VIEW ACADEMY
YOUR BEST WAY

Pharmacology
Med – Lecture 4

Pharmacokinetics I

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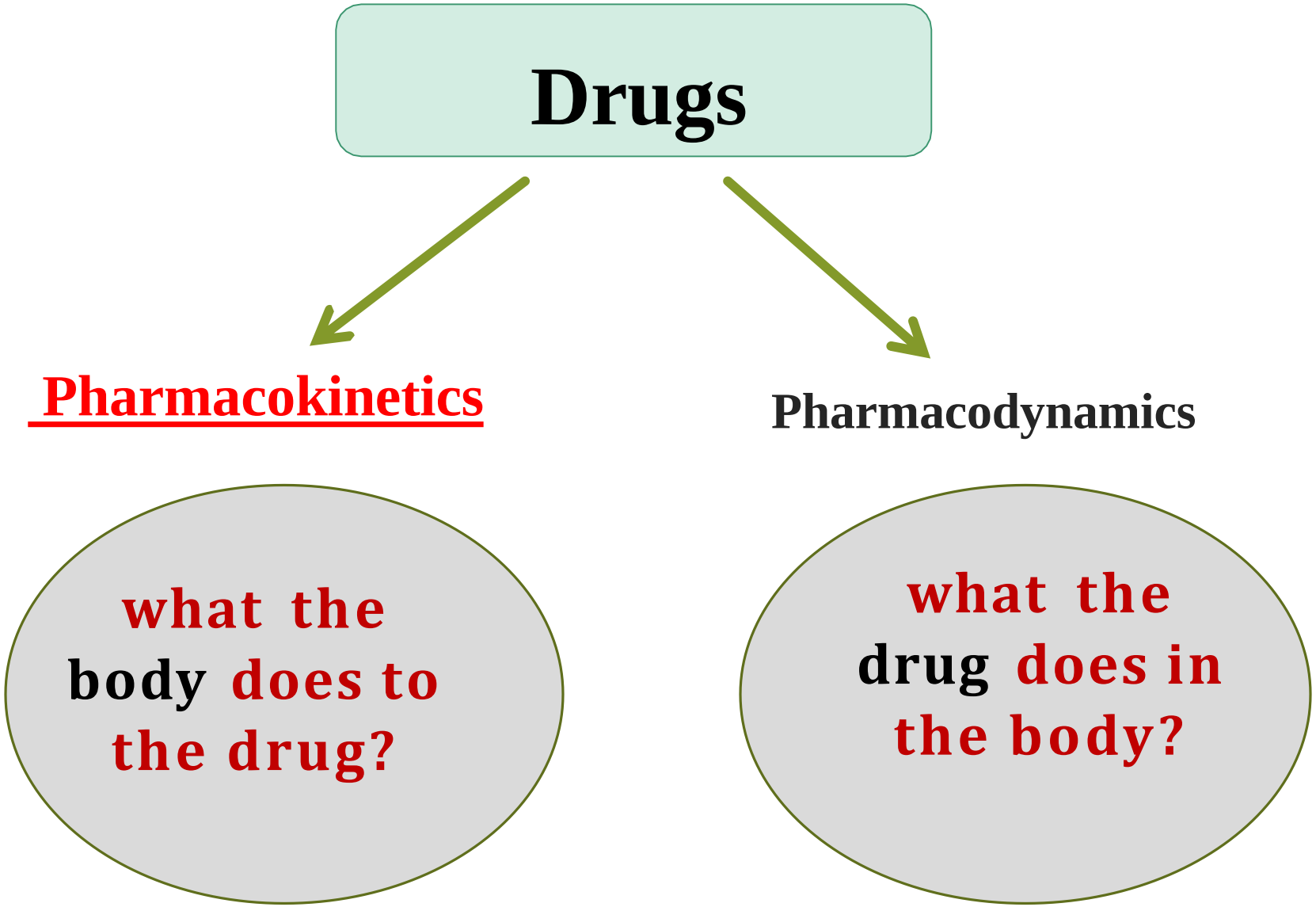
Original Slides for Dr. Heba Ahmed Hassan

