PHARMACOLOGY
433

King Saud University
College of Medicine
Foundation Block

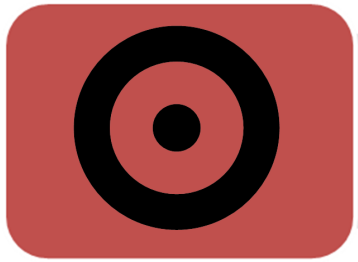
Pharmacokinetics II ; Bioavailability and Distribution

2

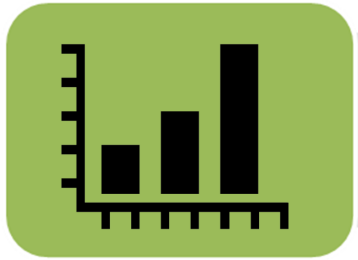
KEY WORDS

*Bioavailability
*Bioequivalence
*Distribution
*Body fluids
*Concentration
*Permeability
*Barriers
*Binding

OBJECTIVES

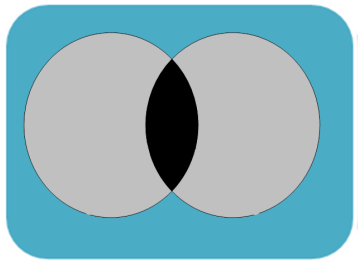


Define the apparent volume of distribution (Vd).

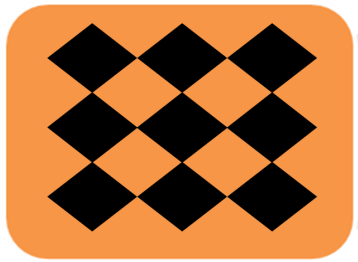


Define the concept of compartments.

Define the Major body fluid compartments.

