تفريغ فارما ١

اسم الموضوع: lec 2

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لجان الدفعات

General principles

When a drug is ingested in the body, what happens?

- The body acts on the drug :Pharmacokinetics → effect of the Body on drug
- The drug act on the body : Pharmacodymanics ارتباط الدواء بالمستقبلات
  ↳ effect of drug on the body

- In these two complex processes, numerous factors interfere to give the final outcome.

Pharmacokinetics ⇒ (ADME)

- Absorption → the process by which a drug enters the blood stream after administration
- Distribution → ~~irreversible~~ → reversible
- Metabolism (transformation) → ① transformation the drug from lipophilic into hydrophilic
- Elimination → metabolisim + excreation
  - excreation لذلك لابد أن نقول
  - يعمل على تسهيل خروج الدواء من الجسم

*Volume of distribution ↑, the amount of drug reaches into tissue ↑

*Metabolism ⇒ ② transformation of the drug from active to inactiv or inactive to active (prodrug)

Phase I Phase II

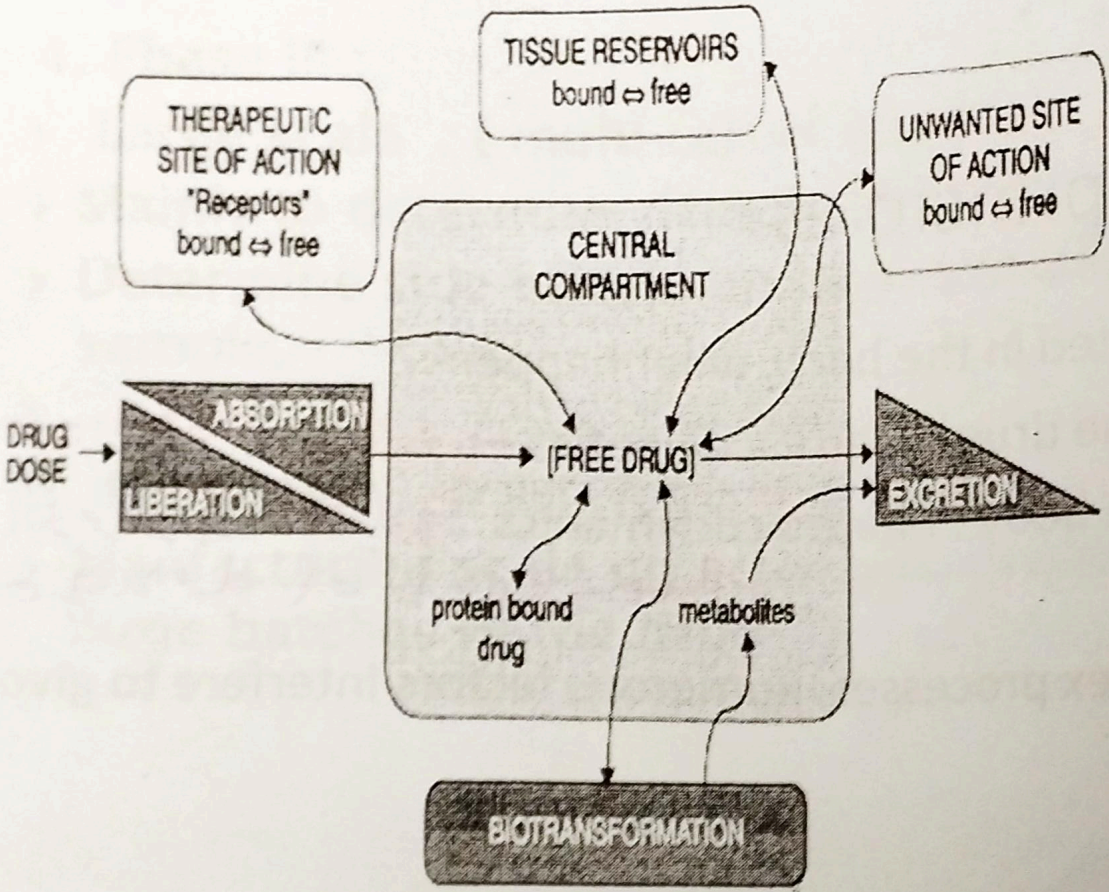


Figure 1-1. *The interrelationship of the absorption, distribution, binding, metabolism, and excretion of a drug and its conc sites of action.*

