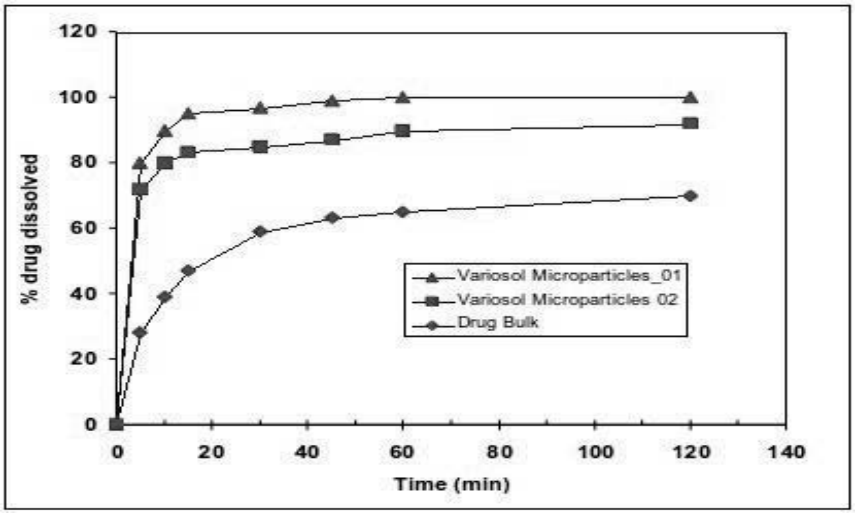
In vitro simulation of *in vivo* dissolution

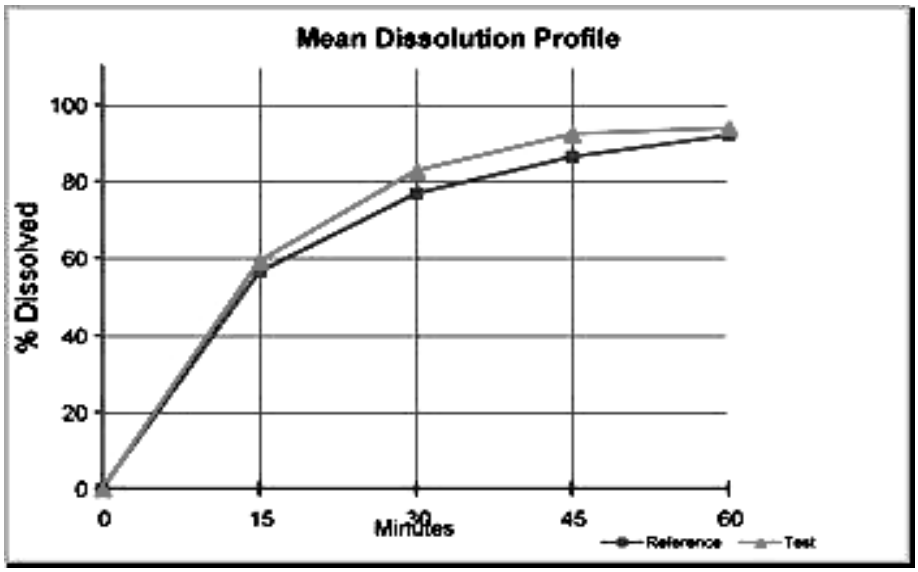
- Hydrodynamics in *in vitro* experiments (to simulate gastrointestinal motility) are reflected by **the design of the apparatus, the agitation intensity, the flow and/or volume, the viscosity of the medium** and practical issues, such as the **position of the dosage form during the experiment.**
- The paddle or basket rotation is designed to produce reproducible hydrodynamics that can be consistent from lab to lab. The real physical purpose of the agitation is to remove the drug-saturated layer of dissolution from around the dosage and replace it with fresh medium.

In vitro simulation of *in vivo* dissolution

- Flask shape has affected the hydrodynamics of systems and consequently it was considered better to have flask of uniform hemispherical shape.
- The distance between the inside bottom of the vessel and the basket is 25 mm to simulate *in vivo* hydrostatic pressure.

Drug dissolution profile





1.6. Drug stability and hydrolysis in GIT

- Acid and enzymatic hydrolysis of drugs in GIT is one of the reasons for poor bioavailability.

Acid hydrolysis

- Both penicillin G and erythromycin are susceptible to acid hydrolysis.
- The extent of hydrolysis and hence the extent of absorption is greatly affected by:
    1. The residence time in the stomach
    2. The dissolution rate.

Follow;1.6. Drug stability and hydrolysis in GIT

- Penicillin G (half life of degradation = 1 min at pH = 1)
- Rapid dissolution leads to poor bioavailability (due to release large portion of the drug in the stomach, pH = 1.2)

Follow1.6. Drug stability and hydrolysis in GIT

- **Techniques to minimize the extent of acid hydrolysis (improve the bioavailability) of unstable drug.**

1. Enteric coating

- This technique delay the dissolution of drug until reaching the small intestine.
- The enteric coat resist dissolution in acidic pH (gastric fluid) and dissolve readily in intestinal fluid pH
- Ex. Erythromycin enteric coated tablets
- The enteric coated tablets showed variable drug bioavailability.

Follow;1.6. Drug stability and hydrolysis in GIT

2- Pro- Drugs

- It is a chemical derivative of the parent drug which exhibit limited solubility in gastric fluids but liberate the parent drug in the small intestine.
- Liberation of parent compound from pro-drug is the rate limiting step in bioavailability, either positively or negatively.
- Ex. 1- erythromycin stearate (liberate the free base in the small intestine).

Follow;1.6. Drug stability and hydrolysis in GIT

Follow; 2- Pro- Drugs

- Ex. 2- erythromycin estolate (Lauryl sulphate salt of erythromycin propionate)
  - The poorly soluble lauryl sulfate salt remains un-dissolved in the stomach.
  - It dissolves and dissociate to give ester erythromycin propionate in the intestine.
  - The ester is better absorbed than the free erythromycin due to its increased lipid solubility.
  - In blood, the ester hydrolysis to release erythromycin.

1.7. Complexation

- Complexation of a drug in the GIT fluids may alter rate and extent of drug absorption.
- Complexation affects the effective drug concentration of GIT fluids

1.7.1- Complexation between a drug and normal components of the GIT:

- Mucin (Intestinal mucosa) + streptomycin = poorly absorbed complex
- Mucin is a various muco-polysaccharide lining the mucosal surface of the GIT
- This leads to reduced effective drug concentration at the site of absorption and reduced drug bioavailability.

Follow; 1.7. Complexation

1.7.2- Complexation between a drug and dietary components:

- Calcium (dairy products, milk, antacids, …..etc) + Tetracycline = poorly soluble and absorbed complex (food-drug interaction)

Follow; 1.7. Complexation

1.7.3- Complexation between a drug and excipients present in the dosage forms:

(A) leading to reduced bioavailability

- Tetracycline + dicalcium phosphate (diluent in tablets and capsules) = poorly soluble and absorbed complex
- Amphetamine + Carboxyl methylcellulose (tablet additive) = poorly absorbed complex
- Phenobarbitone + PEG 4000 = poorly absorbed complex

Follow; 1.7. Complexation

1.7.3- Complexation between a drug and excipients present in the dosage forms:

(B) leading to beneficial effect

- Polar drugs + complexing agent = well-absorbed lipid soluble complex (dialkylamides + prednisone)
- Lipid soluble drug + water soluble complexing agent = well-absorbed water soluble complex (cyclodextrine)

Follow; 1.7. Complexation

1.7.3- Complexation between a drug and excipients present in the dosage forms:

(C) leading to no effect

- Drug + excipients = soluble complexes rapidly dissociate to liberate the free drug
- The effect on drug absorption is determined by the rate of complex dissociation

1.8- Adsorption

- Certain insoluble substance may adsorb co-administered drugs leading to poor absorption
- Charcoal (antidote in drug intoxication)
- Cholestyramine (insoluble anionic exchange resins)
- Adsorption decreases the effective drug concentration in solution at the site of absorption.
- The readily reversible drug- adsorbent interaction will have no effect or affect only the rate not the extent of drug absorption.

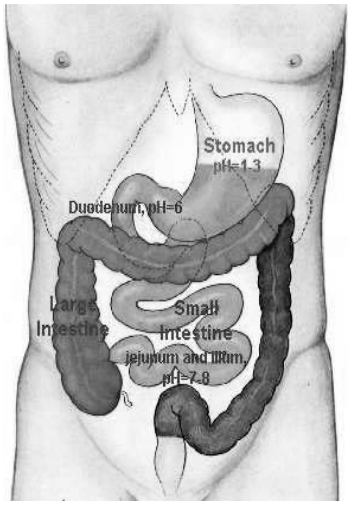
Follow; 1.8- Adsorption

- Ex.1. Promazine + attapulgite = readily reversible complex (affect only the rate of absorption)
- Ex.2. Promazine + charcoal = not readily reversible complex (affect the rate and extent of drug absorption)
- Cyanocobolamin + Talc (a glidant in tablet) = affect both the rate and extent of drug absorption

2- Physiological factors affecting oral drug absorption

2.1- pH of the GIT fluids

- The pH of GI fluids varies considerably along the length of the gastrointestinal tract.
- Gastric fluid is highly acidic (**1 – 3.5**) in healthy people in the fasted state.
- The duodenum (**6 to 6.5**)
- Jejunum and ileum (**7- 8**)
- Large intestine (**7- 8**)



2- Physiological factors affecting oral drug absorption

Follow; 2.1- pH of the GIT fluids

Factors affecting the normal pH ranges of GIT fluids

- ***1- Food ingestion***
  - Following the ingestion of a meal, the gastric juice is buffered to a less acidic pH, which is dependent on meal composition
  - Typical gastric pH values following a meal are in the range 3- 7.
  - Depending on meal size, the gastric pH returns to the lower fasted-state values within 2 -3 hours.
  - Thus, only a dosage form ingested with or soon after a meal will encounter theses higher pH values, which may affect the chemical stability of a drug, drug dissolution or absorption.