Pharmacology

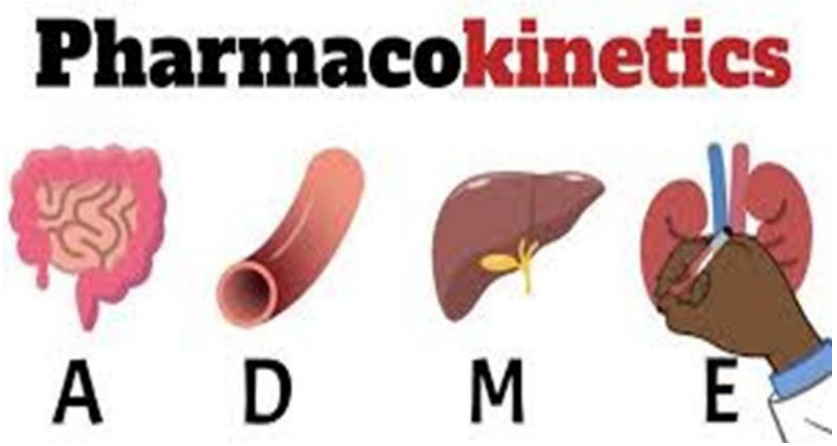
The science that deals with drugs.

Drugs

Substances used to prevent and treat diseases.


Drugs
Pharmacokinetics
Pharmacodynamics
what the body does to the drug?
what the drug does in the body?

Pharmacokinetics



What the body does to the drug?

- Absorption
  - The ‘entrance’ of the drug from the site of administration to allow it to get (either directly or indirectly) to the plasma
- Distribution
  - Being in blood (plasma) after absorption
- Metabolism
  - whether in the liver or other tissues, plays a crucial role in determining the drug's effectiveness and duration.
- Excretion (Whatever the type)

Absorption

- Passage of drug from site of administration to systemic circulation.

