BP604T

(BIOPHARMACEUTICS & PHARMACOKINETICS)

Course Content:

UNIT-I 10 Hours

Introduction to Biopharmaceutics

Absorption; Mechanisms of drug absorption through GIT, factors influencing drug absorption though GIT, absorption of drug from Non per oral extra-vascular routes, **Distribution** Tissue permeability of drugs, binding of drugs, apparent, volume of drug distribution, **plasma and tissue protein binding** of drugs, factors affecting protein-drug binding. Kinetics of protein binding, Clinical significance of protein binding of drugs

UNIT- II 10 Hours

Elimination: Drug metabolism and basic understanding metabolic pathways renal excretion of drugs, factors affecting renal excretion of drugs, renal clearance, Non renal routes of drug excretion of drugs **Bioavailability and Bioequivalence:** Definition and Objectives of bioavailability, absolute and relative bioavailability, measurement of bioavailability, in-vitro drug dissolution models, in-vitro-in-vivo correlations, bioequivalence studies, methods to enhance the dissolution rates and bioavailability of poorly soluble drugs.

UNIT- III 10 Hours

Pharmacokinetics: Definition and introduction to Pharmacokinetics, Compartment models, Non compartment models, physiological models, One compartment open model. (a). Intravenous Injection (Bolus) (b). Intravenous infusion and (c) Extra vascular administrations. Pharmacokinetics parameters - KE ,t1/2,Vd,AUC,Ka, Clt and CLR- definitions methods of eliminations, understanding of their significance and application.

UNIT- IV 08 Hours

Multicompartment models: Two compartment open model. IV bolus Kinetics of multiple dosing, steady state drug levels, calculation of loading and mainetnance doses and their significance in clinical settins.

UNIT- V 07 Hours

Nonlinear Pharmacokinetics: a. Introduction, b. Factors causing Non-linearity. c. Michaelis-menton method of estimating parameters, Explanation with example of drugs.

Unit-1 : Introduction to Biopharmaceutics

Absorption; Mechanisms of drug absorption through GIT, factors influencing drug absorption though GIT, absorption of drug from Non per oral extra-vascular routes, **Distribution** Tissue permeability of drugs, binding of drugs, apparent, volume of drug distribution, **plasma and tissue protein binding** of drugs, factors affecting protein-drug binding. Kinetics of protein binding, Clinical significance of protein binding of drugs

Cell membrane

Also called the plasma membrane, plasmalemma or phospholipid bilayer.

- The plasma membrane is a flexible yet sturdy barrier that surrounds & contains the cytoplasm of a cell.
- Cell membrane mainly consists of:

1. Lipid bilayer-
-phospholipid
-Cholesterol
-Glycolipids.

2. Proteins-
-Integral membrane proteins
-Lipid anchored proteins
-Peripheral Proteins

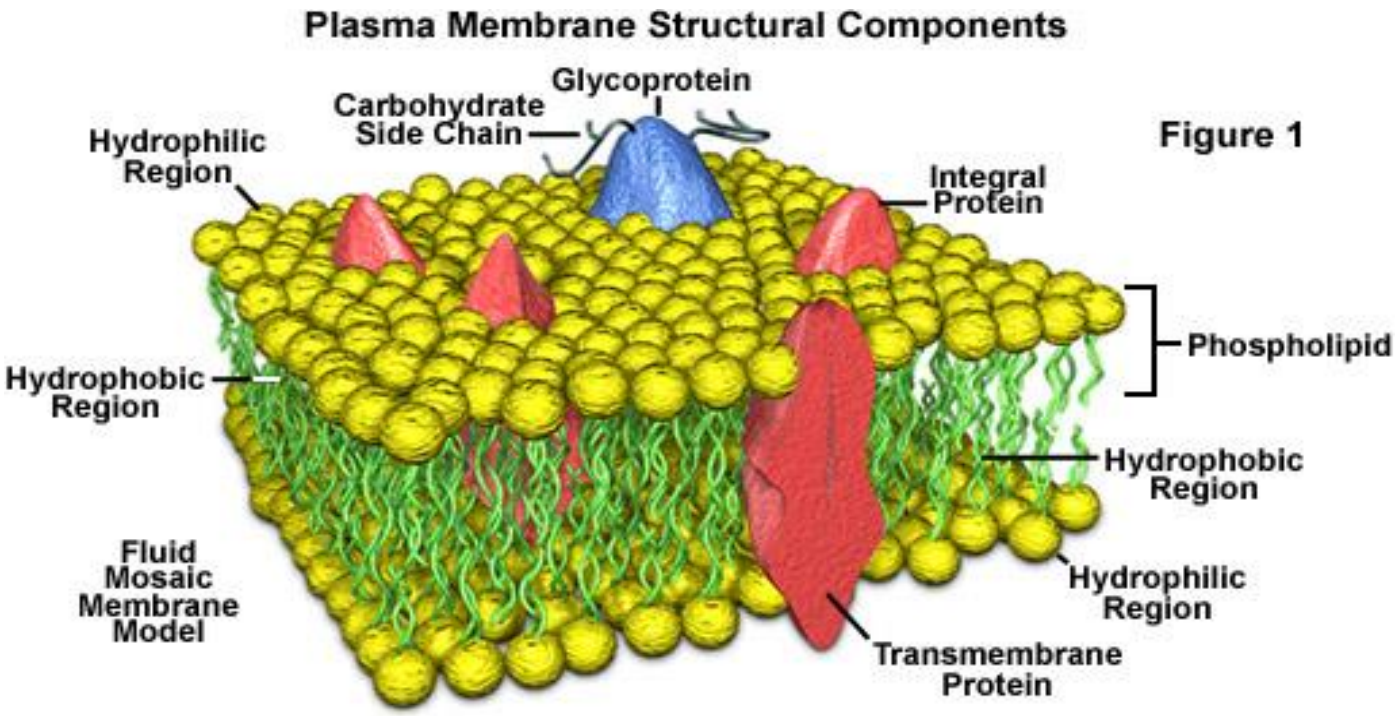


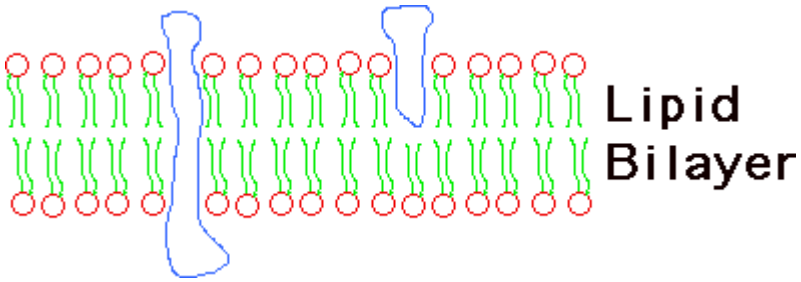
Figure 1

A. Membrane physiology

Membrane structure

In 1900 Overton performed some simple but classic experiments related to cell membrane structure. By measuring the permeability of various types of compounds across the membranes of a frog muscle he found that lipid molecules could readily cross this membrane, larger lipid insoluble molecules couldn't and small polar compounds could slowly cross the membrane. He suggested that membranes were similar to lipids and that certain molecules (lipids) moved across membranes by dissolving in the membrane.

These results suggest that the biologic membrane is mainly lipid in nature but contains small aqueous channels or pores.



The Fluid Mosaic Model

The membrane then acts as a lipid barrier with protein formed pores. The protein within the membrane can act transport enhancers in either direction depending on the protein.

The barriers between various organs, tissues and fluids areas will consist of cells of different structure and membranes characteristics. In some cases the cells are loosely attached with extracellular fluid freely moving between the cells. Drugs and other compounds, lipid or not, may freely move across this barrier. In other cases there may be tight junctions between the cells which will prevent non lipid movement.

Loosely Attached Cell Barrier

Cell Barrier with Tight Junctions

These are general structures of the cellular layer. Layers in different parts of the body have somewhat different characteristics which influence drug action and distribution. In particular, membrane protein form and function, intracellular pore size and distribution is not uniform between different parts of the body.

Examples of some barrier types:

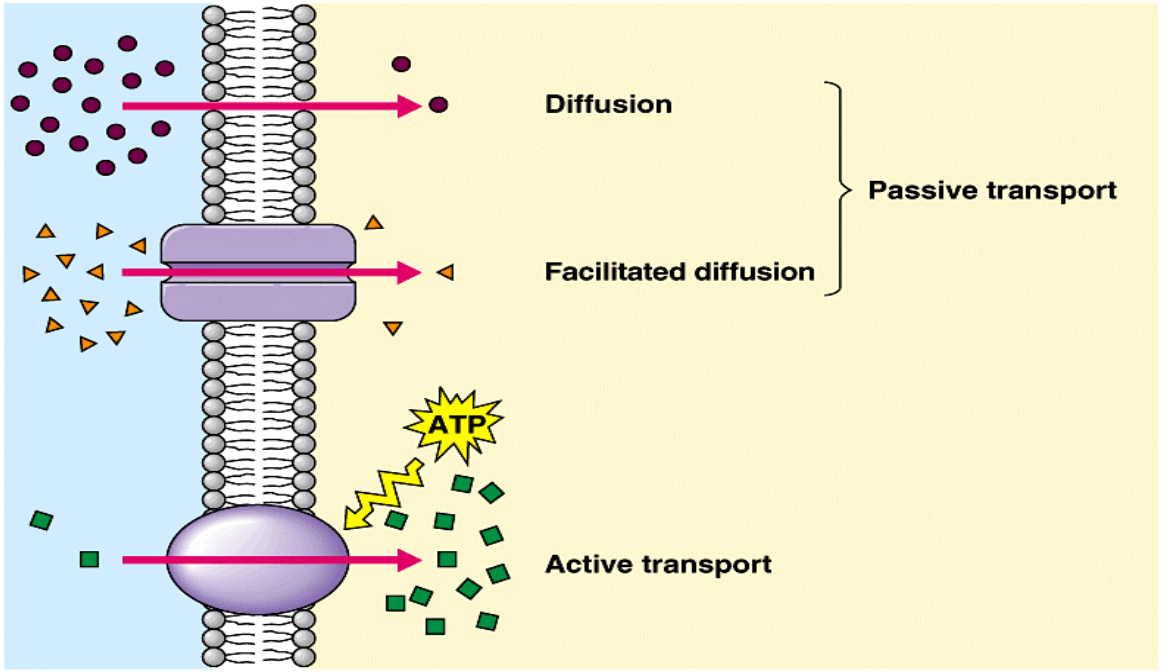
Blood-brain barrier: The cellular barrier between the blood and brain have very tight junctions effectively eliminating transfer between the cells. Additionally there are specific transport mechanisms, such as P-glycoproteins which actively causes the removal of drugs and other compounds from the brain. This will prevent many polar (often toxic materials) materials from entering the brain. However, smaller lipid materials or lipid soluble materials, such as diethyl ether, halothane, can easily enter the brain across the cellular membrane. These compounds are used as general anesthetics.