2- Physiological factors affecting oral drug absorption

Follow; 2.1- pH of the GIT fluids

- ***2- Diurnal cycle of gastric acidity***
  - A circadian rhythm of basal gastric acidity is known to occur with acid output being highest in the evening and lowest in the morning.
- ***3- General health of the individual***
- ***4- The presence of localized disease*** (gastric and duodenal ulcers)

2- Physiological factors affecting oral drug absorption

Follow; 2.1- pH of the GIT fluids

- ***5- Drug therapy***
  - Ex. Anti-cholinergic drugs inhibits gastric secretion
  - Ex. Antacid increase pH
- ***6- Gender***
  - There is a sex-related difference in human gastric acid secretion
  - (pH of 2.16 for men and 2.79 in women)
- ***7- Age***
  - It has always been assumed that gastric acid secretion decreased with age.

2- Physiological factors affecting oral drug absorption

Follow; 2.1- pH of the GIT fluids

- *The effect of pH on drug absorption:*
  - 1- The GI pH may influence the chemical stability of the drug in the lumen
  - Chemical degradation due to pH-dependent hydrolysis can occur in the GI tract.
  - The result of this instability is incomplete bioavailability, as only a fraction of the administered dose reaches the systemic circulation in the form of intact drug.

2- Physiological factors affecting oral drug absorption

Follow; 2.1- pH of the GIT fluids

- *Follow; The effect of pH on drug absorption:*
  - 2- Affects the degree of ionization of weak electrolytes.
  - 3- Affects the dissolution rate and /or absorption, if the drug is a weak electrolyte.

2- Physiological factors affecting oral drug absorption

2.2- Surface area of GIT absorption site

- The small intestine has the largest effective surface area due to presence of villi and microvilli
- The stomach and large intestine have relatively small absorptive surface areas due to absence of villi and microvilli.
- Certain drugs are absorbed from the stomach but with lower extent compared with the small intestine
- Large intestine plays a significant role in absorption of slowly absorbed drug and drugs need to be degraded by bacterial flora before absorption (ex. Sulphasalazine.)

2- Physiological factors affecting oral drug absorption

2.3- Gastric emptying rate

- The process of gastric emptying is extremely complex and is influenced by many factors.
- Most drugs are not absorbed from the stomach and are therefore dependent on the gastric emptying process to deliver them to their site of absorption.

2- Physiological factors affecting oral drug absorption

Follow; 2.3- Gastric emptying rate

- Factors enhancing gastric emptying rate:
  - Intake of fluids
  - Hunger
  - Anxiety
  - The patient's body position (lying on the right side)
  - Intake of antiemetics (ex. Metoclopramide)

2- Physiological factors affecting oral drug absorption

Follow; 2.3- Gastric emptying rate

- Factors retarding gastric emptying rate:
- Meals that contain large fragments of food or are nutrient-dense will take longer to empty and hence will delay the passage of dosage forms to the small intestine (fatty foods, highly viscous meal).
  - Hence, unless the drug is irritating to gastric mucosa, it should not be administered with bulky meal
- Mental depression
- Gastric ulcers
- Pyloric stenosis
- Hypothyroidism
- Patient body position (lying on the left side)
- Anticholinergic drugs

2- Physiological factors affecting oral drug absorption

Follow; 2.3- Gastric emptying rate

- **Gastric emptying follows a circadian rhythm with slower emptying occurring in the afternoon compared with the morning.**
- These numerous factors contribute to high inter-subject and intra-subject variations in oral drug bioavailability
- The gastric emptying rate of solution type dosage forms and suspensions of fine particles is generally much faster and less variable than solid, non-disintegrating unit dosage forms.

2- Physiological factors affecting oral drug absorption

Follow; 2.3- Gastric emptying rate

- **Delay in gastric emptying rate may lead to:**
- 1- Delay the rate of drug absorption (reduction in the rate not the extent of absorption):
  - Decrease the intensity of the therapeutic response.
  - Increase the onset of action
  - Ex. Aspirin, barbiturate and cephalosporin

2- Physiological factors affecting oral drug absorption

Follow; 2.3- Gastric emptying rate

- **Delay in gastric emptying rate may lead to:**
- 2- Decreasing the effective drug concentration at the site of absorption
  - By decreasing the stability of drugs susceptible to chemical (acidic pH) or enzymatic degradation in the stomach
  - Leading to reduction in the rate and extent of drug absorption.
  - Ex. Penicillin

Follow; 2.3- Gastric emptying rate

- **Delay in gastric emptying rate may lead to:**
- 3- Delay the onset of therapeutic activity without affecting the intensity
  - Ex. Enteric coated tablets
- 4- Increase the drug dissolution (enhance bioavailability)
  - Ex. Poorly soluble weak basic drugs (nitrofurantoin)
  - Exhibited enhanced bioavailability in presences of food

2.4- Food

A- Reducing gastric emptying rate

- Food (especially fatty, solid and hot food) slows the gastric emptying rate under normal physiological conditions.
- Consequently, the gastric residence time of the concurrently administered drugs is prolonged.
- This may lead to:
  - **1- Reduced rate of absorption** of the concurrently administered drug

Follow**; 2.4- Food**

Follow; A- Reducing gastric emptying rate

- **2- A delay in the onset of therapeutic action.** This is of clinical concern when a rapid onset of action is required, as for analgesics, sedatives, and hypnotics. For this group of drugs, administration under fasting condition may be preferable**.**

2- Physiological factors affecting oral drug absorption

Follow; **2.4- Food**

Follow; A- Reducing gastric emptying rate

- **3- Reduced extent of absorption** for those acid-labile drugs such as penicillin, erythromycin, and cephalosporin, (hydrolysis is increased as a result of increased gastric residence time).
- **4- Increased extent of absorption** for poorly aqueous soluble drugs (Increased dissolution due to prolonged gastric residence time and increased gastric secretion in response to food administration)

Follow; **2.4- Food**

B- Stimulation of gastrointestinal secretion

- Increased acidic and enzymatic secretions in response to ingestion of food may lead to:
  - Reduced drug bioavailability; For drugs susceptible to chemical or enzymatic degradation.
  - Enhanced absorption of poorly soluble drugs (griseofulvin) due to secretion of bile salts (S.A.A.) in response to ingestion of fatty meal.

2- Physiological factors affecting oral drug absorption

Follow; **2.4- Food**

C- Competition between food components and drugs specialized absorption mechanisms

- Between nutrients and drugs of similar chemical structures leading to competitive inhibition of drug absorption
  - Ex. L-Dopa + amino-acids (resulted from breakdown of ingested proteins) = competitive inhibition of L-Dopa absorption

Follow; **2.4- Food**

D- Complexation of drugs with components in the diet

- Tetracycline will form poorly soluble complexes with metal ions such as Ca^{++}, Mg^{++}, Fe^{++}, and Al^{+++} .
- Therefore, concurrent administration of tetracycline and foods or drugs that contain these metal ions should be avoided.
- Reduced oral bioavailability may lead to sub-therapeutic drug level and treatment failure.

Follow**; 2.4- Food**

E- Increased viscosity of the GIT fluids

- This result in reduction of drug dissolution rate by decreasing ***D*** and by reducing drug diffusion from the lumen to the absorbing membrane lining the GIT.
- These effects tend to decrease drug bioavailability if the drug bioavailability is dissolution limited.

Follow; **2.4- Food**

F- Food induced changes in blood flow

- Blood flow to the GIT and liver increases shortly after a meal. This will increase the rate of drug presentation to the liver.
- Consequently, a larger fraction of drug escape first pass metabolism.
- This is because the enzyme systems responsible for drug metabolism become swamped (saturated by the increased rate of drug presentation to the site of biotransformation).
- So, food increases the amount of intact drug reaching the systemic circulation.
- An increase in oral bioavailability has been observed for several drugs including hydralazine and some beta-adrenergic blocking agents such as labetolol, metoprolol and propranolol.

2.5- Malabsorption

- Malabsorption is any disorder with impaired absorption of fat, carbohydrate, proteins and vitamins.
- Drug induced malabsorption has been observed after administration of neomycin, phenytoin and anticancer agents.
- Results in impaired absorption of vitamins (B_{12}, D, K) folic acid, iron, calcium….

3- Dosage form factors affecting oral drug absorption

3.1- Role of dosage forms

- The bioavailability of a drug decrease in the following order: solution > suspension > capsule > tablet > coated tablet.
- The type of oral dosage forms affects the possible number of intervening steps between administration and appearance of dissolved drug in the GIT fluids.
- The greater the number, the lower the bioavailability of a given drug.

