III Formulation Factors Affecting Oral Absorption:

- The role of the drug formulation in the delivery of drug to the site of action should not be ignored.
- Since a drug must be in solution to be absorbed efficiently from the G-I tract, you may expect the bioavailability of a drug to decrease in the order solution > suspension > capsule > tablet > coated tablet.

A. *Solution dosage forms:*

- In most cases absorption from an oral solution is rapid and complete, compared with administration in any other oral dosage form.

III Formulation Factors Affecting Oral Absorption (Cont.):

- Some drugs which are poorly soluble in water may be:

1- dissolved in mixed water/alcohol or glycerol solvents (cosolvency),

2- given in the form of a salt (in case of acidic drugs)

3- An oily emulsion or soft gelatin capsules have been used for some compounds with lower aqueous solubility to produce improved bioavailability.

III Formulation Factors Affecting Oral Absorption (Cont.):

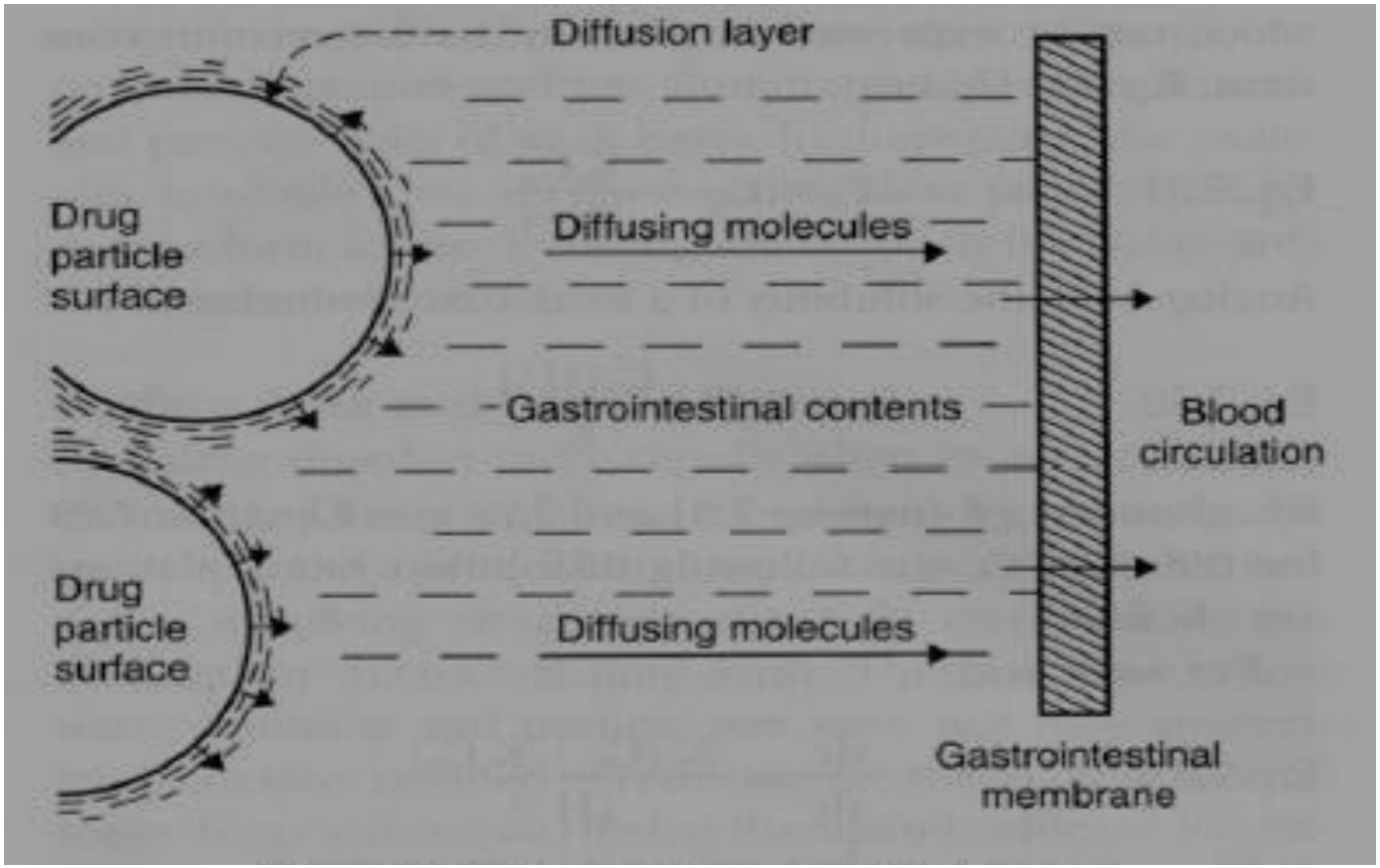
B. Suspension dosage forms:

- A well formulated suspension is second to a solution in terms of superior bioavailability.

