Lecture (2)

Bioavailability and distribution

pharmacology
Team 438

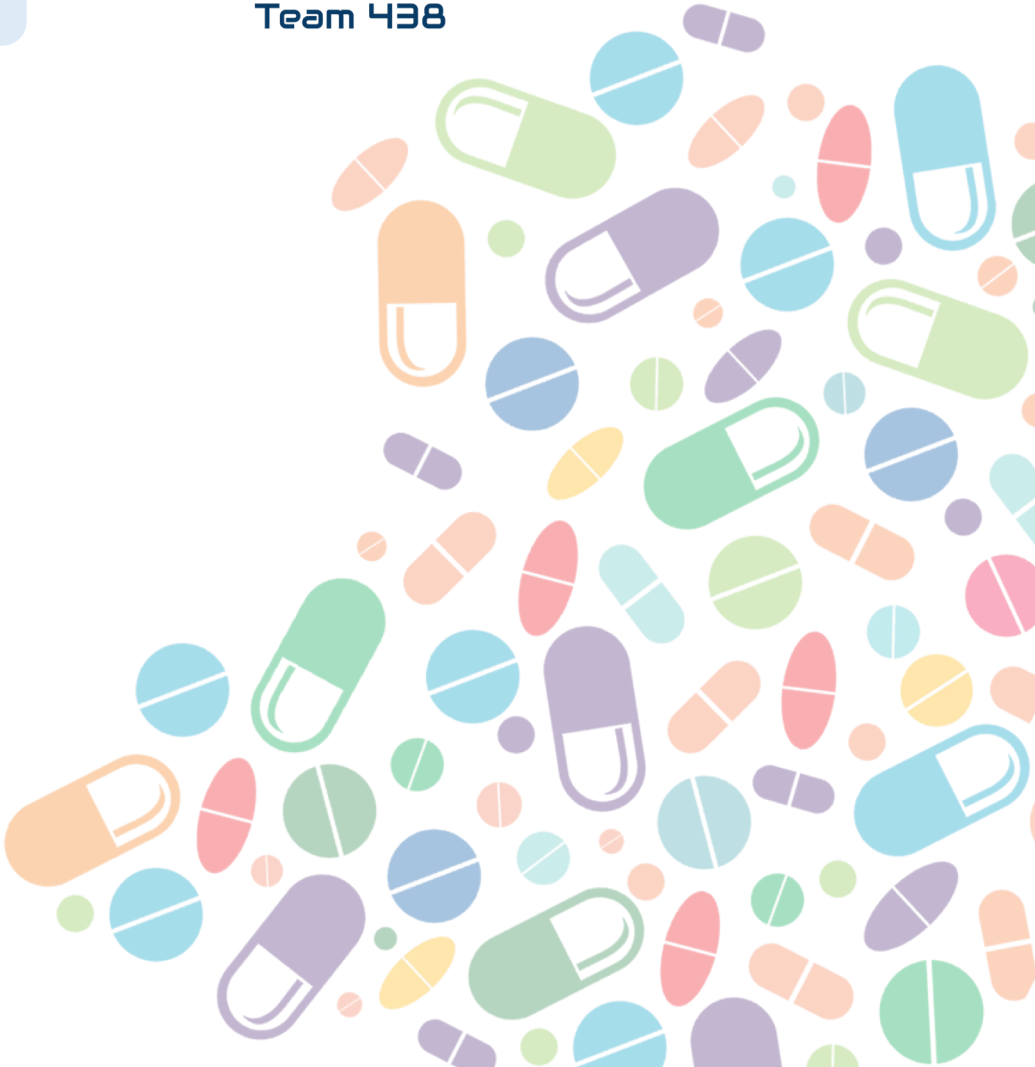
MED438
KING SAUD UNIVERSITY

- Red : important
- Black : in male / female slides
- Pink : in girls slides only
- Blue : in male slides only
- Green : notes, Extra

Editing File:

https://docs.google.com/document/d/1WvdeC1atp7J-ZKWOUSukSLsEcosjZ0AqV4z2VcH2TA0/edit?ts=5bb8d759

Reviewed by Razan AlRabah & Khalid Alkhani



Objectives:

- Major body fluid compartments
- Concept of compartments.
- Apparent volume of distribution (Vd).
- Plasma protein binding.
- Tissue binding.