Follow; 3- Dosage form factors affecting oral drug absorption

3.1- Role of Excipients

Diluents

- Australian outbreak of phenytoin intoxication.
- Many epileptic patients who had been stabilized with sodium phenytoin capsules containing calcium sulphate dihydrate as the diluent, developed clinical features of phenytoin over dosage when given sodium phenytoin capsules containing lactose as the diluent
- This is because the excipient calcium sulphate dihydrate forms a poorly absorbed calcium-phenytoin complex

Follow; 3- Dosage form factors affecting oral drug absorption

Follow; **3.1- Role of Excipients**

Lubricants and Glidants

- **Talc** (in tablets as a glidant) + Cyanocobolamin = Adsorbed drug = decreased drug absorption
- Excessive quantities of **magnesium stearate** in drug formulation = retard drug dissolution = slow rate of drug absorption

Follow; 3- Dosage form factors affecting oral drug absorption

Follow**; 3.1- Role of Excipients**

Surfactants

(Emulsifying, solubilizing, suspension stabilizer and wetting agents)

- Generally increase the dissolution rate and drug absorption rate.
- Ex. Phenacetin + Tween 80 (to prevent aggregation in aqueous suspension) = prevent aggregation = increase effective surface area = increase dissolution rate = increase drug absorption

Bio-pharmaceutics Classification System (BCS)

- The (BCS) has been developed to provide a scientific approach to allow for the prediction of *in vivo* pharmacokinetics of oral immediate release (IR) drug products by classifying drug compounds based on their solubility related to dose and intestinal permeability in combination with the dissolution properties of the dosage form.

Follow; Introduction

- The importance of drug dissolution in the gastrointestinal tract and permeability across the gut wall barrier in the oral absorption process has been well known since the 1960s, but the research carried out to constitute the BCS has provided new quantitative data of great importance for modern drug development especially within the area of drug permeability.

According to BCS, drug substances are classified as follows:

- Class I - High Permeability, High Solubility
- Class II - High Permeability, Low Solubility
- Class III - Low Permeability, High Solubility
- Class IV - Low Permeability, Low Solubility

Class Boundaries

- A drug substance is considered HIGHLY SOLUBLE when the highest dose strength is soluble in $\leq$ 250 ml water over a pH range of 1 to 7.5
- A drug substance is considered HIGHLY PERMEABLE when the extent of absorption in human is determined to be $\geq$ 90% of an administered dose.

Class Boundaries

- A drug product is considered to be RAPIDLY DISSOLVING when $\geq$ 85% of the labeled amount of drug substance dissolves within 30 minutes using USP apparatus I or II in a volume of $\leq$ 900 ml buffer solutions.

Class I Drugs

- The rate limiting step is drug dissolution
- If dissolution is very rapid, then gastric emptying rate becomes the rate determining step.
- E.g. Metoprolol, Diltiazem, Verapamil, Propranolol.

Class II Drugs

- In vivo drug dissolution is the rate limiting step for absorption
- The absorption for class II drugs is usually slower than class I and occurs over a longer period of time.
- In vitro- in vivo correlation (IVIVC) is usually expected for class I and class II drugs.
- E.g. Phenytoin, Danazol, Ketoconazole, Mefenamic acid, Nifedipine.

Class III Drugs

- For class III drugs, permeability is rate limiting step for drug absorption.
- These drugs exhibit a high variation in the rate and extent of drug absorption.
- Since the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the dosage form factors.
- E.g. Cimetidine, Acyclovir, Neomycin B, Captopril.

Class IV Drugs

- Class IV drugs exhibit a lot of problems for effective oral administration.
- Fortunately, extreme examples of class IV compounds are the exception rather than the rule and are rarely developed and reach market.
- Nevertheless a number of class IV drugs do exist. E.g. Taxol.

Applications of BCS in oral drug delivery technology

- Once the solubility and permeability characteristics of the drug are known it becomes an easy task for the research scientist to decide upon which drug delivery technology to follow or develop.

Class I Drugs

- The major challenge in development of drug delivery system for class I drugs is to achieve a target release profile associated with a particular pharmacokinetic and/or pharmacodynamic profile.
- Formulation approaches include both control of release rate and certain physicochemical properties of drugs like pH-solubility profile of drug.

Class II Drugs

- The system that are developed for class II drugs are based on micronisation, lyophilization, addition of surfactants, formulation as emulsions and micro emulsions systems, use of complexing agents like cyclodextrins.

Class III Drugs

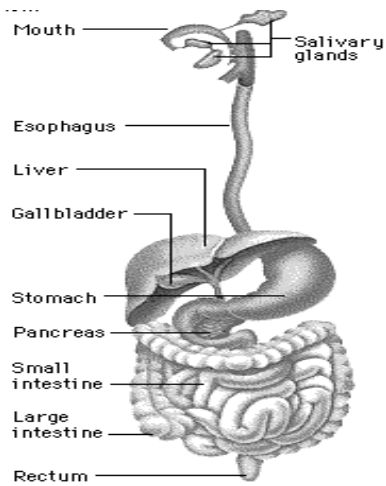
- Class III drugs require the technologies that address to fundamental limitations of absolute or regional permeability. Peptides and proteins constitute the part of class III and the technologies handling such materials are on rise now days.

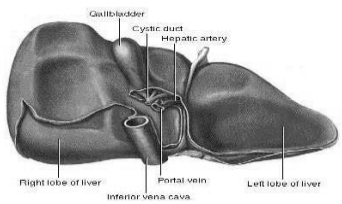
Class IV Drugs

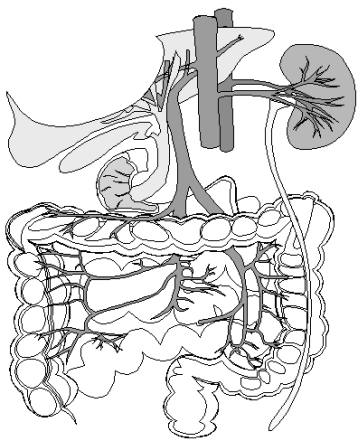
- Class IV drugs present a major challenge for development of drug delivery system and the route of choice for administering such drugs is parenteral with the formulation containing solubility enhancers.

Biopharmaceutics (LADME)

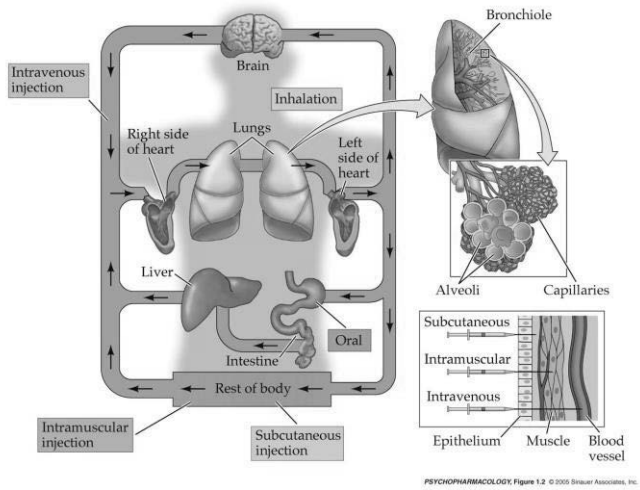
Introduction







Introduction:
Routes of administration



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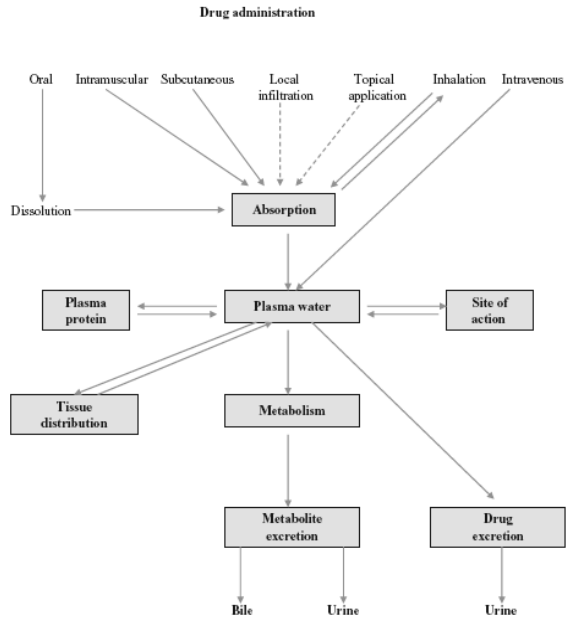
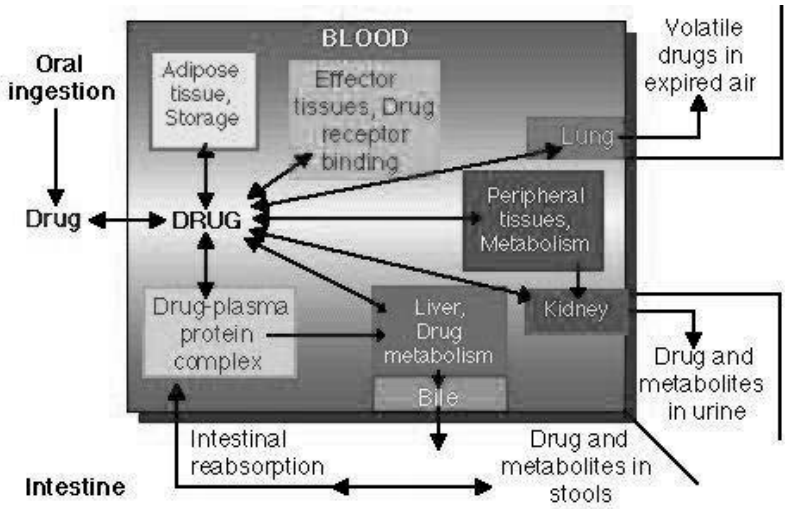


Introduction



Drug distribution

- After a drug is absorbed into plasma, the drug molecules are distributed throughout the body by the systemic circulation.
- The drug molecules are carried by the blood to the target site (receptor) for drug action and to other (non-receptor) tissues as well, where side effects or adverse reactions may occur.
- Drug molecules are distributed to eliminating organs, such as the liver and kidney, and to non-eliminating tissues, such as the brain, skin, and muscle.