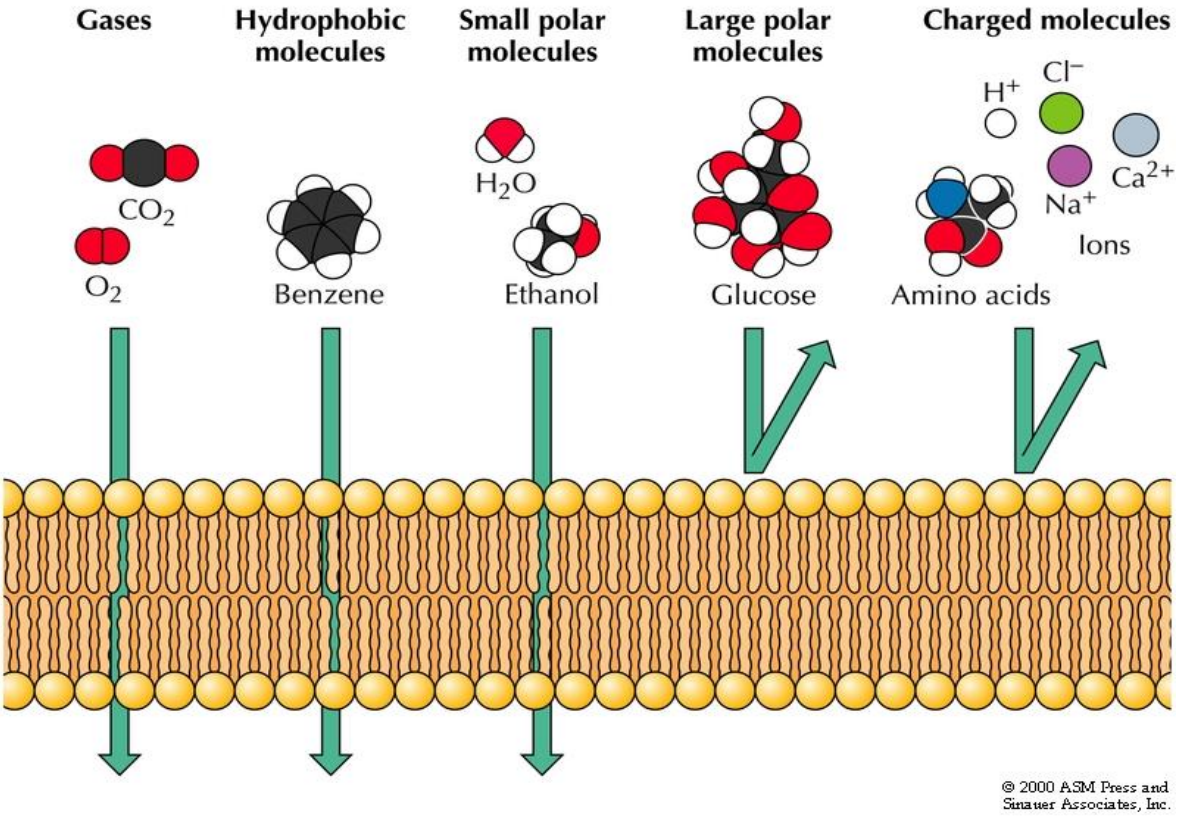
Renal tubules: In the kidney there are a number of regions important for drug elimination. In the tubules drugs may be reabsorbed. However, because the membranes are relatively non-porous, only lipid compounds or non-ionized species (dependent of pH and pKa) are reabsorbed.

Hepatic blood vessels: The capillaries are lined with a basement membrane broken in part by sinusoids and fenestrations interspersed with cells held together with tight junctions. The result is a barrier that allows considerable transfer between the blood and hepatocytes.

Blood capillaries and renal glomerular membranes: These membranes are quite porous allowing non-polar and polar molecules (up to a fairly large size, just below that of albumin, M.Wt 69,000) to pass through. This is especially useful in the kidney since it allows excretion of polar (drug and waste compounds) substances.