* أي مكان في الجسم يوجد فيه انزيمات يكون الدواء فيه معرض للـ metabolism

Absorption ⇒ يحدث اذا كان في barrier يمنع وصول الدواء الى blood stream مثل GI

- A drug should be absorbed from the site of adminstration into the plasma

- To produce its effect, a drug much reach its site of action at appropriate concentration.

*IM (Intramuscular) → يحدث له absorption

*IV (Intravenous) → لا يحتاج أن يحدث له امتصاص لانه يذهب مباشرة الى مجرى الدم

Factors affecting Drug Absorption

- Drug physicochemical properties → Physical: particle size, solubility, stability, Partition coefficient
- Route of drug administration
- Effect of pH on drug absorption
- Blood flow to the absorption site → Blood flow ↑ ⇒ absorption ↑
- Total surface area available for absorption → surface area ↑ ⇒ absorption ↑
- Contact time at the absorption surface
- Expression of drug carriers such as " P-glycoprotein"

*Ionized drug → Hydrophilic لا يدخل بسهولة الى الخلايا لانه

*Un-ionized drug → يدخل بسهولة الى الخلايا لانه lipophilic

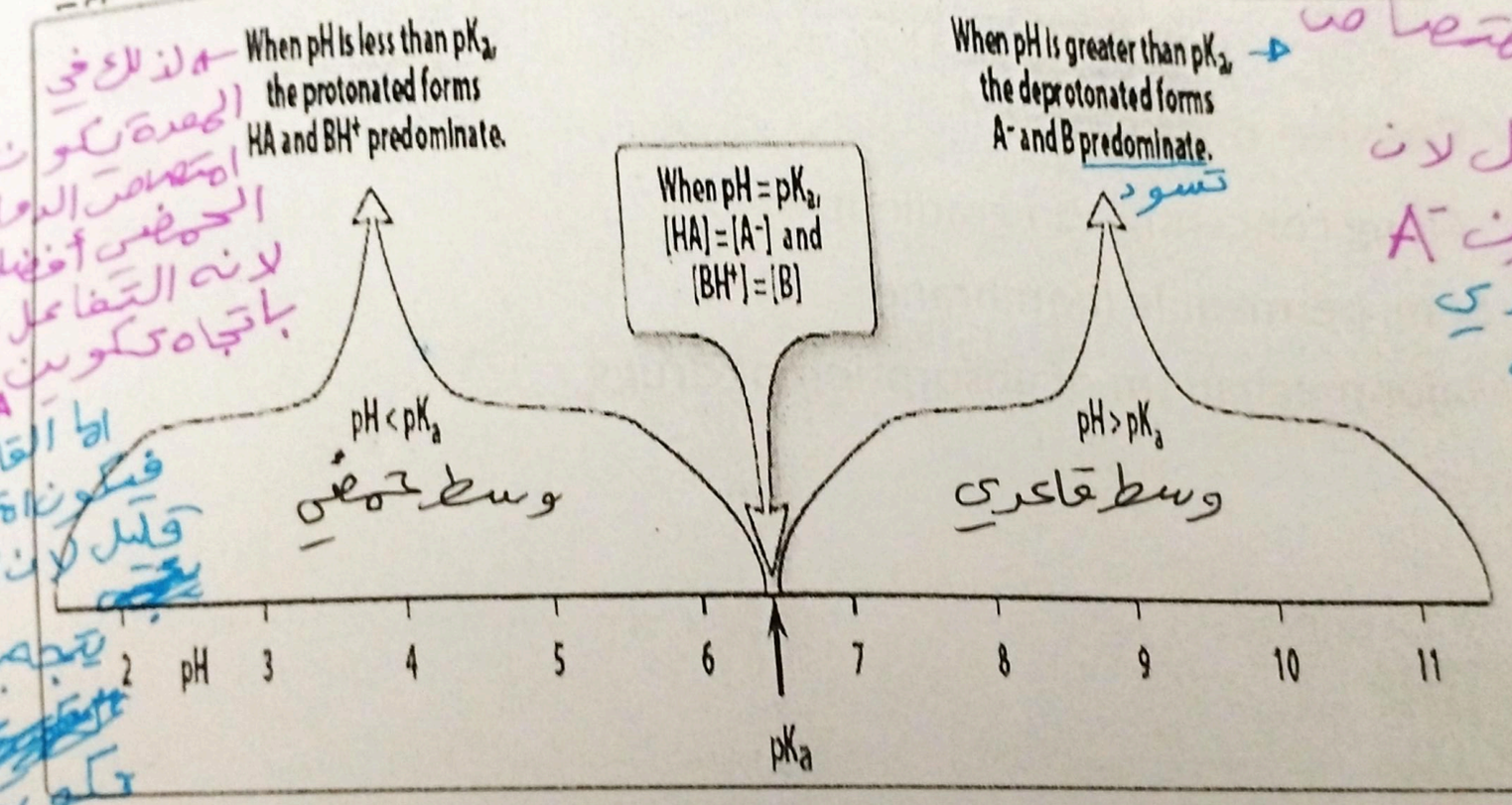
weak acid $X = -1$

weak base $X = +1$

$$\%\ ionization = \frac{100}{1+10^{-X(PH-Pka)}}$$

خاص بالدواء ← pka

خاص بالوسط ← PH



لذلك في الجهة يكون امتصاص الدواء الحمضي أفضل لانه التفاعل يتجه باتجاه تكوين HA

اما القاعدة فيكون امتصاصها قليل لان التفاعل يتجه باتجاه تكوين BH^+

في small intestine يكون امتصاص الدواء الحمضي أقل لان التفاعل يتجه لتكوين A^-

اما الدواء القاعدي فيكون امتصاصه أفضل لان التفاعل يتجه لتكوين B

تسود

$$AH \rightleftharpoons A^- + H^+$$

$$B + H^+ \rightleftharpoons BH^+$$

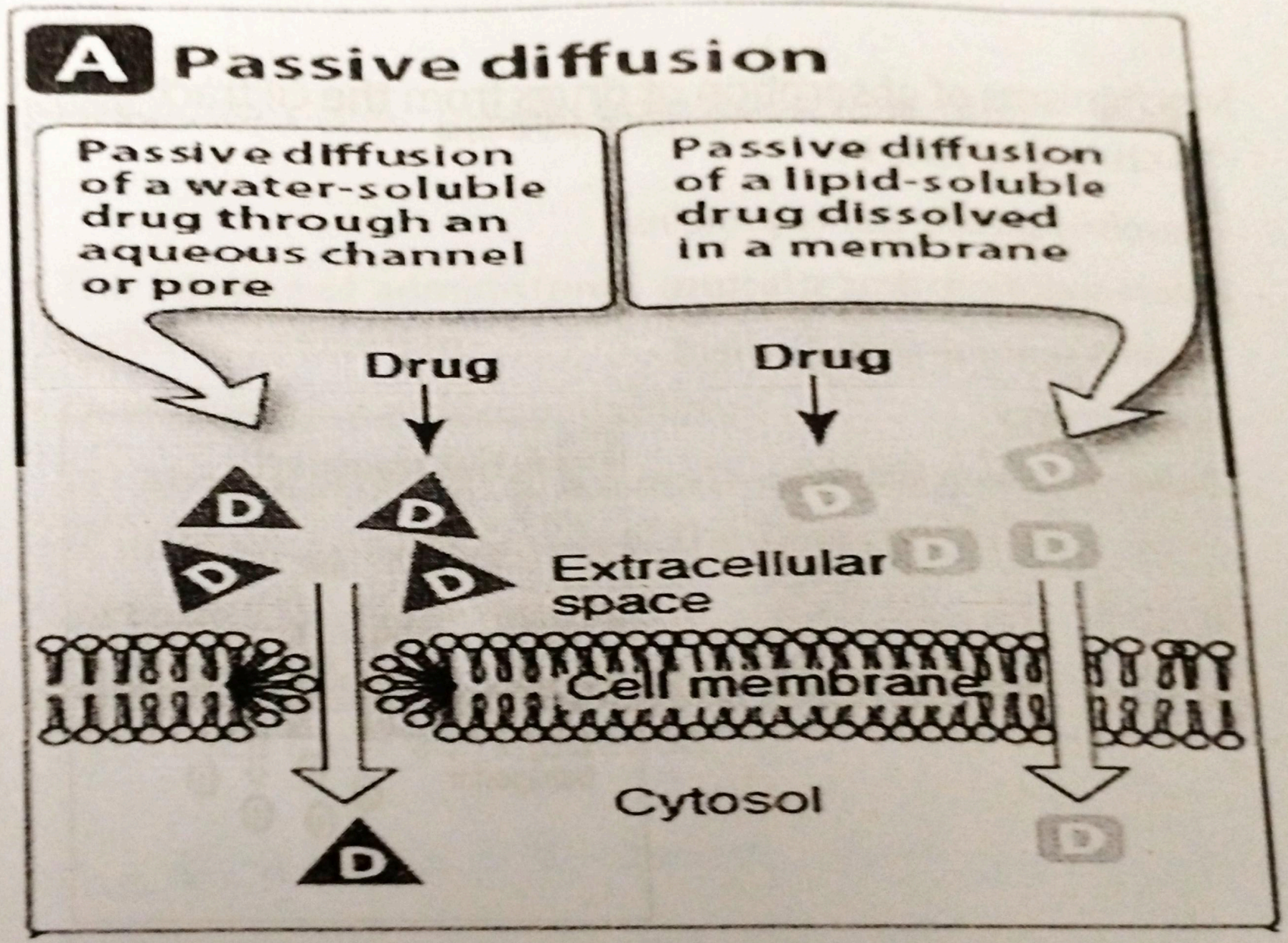
P-glycoprotein

- Multidrug transmembrane transporter protein
- Transports various drugs and causes drug resistance!

Liver	transporting drugs into bile for elimination
Kidney	Pumping drugs into urine for excretion
placenta	transporting drugs back into maternal blood
intestine	transporting drugs into the intestinal lumen and reducing drug absorption
Brain capillaries	Pumping drugs back into blood/limiting drug access to the brain

Mechanisms of absorption of drugs from the GI tract

- ✓ **Passive diffusion :**
  - Along concentration gradient
  - Semi permeable membrane
  - Major mechanism of absorption of drugs


A Passive diffusion
Passive diffusion of a water-soluble drug through an aqueous channel or pore
Passive diffusion of a lipid-soluble drug dissolved in a membrane
Drug
Drug
D
Extracellular space
Cell membrane
Cytosol