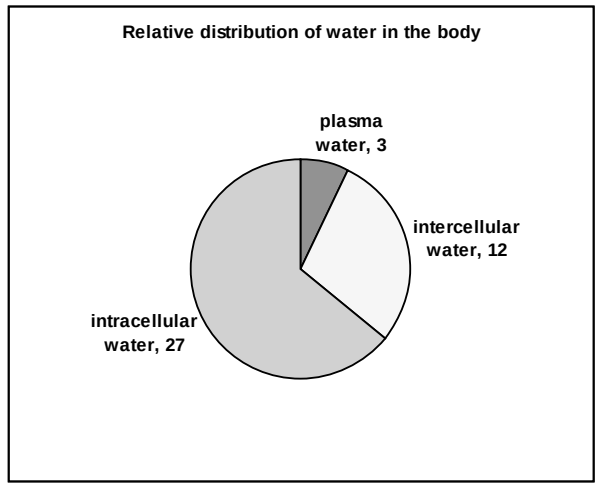
Drug distribution

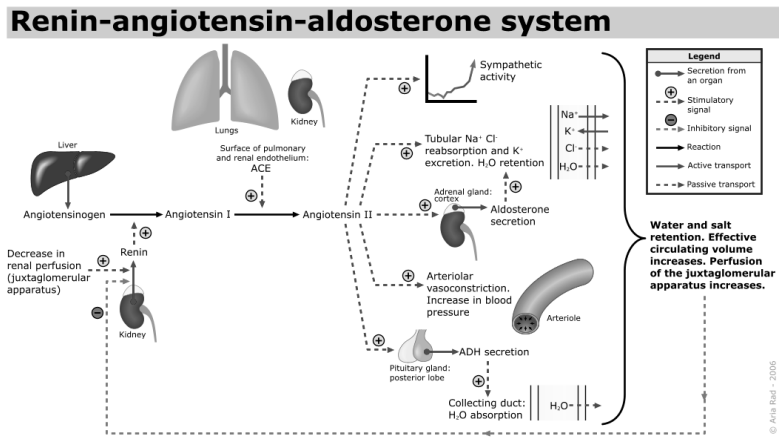
- In pregnancy, drugs may cross the placenta and may affect the developing fetus.
- Drugs can also be secreted in milk via the mammary glands.
- A substantial portion of the drug may be bound to proteins in the plasma and/or tissues.
- Lipophilic drugs deposit in fat, from which the drug may be slowly released

Drug distribution: Body fluids

- Mixing of a drug solution in the blood occurs rapidly due to high flow rate and rapid turn-over.
- Drug molecules rapidly diffuse through a network of fine capillaries to the tissue spaces filled with interstitial fluid.
- The interstitial fluid plus the plasma water is termed *extracellular water,* because these fluids reside outside the cells.
- Drug molecules may further diffuse from the interstitial fluid across the cell membrane into the cell cytoplasm

Drug distribution:
Body fluids



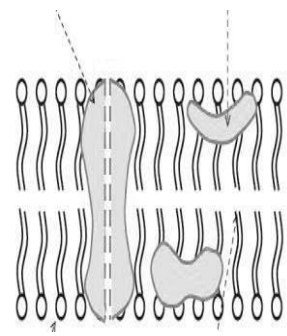


Drug distribution:
Diffusion through cell membrane

- Drug distribution is generally rapid, and most small drug molecules permeate capillary membranes easily.
- The passage of drug molecules across a cell membrane depends on the physicochemical nature of both the drug and the cell membrane.
- The molecular size plays an important role in drug diffusion across the membrane.

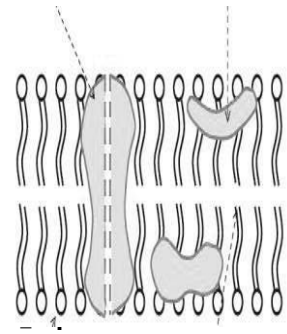
Drug distribution:
Diffusion through cell membrane

- Cell membranes comprise protein and a bilayer of phospholipid, which acts as a lipid barrier to drug uptake.
- Thus, lipid-soluble drugs generally diffuse across cell membranes more easily than highly polar or water-soluble drugs.
- Accordingly, non-ionized form of the drug can permeate.



Drug distribution:
Diffusion through cell membrane

- Small drug molecules generally diffuse more rapidly across cell membranes than large drug molecules.
- If the drug is bound to a plasma protein such as albumin, the drug–protein complex becomes too large for easy diffusion across the cell or even capillary membranes



Drug distribution $\frac{dm}{dt} = \frac{DKA\ (Cp - Ct)}{h}$

- Diffusion and Hydrostatic Pressure
  - The processes by which drugs transverse capillary membranes include passive diffusion and hydrostatic pressure.
  - Passive diffusion is the main process by which most drugs cross cell membranes.
  - The driving force for passive diffusion is the concentration gradient.
  - Passive diffusion is described by *Fick's law of diffusion*
  - So the contributing factors include the partition coefficient, diffusion coefficient and the plasma concentration.
  - Additional factors include membrane permeability and tissue affinity to drug.

Drug distribution

- Diffusion and Hydrostatic Pressure
  - *Hydrostatic pressure* represents the pressure gradient between the arterial end of the capillaries entering the tissue and the venous capillaries leaving the tissue.
  - The pressure of arterial end of the capillaries is 8 mmHg higher than the tissue. This will lead to filtration of the fluid into the tissue.
  - The filtered fluid returns to the venous capillaries leaving the tissue (venous capillaries has lower pressure).
  - Hydrostatic pressure is responsible for penetration of water-soluble drugs into spaces between endothelial cells and possibly into lymph.

Drug distribution

- Distribution Half-Life, Blood Flow, and Drug Uptake by Organs
  - Because the process of drug transfer from the capillary into the tissue fluid is mainly diffusional, the membrane thickness, diffusion coefficient of the drug, and concentration gradient across the capillary membrane are important factors in determining the rate of drug diffusion.
  - Kinetically, if a drug diffuses rapidly across the membrane in such a way that blood flow is the rate-limiting step in the distribution of drug, then the process is *perfusion* or *flow limited*.
  - In congestive heart failure, decreased cardiac output, results in impaired blood flow, which may reduce renal clearance through reduced filtration pressure and blood flow.

Drug distribution

- Distribution Half-Life, Blood Flow, and Drug Uptake by Organs
  - If drug distribution is limited by the slow diffusion of drug across the membrane in the tissue, then the process is termed *diffusion* or *permeability limited*.
  - Drugs that are permeability limited may have an increased distribution volume in disease conditions that cause inflammation and increased capillary membrane permeability.
  - The delicate osmotic pressure balance may be altered due to albumin and/or blood loss or due to changes in electrolyte levels in renal and hepatic disease, resulting in net flow of plasma water into the interstitial space (edema).
  - This change in fluid distribution may partially explain the increased extravascular drug distribution during some disease states

Drug distribution

- Distribution Half-Life, Blood Flow, and Drug Uptake by Organs

$$K_d = \frac{Q}{VR}$$

K_d = distribution rate constant

Q = blood flow to the organ

V = volume of the organ

R = ratio of drug conc in the organ to that in the venous blood

$$\text{distribution half life} = \frac{0.693}{K_d}$$

Drug distribution

- Distribution Half-Life, Blood Flow, and Drug Uptake by Organs
  - If each tissue has the same ability to store the drug, then the distribution half-life is governed by the blood flow.
  - Vascular tissues such as the kidneys and adrenal glands achieve 95% distribution in less than 2 minutes.
  - In contrast, drug distribution time in fat tissues and other less vascular organs takes 4 hours
  - Under normal conditions, limited blood flow reaches the muscles.
  - During exercise, the increase in blood flow may change the fraction of drug reaching the muscle tissues. Diabetic patients receiving intramuscular injection of insulin may experience the effects of changing onset of drug action during exercise.
  - During injury or when blood is lost, constriction of the large veins redirect more blood to needed areas and, therefore, affect drug distribution.

Drug distribution

- Distribution Half-Life, Blood Flow, and Drug Uptake by Organs
  - Some tissues have great ability to store and accumulate drug.
  - For example, the antiandrogen drug flutamide and its active metabolite are highly concentrated in the prostate. The prostate drug concentration is 20 times that of the plasma drug concentration; thus, the antiandrogen effect of the drug is not fully achieved until distribution to this receptor site is complete.
  - Digoxin is highly bound to myocardial membranes.
  - Iodine is concentrated in the thyroid gland and tetracycline in developing teeth and bone.

Drug distribution

- Drug accumulation
  - This is not only dependent on tissue perfusion but also dependent on the affinity of drug to the tissue.
  - Drugs with a high lipid solubility tend to accumulate in adipose tissue. This process is reversible. Because the adipose tissue is poorly perfused with blood, drug accumulation is slow. However, once the drug is concentrated in fat, drug removal may also be slow. For example DDT (dichlorodiphenyltrichloroethane) is highly lipid soluble and remains in fat tissue for years.

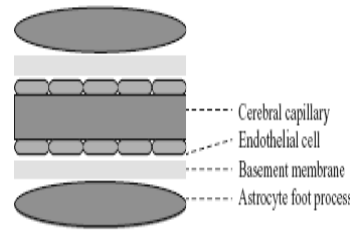
Drug distribution

- Permeability of capillaries and cell membrane (diffusional barrier)
  - The brain is well perfused with blood, but many drugs with good aqueous solubility have high kidney, liver, and lung concentrations and yet little or negligible brain drug concentration.
  - This is due to the high diffusional resistance from the blood brain barrier (BBB)

Drug distribution:
diffusional barrier to the brain

- In cerebral capillaries, endothelial cells have overlapping 'tight' junctions restricting passive diffusion.
- The surrounding capillary basement membrane is closely applied to the peripheral processes of astrocytes, which play an important part in neuronal nutrition.