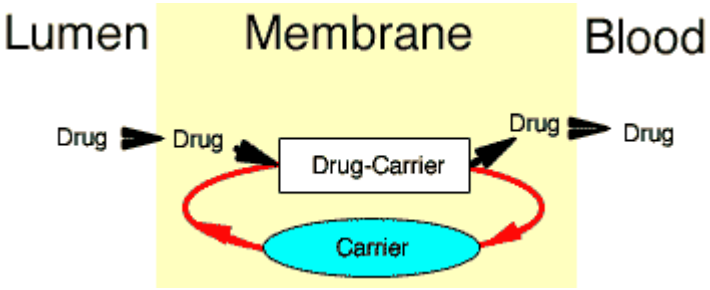
B. Passage of drugs across membranes





Movement of substance across the cell membrane

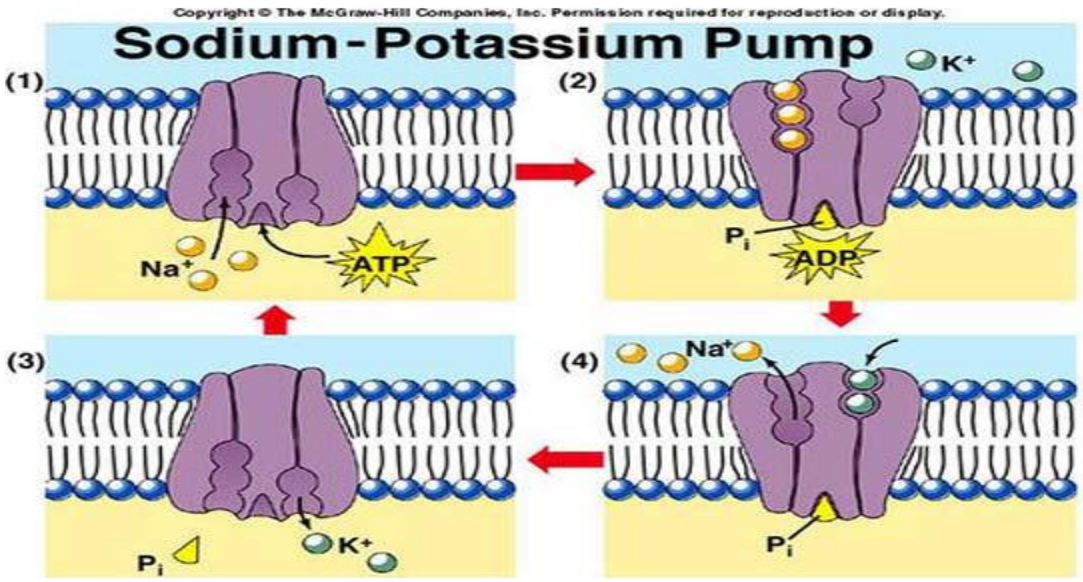
1.Active transport or carrier mediated transport:



Carrier-Mediated Transport Process

The body has a number of specialized mechanisms for transporting particular compounds; for example, glucose and amino acids. Sometimes drugs can participate in this process; e.g. 5-fluorouracil. Active transport requires a carrier molecule and a form of energy.

- the process can be saturated
- transport can proceed against a concentration gradient
- competitive inhibition is possible
- **Active Transport**
- Active transport is the energy-demanding transfer of a substance across a cell membrane **against** its concentration gradient, i.e., from lower concentration to higher concentration.
- Special proteins within the cell membrane act as specific protein 'carriers'. **The energy for active transport** comes from ATP generated by respiration (in mitochondria).
- **Major examples of Active Transport** Re-absorption of glucose, amino acids and salts by the proximal convoluted tubule of the nephron in the kidney.
- Sodium/potassium pump in cell membranes (especially nerve cells)



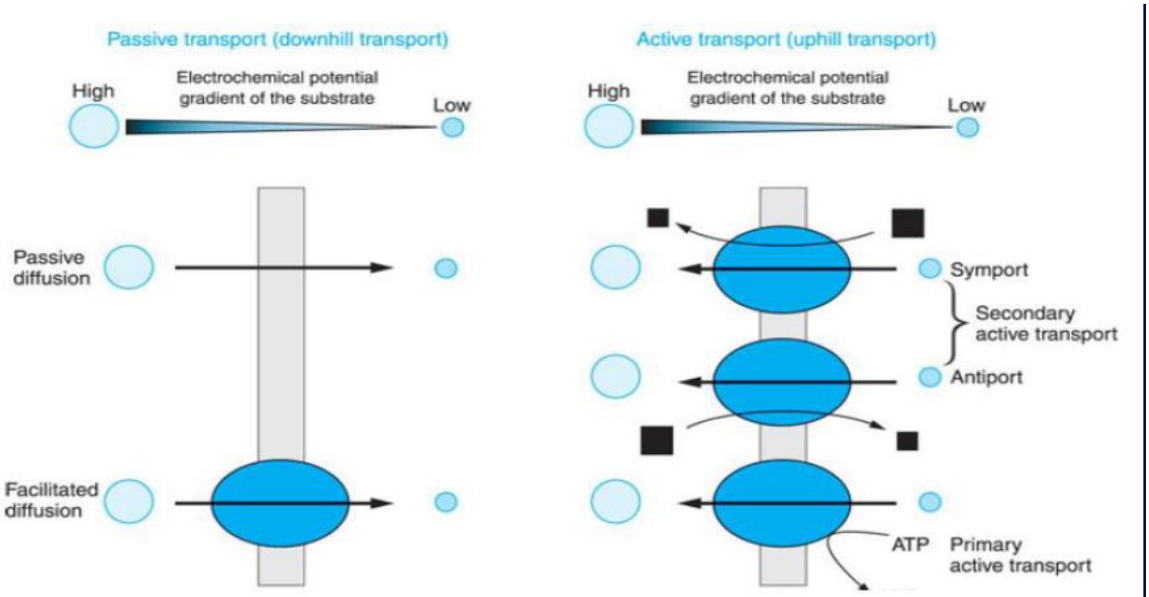


FIGURE 2–4 ***Classification of membrane transport mechanisms.*** *Light blue circles* depict the substrate. Size of the circles is proportional to the concentration of the substrate. *Arrows* show the direction of flux. *Black squares* represent the ion that supplies the driving force for transport (size is proportional to the concentration of the ion). *Dark blue ovals* depict transport proteins.