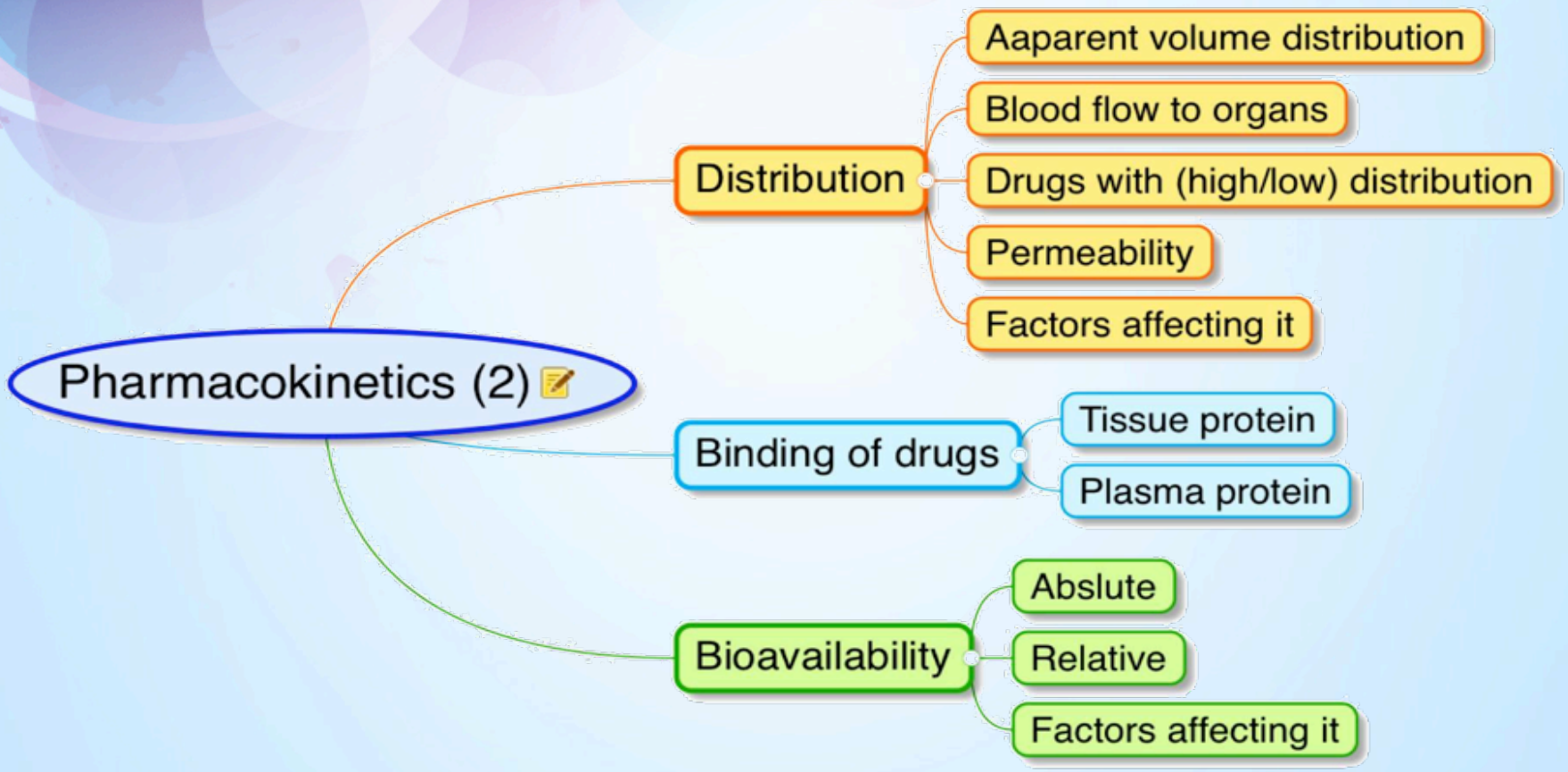


Define the Plasma protein binding and the Tissue binding.



Define the bioavailability of drugs.

LECTURE CONTENT



Bioavailability

Is the fraction of unchanged drug that enters systemic circulation after administration and becomes available to produce an action.

The rate (time) and extent (amount) of drugs reaching Systemic Circulation.

"Concentration of a drug in the blood"

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

The drug is more suitable when the resultant number is closer to 1 (0.9 , 0.8).

* Subcutaneous (S.C), intramuscular (I.M), oral, rectal, and other extra vascular routes of administration have incomplete absorption and go through the Portal Circulation (first pass metabolism) which reduce bioavailability.

Absolute Bioavailability

The bioavailability of a drug after Administration by any route is compared to its intravenous (I.V) standard formulation.

***We compare it with I.V because it is the best possible standard**

Pharma industries usually determine absolutes bioavailability by giving drug orally and compare it to the same drug standard preparation given by intravenously

Remember that : when comparing by relative bioavailability, the two drugs must have the same route of administration.
Orally with orally, rectally with rectally…. And so on.

Relative Bioavailability

Determined when two products (drugs) are compared to each other, not to an intravenous (I.V.) standard.

It is commonly calculated in the drug industry to determine that the generic formulation is Bioequivalent to another formulation.

- To get an idea of how different formulations differ in their bioavailability
- Dosage adjustment is required when changing formulations.

Tylenol compared to Panadol

Both paracetamol 500 mg

Bioequivalence

What is it ?

