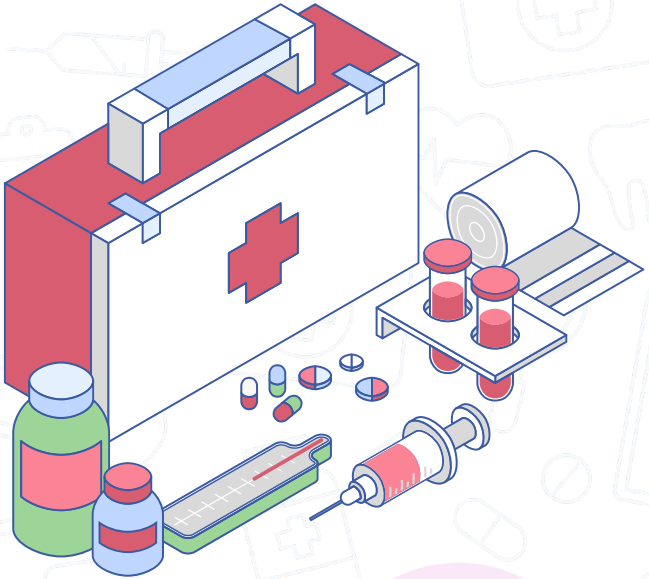
Click for useful **video**!

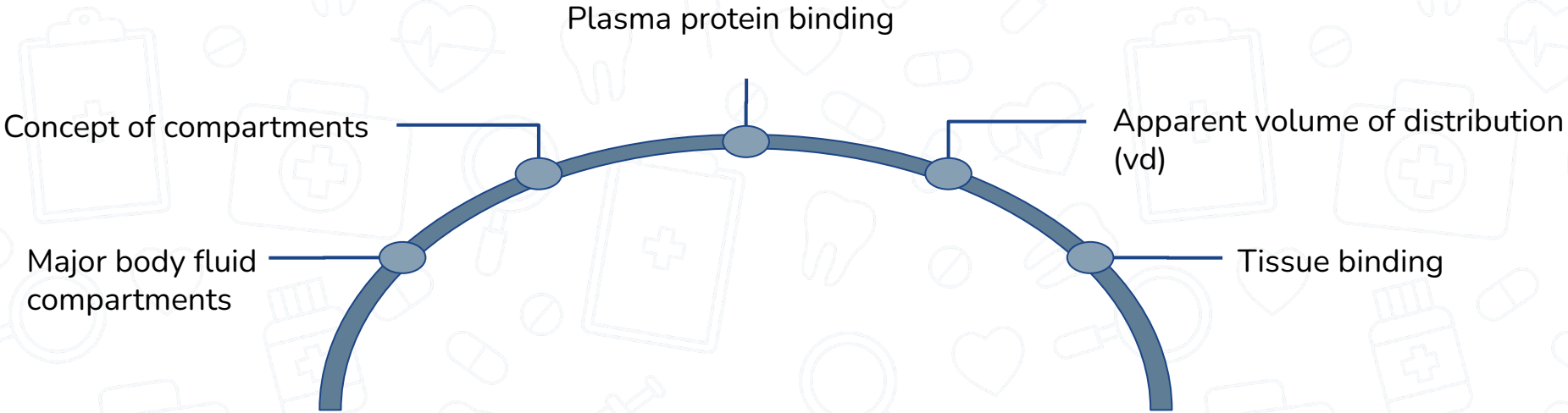
BIOAVAILABILITY AND DISTRIBUTION 442



EDITING FILE

Important
Main text
Male slide
Female slide
Extra info
Doctor notes

OBJECTIVES


Plasma protein binding
Concept of compartments
Apparent volume of distribution (vd)
Major body fluid compartments
Tissue binding

BIOAVAILABILITY

Click for useful **video**!