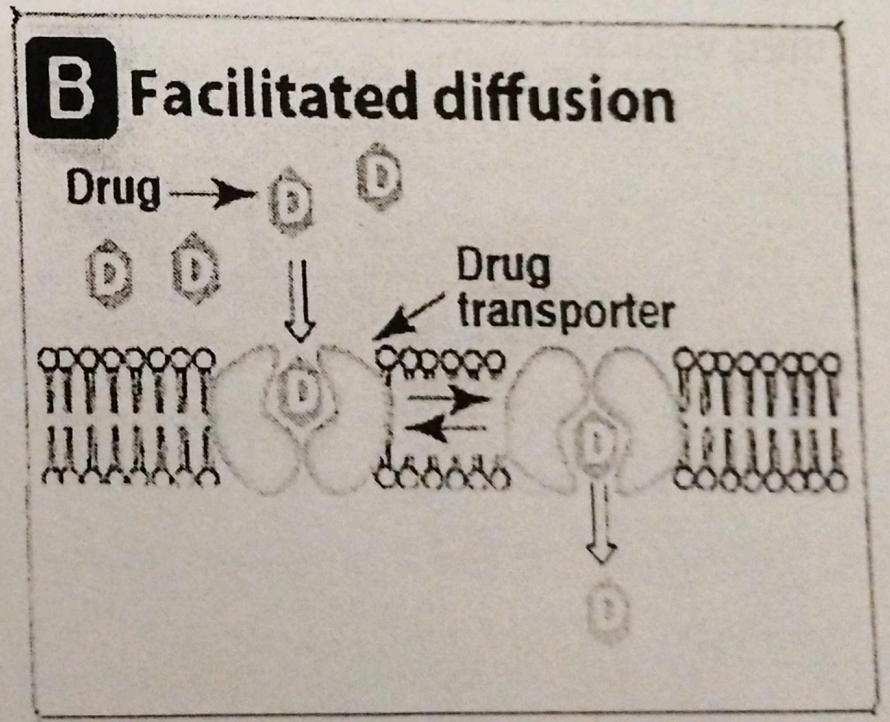
Mechanisms of absorption of drugs from the GI tract

✓ **Facilitated diffusion :**

More specific mechanism

Specific transmembrane protein carriers

Along concentration gradient, No energy needed



Mechanisms of absorption of drugs from the GI tract

✓ **Active transport :**

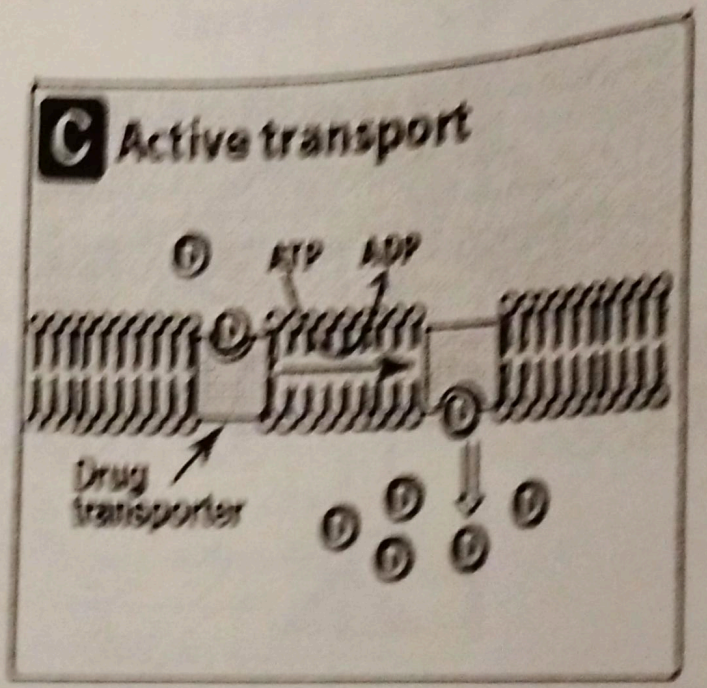
Involves specific carrier proteins

More specific to drug structure

Against concentration gradient

Needs energy

Shows saturation kinetics

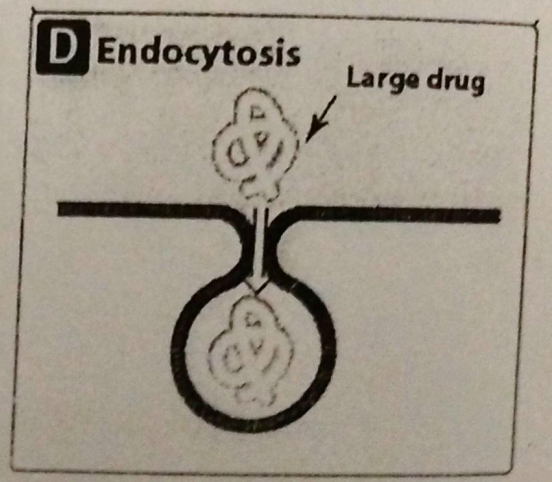


Mechanisms of absorption of drugs from the GI tract

- ✓ **Endocytosis and exocytosis :**

Large sized drugs

Endocytosis involves engulfment of a drug molecule by the cell membrane and transport into the cell by pinching off the drug filled vesicle