Bioavailability :

Is the amount of unchanged drug that enters systemic circulation after administration and becomes available to produce pharmacological actions. (rate and extent of active reaching systemic circulation)

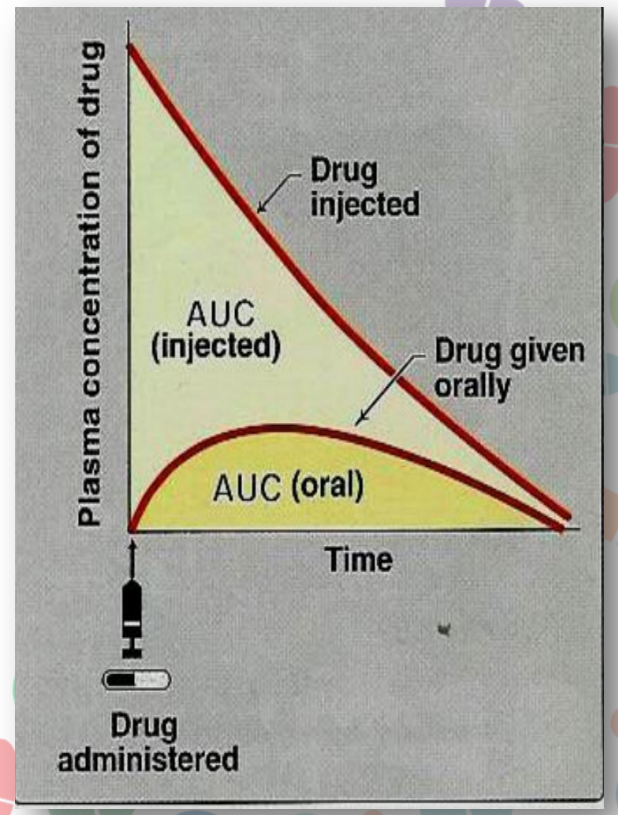
Factors affecting Bioavailability:

1.Same factors affecting Absorption MW, dosage forms, drug solubility, etc.
2.First Pass Metabolism

$$\text{Bioavailability(F)} = \frac{\text{AUC (Oral) or rectal or sublingual or I.M etc..}}{\text{AUC (I.V)}} \times 100$$

AUC = Area Under Curve

- I.V. provides 100% bioavailability
  i.e. F= 1.
- Subcutaneous, intramuscular, oral, rectal,
  and other extra vascular routes of administration require
  that the drug be absorbed first, which can reduce bioavailability



Bioavailability

Absolute (FA)