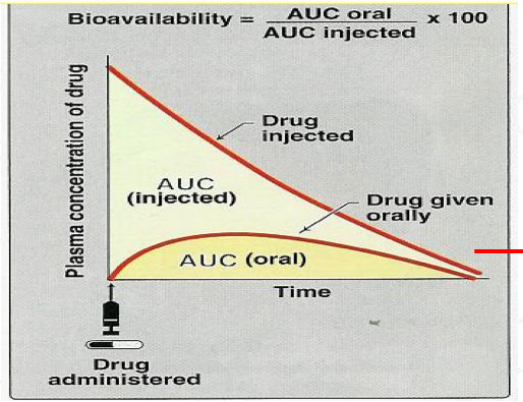
- The amount of **unchanged** drug that enters systemic circulation after administration and becomes available to produce pharmacological actions(treatment)
- Rate and extent of active reaching systemic circulation

Equation : → $\text{Bioavailability (F)} = \frac{\text{AUC (oral)}}{\text{AUC (I.V.)}} \times 100$

AUC = Area Under the Curve

Note: Its the standard because IV rate is (1 or 100%)

Note439:
For drugs administered orally: Bioavailability may be less than 100% for 2 main reasons: **incomplete absorption & first pass metabolism**



Excretion

لما يوصل عند الصفر يعني ان تم امتصاصه ويطلع من الجسم

I.V. provides 100% bioavailability i.e. F= 1

Subcutaneous, intramuscular, oral, rectal, and other extravascular routes of administration require that the drug be absorbed first, which can reduce bioavailability

BIOAVAILABILITY

ABSOLUTE

Note: With standard

The bioavailability of a drug after administration by any route is **compared to its intravenous standard** formulation.

Note439: Generic formulation is the actual name of a drug e.g Paracetamol

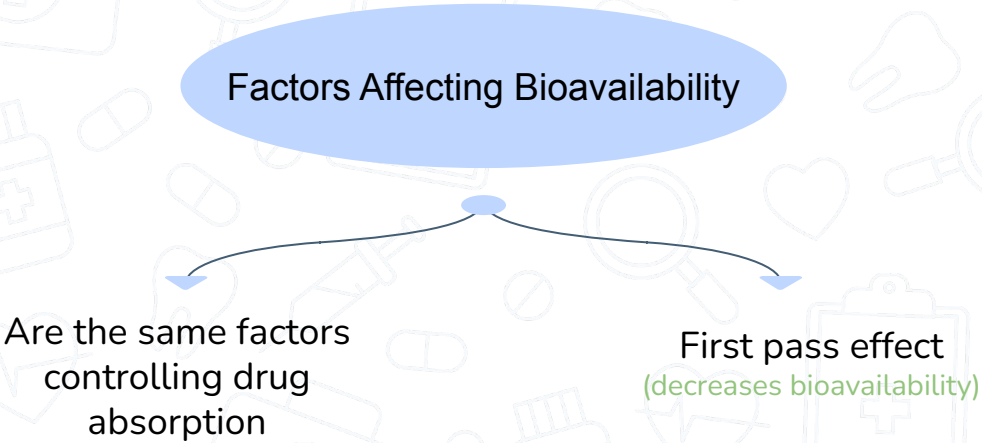
RELATIVE

- Is determined when two products are compared to each other **not to an intravenous standard.**
- This is commonly calculated in the drug industry to determine that the generic formulation is **bioequivalent** to another formulation
- **Bioequivalent = Same bioavailability**
- **E.g** **Tylenol** (paracetamol 500 mg) compared to **Panadol** (paracetamol 500 mg)
- Relative bioavailability Is important to get an idea of how different formulation or routes of administration differ in their bioavailability

BIOEQUIVALENCE

Two pharmaceutical products are **bioequivalent** when the rate and extent of bioavailability of active ingredients in two product are the same

Dosage adjustment is required when changing formulation or routes of administration .



no need to remember any drug name

FACTORS AFFECTING ABSORPTION

(GIRLS' SLIDES)

1-Route of administration

2-Dosage forms (depending on particle size and disintegration, ease of dissolution).
(suspension > capsule > tablet)

3-Molecular weight of drugs

4-Lipid solubility

5- Degree of ionization

6-Drug solubility (aqueous preparation better than oily, suspension preparations)

7-Chemical instability in gastric pH
(Penicillin & insulin)

8-Surface area available for absorption.
- small intestine has large surface area than stomach due to intestinal microvilli.