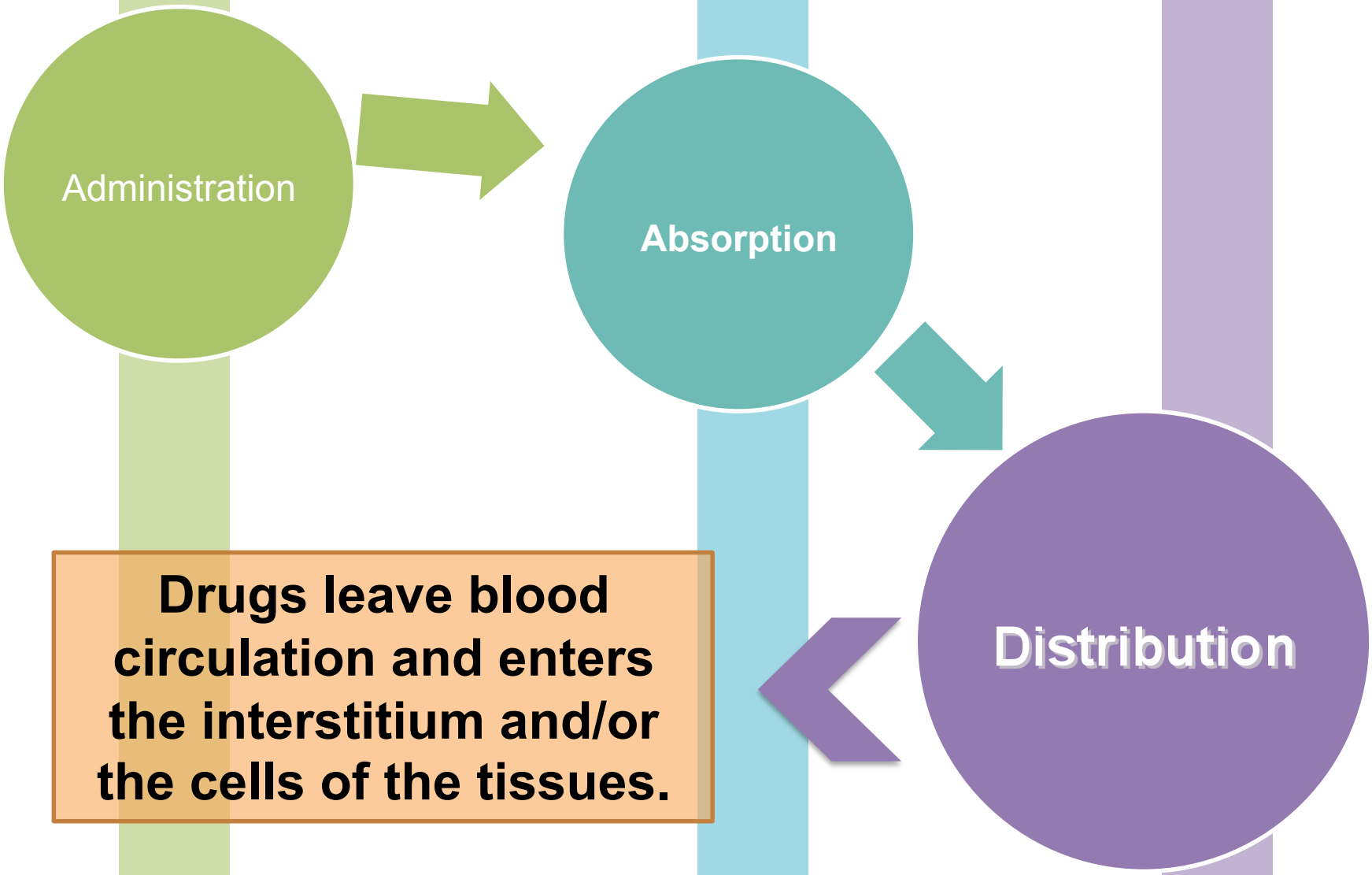
- Drug considered to be Bioequivalent when the Rates and Extents of bioavailability of the two products are not significantly different. (When their bioavailabilities are the same)