Bioavailability

- The fraction of administered drug that reaches the systemic circulation.
- **Determination of bioavailability :**

  (1) Absolute B.A: Drug plasma levels of a given route (PO)/Drug plasma levels of the IV route(100%).

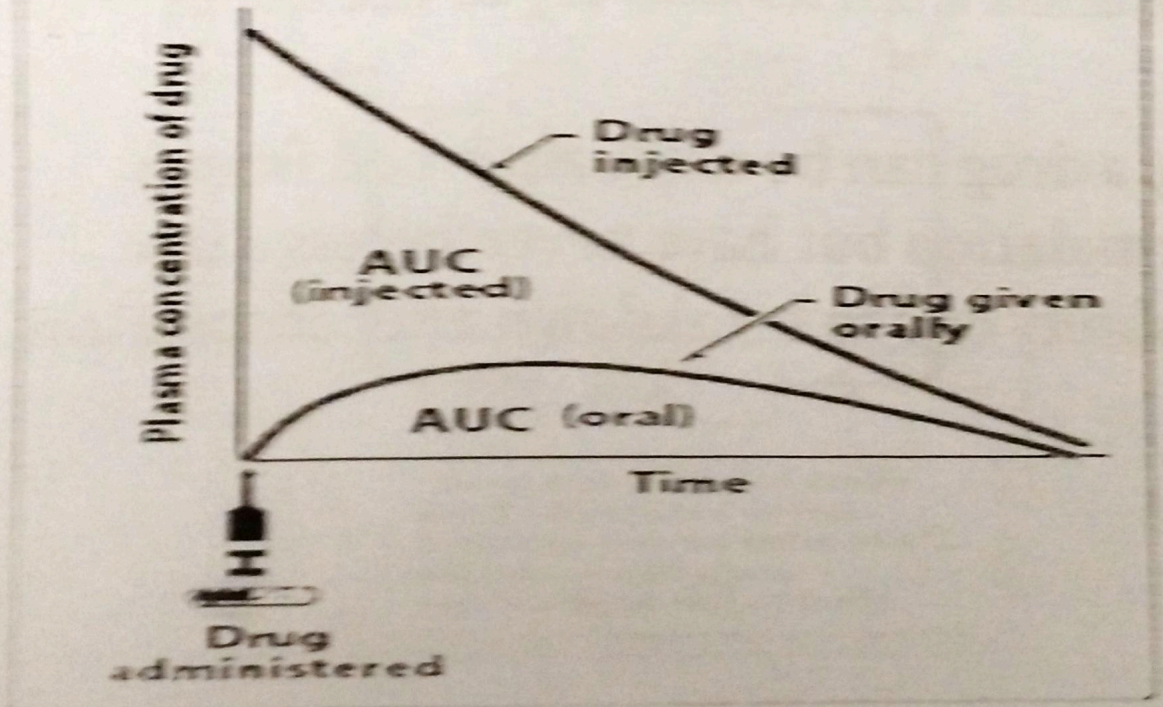
  (referred to the I.V route)

  Absolute Bioavailability is used when the drug is approved for IV adminstration

The fraction of drug that been absorbed
الباقي و metabolism غلط لان جزء من الدوا يحدث له
يذهب الى الدم

Absolute Bioavailability → هو مقارنة اي دواء من طرق الاعطاء ب IV

$$\text{Bioavailability} = \frac{\text{AUC oral}}{\text{AUC injected}} \times 100$$



AUC ▷ area under the curve

مقارنة دوائين مع بعض

Relative Bioavailability:

Many drugs are not approved for intravenous administration.