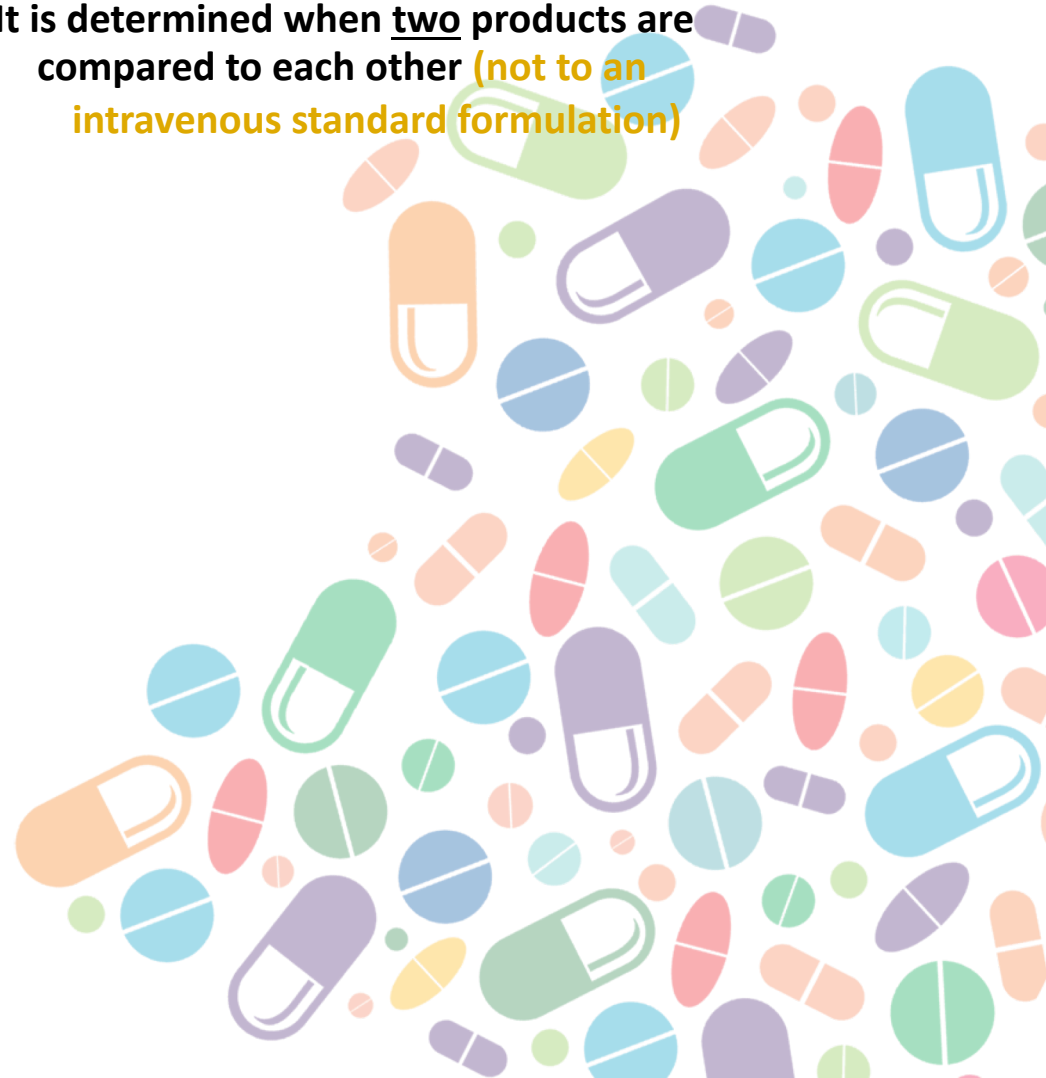
The bioavailability of a drug after administration by any route is compared to its intravenous standard formulation

Relative (FR)

It is determined when <u>two</u> products are compared to each other (not to an intravenous standard formulation)

Relative Bioavailability:

- This is commonly calculated in the drug industry to determine that the generic formulation is bioequivalent to another formulation.
- Example: Tylenol (Paracetamol 500g) compared to Panadol (Paracetamol 500g).
- It is important to get an idea of how different formulations or routes of administration differ in their bioavailability.
- Dosage adjustment is required when changing formulations or routes of administration.



Bioequivalence

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

Distribution

-Is the process by which drugs leave blood circulation and enter the Interstitium and/or the cells of the tissues.