Factors affecting Bioavailability

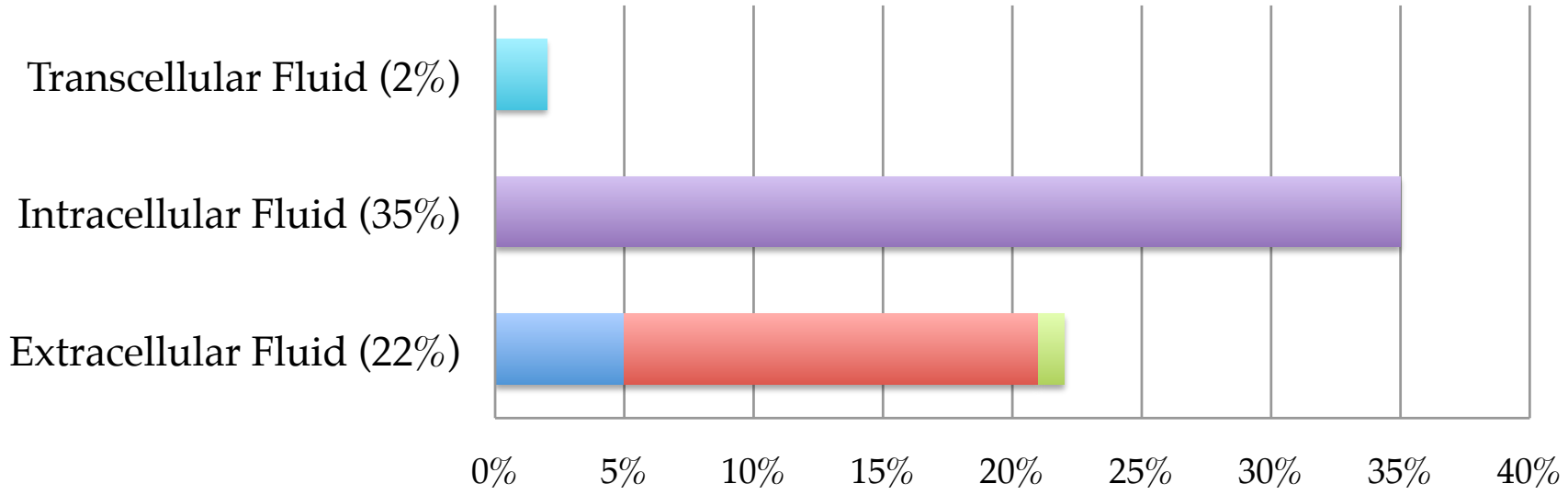
- Route of administration, Dosage forms, Molecular weight of drug, Lipid solubility, Degree of ionization, Drug solubility, Chemical instability in gastric pH, Surface area available for absorption, Blood flow to absorptive site, Intestinal motility, Drug interactions, Food, Concentration of drugs.

Rate and Extent means : the amount of drugs and the time required to reach the Systemic Circulation.

After administration, and after the drug has been absorbed into the blood circulation, it needs to get distributed..



THE MAJOR BODY FLUID COMPARTMENTS



	Extracellular Fluid (22%)	Intracellular Fluid (35%)	Transcellular Fluid (2%)
Plasma	5%	0	0
Interstitial Fluid	16%	0	0
Lymph	1%	0	0
Intracellular Fluid	0	35%	0
cerebrospinal, intraocular, synovial, peritoneal, pleural & digestive secretions.	0	0	2%

Apparent Volume Distribution (Vd)

Is the ratio of drug amount in the body to the concentration of drug in blood.

Large Vd = means long duration of action.

$$Vd\ (L) = \frac{\text{total amount of drug in body (mg)}}{\text{concentration in blood (mg/L)}}$$