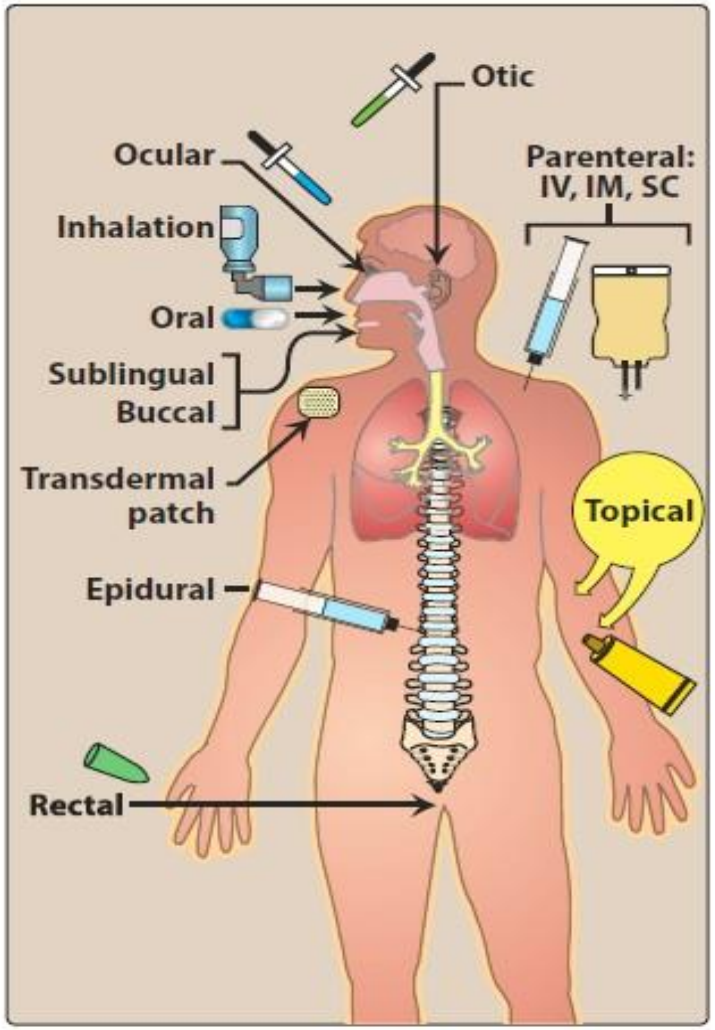
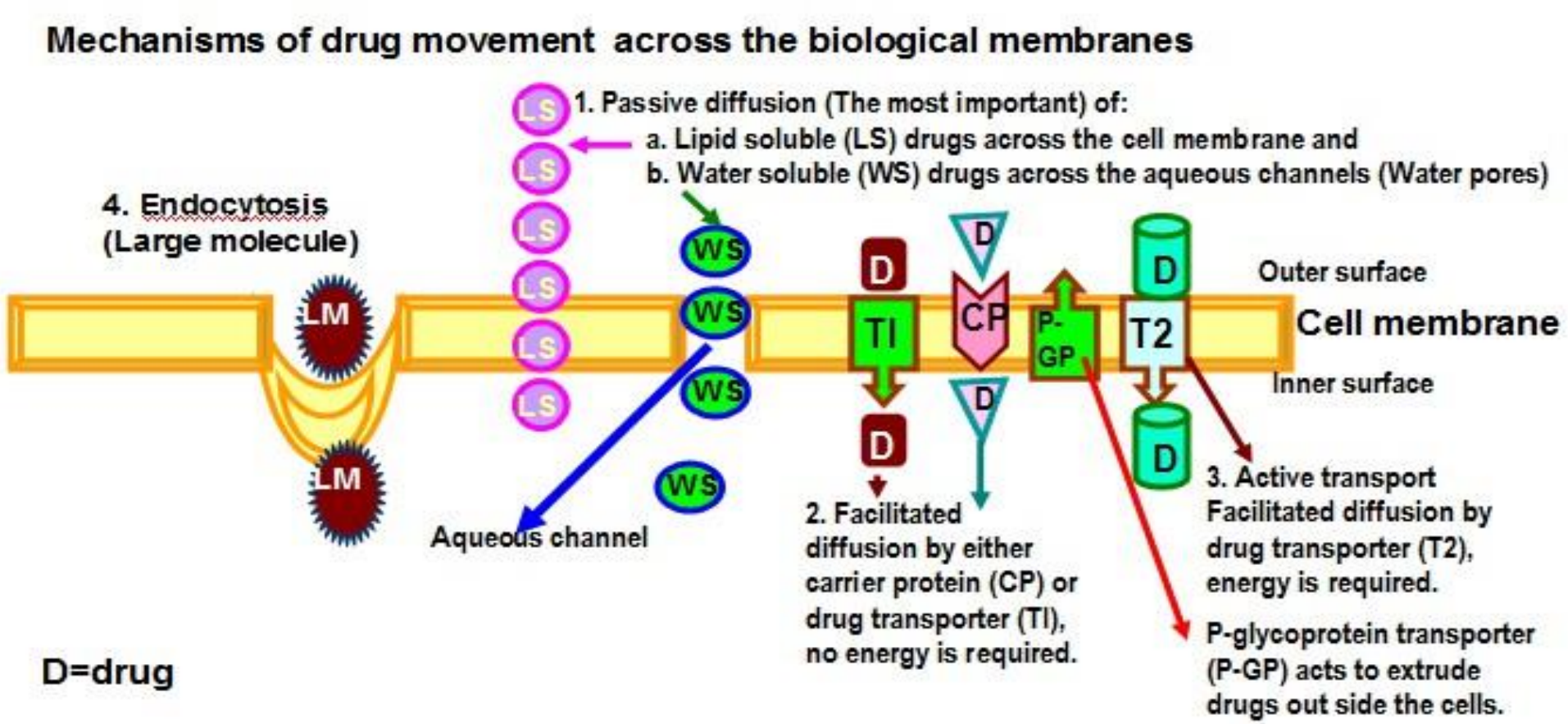