9-Blood flow to absorptive site
- **greater** blood flow increases bioavailability
- Intestine has **greater** blood flow than stomach

10-Intestinal motility (transit time)
- Diarrhea reduce absorption

11- Gastric emptying
- drugs that increase gastric emptying enhances absorption (metoclopramide). To be adsorb in the intestinal

12-Drug interactions

13-Food
- **Slow** gastric emptying
- generally slow absorption
- Tetracycline, aspirin, penicillin
- **A fatty meal** increase the absorption of fat soluble antifungal drug (e.g. griseofulvin)

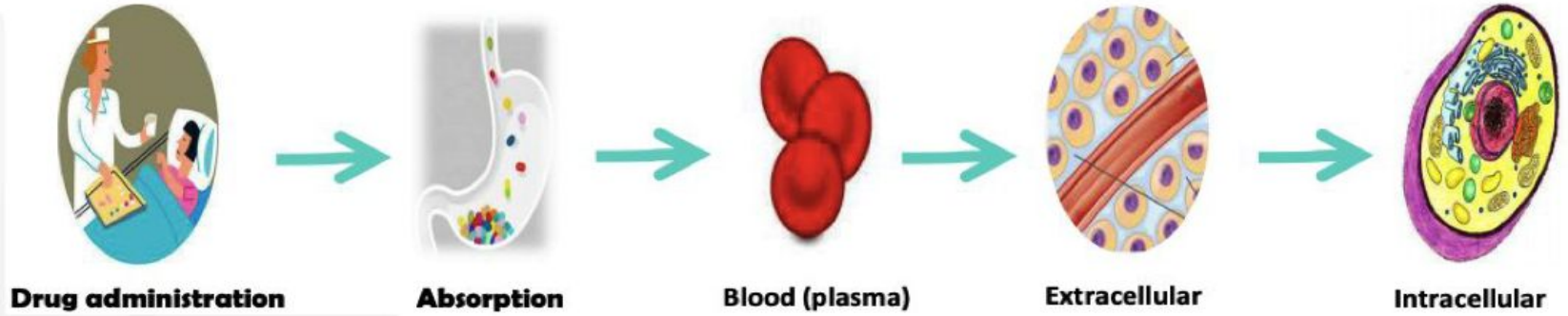
DISTRIBUTION

Is the process by which drugs leave blood circulation and enters the interstitium and/or the cells of the tissues. Distributed either intracellular or extracellular

- Lipid soluble drugs are distributed in the intracellular region. Because they can cross the cell membrane

- Water soluble drugs are distributed in the extracellular region. Because they can not cross the cell membrane . Med439

Note: Not necessary to pass through all stages may stop at the stage of blood only



APPARENT VOLUME OF DISTRIBUTION (VD)

Apparent Volume of Distribution (Vd) : Is the ratio of drug amount in the body (dose) to the concentration of the drug in blood .

$$Vd(L) = \frac{\text{dose (mg)}}{\text{Plasma concentration (mg/L)}}$$

Explanation:
-Drug A: (100mg dose) Has high Molecular weight so it will stay in the plasma

Plasma concentration ↑ Vd ↓

-Drug B: (100mg dose) low molecular weight and lipid soluble so it will go into the tissue

Plasma concentration ↓ Vd ↑

Note: drugs which are in other compartments (extracellular or intracellular) are not available for metabolism, they should come in the plasma to be metabolized by the liver and excreted by the kidney

Why is Vd important ?

- To calculate loading dose الجرعة الاولى
- Large Vd mean long duration of action .