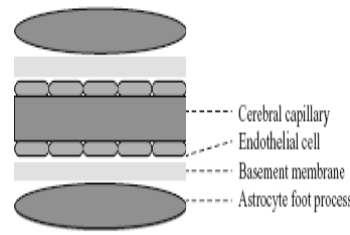
Blood-brain barrier



Drug distribution:
diffusional barrier to the brain

- To pass from capillary blood to the brain, most drugs have to cross the endothelium, the basement membrane and the peripheral processes of astrocytes by simple diffusion or filtration.
- Some drugs cannot readily cross these restrictive barriers, which are collectively referred to as the blood–brain barrier.

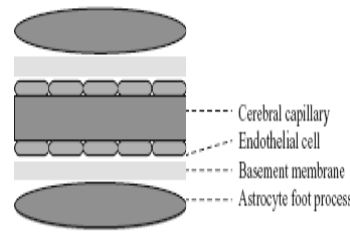
- Blood-brain barrier



Drug distribution:
diffusional barrier to the brain

- Enzymatic barrier
- In addition to this structural barrier, there is also a metabolic or enzymatic blood–brain barrier, which is mainly associated with the peripheral processes of astrocytes.
- Many neurotoxic agents (e.g. free fatty acids, ammonia) can readily cross the capillary endothelium, but are metabolized before they reach the CNS.
- In addition, capillary endothelial cells express a transport protein (P-glycoprotein), which actively extrudes many drugs, including most opioids, from the CNS.

- Blood-brain barrier



Drug distribution

- Permeability of BBB to drugs
  - Certain metabolic substrates and hormones, such as glucose, insulin, l-amino acids, l-thyroxine and transferrin, normally cross the BBB by endocytosis or carrier transport.
  - In addition, many low molecular weight, lipid-soluble drugs (e.g. general anaesthetics, local anaesthetics, opioid analgesics) can cross the barrier and enter the CNS, although their access may be restricted by P-glycoprotein.
  - In contrast, when drugs are highly protein bound (e.g. tolbutamide, warfarin), only the unbound fraction can readily diffuse from blood to the CNS, so that the concentration of these drugs in the brain may be 1–2% of the total plasma level.

Drug distribution

- Drug permeability of BBB
  - Approximately 25% of thiopental is initially taken up by the brain due to its high lipid solubility and the extensive blood supply of the CNS. As the plasma concentration falls, thiopental is progressively taken up by less well-perfused tissues which have a higher affinity for the drug. In consequence, intravenous thiopental is rapidly redistributed from brain to muscle and finally to subcutaneous fat.
  - Redistribution is mainly responsible for its short duration of action, and its final elimination from the body may be delayed for24 hours.
  - The normal impermeability of the BBB can be modified by diseases as inflammation, oedema and acute and chronic hypertension.

Drug distribution:
Apparent volume of distribution

- The concentration of drug in the plasma or tissues depends on the amount of drug systemically absorbed and the volume in which the drug is distributed.
- The *apparent volume of distribution* (VD) is used to estimate the extent of drug distribution in the body.
- Although the VD does not represent a true anatomical, or physical volume, it represents the result of dynamic drug distribution between the plasma and the tissues and accounts for the mass balance of the drug in the body.

$$VD = \frac{\text{amount of drug (mg) added to the system}}{\text{Plasma concentration (mg/L) after equilibrium}}$$

Protein binding of drugs

- Many drugs interact with plasma or tissue proteins or with other macromolecules, such as melanin and DNA, to form a *drug–macromolecule complex*.
- The formation of a drug protein complex is often named *drug–protein binding*.
- Drug–protein binding may be a reversible or an irreversible process.
- *Irreversible* protein binding results from covalent chemical bonding.
- Irreversible drug binding accounts for certain types of drug toxicity that may occur over a long time period, as in the case of chemical carcinogenesis, or within a relatively short time period, as in the case of drugs that form reactive chemical intermediates.
- For example, the hepatotoxicity of high doses of acetaminophen is due to the formation of reactive metabolite intermediates that interact with liver proteins.

Protein binding of drugs

- Most drugs bind or complex with proteins by a reversible process.
- *Reversible drug–protein binding* implies that the drug binds the protein with weaker chemical bonds, such as hydrogen bonds or van der Waals forces.
- Reversible drug–protein binding is of major interest in pharmacokinetics.
- $$\text{unbound drug} + \text{protein} \rightleftarrows \text{drug} - \text{protein complex}$$

Protein binding of drugs

- Only the free drug can diffuse to the tissue and as its concentration in plasma falls, protein-bound drug rapidly dissociates. Consequently, a continuous concentration gradient is present for the diffusion of drugs from plasma to tissues.
- Albumin binds drugs as salicylates, indomethacin, tolbutamide and oral anticoagulants.
- Globulins bind many basic drugs (e.g. bupivacaine, opioid analgesics). Plasma globulins also play an important role in the binding of minerals, vitamins and hormones.

Protein binding of drugs: drug displacement and competition

- Drugs and endogenous substrates that are extensively bound to proteins may compete for (and be displaced from) their binding sites.
- Displacement of drugs from plasma proteins can affect the pharmacokinetics of a drug in several ways:
  - (1) Increase the free drug concentration
  - (2) Increase the free drug concentration that reaches the receptor sites directly, causing a more intense pharmacodynamic (or toxic) response.
  - (3) Transient increase in VD and decreasing partly some of the increase in free plasma drug concentration
  - (4) increase the free drug concentration, resulting in more drug diffusion into tissues of eliminating organs, particularly the liver and kidney, resulting in a transient increase in drug elimination.

Protein binding of drugs: drug displacement and competition

- However, it is now believed that, binding of drugs at clinical concentrations only occupies a small proportion of the available binding sites and does not approach saturation. Consequently, competition between drugs resulting in clinically significant displacement from plasma protein binding is rare.

Plasma protein binding and drug distribution and elimination

- In general, drugs that are highly bound to plasma protein have reduced overall drug clearance.
- For a drug that is metabolized mainly by the liver, protein binding prevents the drug from entering the hepatocytes, resulting in reduced drug metabolism by the liver.
- In addition, molecularly bound drugs may not be available as substrates for liver enzymes, thereby further reducing the rate of metabolism.

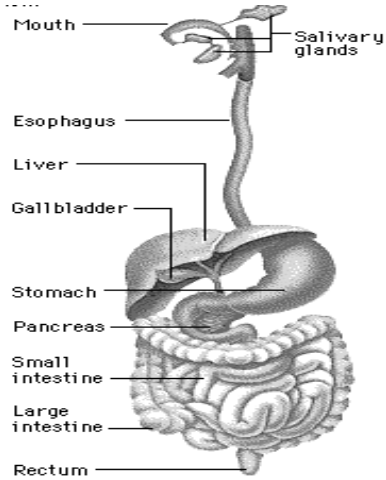
Plasma protein binding and drug distribution and elimination

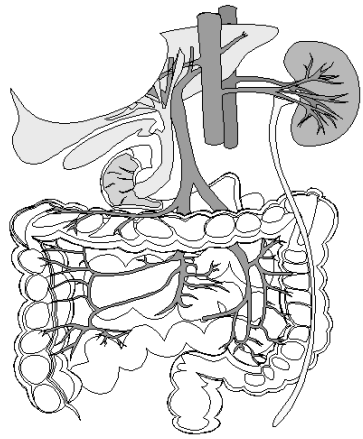
- Protein-bound drugs act as larger molecules that cannot diffuse easily through the capillary membranes in the glomeruli.
- The elimination half-lives of some drugs, such as the cephalosporins, which are excreted mainly by renal excretion, are generally increased when the percent of drug bound to plasma proteins increases.
- Other examples include:
  - Doxycycline, which is 93% bound to serum proteins, has an elimination half-life of 15.1 hours, whereas oxytetracycline, which is 35.4% bound to serum proteins, has an elimination half-life of 9.2 hours.
  - In contrast drug that is both extensively bound and actively secreted by the kidneys, such as penicillin, has a short elimination half-life, because active secretion takes preference in removing or stripping the drug from the proteins as the blood flows through the kidney.

Protein Binding and pathological state

- Binding to plasma proteins is modified in pathological conditions associated with hypoalbuminaemia, as in liver cirrhosis, nephrosis, trauma or burns. In these conditions, the concentration of the unbound drug tends to increase and may result in toxic effects (e.g. with phenytoin or prednisolone).
- Significant changes are more likely when high doses of drugs are used, or when drugs are given intravenously. In these conditions, plasma proteins may be saturated, causing a disproportionate increase in the concentration of the unbound drug.
- Tissues and organs that are well perfused (e.g. brain, heart, abdominal viscera) may receive a higher proportion of the dose, increasing the potential of toxic effects.
- Similar effects may occur in elderly patients and in subjects with renal impairment, possibly due to alterations in the affinity of drugs for albumin.