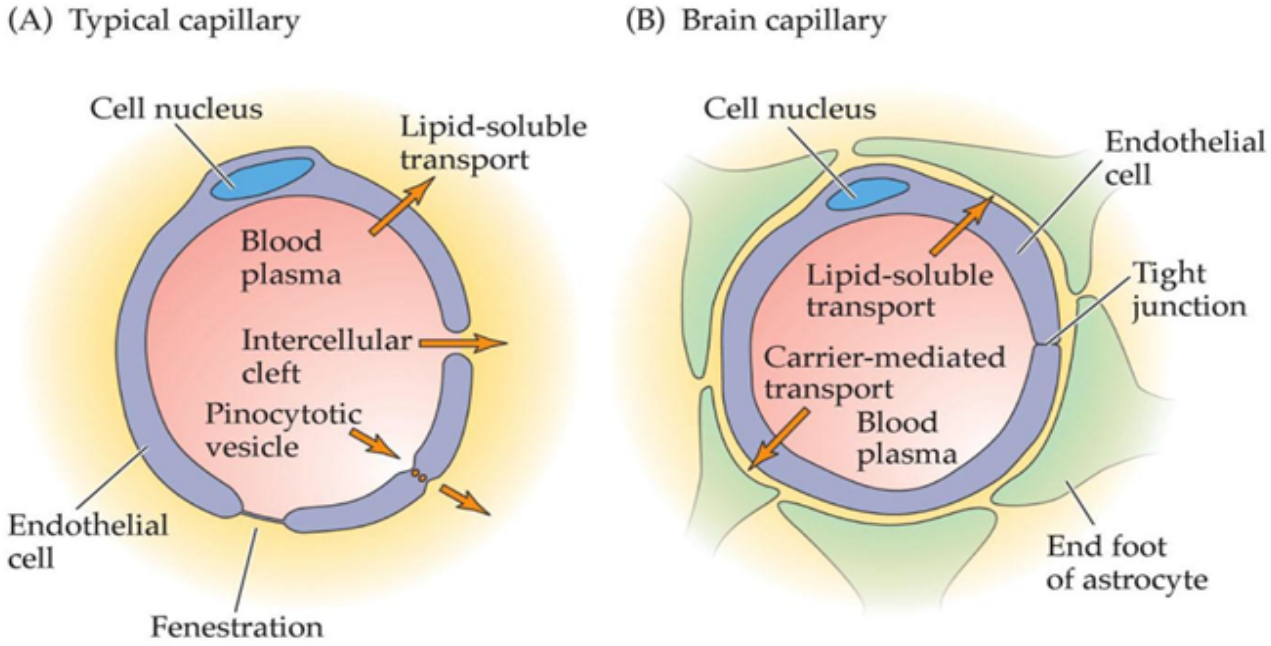
FACTORS AFFECTING DISTRIBUTION

1. Blood Flow to Organs	2. Physiochemical Properties of the Drug	3. Capillary Permeability	4. Tissue and plasma protein Binding of Drugs.
The greater the blood flow to tissues, the more distribution that occurs from plasma to interstitial fluids.	Molecular weight	1. Endothelial cells of capillaries in tissues (Except the brain) ↓ wide slit junctions ↓ easy movement & distribution	**Plasma Proteins Binding** -acidic drug bind to Albumin. e.g. : Warfarin, Phenytoin, Aspirin. -basic drugs bind to Glycoprotein. e.g. : Diazepam, Quinidine. -Unbound drug (free) ⇄ bound drug. (Equilibrium)
Drugs distribute more rapidly to brain, liver and kidney more than skeletal muscles and fat.	Lipid solubility: - Most lipid soluble drugs cross biological membranes. - Hydrophilic drugs do not readily cross membranes.	2. Brain tight junction *Blood Brain Barrier (BBB)*.	**Tissue Proteins Binding** -Tetracycline bind to Bones -Iodides accumulate in Salivary & Thyroid Glands.
	Pka.		

Volume of Distribution (Vd)