Diffusion

Diffusion is the net passive movement of particles (atoms, ions or molecules) from a region in which they are in higher concentration to regions of lower concentration. It continues until the concentration of substances is uniform throughout. **Some major examples of diffusion in biology:**

- Gas exchange at the alveoli — oxygen from air to blood, carbon dioxide from blood to air.
- Gas exchange for photosynthesis — carbon dioxide from air to leaf, oxygen from leaf to air.
- Gas exchange for respiration — oxygen from blood to tissue cells, carbon dioxide in opposite direction.
- Transfer of transmitter substance — acetylcholine from presynaptic to postsynaptic membrane at a synapse.
- Osmosis — diffusion of water through a semipermeable membrane.

High Diffusion Rate: short distance, large surface area, big concentration difference (Fick's Law).
High temperatures **increase** diffusion; large molecules **slow** diffusion.

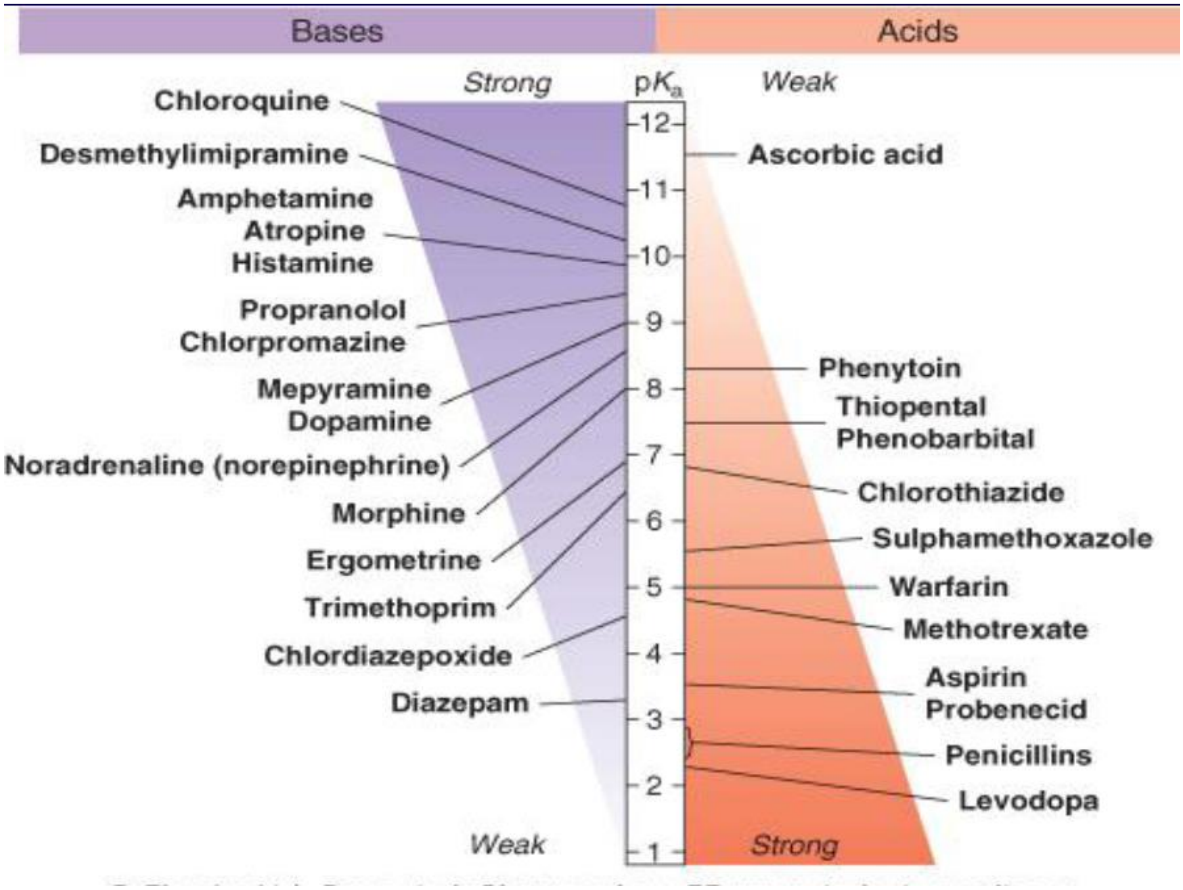
- ❖ *Lipid soluble drugs along concentration gradient cross lipid by layer. Is directly proportional to concentration gradient,require no carrier,no energy.*
- ❖ *•Non-ionized drugs are lipid soluble. Diffusion expresses in term of lipid/ water partitioned coefficient. Lipid solubility is determined by permeability coefficient, Coefficient is ratio of concentration of drug in two immiscible phages. Partition coefficient reflect solubility in a lipid*

solvent relative to solubility in water. Greater lipid solubility reflected in greater partitioned coefficient.

