جامعة الملك سعود
King Saud University

PHARMACOLOGY

Team 434

Foundation Block

2- Bioavailability and Distribution

Color Index

Red: Important Notes.

Orange: Further Explanation.

Purple: Additional Notes.

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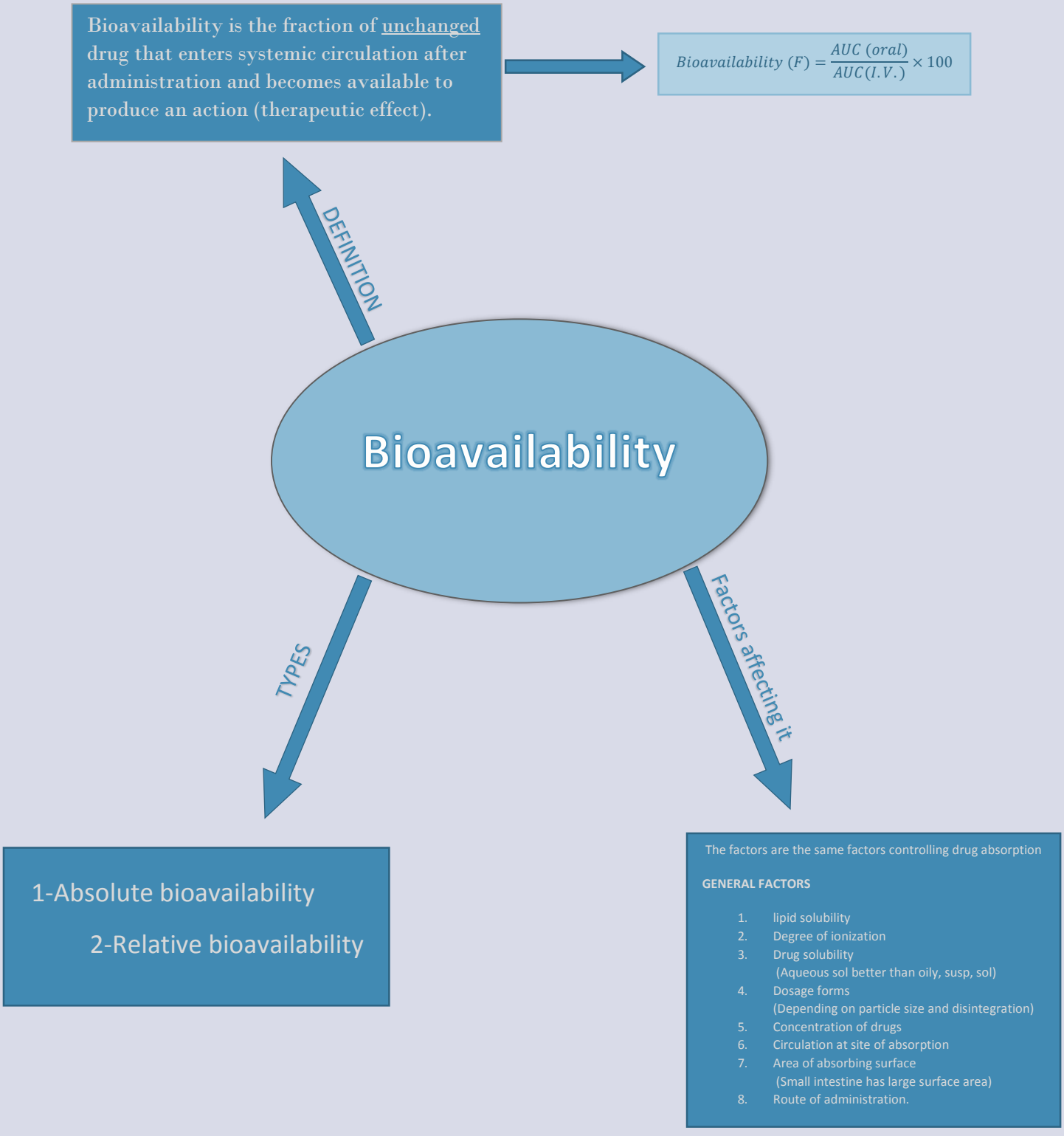
Objectives

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


Bioavailability is the fraction of unchanged drug that enters systemic circulation after administration and becomes available to produce an action (therapeutic effect).
$Bioavailability\ (F) = \frac{AUC\ (oral)}{AUC\ (I.V.)} \times 100$
DEFINITION
Bioavailability
TYPES
Factors affecting it
1-Absolute bioavailability
2-Relative bioavailability
The factors are the same factors controlling drug absorption
GENERAL FACTORS
1. lipid solubility
2. Degree of ionization
3. Drug solubility
(Aqueous sol better than oily, susp, sol)
4. Dosage forms
(Depending on particle size and disintegration)
5. Concentration of drugs
6. Circulation at site of absorption
7. Area of absorbing surface
(Small intestine has large surface area)
8. Route of administration.