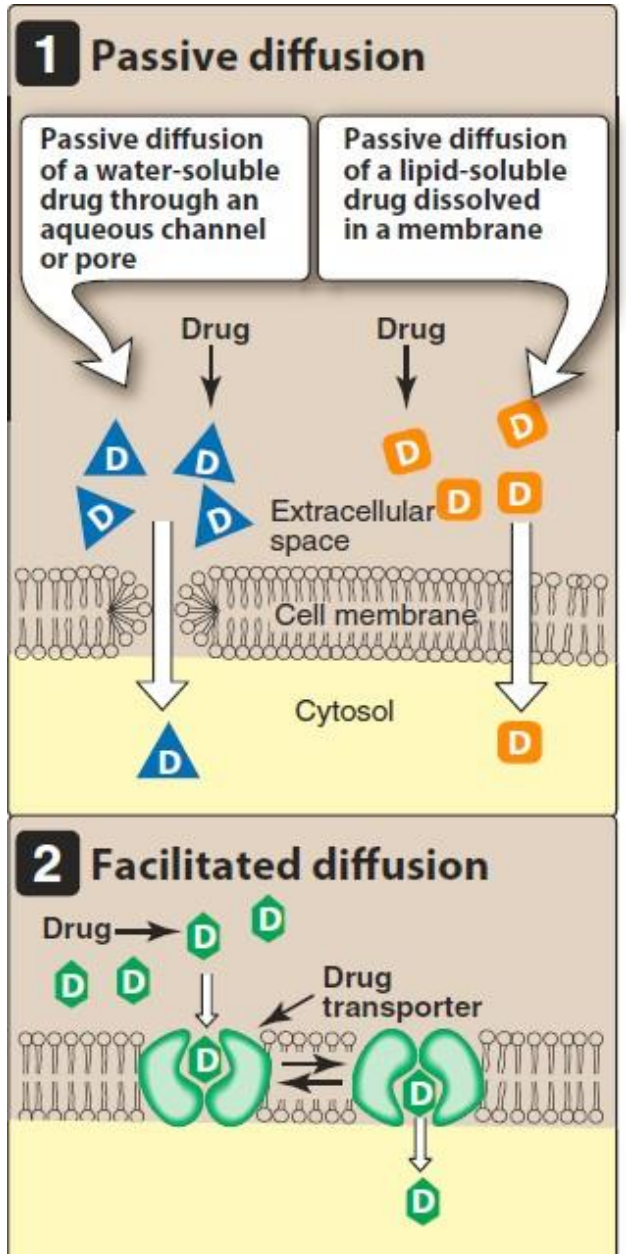
Figure 1.2
Commonly used routes of drug administration. IV = intravenous; IM = intramuscular; SC = subcutaneous.

Mechanisms of drug absorption
(how drugs cross biological membranes)



1. Passive diffusion:

- Rapid movement of lipid-soluble drugs across the **cell membrane**
- Movement of the water-soluble drugs across the aqueous channels (water pores).
- **No energy** needed and with concentration gradient.
- No carrier needed
-

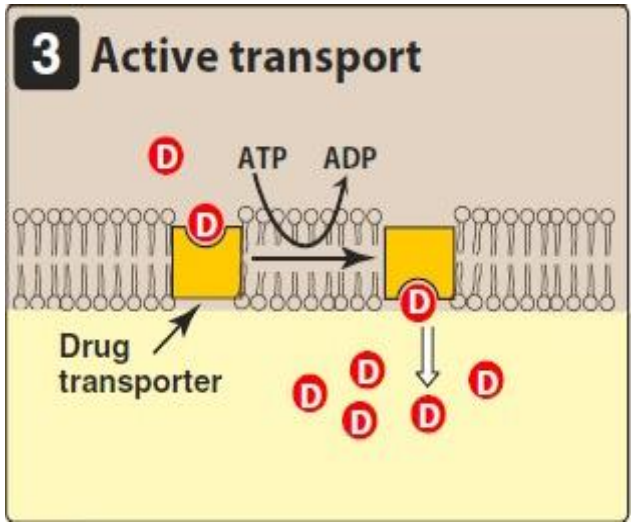


2. Facilitated diffusion

- The drugs are carried into inside the cell by **carrier** or **transporter**.
- **No** energy is required and according to the concentration gradient
- Large molecule