- *Most drugs are either weak acid or bases with molecular weight < 600. In solution present both ionised and un-ionised form.*
- *•Weak acids partially dissociate,is bi- directional ; CH3COOH CH3COO- + H+*
- *•Strong acids are completely dissociated ; is unidirectional; HCl Cl- +H +*
- *Fraction of ionised & unionised drug is determined by pKa of drug and pH of media.*
- *•HA H+ + A - HA –nonionised weak acid*
    - *ionised weak acid*
- *•BH+ H+ + B B - nonionized weak base*

- *BH+ - ionised weak base*
- *•If pK and pH is known fraction of ionised and unionised can be calculated by Henderson – Hasselbalch equation:*
    - *•pKa = pH + log [HA] = pH + log [unionised] /[ionised]*
    - *•pKb = pH + log [BH+] = pH + log [ionised] /B [unionised]*

  So diffusion is determined by pK and pH
- *•In general presence of lipophilic group benzene ring, hydrocarbon chain, steroid neucleus or halogen groups favours lipid solubility and presence of ionisable group e.g. -OH, -CONH2, -COOH decrease L/W partition coefficient, favour water solubility.*
- *•Acidic drugs are aspirin(pK 3.5), phenobarbitone, frusemide, cromolyn sodium, naproxen; Basic drugs are diazepam ,morphine,pethidine (pK 8.6), while neutral drugs are prednisolone, ethanol.*
- *•Acidic drug have pKa ranging 2.5 –8 ,while for basic drug pKb range 6-10.*
- *Acidic drugs are more ionised and less lipid soluble (less diffusible) in basic media. On the contrary is less ionised and more lipid soluble in acidic media.*
- *•pH of stomach is 1.5 –6, ileum 7.6 ,urine is 4.6 –8.2.*
- *•pK of aspirin is 3.5; In stomach with pH 1.5 remain mostly unionised & readily absorbed. In kidney tubules with pH 5.5 aspirin is mostly ionised will not be reabsorbed, rather readily excreted.*
- *•In general alkalisation of urine will increase excretion of acidic drug (aspirin, phenobarbitone, sulfonamide) & will decrease excretion of basic drugs (amphetamine).*



2. **Facilitated Diffusion**

This is the movement of **specific** molecules **down a concentration gradient**, passing through the membrane via a **specific carrier protein.** Thus, rather like enzymes, each carrier has its own shape and only allows one molecule (or one group of closely related molecules) to pass through.

Selection is by size; shape; charge.

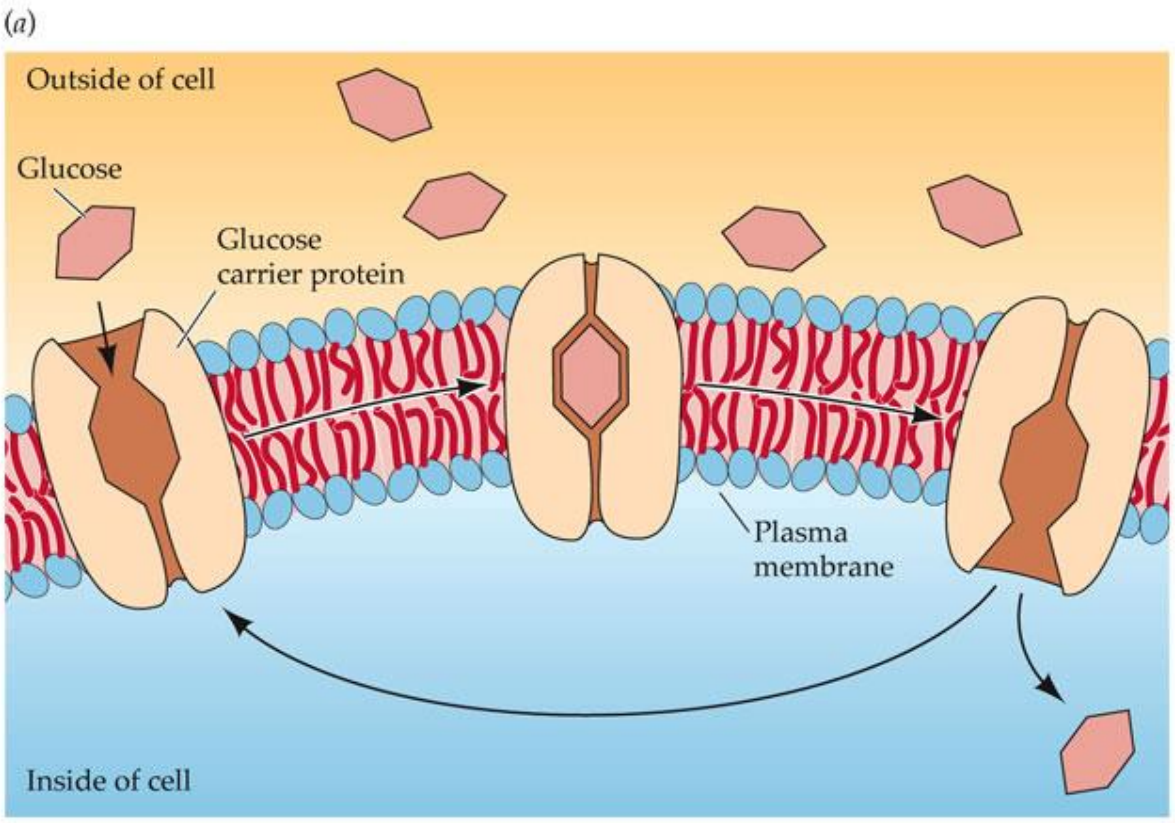
Common molecules entering/leaving cells this way include glucose and amino-acids.

It is **passive** and requires no energy from the cell.