- A suspension of a finely divided powder will maximize the potential for rapid dissolution.
- A good correlation can be seen for particle size and absorption rate.

- The addition of a surface active agent will improve the absorption of very fine particle size suspensions.

III Formulation Factors Affecting Oral Absorption (Cont.):



Absorption of drugs from aqueous suspensions

III Formulation Factors Affecting Oral Absorption (Cont.):

C. Capsule dosage forms:

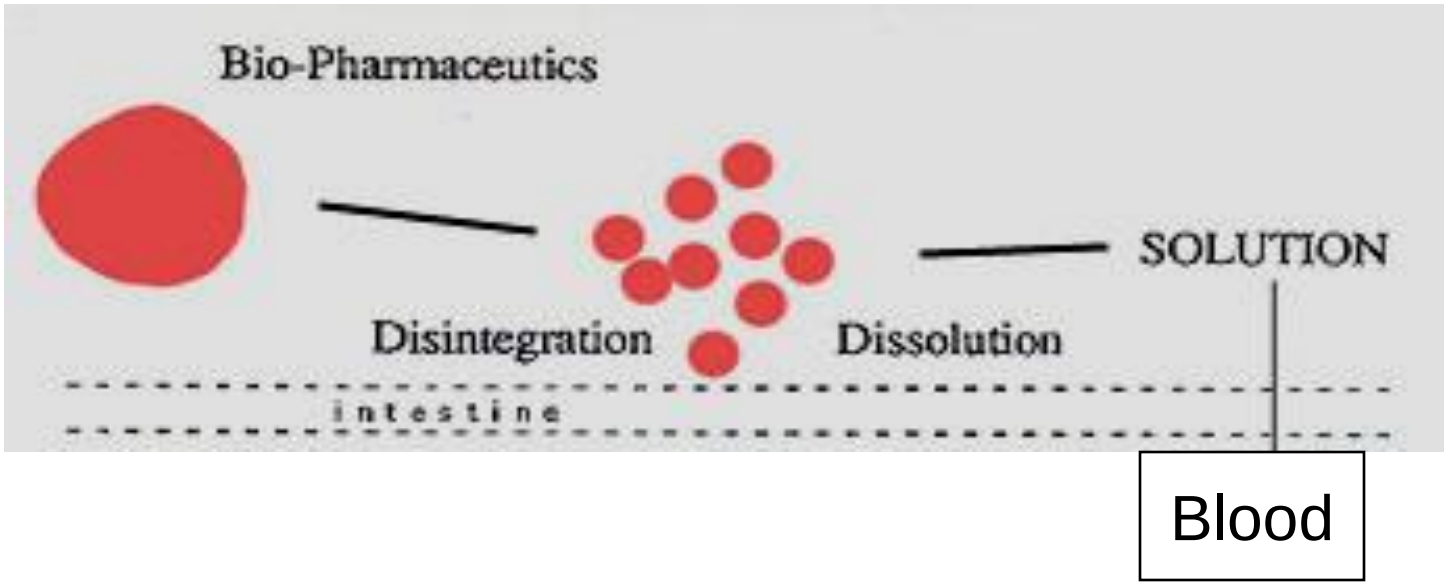
- The hard gelatin shell should disrupt rapidly and allow the contents to be mixed with the G-I tract contents.

- If a drug is hydrophobic a dispersing agent should be added to the capsule formulation. These diluents will work to disperse the powder, minimize aggregation and maximize the surface area of the powder.

- Tightly packed capsules may have reduced dissolution and bioavailability.

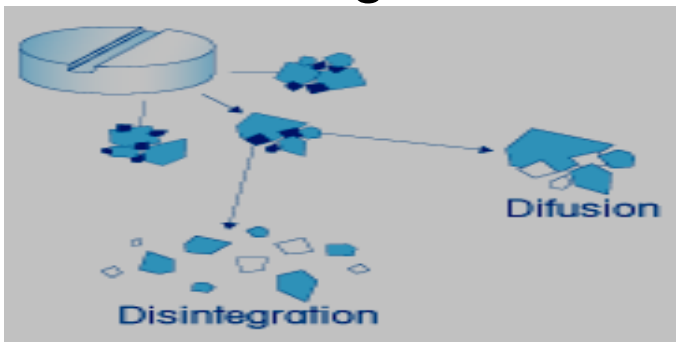
III Formulation Factors Affecting Oral Absorption (Cont.):

D. Tablet dosage forms:



III Formulation Factors Affecting Oral Absorption (Cont.):

- The tablet is the most commonly used oral dosage form.
- It is also quite complex in nature.