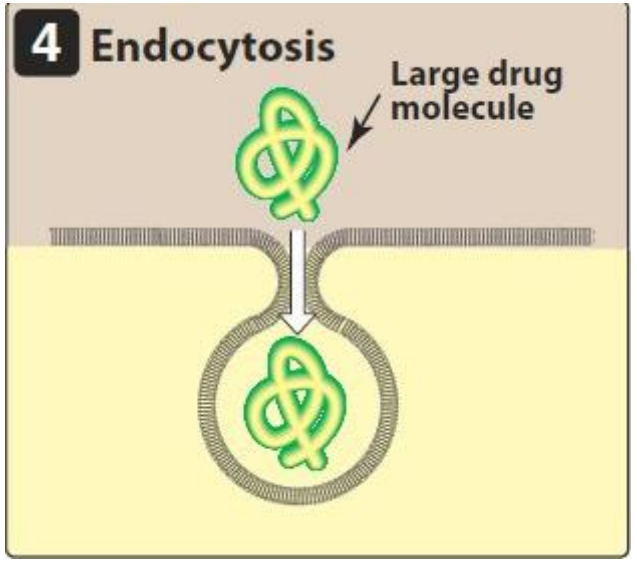
3. Active Transport:

- The drug movement may be **against** the concentration gradient <u>by drug carrier or transporter.</u>
- **Energy** is required



4. Endocytosis

- Drugs of high molecular weight, the drug binds to the cell membrane, dips in and enveloped by the cell membrane.



Factors affecting absorption:

- Route of Administration
- Absorbing surface
- Co Administration of food or drugs
- Systemic circulation
- Specific factors

- 1-Water & lipid solubility
- 2- Pharmaceutical preparation
- 3- Ionization of the drugs

A. Factors related to the patient

1- Route of Administration

I.V. and inhalation > I.M. > S.C. > Oral >Topical

2- Absorbing surface

- **Vascularity:** (Alveoli > S.C. tissue). **- Direct relationship**
- **Surface area:** (Alveoli > Intestine > Stomach) **- Direct relationship**
- **Pathological conditions**: Diarrhea decrease oral absorption

A. Factors related to the patient

3- Systemic *Circulation*

- **Shock** decrease absorption; oral and subcutaneous routes are not suitable.

4- Specific factors

- Intrinsic factor is essential for vitamin B12 absorption.

5- Co Administration of other drugs& food

- **S.C. adrenaline (added to local anesthetics) → V.C. absorption of local anesthetics → longer duration of action of local anesthetics.**
- **Ca+2 (e.g. in milk) ▼ oral absorption of tetracyclines (antibiotics).**

B. Factors related to the drug

1. Water and lipid solubility

► **Completely water-insoluble compounds are** not absorbed (e.g. barium chloride).

► **increase lipid solubility** lead to increase absorption (lipid/water partition coefficient).