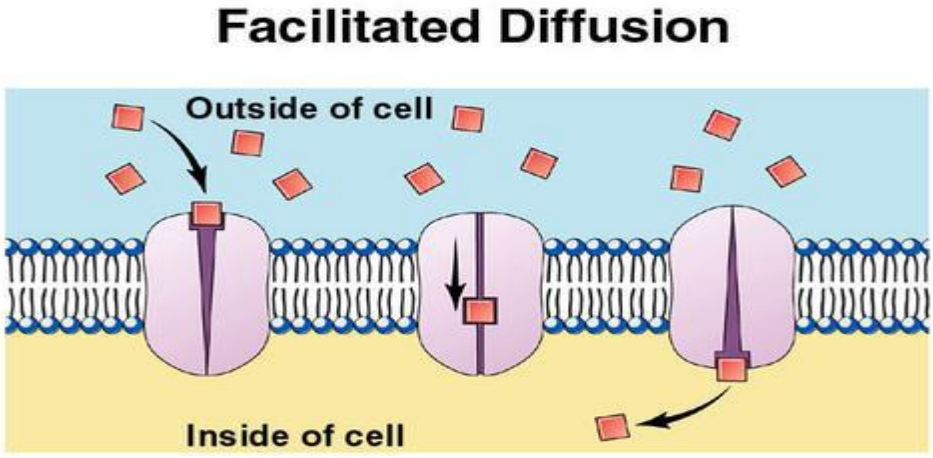
If the molecule is changed on entering the cell (glucose + ATP → glucose phosphate + ADP), then the **concentration gradient of glucose** will be kept high, and there will a steady one-way traffic.

A drug carrier is required but no energy is necessary. e.g. vitamin B12 transport.

- saturable if not enough carrier
- no transport against a concentration gradient only downhill but faster



LIFE: THE SCIENCE OF BIOLOGY, Seventh Edition, Figure 5.11 A Carrier Protein Facilitates Diffusion (Part 1)



P-glycoprotein

P-glycoprotein transporters (PGP, MDR-1) are present throughout the body including liver, brain, kidney and the intestinal tract epithelia. They appear to be an important component of drug absorption acting as reverse pumps generally inhibiting absorption. This is an active, ATP-dependent process which can have a significant effect on drug bioavailability. P-glycoprotein works against a range of drugs (250 - 1850

Dalton) such as cyclosporin A, digoxin, β-blockers, antibiotics and others. This process has been described as multi-drug resistance (MDR). Additionally P-glycoprotein has many substrates in common with cytochrome P450 3A4 (CYP 3A4) thus it appears that this system not only transports drug into the lumen but causes the metabolism of substantial amounts of the drug as well (e.g. cyclosporin).

Clinically significant substrates of PGP include digoxin, cyclosporine, fexofenadine, paclitaxel, tracrolimus, nortriptyline and phenytoin. A number of compounds can act as PGP inhibitors including atorvastatin (digoxin AUC increased), cyclosporine (increased paclitaxel absorption), grapefruit juice (increased paclitaxel absorption) and verapamil. Rifampin and St. John's wort have been reported to induce PGP expression.

The distribution of PGP polymorphism varies by race. The 'normal' 3435C allele is found in 61% African American and 26% in European American. The clinically important 3435T polymorph is found in 13% of African American and 62% of European American. The 3435T allele has been associated with reduced PGP expression (concentration) and consequently higher absorption. Digoxin levels were higher in healthy subjects with the 3435T allele compared with results in subjects with the 3435C allele.

1.Passive diffusion:

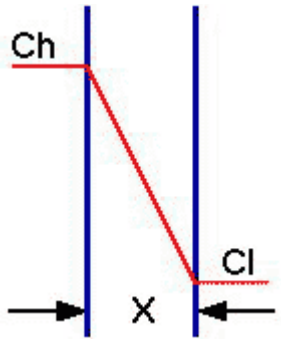


Diagram of Passive Transport with a Concentration Gradient

Most (many) drugs cross biologic membranes by passive diffusion. Diffusion occurs when the drug concentration on one side of the membrane is higher than that on the other side. Drug diffuses across the membrane in an attempt to equalize the drug concentration on both sides of the membrane.

If the drug partitions into the lipid membrane a concentration gradient can be established. The rate of transport of drug across the membrane can be described by Fick's first law of diffusion:-

$$\text{Rate of diffusion} = \frac{dM}{dt} = -\frac{D \bullet A \bullet (Ch - Cl)}{x}$$

Fick's First Law, Rate of Diffusion

The parameters of this equation are:-

D: diffusion coefficient. This parameter is related to the size and lipid solubility of the drug and the viscosity of the diffusion medium, the membrane. As lipid solubility increases or molecular size decreases then D increases and thus dM/dt also increases.

A: surface area. As the surface area increases the rate of diffusion also increase. The surface of the intestinal lining (with villae and microvillae) is much larger than the stomach. This is one reason absorption is generally faster from the intestine compared with absorption from the stomach.

x: membrane thickness. The smaller the membrane thickness the quicker the diffusion process. As one example, the membrane in the lung is quite thin thus inhalation absorption can be quite rapid.

(Ch -Cl): concentration difference. Since V, the apparent volume of distribution, is at least four liters and often much higher the drug concentration in blood or plasma will be quite low compared with the concentration in the GI tract. It is this concentration gradient which allows the rapid complete absorption of many drug substances.