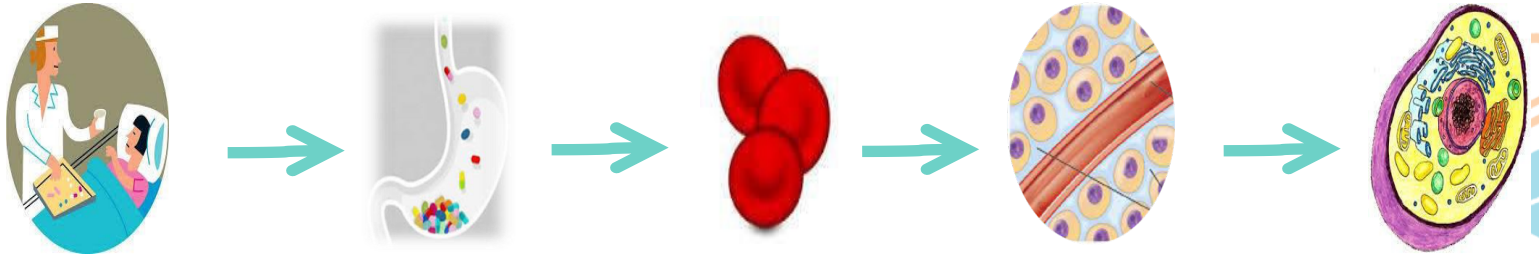
-Apparent Volume of Distribution (VD): is the ratio of drug amount in body (dose) to the concentration of drug in blood.

$$Vd\ (L) = \frac{\text{Dose (mg)}}{\text{Plasma Concentration (mg/L)}}$$

If plasma conc. > Dose
then the conc. of the drug in the blood is high
and VD is low

Vd is important to:

1. Calculate the loading dose
2. Predict the duration of action:
   - High Vd means long duration of action.
   - Low Vd means short duration of action.



Drug administration → **Absorption** → **Blood (plasma)** → **Extracellular** → **Intracellular**

Major body fluid compartments

Intracellular fluid (35%)

Fluid present inside all cells in the body (28 L).

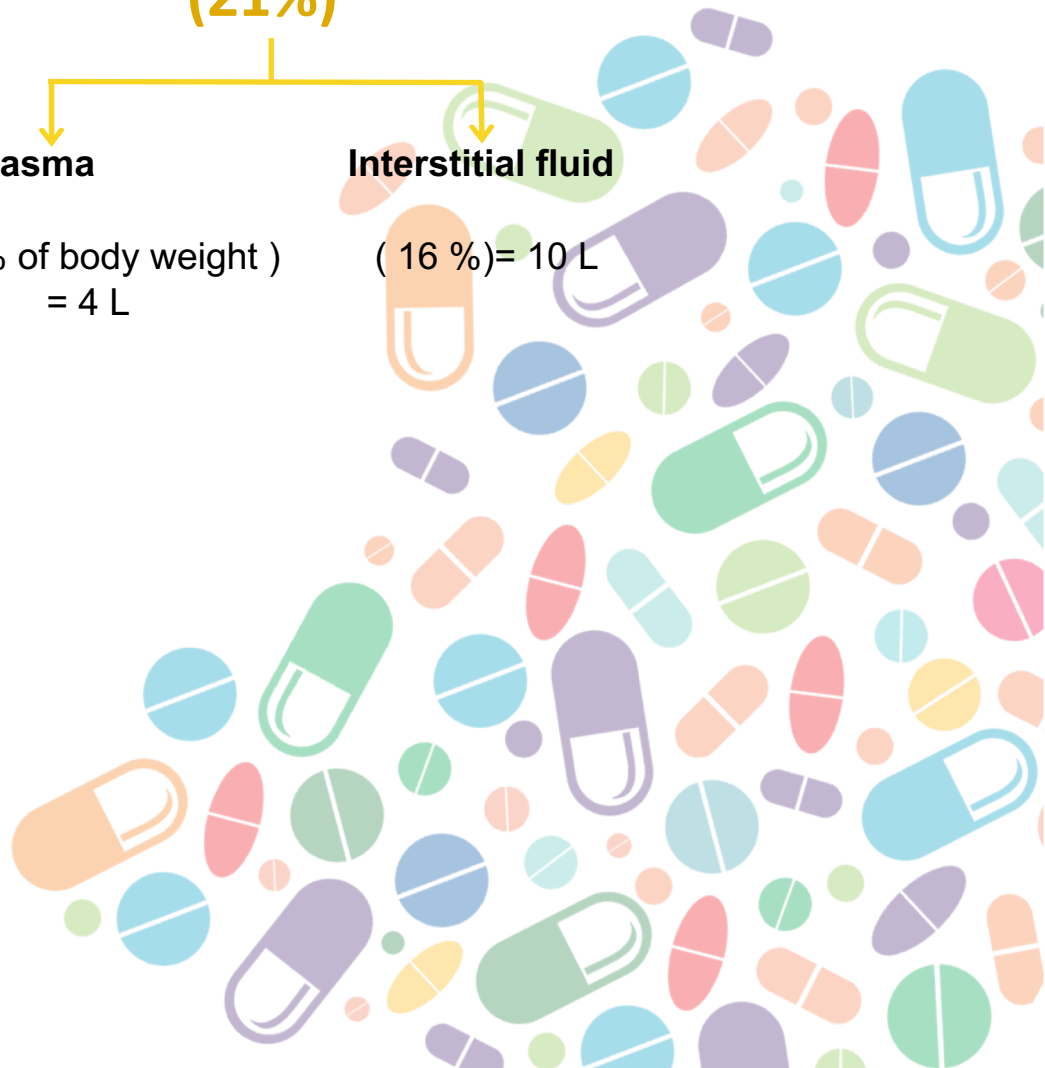
Extracellular fluid (21%)