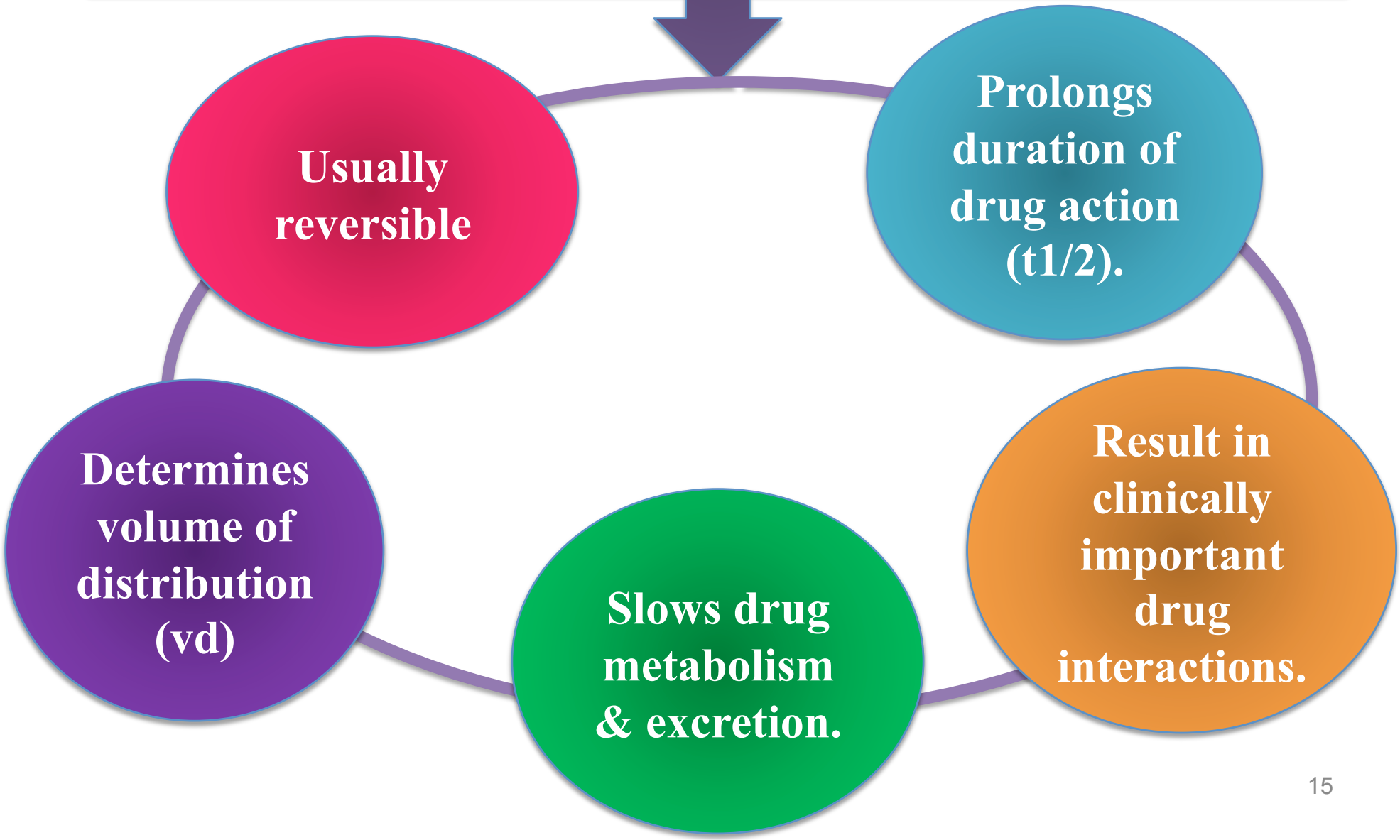
Drugs with high Vd Eliminated slowly = long duration of action	Drugs with low Vd Eliminated quickly
Have higher concentrations in tissues than in plasma.	Confined to plasma & interstitial fluid.
Relatively lipid soluble	Polar comp or lipid insoluble drugs e.g. Carbenicillin, Vecuronium, Gentamycin.
Distributed intracellularly	Distributed in extracellular compartments.
Not efficiently removed by haemodialysis	High MW e.g. Heparin, Insulin.
e.g. Phenytion, Morphine, Digoxin	High plasma protein binding e.g. Warfarin.
	Do not cross BBB or Placental Barriers

Blood brain barrier (BBB)	Placental barrier
Only lipid soluble drugs or actively transported drugs can cross BBB.	Lipid soluble drugs can cross placental barrier and enter the fetal blood.
Hydrophilic drugs (ionized or polar drugs) can not cross BBB.	
Inflammation as in meningitis increase permeability to hydrophilic drugs e.g. Penicillin & Gentamycin.	



	Bound form of Drugs	Unbound form of Drugs
Form	Non-diffusible	Diffusible
Combination with receptors	Cannot combine	Combine
Activity	Inactive	Active
Metabolism & Excretion	Not available	Available
Duration of Action (t ½).	Long	Short

Characters & consequences of Binding



Displacement

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

SUMMARY

Major Body Fluid Compartments.

The major body fluid compartments are:

- **Extracellular Fluid (22%):**
  Plasma (5%), Interstitial Fluid (16%) & Lymph (1%).
- **Intracellular Fluid (35%).**
- **Transcellular Fluid (2%):**
  Cerebrospinal, intraocular, synovial, peritoneal, pleural & digestive secretions.