Loading dose is the large initial dose That is given to achieve rapid therapeutic plasma level

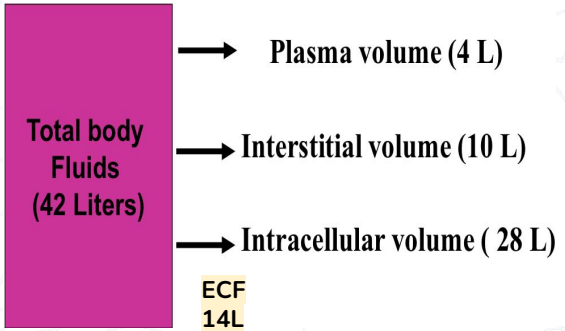
Note: when (Vd) is inside the plasma blood it will decrease due to metabolic reactions, but (Vd) will be high inside cells and organs. med439

APPARENT VOLUME OF DISTRIBUTION (VD)

The major body fluid compartment are	
extracellular fluid(22%)	intracellular fluid (35%)
1-Plasma (5% of body weight =4L) 2-Interstitial fluid (16%=10L) **14L**	Fluid present inside all cells in the body (28L)

percentage Is not important

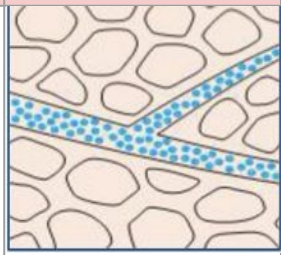
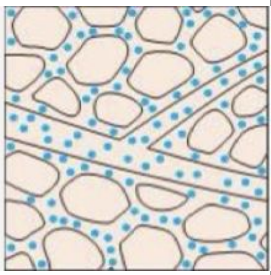
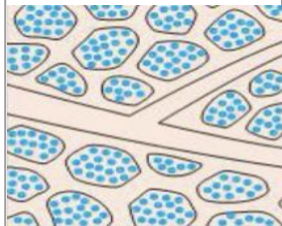
But Important to know :
1- intracellular **more than** extracellular
2- must to know **L**



Extra information : ECF is 22% of the body fluids the plasma(5%) and interstitial fluids(16%) = 22% (اللي يوصلها drug)
The remaining 1% is for TCF (Transcellular fluids)

Very important slide

Drugs may distribute through:

Compartment	Distribution through	Volume of distribution (Vd)	Drug characteristics	Crossing	Example	Picture
One Compartment	**Plasma (Trapped in blood)**	around **4 L** (Very low because of high molecular weight)	**Very high molecular weight drugs**, or drugs that bind to plasma proteins	**Can not** move across endothelial cells of capillaries (due to **high molecular weight**)	Heparin 4L (Anticoagulant)	
Two Compartments Inside capillary	**Extracellular fluid**	between **4 and 14 L**	Drugs that have a **low molecular weight** but are **hydrophilic** (Not lipid soluble)	Can pass through endothelium into interstitial fluids **BUT can not cross cell membranes to intracellular fluids.** (because its **hydrophilic**)	Atracurium 11L (muscle relaxant)	
Multi Compartments	**Total Body Water (Extracellular & Intracellular fluid) Diffusion to intracellular fluid**	**For Lipid soluble drugs** a) Vd = Total Body Water **Drugs that bind strongly to tissues** b) Vd > Total Body Water		Difusion to intracellular fluid (can pass through membranes because it's **lipid soluble**)	a) Ethanol 38 L b) Digoxin 385 L	

No need to remember any drug name

Volume of distribution (Vd)

Drugs With **Low Vd**

These types of drugs are safe for pregnant women to use because they can not cross to placental barrier

- distributed in extracellular compartments (plasma & interstitial fluid).
- **Polar comp** or **lipid insoluble** drugs. e.g. gentamicin, atracurium
- **High MW** (molecular weight) e.g. heparin – insulin.
- **High plasma protein binding** e.g. warfarin (anticoagulant).
- **Do not cross BBB** (Blood Brain Barrier)or **placental barriers.**

Note: Drugs that cross the blood brain barrier, will cross placental barrier and vice versa. Med(439)

Drugs With **High Vd**

-Low molecular weight
-Free drugs (not bounded to plasma proteins)

- Have **higher concentrations in tissues** than in plasma.
- **Lipid soluble.**
- Distributed **intracellularly**
- e.g. digoxin, phenytion, morphine (يستخدمونهم لعلاج الصرع و التشنجات)