Drug metabolism: Presystemic disposition





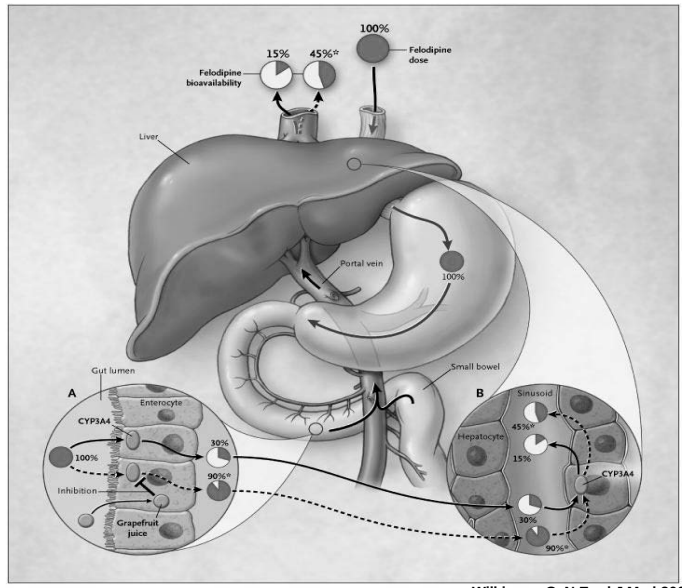
Drug metabolism: Presystemic disposition

- First pass effect
  - After oral administration drugs permeate through the enterocytes then pass through the mesentric vein to the portal vein which will take the drug to the liver where it will be subjected to extensive metabolism. This metabolism may take place in the intestinal mucosal cells.
  - This effect is termed the first pass effect and is responsible for rapid metabolism of the drug leading to poor oral bioavailability.

Drug metabolism: Presystemic disposition

- First pass effect
  - This effect may be altered by food or drink.
  - E.g. food intake will increase the blood flow to the liver. This will result in more drug molecules reaching the liver at the same time. This will give a chance for more drug to escape from the hepatic first pass metabolism.

First-Pass Metabolism after Oral Administration of a Drug, as Exemplified by Felodipine and Its Interaction with Grapefruit Juice

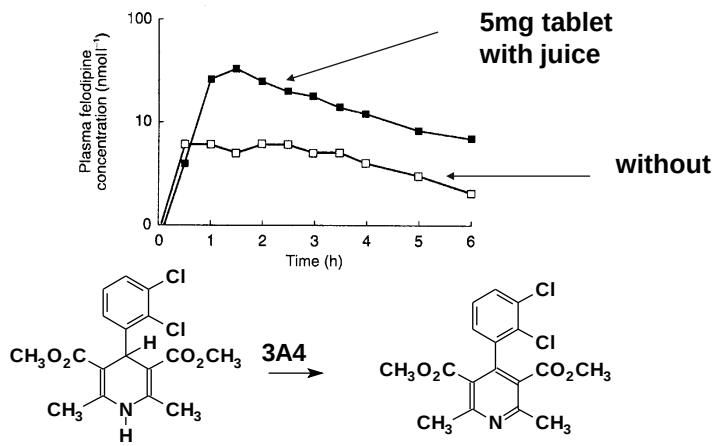


Wilkinson G. N Engl J Med 2005;352:2211-2221

First-Pass Metabolism after Oral Administration of a Drug, as Exemplified by Felodipine and Its Interaction with Grapefruit Juice

- The previous figure shows the first-pass metabolism after oral administration of a Drug, as Exemplified by Felodipine and Its Interaction with Grapefruit Juice.
- CYP3A enzymes (e.g., CYP3A4) present in enterocytes of the intestinal epithelium extensively metabolize felodipine during its absorption, and on average only 30 percent of the administered dose enters the portal vein (solid line). Subsequently, CYP3A enzymes in the liver further metabolize the drug so that only 15 percent of the dose is bioavailable and finally reaches the systemic circulation and is able to exert its effects. Grapefruit juice selectively inhibits CYP3A in the enterocyte, with the net result being an increase in the oral bioavailability of felodipine by a factor of three, denoted by the asterisks and the dashed lines.

Effect of Grapefruit Juice on Felodipine Plasma Concentration (from Bailey et al., Br. J. Clin Pharmacol, 1998, 46: 101-110)



Grapefruit Juice Facts

- GJ elevates plasma peak drug concentration but not the elimination $t_{1/2}$
- GJ reduced metabolite/parent drug AUC ratio
- GJ caused 62% reduction in small intestinal enterocyte 3A4 and 3A5 protein. It does not affect the liver to the same extent (i.v. pharmacokinetics unchanged)
- GJ effects last ~4 h. This requires new enzyme synthesis
- The effect may be up to 5x C_{max} and is highly variable among individuals depending upon the level of 3A4 in the small intestine.

Systemic metabolism (biotransformation)

- Drug molecules are processed by enzymes evolved to cope with natural compounds
- The drug actions may be increased, decreased or unchanged.
- Individual variation in the metabolism is genetically determined.
- There may be several routes of metabolism.
- May not lead to termination of drug action.
- May take place anywhere BUT the **liver** is main site.
- Not constant - can be changed by other drugs providing the base of many drug-drug interactions.

Biotransformation of drugs

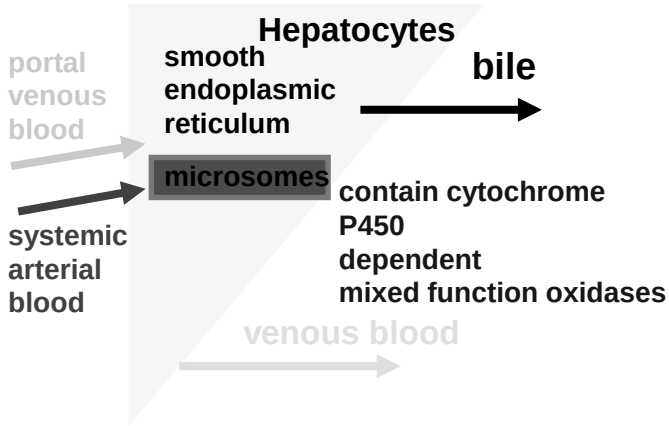
- Process by which the drug is chemically converted in the body to a metabolite with the goal of de-toxification.
- Biotransformation is usually enzymatic but some drugs may be changed in non-enzymatic process.
- Drugs may converted to less toxic/effective materials, more toxic/effective materials

  materials with different type of effect or toxicity

Sites of biotransformation

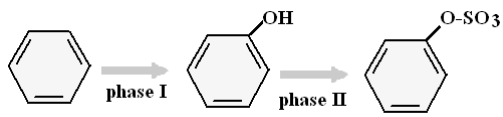
- Where ever the appropriate enzymes occur (plasma, kidney, lung, gut wall and LIVER).
- The liver is ideally placed to intercept natural ingested toxins and has a major role in biotransformation

The liver

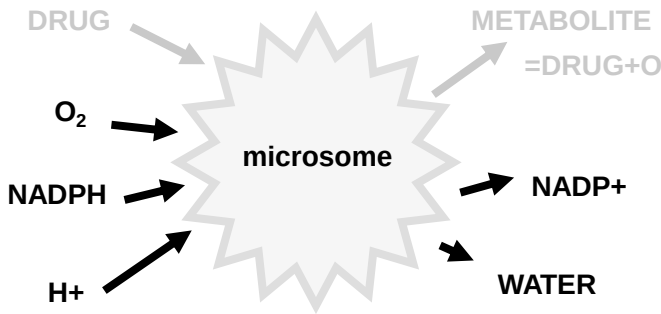


Types of biotransformation reactions

- Any structural change in a drug molecule may change its activity
- Phase I - changes drugs and creates site for phase II. oxidation (adds O) eg. Microsomes (P450); reduction; hydrolysis (eg. by plasma esterases) and others
- Phase II - couples group to existing (or phase I formed) conjugation site. E.g. glucuronide (with glucuronic acid), sulphate and others



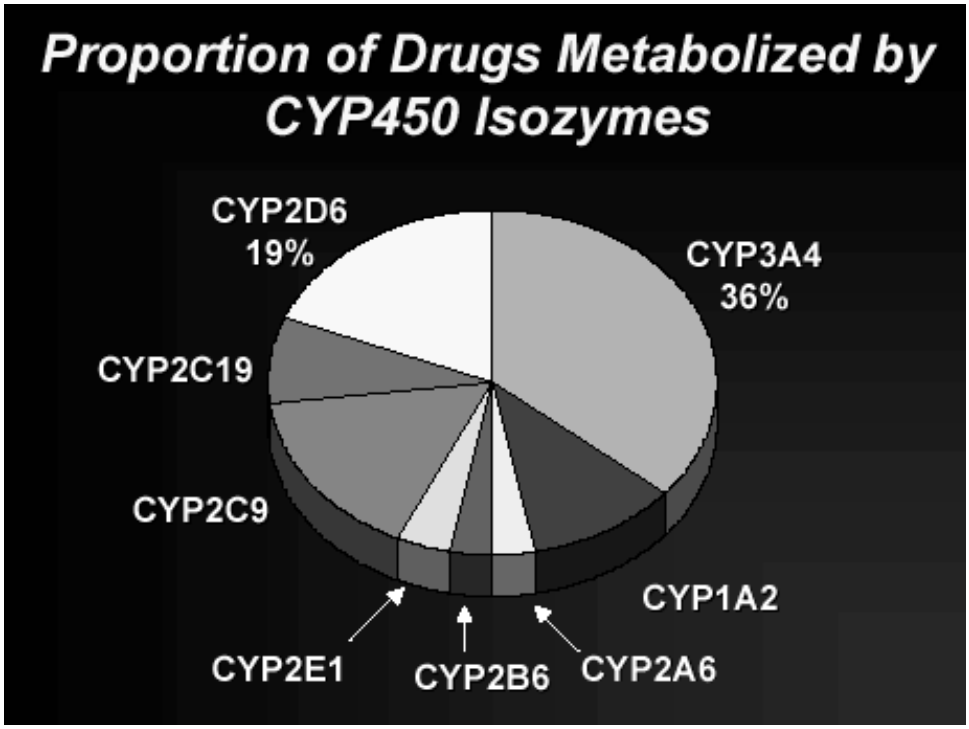
Cytochrome P450 dependent mixed function oxidases