	Absolute Bioavailability	Relative Bioavailability
Definition	The bioavailability of a drug after Administration by any route is compared to its Intravenous (I.V.) standard formulation.	It is determined when two products are compared to each other, not to an intravenous standard.
Compare	A drug compare to the I.V. route of the same drug E.g. (oral & I.V.)	Same drugs Same dosage different companies. E.g. (**Tylenol** & **Panadol**)

Notes:

- 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
- Relative bioavailability is important to get an idea of how different formulations or routes of administration differ in their bioavailability.
- This is commonly calculated in the drug industry to determine that the generic formulation is bioequivalent to another formulation.

Intro to Bioavailability: http://youtu.be/W8aVzlXPgCQ

Bioequivalence

- Two drug products are considered to be bioequivalent when the rates and extents of bioavailability (F) of the two products are not significantly different under suitable test conditions.
- Drug X has bioavailability 85% and Drug Y has bioavailability 80% ; Drug X & Drug Y are bioequivalent because there is no a big deference between their bioavailability .

Rate and Extent

- means the amount of drugs and the time required reaching the systemic circulation.

DISTRIBUTION

DEFINITION

It is the process by which drugs leave blood circulation and enters the interstitium and/or the cells of the tissues.

Factors affecting it

1. Cardiac output and blood flow.
2. Physiochemical properties of the drug.
3. Molecular weight
4. Pka.
5. Lipid solubility.
6. Capillary Permeability
7. Plasma protein binding
8. Tissue binding.

Dose of drug administered.

ABORPTION

Drug concentration in systemic circulation.

DISTRIBUTION

Drug in tissues of distribution.

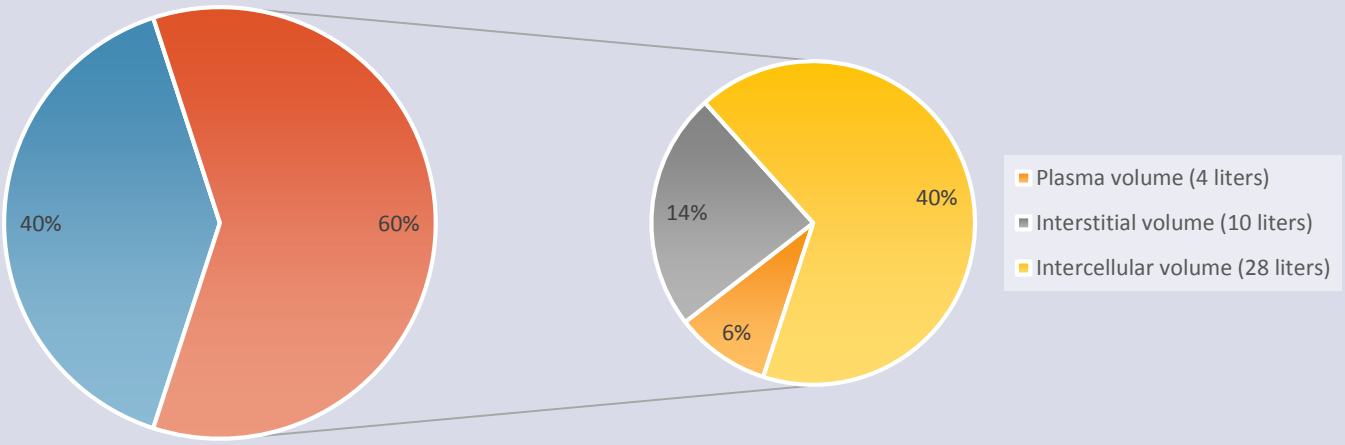
Apparent Volume of Distribution (VD)

It is the ratio of drug amount in the body to the concentration of drug in blood

$$Vd\ (L) = \frac{Dose\ of\ the\ drug\ (mg)}{Concentration\ in\ blood\ (mg/L)}$$

TOTAL BODY FLUIDS

(60% of body weight in 70-kg individual)



Drugs with **high** Vd	Drugs with **low** Vd
Have higher concentrations in tissues than in plasma.	Confined to plasma & interstitial fluid.
Distributed in intracellular	Distributed in extracellular compartments.
Relatively lipid soluble.	Polar comp or lipid insoluble drugs
Not efficiently removed by haemodialysis.	Do not cross BBB or placental barriers.
e.g. phenytion, morphine, digoxin	High MW e.g. heparin – insulin. High plasma protein binding e.g. warfarin.