Factors Affecting Distribution

1-Cardiac output and blood flow

- The greater the blood flow to tissues, the more distribution that occurs from plasma to interstitial fluids.
- Drugs distribute more rapidly to brain, liver & kidney > more than skeletal muscles & fat

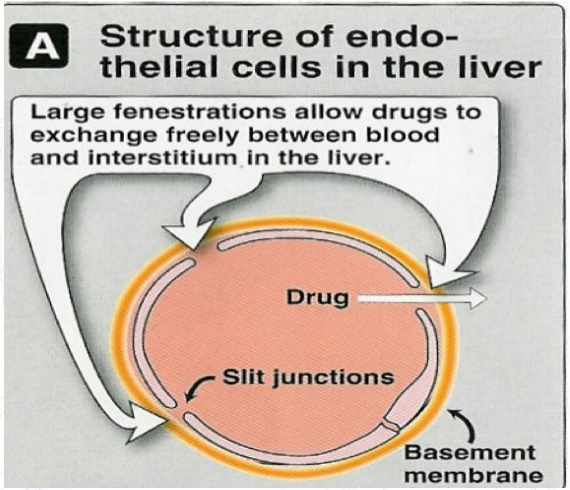
2-Physical and chemical properties of the drug

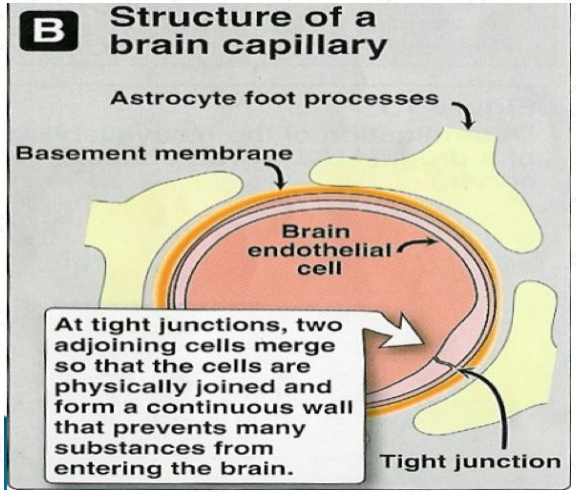
- Molecular Weight
- PKa
- Lipid Solubility
  - Hydrophilic drugs (Ionized, Charged, Polar) do not readily cross cell membranes but go through slit junctions in endothelial cells of capillaries
  - Most lipid soluble drugs (unionized, uncharged, nonpolar) cross biological membranes

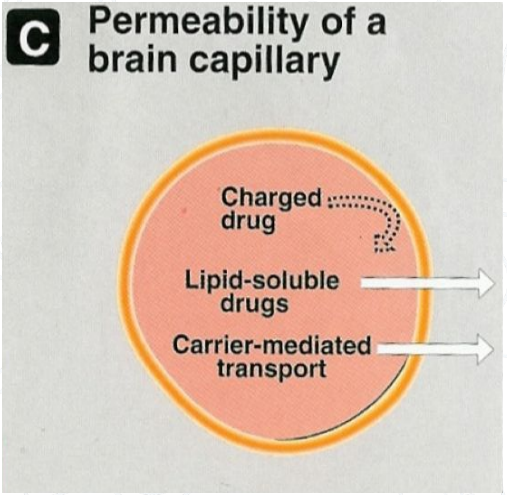
3-Capillary permeability

- Endothelial cells of capillaries in tissues other than brain have wide slit junctions allowing easy movement, permeation and distribution.
- Blood brain barrier (BBB):
  - Brain has tight junction Blood Brain Barrier(BBB).
  - Only lipid soluble drugs or actively transported drugs can cross BBB.
  - Hydrophilic drugs (ionized or polar drugs) cannot cross BBB.
  - Inflammation as in meningitis (التهاب السحايا) increase permeability to hydrophilic drugs
    - e.g. penicillin & gentamycin
- Placental barrier
  - Lipid soluble drugs can cross placental barrier and enter the fetal blood.