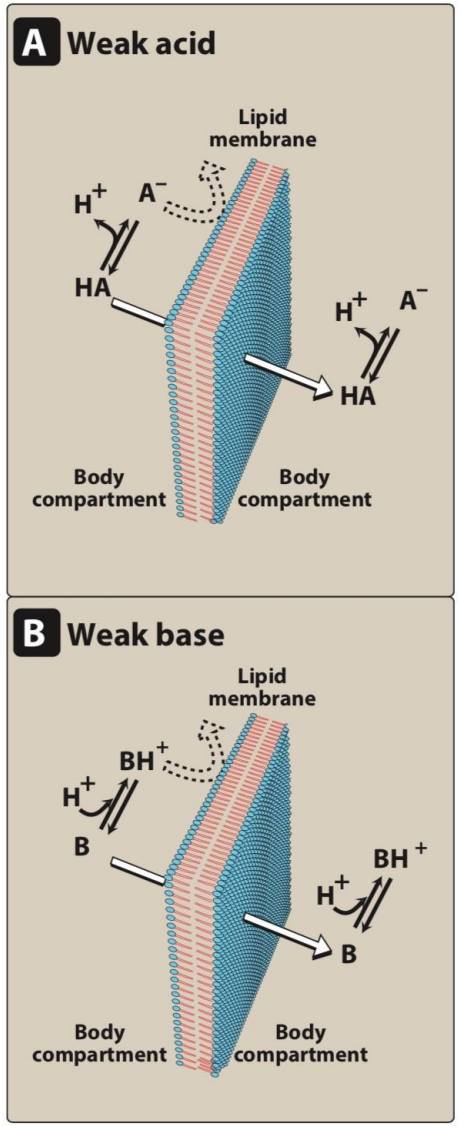
2. Pharmaceutical preparation

- **Dosage form**: Solution > Suspension > tablet.
- **Shape, size of particles and rate** of dissolution of tablets.
- **Excepient (filler)** containing Ca+2 decreases oral absorption of tetracyclines.

3- Ionization of the drug:

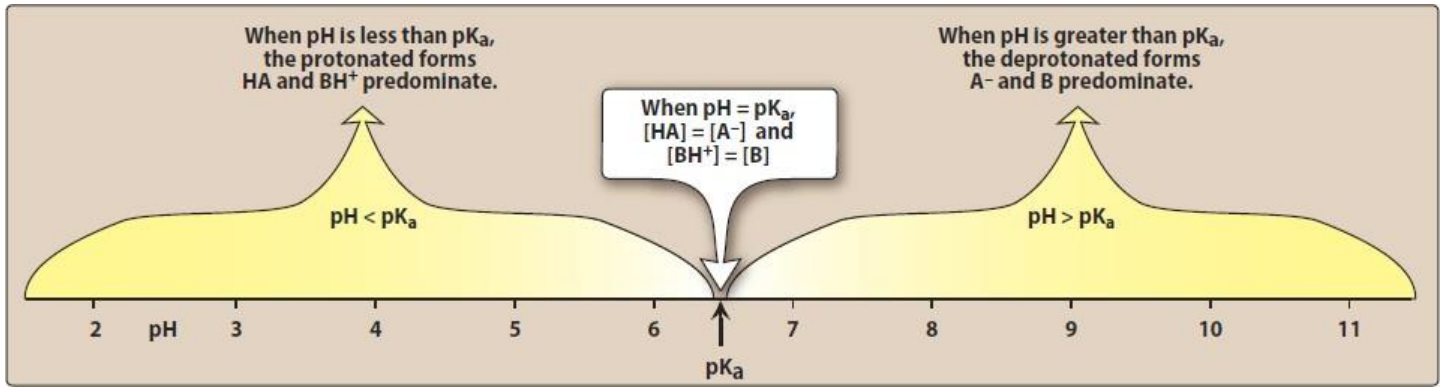
سلايد اضافي لترتيب الأفكار وتوضيحات افضل

- Most drugs are **weak acids** or **weak bases** that are present in solution as both the **ionized** and **non-ionized** form
- Protonated form of ACIDIC drugs are non-charged (unionized): $HA \rightleftharpoons H^+ + A^-$
- Protonated form of BASIC drugs are charged (ionized): $BH^+ \rightleftharpoons B + H^+$
- **For a weak acid,** the uncharged, protonated HA can permeate through membranes and A- cannot
- **For a weak base,** the uncharged form B penetrates through membranes, but the protonated BH+ does not
- Non-ionized molecules are usually lipid soluble and can diffuse across cell membranes but ionized molecules are usually unable to penetrate the lipid membrane because of their low lipid solubility.
- The ratio of ionized to unionized species depends on the pH of the environment, and the **strength of the weak acid or base which represented by** pKa of the drug
- **When pKa = pH (50% ionized: 50% unionized)**