Plasma

(5 % of body weight) = 4 L

Interstitial fluid

(16 %)= 10 L



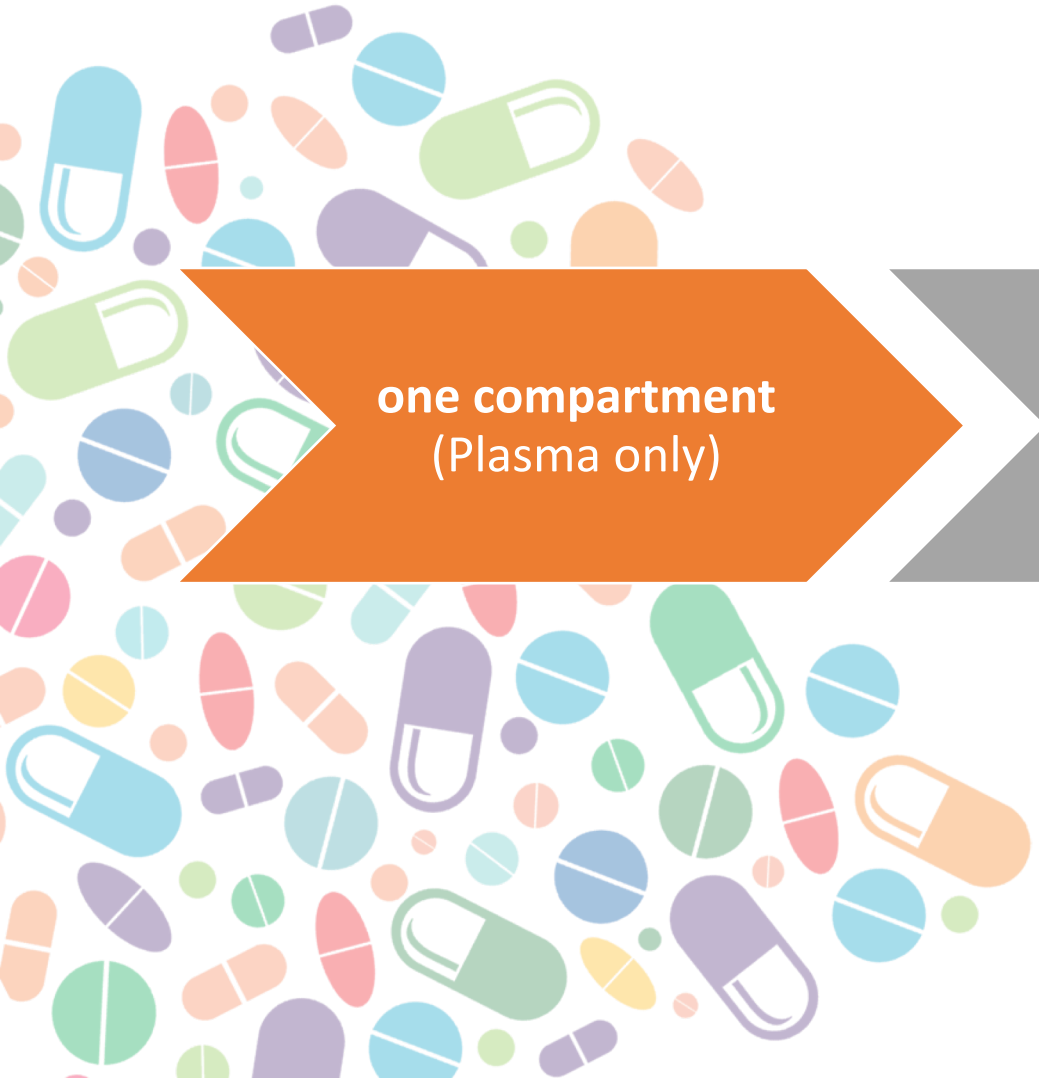
Cases for drug distribution:

Case 1: The drug stays in the blood. In this case the drug is in one compartment (plasma compartment).

Case 2: It crosses the endothelial cells of the capillaries and the drug reaches the interstitial fluids surrounding the cell BUT it does not enter the cell yet. It is considered two compartments and we say (extracellular) around the cells.

Case 3: It enters the cells and in this case it's considered multi compartments (intracellular+Extracellular).

Drug may be distributed through:



one compartment
(Plasma only)

Two compartments
(Plasma + interstitial fluid = Extracellular)

Multi compartments
(Extracellular + Intracellular)

Distribution

	Plasma compartment	Extracellular compartment	Intracellular + Extracellular compartment
VD	4 L	4 – 14 L	Equal to total body fluids or might be higher 42 ≥ L
Properties	▪ High molecular weight drugs ▪ Drugs binding to plasma proteins	Drugs with Low molecular weight but are hydrophilic	▪ Lipid soluble drugs (hydrophobic) ▪ Drugs that bind strongly to tissues (have Vd > TBW)
Distribution	Cannot move across endothelial capillaries (trapped in the blood)	Pass endothelium into interstitial fluid BUT can not cross cell membrane to intracellular fluids	Pass the cell membrane and enters the cell
Example	Heparin 4 L	Atracuronium 11 L	Digoxin (385 L) > TBW Ethanol (34-41 L) =TBW

Drugs with low Vd:

- Distributed in extracellular compartments (plasma & interstitial fluid).
- Polar Compound or Lipid insoluble drug e.g. **Gentamycin** and **Atracuruim**
- High molecular weight drugs e.g. **heparin** – **insulin**
- High plasma protein binding e.g. **warfarin** (anticoagulant)
- Do not cross BBB or placental barrier (BBB = Blood Brain Barrier)

Drugs with high Vd:

- They have higher concentration in tissue than in plasma
- Lipid Soluble
- Distributed Intracellularly
- Example: **Digoxin**, **Phenytion** and **Morphine**.

Factors that mainly affect Distribution:

- **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 and kidney than skeletal muscles & fat)

- **Capillary Permeability.**

  Endothelial cells of capillaries in tissues other than brain have **wide slit junctions** allowing easy movement, permeation and distribution. (Brain has tight junctions -Blood Brain Barrier-)

- **Physical & Chemical properties of the drug:**

  -Molecular weight.

  -Pka (Acidic or basic)

  -Lipid solubility:

  Most lipid soluble drugs (unionized, uncharged, non-polar) cross biological membranes.
  Hydrophilic drugs (ionized, charged, polar) do not readily cross membranes but go through slit junctions in endothelial cells of capillaries.