There are several different types of mixed function oxidase - different specificity

Cytochrome P450 dependent mixed function oxidases

CYP
FOUR families 1-4
SIX sub-families A-F
up to TWENTY isoenzymes 1-20
CYP3A4 : CYP2D6 : CYP2C9 : CYP2C19 :CYP2A6



Biotransformation reactions

PHASE 1 reactions

Hydroxylation $-CH_2CH_3 \rightarrow -CH_2CH_2OH$

Oxidation $-CH_2OH \rightarrow -CHO \rightarrow -COOH$

N-de-alkylation $-N(CH_3)_2 \rightarrow -NHCH_3 + CH_3OH$

Oxidative deamination $-CH_2CHCH_3 \rightarrow -CHCOCH_3 + NH_3$ (with NH_2 on the CH)

PHASE 2 reactions

Conjugations with glucuronide, sulphate

.... alters activity, made less lipid soluble so excreted

Phase II reactions (not all in the liver)

- Conjugation of -OH, -SH, -COOH or -CONH with glucuronic acid to give glucuronides
- Conjugation of -OH with sulphate to give sulphates
- Conjugation of $-NH_2$, $-CONH_2$, aminoacids, sulpha drugs with acetyl- to give acetylated derivatives
- Conjugation of -halo, -nitrate, epoxide, sulphate with glutathione to give glutathione conjugates
- All tend to be less lipid soluble and thus easily excreted and less reabsorbed.

Other (non-microsomal) reactions

- Hydrolysis in plasma by esterases (suxamethonium by cholinesterase)
- Alcohol and aldehyde dehydrogenase in cytosolic fraction of liver (ethanol)
- Monoamine oxidase in mitochondria (noradrenaline, dopamine, amines)
- Xanthene oxidase (6-mercaptopurine, uric acid production)
- enzymes for particular drugs (dopa-decarboxylase etc)

Factors affecting biotransformation

- Genetic polymorphism
  - This depends on the race.
  - N-acetylation of isoniazid is genetically determined with at least two groups being identified including rapid and slow acetylators.
  - Individuals with slow acetylation are subject to isoniazid-induced toxicity.
  - Procainamide and hydralazine are other drugs undergoing acetylation and demonstrating genetic polymorphism.

Factors affecting biotransformation

- age (reduced in aged patients & children)
- sex (women slower ethanol metabilizers)
- species (animal model are usually used in early stages of drug development. However different animal species may have different metabolic pathways. E.g. Amphetamine is mainly hydroxylated in rats but deaminated in human and dogs.
- clinical or physiological condition (liver disease may affect the extent of drug metabolism)
- other drug administration (induction or inhibition)
- food (charcoal grill ++CYP1A) (grapefruit juice --CYP3A)
- first-pass (pre-systemic) metabolism

Some basic definitions

- Substrate:
  Drug is metabolised by the enzyme system
- Inducer:
  Drug that will increase the synthesis of CYP450 enzymes. They will shorten action of drugs or increase effects of those biotransformed to active agents
- Inhibitor
  Drug that will decrease the metabolism of a substrate. They prolongs action of drugs or inhibits action of those biotransformed to active agents (pro-drugs).
- BLOCKERS
  Acting on non-microsomal enzymes (MAOI, anticholinesterase drugs)

Enzyme Induction

- Leads to production of more enzyme, usually after 3-4 days of exposure to inducer
- Most CYPs are inducible except CYP2D6
- Time course of interaction depends on half-life of inducer.

Enzyme Induction

- Rifampicin has short half-life and induction apparent within 24 hours after administration.
- Phenobarbitone has longer half life so time to complete induction takes longer.
- Other inducer include carbamazepine, griseofulvin, chronic use of alcohol and polycyclic hydrocarbons (Tobacco smoke and grilled meat).

Enzyme Inhibition

- Enzyme inhibition can take place by many mechanisms
  - Competitive inhibition: in this case the inhibitor and drug-substrate compete for the same active center on the enzyme. The substrate and inhibitor may be structurally related. Increasing the drug-substrate concentration may displace the inhibitor from the enzyme and partially or fully reverse the inhibition.
  - Noncompetitive inhibition: the inhibitor acts at a site on the enzyme different from the active site (allosteric site). The inhibition depends only on inhibitor concentration. Enzyme inhibition cannot be reversed by increasing drug concentration.

Enzyme Inhibition

- Often rapid, reversible and relatively short acting.
  E.g. erythromycin and cyclosporin
  NB erythromycin is a substrate and an inhibitor of CYP 3A4
- May be prolonged due to long half- life of drug.
  E.g. amiodarone and S-Warfarin
  NB amiodarone is an inhibitor of CYP2C9 but not a substrate for this CYP

Extra-hepatic drug metabolism

- The liver is the main site but other sites may be involved.
- These sites include the skin, the lung, the GI mucosal cells, the microbial flora of distal parts of ileum and large intestine. The kidney may play a role also.
- The metabolism is affected by the nature of the drug and the route of administration.
- E.g. isoproterenol forms sulfate conjugate in the GI mucosal cell after oral administration but forms methylated metabolite after i.v. injection. Also sulfasalazine is activated to absorbable form by the microbial flora.

EXCRETION OF DRUGS

Excretion is defined as the process where by drugs or metabolites are irreversibly transferred from internal to external environment through renal or non renal route.

Excretion of unchanged or intact drug may be needed in termination of its pharmacological action.

EXCRETION

- Urine is the main but NOT the only route.
- Glomerular filtration allows drugs of small MW to pass into urine; reduced by plasma protein binding; only a portion of plasma is filtered.
- Tubular secretion active carrier process for cations and for anions; inhibited by probenicid.
- Passive re-absorption of lipid soluble drugs back into the body across the tubule cells (non-ionized form).

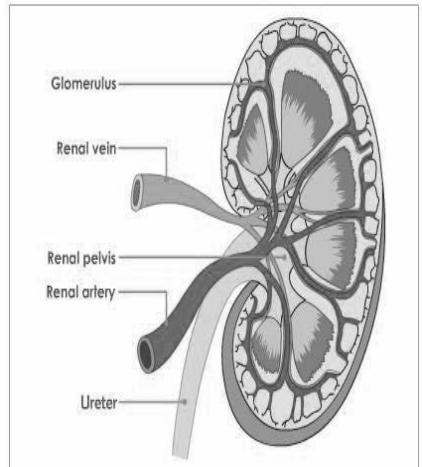
Note: pH of the urine can be modified to control the drug excretion rate. Alkaline urine reduce re-abosorption of weak acid drug and vice verse.

TYPES OF EXCRETION

1. **RENAL EXCRETION**
2. **NON RENAL EXCRETION**
   - **Biliary excretion.**
   - **Pulmonary excretion.**
   - **Salivary excretion.**
   - **Mammary excretion.**
   - **Skin / Dermal excretion.**
   - **Gastrointestinal excretion.**
   - **Genital excretion.**

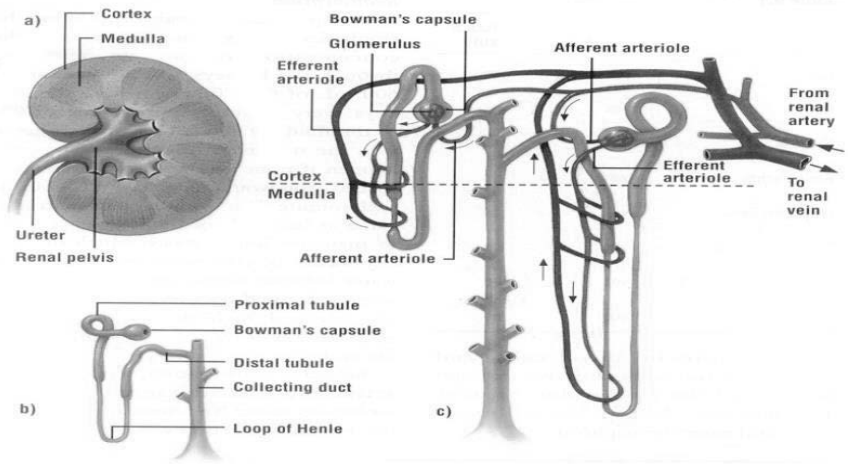
LONGITUDNAL SECTION OF KIDNEY

- The outer zone of the kidney is called the *cortex*, and the inner region is called the *medulla*.
- The *nephrons* are the basic functional units, collectively responsible for the removal of metabolic waste and the maintenance of water and electrolyte balance. Each kidney contains 1 to 1.5 million nephrons.
- The *glomerulus* of each nephron starts in the cortex. *Cortical nephrons* have short *loops of Henle* that remain exclusively in the cortex; m*edullary nephrons* have long loops of Henle that extend into the medulla.



A Longitudinal Section of the Kidney Showing Three Distinct Regions

ANATOMY OF NEPHRON



GLOMERULAR FILTRATION

- ✓ It Is non selective , unidirectional process
- ✓ Ionized or unionized drugs are filtered, except those that are bound to plasma proteins.
- ✓ Driving force for GF is hydrostatic pressure of blood flowing in capillaries.
- ✓ **GLOMERULAR FILTRATION RATE:**

  Out of 25% of cardiac out put or 1.2 liters of blood/min that goes to the kidney via renal artery only 10% or 120 to 130ml/min is filtered through glomeruli. The rate being called as glomerular filtration rate (GFR).e.g. creatinine, inulin.