Notes:

- Large Vd = means long duration of action
- Some drugs remains on our body for a long time because it is lipid soluble.

BLOOD FLOW TO ORGANS

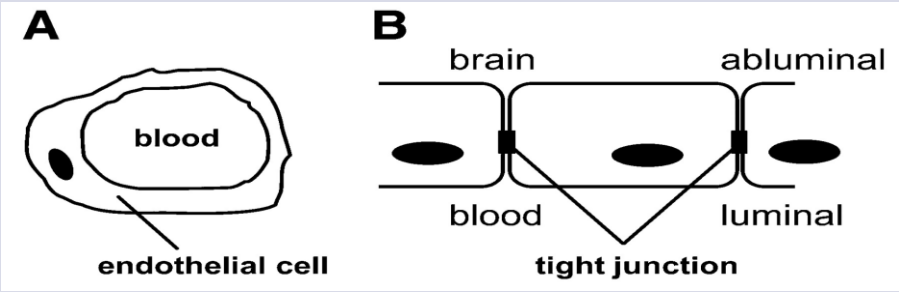
- The greater the blood flow to tissues, the more distribution that occurs from plasma to interstitial fluids.
- Drugs distribute more rapidly to brain, liver and kidney > more than skeletal muscles & fat.

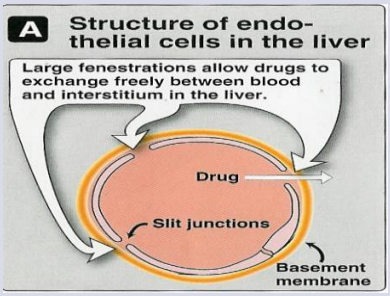
PHYSIOCHEMICAL PROPERTIES

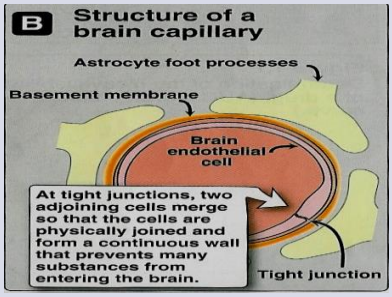
- Most lipid soluble drugs cross biological membranes
- Hydrophilic drugs do not readily cross membranes but go through slit junctions

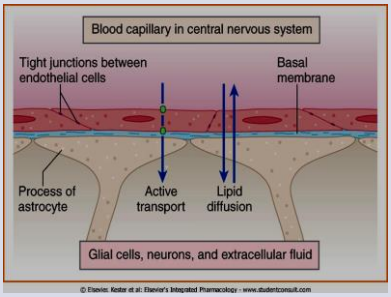
CAPILLARY PERMEABILITY

- Endothelial cells of capillaries in tissues other than brain have wide slit junctions allowing easy movement & distribution.
- Brain has tight junction Blood Brain Barrier (BBB).

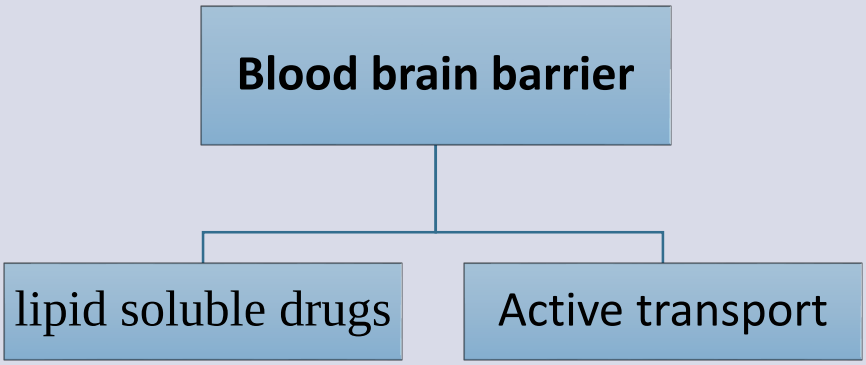








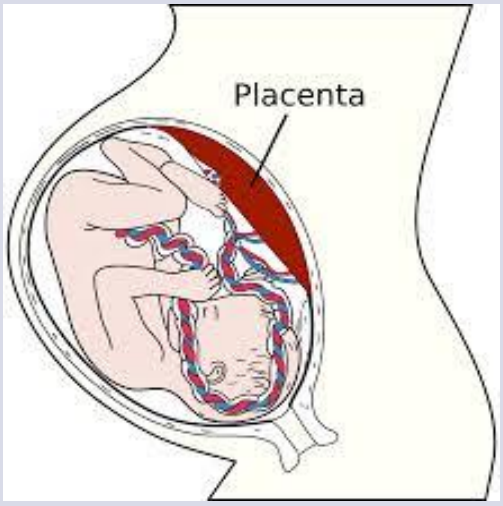
BLOOD BRAIN BARRIER (BBB)