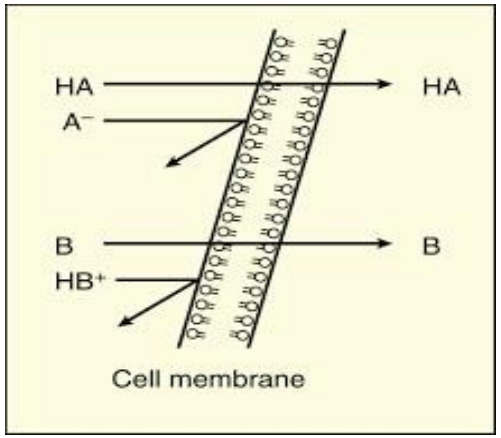


3- Ionization of the drug:

- Ionization decreases lipid solubility and absorption of drugs.
- Non-ionized (uncharged) ⟹ better absorption.
- Depends on pKa of the drug and pH of the medium
- Quaternary ammonium compounds ⟹ Ionized poor absorption.
- **Streptomycin** has high pKa ⟹ always ionized not absorbed orally.



The effect of pH on drug absorption



When drugs bind hydrogen,

- weak acids become unionized (A- + HA)
- while weak base are ionized (B + BH+)
- **At low pH** weak acids become unionized while the weak bases become ionized.
- **At high pH** weak base drugs become unionized while weak acids become ionized.
- Accordingly, weak acid are more absorbed in acidic media while weak bases are more absorbed in alkaline media.
- **The pH at which the concentrations of the ionized and unionized forms of the drug are equal is termed pKa**
- **Each drug has its own pKa.**

Clinical importance of pKa

1- GIT:
Aspirin (acidic drug) has low pKa.

Drug molecules become unionized in the empty stomach (low pH) and can enter gastric mucosal cells. In gastric mucosal cells (high pH) aspirin becomes ionized and trapped in gastric mucosal cell "peptic ulceration"

2- Kidney:
In drug poisoning,

renal elimination could be enhanced by changing urinary pH to increase ionization of drug and inhibit tubular reabsorption of the drug.

- Alkalinization of urine by sodium bicarbonate (to increase urine pH above drug pKa) is useful in acidic drug poisoning e.g. Aspirin and phenobarbital.

- Acidification of urine by ascorbic acid (to decrease urine pH below drug pKa) is used in basic drug poisoning e.g. amphetamine.

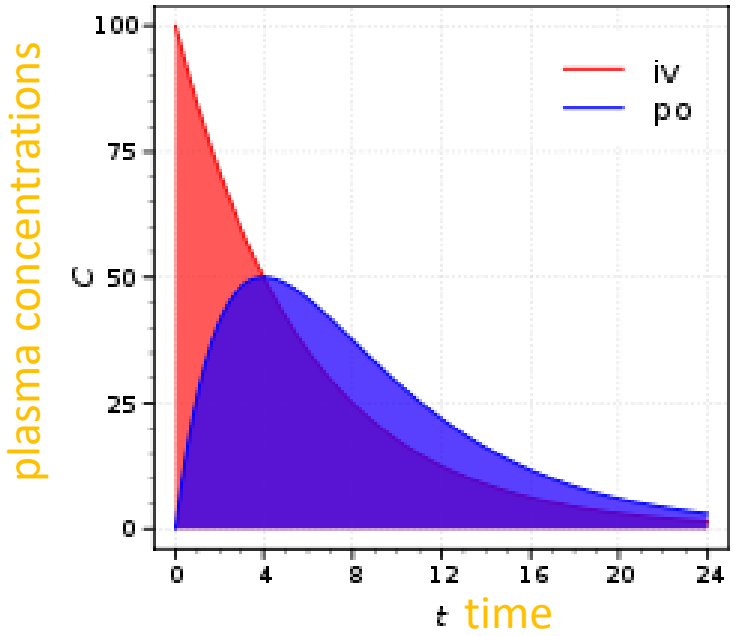
Bioavailability

- It is the percentage of drug that reaches the systemic circulation and becomes available for biological effect.