Apparent volume of distribution (Vd).

- **It is the ratio of drug amount in the body to the concentration of drug in blood.**
- **Large Vd means long duration of action.**
- **Factors Affecting Distribution:**

1. **Cardiac output and blood flow.**
2. **Physiochemical properties of the drug.**
3. **Capillary Permeability**
4. **Plasma protein binding**
5. **Tissue binding.**

Drugs with high Vd	Drugs with low Vd
• **Distributed intracellularly.**	• Distributed in extracellular compartments.
• **Relatively lipid soluble.**	• Polar comp or lipid insoluble drugs.
• **Have higher concentrations in tissues than in plasma.** • **Not efficiently removed by haemodialysis.**	• Confined to plasma & interstitial fluid. • High MW. • High plasma protein binding. • Do not cross BBB or placental barriers.

SUMMARY

BINDING OF DRUGS:

- **Plasma protein binding.**

- **Drugs can bind to plasma proteins (acidic drug bind to albumin while basic drugs bind to glycoprotein).**

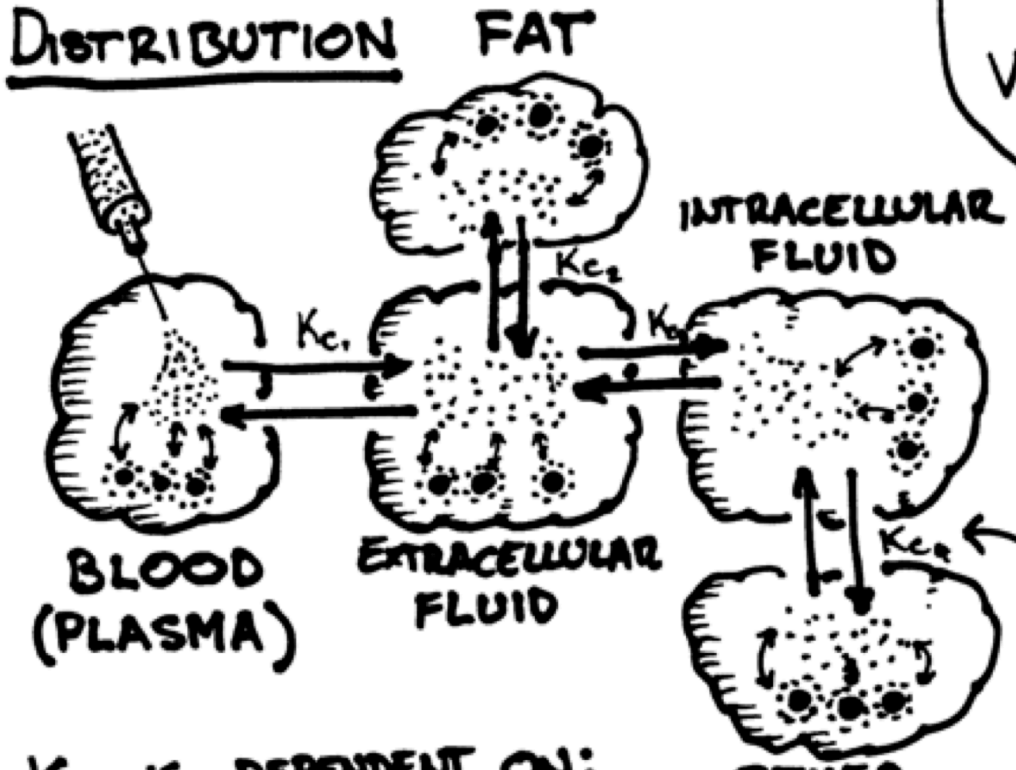
Drugs exist in two forms:

Bounding Form of Drug ⟺	**Unbound Form of Drug**
Non-diffusible form.	Diffusible form.
Cannot combine with receptors.	Combine with receptors.
Inactive	Active.
Not available for metabolism & excretion.	Available for metabolism & excretion.
Has long duration of action (t ½).	Has short duration of action (t ½).