In such cases, the bioavailability of the test drug is compared to a reference standard , both being given by the same route (other than intravenous) and in the same dose. This is known as relative bioavailability

Relative bioavailability=AUC(test)/AUC(std)

Bioavailability is NOT Absorption !!

- *Absorption*

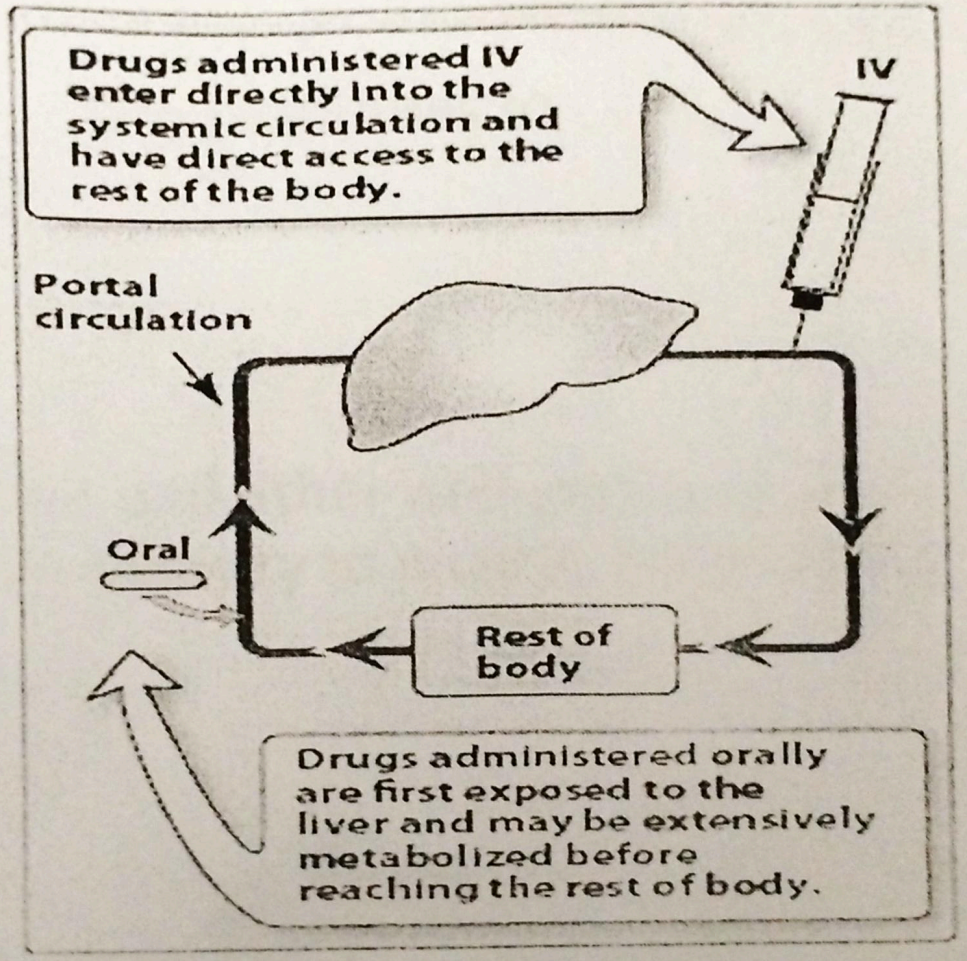
It is only one of the steps separating drug administration from its delivery to the site of action.

e.g. a drug can be 100% absorbed from a given formulation but have nevertheless a low bioavailability due to breakdown after absorption

Factors that influence bioavailability

- **First-pass hepatic metabolism**
- **Solubility of the drug**
- **Chemical instability** → مثل الانسولين
- **Nature of the drug formulation**