- **Plasma protein binding** علاقة عكسية مع VD
- **Tissue binding** علاقة طردية مع VD

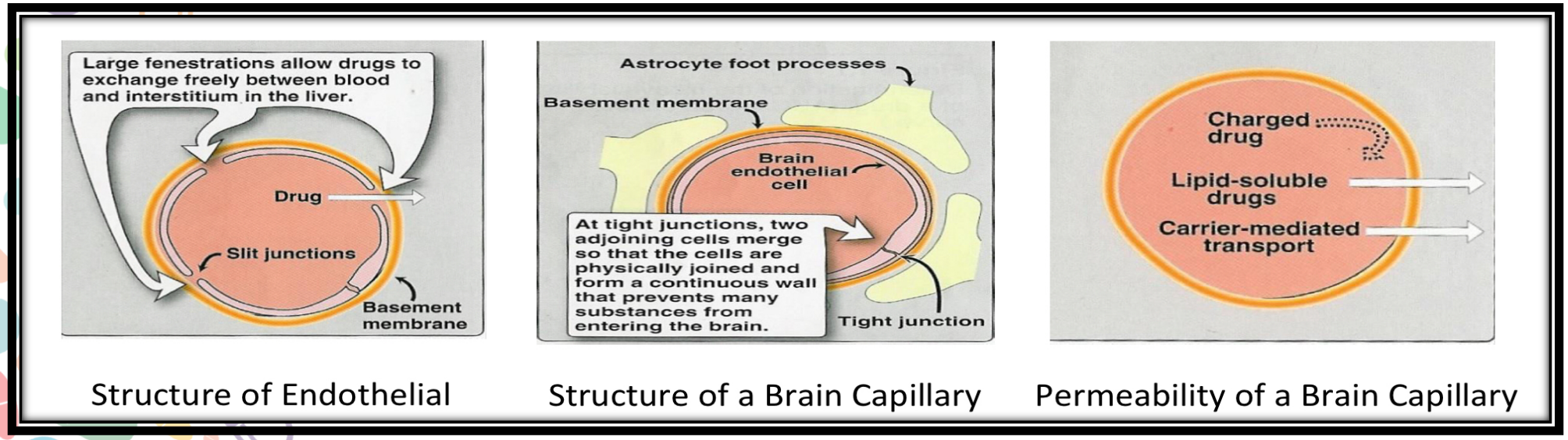
Blood brain barrier (BBB)

- Only lipid soluble (hydrophobic) drugs or actively transported drugs can cross BBB.

- Hydrophilic (ionized, polar Drugs) can't cross BBB However inflammation as meningitis increases the permeability to hydrophilic drugs E.g. penicillin and gentamycine.

Placental barrier

- Lipid soluble drugs can cross placental barrier and enter the fetal blood.



Binding of drugs

Plasma protein binding

- Extensive plasma protein binding will cause more drug to stay in the blood compartment, Therefore, drugs which bind strongly to plasma protein tend to have lower distribution (Vd).
- In blood, drugs exist in two forms bound and unbound (**free form**) forms in **equilibrium** .

(When the free form of drug is consumed, a portion of the bound drug is converted into free form, so the drug can complete its action).

Examples of plasma protein :

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

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

Tissue binding :

Drugs can bind to specific tissues and will have high volume of distribution (Vd).