CAPILLARY PERMEABILITY







Note 439; Slit junctions are seen in this pic

Note 439: No slit junctions. The molecule has to **diffuse** through the membrane (has to be hydrophobic) or it has to be transported **through carriers**

Factors Affecting Distribution (Binding of Drugs)

4)Plasma protein binding

(VD عكسية مع)

Plasma Proteins:

Albumin
Has affinity for acidic drugs as warfarin, phenytoin, aspirin

Alpha 1-acid glycoprotein
Has affinity for basic drugs (cationic) as diazepam, quinidine.

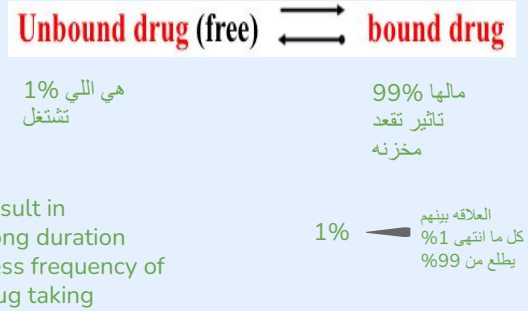
- Extensive & strong plasma protein binding eg. Albumin will cause more drug to stay in the blood compartment. Therefore,they tend to have lower distribution (Vd).

- In blood, drugs exist in two forms bound and unbound forms in equilibrium Bound drugs become free when the unbound drugs run out (so it's as if they are stored while bound to proteins, and they come out when there is a demand)

5)Tissue binding

(VD طردية مع)

- Drugs can bind to specific tissues and will have high volume of distribution (Vd). (because the plasma concentration will be low therefor Vd will be high)
E.g. Tetracycline binds to bone (teeth-ca)



Important slide

Bound form of drug	Unbound form of drug (Free)
non diffusible form	diffusible form
can not cross endothelial barrier	cross endothelial barrier
can not combine with receptors	combine with receptors
inactive	active Cross any membrane
not available for metabolism & excretion	available for metabolism & excretion
has long duration of action (t ½)	has short duration of action (t ½). عطى تاثيره وطلع

CHARACTERS & CONSEQUENCES OF BINDING

- Usually reversible

- determines volume of distribution (vd)

- Slows drug metabolism & excretion

- Prolongs duration of drug action (t1/2).

- Result in clinically important drug interactions.

Displacement

Competition for the same binding site on the plasma proteins may occur between two drugs, displacement of one drug & increasing its concentrations & effects.

Aspirin + Albumin-warfarin →

Albumin-aspirin + free warfarin → bleeding.

Explanation: Replacement of warfarin by aspirin will cause an abundance of free warfarin (anticoagulant) in the blood circulation and that will lead to bleeding.Med439

Extra info: The reason for displacement is the difference in protein affinity to drugs. The affinity of albumin to aspirin is higher than the affinity of albumin and warfarin. That's why when aspirin is freely present in the circulation. It throws warfarin out of albumin and binds to it instead.Med439

MCQ

Q-1 Lipid soluble drugs are distributed in : *{from Med39}*
A)Extracellular region B)Intracellular region C) Plasma D)Interstitial fluid
Q-2 which compartment has more fluid ? (From the Dr)
A)Extracellular fluid B) Plasma C) Intracellular fluid.
Q-3 An unbound form of drug is ? *{from Med39}*
A) Diffusible. B)Inactive. C) Non Diffusible. D) Has long t(½)
Q-4 If a root of administration has 100% Bioavailability. F would be ? *{from Med39}*
A) F > 1 B) F <1 C) F = 100 D) F = 1
Which compartment has 14L ? (From the Dr)
A) One B) two C) three D) multi

1-B
2-C
3-A
4-D
5-B

SAQ

Q-1 What are the characters of an unbound form of drug?

Q-2 Name 3 factors affecting distribution.

Q-3 why VD is higher than TBW in Intracellular (compartment multi) ? (from the Dr)

Answers

1- Diffusible, active, can cross endothelial barrier, has short (t1/2)

2- Capillary permeability, plasma protein binding & tissue binding.

3- drugs will bind strongly with tissue

DONE BY THE AMAZING TEAM

You GOT THIS!

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