First-pass hepatic metabolism



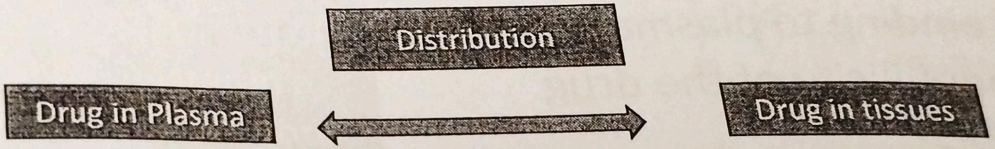
Bioequivalence:

- Two related drug preparations are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations.
- Used to compare generic products with original brands

✓ Differences of **less than 25%** in bioavailability among several formulations of one drug will usually have *no significant effect on clinical outcome* , hence such formulations can be called as bioequivalent.

Distribution

- After reaching plasma, drug has to leave it to be distributed into the interstitial and intracellular fluids



- "Distribution is the dispersion of the drug among the various organs or compartments within the body"

DISTRIBUTION OF DRUGS

- After absorption, drug distributes to
  - Interstetial fluid
  - Intracelluar fluid

❖liver, kidney, brain, and other well-perfused organs receive most of the drug, whereas delivery to muscle, most viscera, skin, and fat is slower

➢The **rate** of delivery and potential **amount** of drug distributed into tissues depend on :

- Cardiac output
- Regional blood flow
- Capillary permeability
- Degree of binding to plasma and tissues protein
- Relative lipophilicity of the drug

➢Well perfused organs **(liver, kidney, brain)** initially receive most of the drug

➢Less perfused organs: (**muscles ,most viscera, skin, and fat)** initially receive less drug

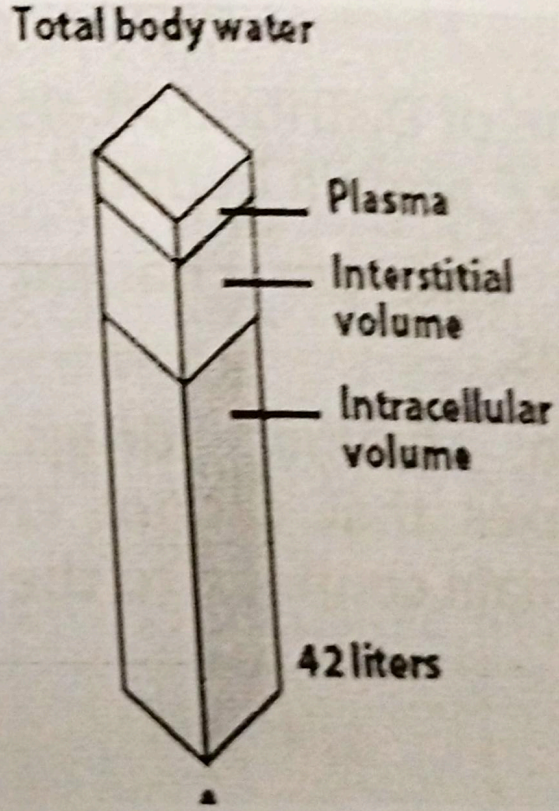
Volume of distribution (V_d)

- Fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma at time zero.

- Importance : it can be useful to compare the distribution of a drug within the volumes of the water compartments in the body

Water presence in various body compartments :

Schematic representation of body water in a 70kg adult. A total of 42 L. Intracellular volume 28L, Interstetial 13 L and plasma about 4L



Vd

- V_d= Dose/ C_p
- Water soluble drugs will reside in the blood, and fat soluble drugs will reside in cell membranes, adipose tissue and other fat-rich areas.
- Drugs distributed mainly in plasma will have lower Vd values compared to drugs distributed mainly in tissues

- Volume of Distribution also relates to whether a drug is Free / protein bound
- Drugs that are charged tend to bind to serum proteins.
- Protein bound drugs form macromolecular complexes that cannot cross biological membranes and remain confined to the bloodstream.