1-Ingredients

Drug : may be poorly soluble, hydrophobic

Lubricant : usually quite hydrophobic

Granulating agent : tends to stick the ingredients together

Filler: may interact with the drug, etc., should be water soluble

Wetting agent : helps the penetration of water into the tablet

Disintegration agent: helps to break the tablet apart

III Formulation Factors Affecting Oral Absorption (Cont.):

- Coated tablets are used to mask an unpleasant taste, to protect the tablet ingredients during storage, or to improve the tablets appearance.

This coating can add another barrier between the solid drug and drug in solution. This barrier must break down quickly or it may hinder a drug's bioavailability.

- ***Sustained release tablet***

Another form of coating is enteric coated tablets which are coated with a material which will dissolve in the intestine but remain intact in the stomach.

Distribution:

Drug distribution: means the reversible transfer of drug from one location to another within the body.

- The distribution of drugs in the body depends on:

1- their lipophilicity

2- protein binding.

Low plasma binding or high tissue binding or high lipophilicity usually means an extensive tissue distribution.

Distribution:

- In pharmacokinetics, the distribution is described by the parameter V, the apparent volume of distribution.

- At equilibrium, V will theoretically not be lower than 7 L in a 70-kg person, but it has no upper limit.

Drug distribution patterns:

-The extent to which a drug distributes affects the half-life of the drug and the fluctuation of the concentration at steady state.

Distribution can be thought of as following one of four types of patterns:

1-The drug may remain largely within the vascular system. Plasma substitutes such as dextran are an example of this type, but drugs which are strongly bound to plasma protein may also approach this pattern.

Drug distribution patterns (Cont.):