- Only lipid soluble drugs or actively transported drugs can cross BBB.
- Hydrophilic drugs (ionized or polar drugs) can not cross BBB.
- Inflammation as in meningitis increase permeability to hydrophilic drugs
- It can transport Hydrophilic drugs only when Inflammation.
- e.g. penicillin & gentamycin

PLACENTAL BARRIER

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



BINDING OF DRUGS

Drug binding: drugs have a tendency to bind to tissue or certain plasma.

1. Plasma proteins binding:

- **Albumin:** Has affinity for acidic drugs as warfarin, phenytoin, aspirin
- **Glycoprotein:** Has affinity for basic drugs(cationic) as diazepam, quinidine.

- Drugs can bind to plasma proteins (**acidic** drug bind to **Albumin** while **basic** drugs bind to **Glycoprotein**)

2. Tissue proteins binding:

- **Tetracycline** bind to bone
- **Iodides** accumulate in salivary & thyroid glands

- Drugs can bind to specific tissue

Drugs exist in two forms inside the body: bound and unbound, the unbound form exhibits the pharmacologic effects.

BOUND	UNBOUND
Non diffusible form	Diffusible form
Cannot combine with receptors	Can combine with receptors
not available for metabolism & excretion	Available for metabolism and secretion
Has long duration of action (t ½).	Has short duration of action (t½)
inactive	Active form (participate in therapeutic effect)

- Bound forms act as a reservoir or storing method for the drug, as unbound drugs exit the body chemical equilibrium takes place releasing more bound drugs in the body.
- Each drug has a specific bound-unbound rate, resulting in different durations of action.

BINDING OF DRUGS AND ITS EFFECT ON DRUG ACTION

- Usually reversible.

  (From bound to unbound forms to reach equilibrium)

- determines volume of distribution (vd)

  (The higher the bound:unbound rate the lower the VD)

- Slows drug metabolism & excretion.

  (The higher the bound:unbound rate the lower the excretion and metabolism)

- Prolongs duration of drug action (t1/2).
- Result in clinically important drug interactions.

1) Which one of the following routes of administrations used in a case of no emergency?

A. Sublingual administration **B.** Oral administration

C. Rectal administration **D.** Parenteral administration

E. Both B and D

2) Which one of the following routes of administration that mostly has no systemic effect?

A. Parenteral administration **B.** Topical application

C. Inhalation **D.** Both B and C

E. Both A and B

3) ..... are studies of mechanisms and effects of drug action.

A. Pharmacodynamics **B.** Pharmacokinetics

C. Pharmacogenomics **D.** None of the above.

4) Route of administration that avoid "first-pass" hepatic effects:

A. Sublingual **B.** Oral

C. Transdermal **D.** Rectal

E. Both A and C

5) ..... is not suitable for oily solutions or poorly soluble substances.

A. Intravenous administration **B.** Subcutaneous administration

C. Intradermal administration **D.** Intramuscular administration

6) Which one of the following is a character of active transport?

A. Unspecific and not saturable

B. Requires no energy and no carrier

C. Absorption of amino acids

D. Occurs along concentration gradient

Answers in the last page

7) Drug is most absorbable if it is:

A. Non ionized **B.** Ionized

C. Water soluble **D.** Both B and C

8) Penicillin (pKa: 2.74) is best absorbed in the:

A. Small intestine **B.** Large intestine

C. Stomach **D.** None of the above

9) Most drugs are either ____ acids or ____ bases.

A. Strong; Strong **B.** Strong; Weak

C. Weak; Weak **D.** Weak; Strong

10) Which of the following drug permeation mechanisms involves polar substances too large to enter cells by other means, such as iron or vitamin B12?

A. Aqueous diffusion **B.** Lipid diffusion

C. Carrier molecules **D.** Endocytosis and exocytosis

11) The order of hardest absorbed drug forms (from most to least) is:

A. Capsule>tablet>suspension>solution

B. Tablet>capsule>suspension>solution

C. Capsule>tablet>solution>suspension

D. Tablet>capsule>solution>suspension

Answers in the last page

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Answers

1-**B**

2-**D**

3-**A**

4-**E**

5-**A**

6-**C**

7-**A**

8-**C**

9-**C**

10-**D**

11-**B**