Determination of bioavailability: Bioavailability is determined by comparing plasma levels of a drug after a particular route of administration (for example, oral administration) with levels achieved by IV administration of the same dose.

If 100mg are given orally, and only 70mg are absorbed unchanged, the bioavailability would be 70%.

$$\text{Bioavailability} = \frac{\text{Area under the curve (AUC) after oral route}}{\text{Area under the curve (AUC) after IV. route}} \times 100$$

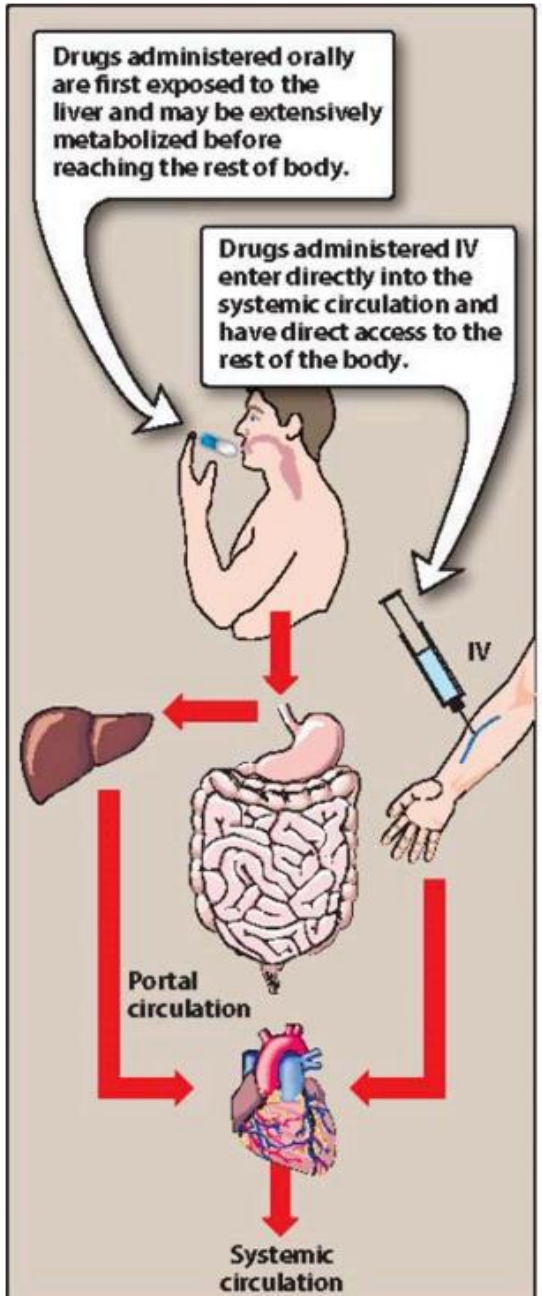


Factors affecting bioavailability:

1 The extent of drug absorption.

1 1st pass effect (1st pass metabolism):

- It is the metabolism of some drugs in a single passage through gut wall, liver or lungs before reaching systemic circulation
- 1st pass metabolism **(Mainly in Liver)**



A. Hepatic 1st Pass Effect :

- **Nitroglycerin** and **propranolol** pass from GIT to liver where they are extensively metabolized in their 1st pass through liver before reaching systemic circulation.

B. Intestinal 1st pass effect:

- **Estrogens** are extensively metabolized in their 1st pass through intestinal wall.

C. Pulmonary metabolism:

- After inhalation, **nicotine** is partially metabolized in the lung.