ACTIVE TUBULAR SECRETION

- This mainly occurs in proximal tubule.
- It is carrier mediated process which requires energy for transportation of compounds against conc. Gradient

Two secretion mechanisms are identified.

- System for secretion of organic acids/anions

E.g. Penicillin, salicylates etc uric acid secreted

- System for organic base / cations

E.g. morphine

- Active secretion is Unaffected by change in pH and protein binding.
- Drug undergoes active secretion have excretion rate values greater than normal GFR e.g. Penicillin.

TUBULAR RE-ABSORPTION

- It occurs after the glomerular filtration of drugs. It takes place all along the renal tubules.
- Re-absorption of drugs indicated when the excretion rate value are less than the GFR 130ml/min.e.g. Glucose
- TR can be active or passive processes.
- Re-absorption results in increased half life of the drug.

TUBULAR RE-ABSORPTION

Active Tubular Re-absorption:

Its commonly seen with endogenous substances or nutrients that the body needs to conserve e.g. electrolytes, glucose, vitamins.

Passive Tubular Re-absorption:

- It is common for many exogenous substances including drugs.
- The driving force is Conc. Gradient which is due to re-absorption of water, sodium and inorganic ions.
- If a drug is neither excreted or re-absorbed its conc. in urine will be 100 times that of free drug in plasma.
- only non-ionized form is reabsorbed.
- Affected by pH of the urine.

pH OF THE URINE

- It varies between 4.5 to 7.5
- It depends upon diet, drug intake and pathophysiology of the patient .
- Acetazolamide and antacids produce alkaline urine, while ascorbic acid makes it acidic.
- Relative amount of ionized ,unionized drug in the urine at particular pH & % drug ionized at this pH can be given by " HENDERSON-HESSELBACH" equation.

HENDERSON-HESSELBACH EQUATION

1- For weak acids

$$pH - pKa = \log \frac{[\text{ ionized }]}{[\text{unionized}]}$$

2- For weak bases

$$pH - pKa = \log \frac{[\text{unionized}]}{[\text{ ionized }]}$$

FACTORS AFFECTING RENAL EXCRETION

- Physicochemical properties of drug
- Urine pH
- Blood flow to the kidney
- Biological factor
- Drug interaction
- Disease state

PHYSICOCHEMICAL PROPERTIES OF DRUG

- **Molecular size**

  Drugs with Mol. wt <300, water soluble are excreted in kidney. Mol. wt 300 to 500 Dalton are excreted both through urine and bile.

- **Binding characteristics of the drugs**

  Drugs that are bound to plasma proteins behave as macromolecules and cannot be filtered through glomerulus. Only free drug appears in glomerular filtrate. Protein bound drug has long half lives.

BIOLOGICAL FACTORS

- **Sex –** Renal excretion is 10% lower in female than in males.
- **Age –** The renal excretion in newborn is 30-40 % less in comparison to adults.
- **Old age –** The GFR is reduced and tubular function is altered which results in slow excretion of drugs and prolonged half lives.

DRUG INTERACTION

- Any drug interaction that result in alteration of binding characteristics, renal blood flow, active secretion, urine pH, and forced diuresis would alter renal clearance of drug.
- Renal clearance of a drug that is highly bound to plasma proteins can be increased after being displaced with other drug e.g. Gentamicin induced nephrotoxicity by furosemide.
- Alkalinization of urine with bicarbonates promotes the excretion of acidic drugs.

DISEASE STATE

- **RENAL DYSFUNCTION**

Greatly impairs the elimination of drugs especially those that are primarily excreted by kidney. Some of the reasons of renal failure are hypertension, Diabetes, Pyelonephritis.

- **UREMIA**

Characterized by Impaired GFR , accumulation of fluids & protein metabolites, also impairs the excretion of the drugs. Half life is increased resulting in drug accumulation and increased toxicity.

NON-RENAL ROUTE OF DRUG EXCRETION

Various routes are

- Biliary Excretion
- Pulmonary Excretion
- Salivary Excretion
- Mammary Excretion
- Skin/dermal Excretion
- Gastrointestinal Excretion
- Genital Excretion

BILIARY EXCRETION

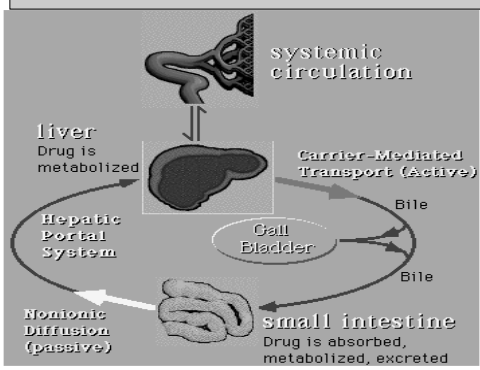
- Bile is secreted by hepatic cells of the liver. The flow is steady 0.5 to 1ml /min.
- It is important in the digestion and absorption of fats.
- 90% of bile acid is re-absorbed from intestine and transported back to the liver for re-secretion.
- Compounds excreted by this route are sodium, potassium, glucose, bilirubin, Glucuronide, sucrose, muco-proteins e.t.c.
- The metabolites are more excreted in bile than parent drugs due to increased polarity.

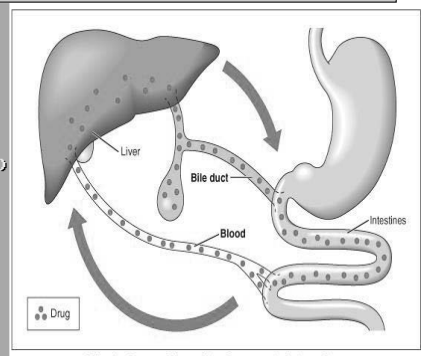
BILIARY EXCRETION

- Phase-II reactions mainly glucuronidation and conjugation with glutathione result in metabolites with increased tendency for biliary excretion.
- Drugs excreted in the bile include chloromphenicol, morphine and indomethacin.
- Glutathione conjugates have larger molecular weight and so not observed in the urine. For a drug to be excreted in bile must have polar groups like –COOH, -SO3H.
- Clomiphene citrate, ovulation inducer is completely removed from the body by BE.

THE ENTEROHEPATIC CIRCULATION

Some drugs which are excreted as glucuronides or glutathione conjugates are hydrolyzed in the intestine to the parent drugs which are reabsorbed.
This phenomenon of drug cycling between the intestine & the liver is called Enterohepatic circulation





THE ENTEROHEPATIC CIRCULATION

- EC is important in conservation of Vitamins, Folic acid and hormones.
- This process results in prolongation of half lives of drugs like Carbenoxolone.
- Some drugs undergoing EC include are cardiac glycosides, rifampicin and chlorpromazine.
- The principle of adsorption onto the resins in GIT is used to treat pesticide poisoning by promoting fecal excretion.

Pulmonary excretion

- Gaseous and volatile substances such as general anesthetics (Halothane) are absorbed through lungs by simple diffusion.
- Pulmonary blood flow, rate of respiration and solubility of substance effect PE.
- Intact gaseous drugs are excreted but not metabolites.
- Alcohol which has high solubility in blood and tissues are excreted slowly by lungs.

Salivary excretion

- The pH of saliva varies from 5.8 to 7.4.
- Unionized lipid soluble drugs are excreted passively.
- The induced bitter taste in the mouth of a patient is indication of salivary excretion.
- Compounds excreted in saliva include Caffeine, Phenytoin, Theophylline.

Mammary excretion

- Milk consists of lactic secretions which are rich in fats and proteins.
- 0.5 to one litre of milk is secreted per day in lactating mothers.
- Excretion of drug in milk is important as it gains entry in breast feeding infants. pH of milk varies from 6.4 to 7.6.Free un-ionized and lipid soluble drugs diffuse passively.
- Highly plasma bound drug like Diazepam is less secreted in milk. Since milk contains proteins. Drugs excreted can bind to it.

Mammary excretion

- Amount of drug excreted in milk is less than 1% and fraction consumed by infant may be too small to produce toxic effects.
- Some potent drugs like barbiturates and morphine may induce toxicity.
- **ADVERSE EFFECTS**
  - Discoloration of teeth with tetracycline and jaundice due to interaction of bilirubin with sulfonamides. Nicotine is secreted in the milk of mothers who smoke.

Skin excretion

- Drugs excreted through skin via sweat follows.
- Excretion of drugs through skin may lead to urticaria and dermatitis.
- Compounds like benzoic acid, salicylic acid, alcohol and heavy metals like lead, mercury and arsenic are excreted in sweat.

GASTROINTESTINAL EXCRETION

- Excretion of drugs through GIT usually occurs after parenteral administration.
- Water soluble and ionized from of weakly acidic and basic drugs are excreted in GIT.
- Example are nicotine and quinine are excreted in stomach. Drugs excreted in GIT are reabsorbed into systemic circulation & undergo recycling.

EXCRETION PATHWAYS, TRANSPORT MECHANISMS & DRUG EXCRETED.

Excretory route	Mechanism	Drug Excreted
Urine	GF/ ATS/ ATR, PTR	Free, hydrophilic, unchanged drugs/ metabolites of MW< 500
Bile	Active secretion	Hydrophilic, unchanged drugs/ metabolites/ conjugates of MW >500
Lung	Passive diffusion	Gaseous &volatile, blood & tissue insoluble drugs
	Passive diffusion Active transport	Free, unionized, lipophilic drugs. Some polar drugs
	Passive diffusion	Free, unionized, lipophilic drugs (basic)
	Passive diffusion	Free, unionized lipophilic drugs
	Passive diffusion	Water soluble. Ionized drugs