Ex. **Tetracycline bind to bone**

Drugs binding to Plasma proteins = decrease in its Vd

Drugs binding to Tissues = increase in its Vd

Bound and unbound forms of drugs:

Bound Form	Unbound Form
Non diffusible form	Diffusible form
Can not cross endothelial Barrier	Cross endothelial barrier
Can not combine with Receptors	Combine with receptors
Inactive (Cannot produce pharmacological action)	Active (Can produce pharmacological action)
Not available for Metabolism & exertion	Available for metabolism & Excretion
Has long duration of Action (t ½)	Has short duration of Action (t ½)

Characters & consequences of Binding:

- **Usually reversible** (When unbound form of drug is consumed, bound form is reversed or converted to unbound form(**Free form**).
- **Determines volume of distribution (Vd).**
- **Slows drug metabolism & excretion.**
- **Prolongs duration of drug action (t ½).**
- **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

NOTE:
Aspirin has a higher binding capacity than the **warfarin**.
Free form of the drug is what causes the side effects. (In this case bleeding).

SUMMARY

The drug	vd	BBB	Placental barrier	Albumin (acidic drugs)	alpha 1 -acid glycoproteins (basic drugs)	TISSUE BINDING
Digoxin	385 L	THE DRUG IS LIPID SOLUBLE.		-----		Yes
Ethanol	38 L	THE DRUG IS LIPID SOLUBLE.				No
atracurium	11 L	THE DRUG IS HYDROPHILIC BUT HAS LOW MOLECULAR WEIGHT.				No
warfarin	LOW VD	NO	NO	YES		No
insulin	LOW VD	IT HAS A HIGH MOLECULAR WEIGHT SO IT CAN NOT BE DIFUSED TO BBB OR PLACENTAL BARRIER.				No
heparin	LOW VD	IT HAS A HIGH MOLECULAR WEIGHT SO IT CAN NOT BE DIFUSED TO BBB OR PLACENTAL BARRIER.				No
Phenytoin	HIGH VD	THE DRUG IS LIPID SOLUBLE.		YES		
morphine	HIGH VD	THE DRUG IS LIPID SOLUBLE.				
gentamycin	LOW VD	THE DRUG IS HYDROPHILIC				No
penicillin	LOW VD	THE DRUG IS HYDROPHILIC				No
quinidine					YES	
diazepam					YES	
Tetracycline						YES with bone
aspirin				yes		

Quiz (MCQ) :

Q1.Which one of these drugs does not require to be absorbed ?

A)Oral B)intravenous C)rectal

Q2.A drug is distributed through 2 compartments is found in ? From 437

A)Plasma B)ICF C)ECF

Q3.Drugs with very high molecular weight are most likely to be found in ?

A)Plasma B)interstitial fluid C)ICF

Q4.A drug with large Vd mean that the drug has ?

A)Short duration of action B)Long duration of action C)No action

Q5.The Vd for Ethanol is ?

A)45 B)38 C)27

Q6.Drugs are distribute rapidly to ?

A)Kidney B)Fat C)Skeletal muscle

Q7.Tetracycline drug bind to ?

A)Heart B)Muscle C)Bone

ANSWER : 1)B - 2)C - 3)A - 4)B - 5)B - 6)A - 7)C

Quiz (SAQ) :

Q1.When the rate and extent of bioavailability of active ingredients in two products are the same the two pharmaceutically products called ?

Q2.What are the factors that affect the bioavailability ?

Q3.What is the ratio of drug amount in the body (dose) to the concentration of drug in blood ?

Q4.How many compartments the drug with low molecular weight may distribute with?

Q5.Give an example to a drug with high Vd ?

Q6.What type of drugs that do not readily cross membranes ?

Q7.What type of drugs that can cross the blood brain barrier (BBB)?

Q8.Give an example to a plasma protein has affinity for acidic drugs ?

Q9.Which type of drug bindings will have high volume of distribution (Vd)?

10.What can the inflammation as in meningitis cause to the permeability of the drug?

1. Bioequivalent 2. same factor controlling absorption + first pass effect 3. apparent volume of distribution 4. two compartments 5. digoxin, phenytion, morphine 6. Hydrophilic drugs (ionized, charged, polar) 7. lipid soluble drugs or actively transported drugs 8. Albumin 9. Tissue binding 10. increase permeability to hydrophilic drugs

Good luck

Thanks to the pharma team 435

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