- **Tissue Binding.**

- **Drugs can bind to specific tissue (bones, salivary & thyroid glands).**

DISTRIBUTION



VOLUME OF DISTRIBUTION (V_D)

$$V_D = \frac{\text{TOTAL AMOUNT OF DRUG IN BODY}}{\text{CONC. OF DRUG IN PLASMA}}$$

E.G. V_D MORPHINE = 5 L/kg BW.

Plasma [ ] = $^3/_{70}$ mg / L

DOSE = V_D x Plasma [ ]

= 5 L/kg BW x $^3/_{70}$ mg / L

= $^{15}/_{70}$ mg / kg BW

∴ 70kg person

Need Dose = 15mg

K_c IS DEPENDENT ON:

- PERMIABILITY OF BARRIERS
- pH OF COMPARTMENTS
- BINDING CAPACITY

HANDWRITTEN TUTORIALS .COM

A helpful tutorial about Drug Distribution !

(http://www.youtube.com/watch?feature=player_embedded&v=sOdVJCNDUTg)

MCQs

1. Relative bioavailability is determined when :

A-Two products are compared to each other.
B- A product is compared to the I.V standard formulation
C-The rates and extents of bioavailability of two products are not significantly different under suitable test conditions.
D- None of the above.

2. Drugs with high volume of distribution :

A-Have higher concentrations in tissues than in plasma.
B-Relatively lipid soluble.
C-Have less concentrations in tissues than in plasma.
D- Both A &B.

3. Bound form of drug :

A-Can't combine with receptors.
B-Active.
C-Non diffusible form.
D-Both A&C.

4. Factors that affect distribution :

A-Cardiac output and blood flow.
B-Tissue binding.
C-Plasma protein binding.
D-All of the above.

5. Large volume of distribution means :

A-Equal duration of action.
B-Short duration of action.
C-Long duration of action.
D-None of the above.

6. All of the following are components of extracellular fluid except :

A-Plasma
B-Peritoneal
C-Interstitial fluid
D-Lymph

1-A , 2-D , 3-D , 4-D, 5-C, 6-B

MCQS

7. which of the following is true :

A- extracellular fluid has 35% of body weight.
B- interstitial fluid has 16% of body weight.
C- transcellular fluid has 4% of body weight.
D- None of the above.

8. which of these factors are affecting bioavailability :

A-blood flow.
B-capillary permeability.
C-route of administration.
D-both A and C.

9. ..... is the fraction of unchanged drug that enters systemic circulation after administration and becomes available to produce an action.

A- absolute bioavailability
B-relative bioavailability
C- bioavailability
D-Both A &B

10. ..... is the ratio of drug amount in body to the concentration of drug in blood.

A- apparent volume of distribution
B- distribution
C- bioavailability
D-relative bioavailability

11. Competition between Aspirin and Warfarin to bind with Albumin can cause :

A- Cell necrosis
B- fetus miscarriage
C- psychological effects
D- Bleeding

12. **Inflammation as in meningitis increase permeability to …… drugs to cross the BBB :**

A- Hydrophilic
B- Hydrophobic
C- Amphipathic
D- High MW

7-B , 8-D, 9-C, 10-A, 11-D, 12-A

Pharmacological Cases

Two patients using the same drug : one of them has Heart Failure and the other has no Cardiovascular Disorders, will the distribution-rate be the same? If not, where would it be less distributed?

Patient with heart failure because ; the cardiac output is low, blood flow will be low, and this factor affects the rate of distribution.

A pregnant woman that needs to use an Anticoagulant (drugs that reduce the risk of blood clot); which drug is better to be prescribed to her **Warfarin or Heparin**?
Known that Warfarin has low MW and Heparin has high molecular weight.

Warfarin has low MW which means it can cross the cell membrane easily and can be distributed better. But, it also means that it will cross the Placental Barrier and will reach the fetus, which will harm it!

So, **Heparin** is more suitable for the patient in this situation.

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We hope that we made this lecture easier for you

THANK YOU ☺