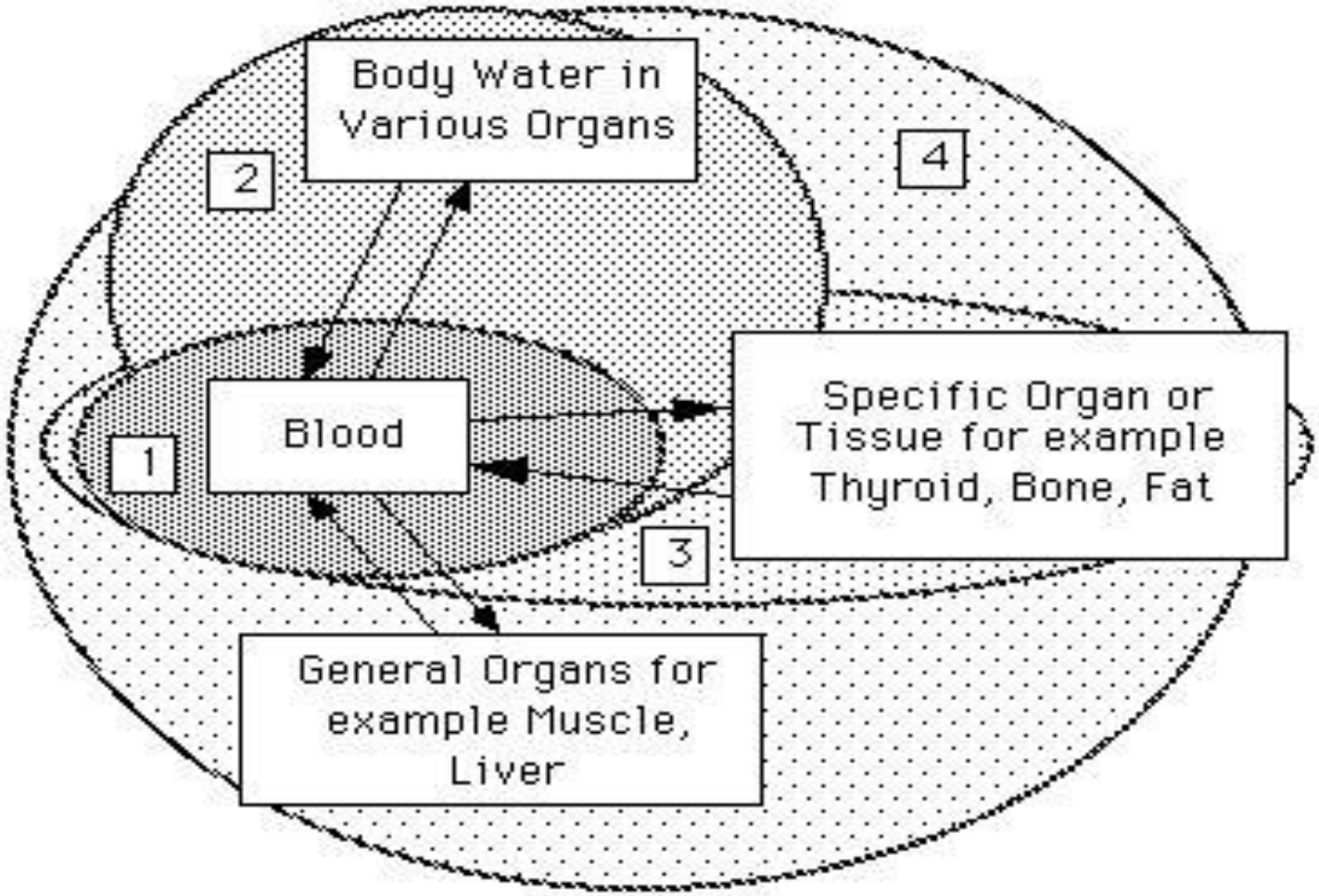


Diagram Representing Various Volumes Distribution Patterns

Drug distribution patterns (Cont.):

2- Some low molecular weight water soluble compounds such as ethanol and a few sulfonamides become uniformly distributed throughout the body water.

Drug distribution patterns (Cont.):

3- A few drugs are concentrated specifically in one or more tissues that may or may not be the site of action.

Iodine is concentrated by the thyroid gland.

The antimalarial drug chloroquine may be present in the liver at concentrations 1000 times those present in plasma.

Drug distribution patterns (Cont.):

Tetracycline is almost irreversibly bound to bone and developing teeth.

Consequently tetracyclines should only be given to young children or infants in extreme conditions as it can cause discoloration and mottling of the developing second set of teeth.

Another type of specific concentration may occur with highly lipid soluble compounds which distribute into fat tissue.

Drug distribution patterns (Cont.):

4- Most drugs exhibit a non-uniform distribution in the body with variations that are largely determined by the ability to pass through membranes and their lipid/water solubility.

The highest concentrations are often present in the kidney, liver, and intestine usually reflecting the amount of drug being excreted.

Drug distribution patterns (Cont.):

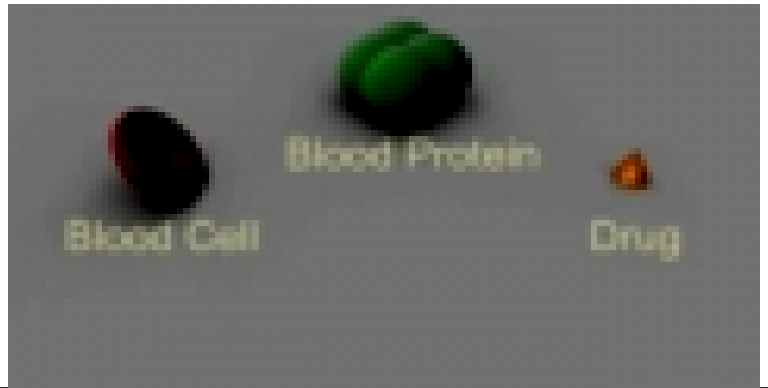
- Apparent volume of distribution (V) is a useful indicator of the type of pattern that characterizes a particular drug.
- A value of V in the region of 3-5 liter (in an adult) would be compatible with pattern 1. This is approximately the volume of plasma.
- Pattern two would be expected to produce a V value of 30 to 50 liter, corresponding to total body water.
- Agents or drugs exhibiting pattern 3 would exhibit very large values of V. Chloroquine has a V value of approximately 115 L/ kg .
- Drugs following pattern 4 may have a V value within a wide range of values.

Drug distribution patterns (Cont.):

Volumes of body fluids	
Fluid substances	**Volume (liter)**
Extracellular Fluid	19
Plasma	3
Interstitial fluids	16
Intracellular fluids	23
Total body water	42

Factors affecting drug distribution:

Factors Affecting Distribution	
A- Rate of distribution	**B- Extent of Distribution**
1. Membrane permeability 2. Blood perfusion	1. Lipid Solubility 2. pH – pKa 3. Plasma protein binding 4. Tissue drug binding



Factors affecting drug distribution (Cont.):

A. Rate of distribution

1. Membrane permeability:

- Capillary walls are quite permeable.
- Lipid soluble drugs pass through very rapidly.
- Water soluble compounds penetrate more slowly at a rate more dependent on their size.
- Low molecular weight drugs pass through by simple diffusion. For compounds with molecular diameter above 100 Å transfer is slow.
- For drugs which can be ionized the drug's pKa and the pH of the blood will have a large effect on the transfer rate across the capillary membrane.

Factors affecting drug distribution (Cont.):

- There are two deviations to the typical capillary structure which result in variation from normal drug tissue permeability.

i) Permeability is greatly increased in the renal capillaries by pores in the membrane of the endothelial cells, and in specialized hepatic capillaries, known as sinusoids which may lack a complete lining. This results in more extension distribution of many drugs out of the capillary bed.