Normally Cl << Ch then:-

$$\frac{dM}{dt} = -\frac{D \bullet A \bullet Ch}{x} = -\frac{D \bullet A \bullet Xg}{x \bullet Vg}$$

constant, ka

Thus the absorption of many drugs from the G-I tract can often appear to be first-order.

3. Pinocytosis = Phagocytosis= Vesicular transport:

Larger particles are not able to move through membranes or interstitial spaces so other processes must be available. These processes involve the entrapment of larger particles by the cell membrane and incorporation into the cell, cytosis. A spontaneous incorporation of a small amount of extracellular fluid

with solutes is called pinocytosis. Phagocytosis is a similar process involving the incorporation of larger particles. Examples include Vitamin A, D, E, and K, peptides in newborn.

Endo/exocytosis

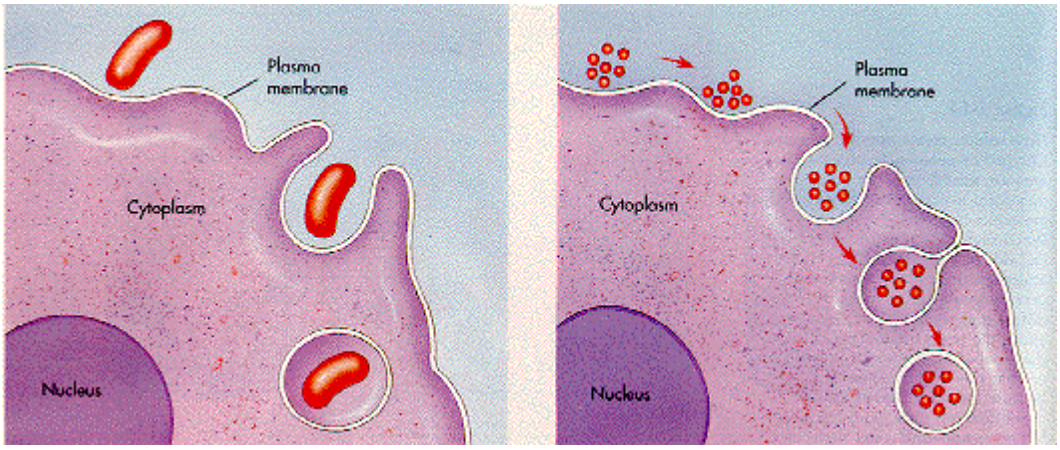
This is the movement of **very large** molecules (or particles, bacteria or other organisms) across the cell membrane. It involves the fusion of vesicles (containing the target/victim) with the cell membrane e.g. bacteria entering **macrophages**. Substances destined for secretion are packaged in the **Golgi body** first.

Pinocytosis ('cell drinking')

This is the uptake of large molecules (DNA, protein) from **solution**, by a form of endocytosis – the vesicles formed are minute and short-lived.

Phagocytosis ('cell eating')

This is the uptake of **solid particles** by a cell e.g. Amoeba feeding, phagocytes engulfing bacteria.



4. Pore transport:

Very small molecules (such as water, urea and sugar) are able to rapidly cross cell membrane as if the membrane contained pores or channels Although, such pores have never been seen by microscope, this model of transportation is used to explain renal excretion of drugs and uptake of drugs into the liver.

Small drug molecules move through this channel by diffusion more `rapidly than at other parts of the membrane. A certain type of protein called transport protein may form an open channel across the lipid membrane of cell.

5. Ion pair formation:

Strong electrolyte drugs are highly ionized (such as quaternary nitrogen compounds) with extreme pKa values, and maintain their charge at physiological pH.

These drugs penetrate membranes poorly. When linked up with an oppositely charged ion, an ion pair is formed in which the overall charge of the pair is neutral. The neutral complex diffuses more easily across

the membrane. An example of this in case of propranolol, a basic drugs that forms an ion pair with oleic acid.

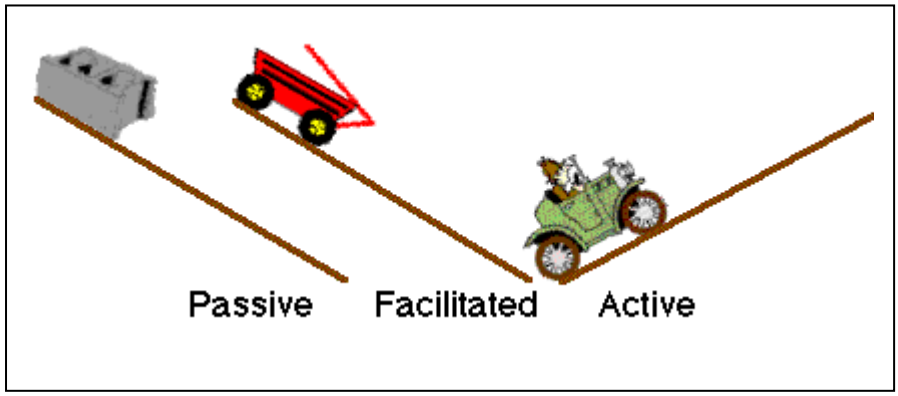


Illustration of Different Transport Mechanisms

C. Gastrointestinal (GI) Physiology

I. Characteristics of GI physiology and Drug Absorption

Organs	**pH**	**Membrane**	**Blood Supply**	**Surface Area**	**Transit Time**	**By-pass liver**
Buccal	approx 6	thin	Good, fast absorption with low dose	small	Short unless controlled	yes
Esophagus	6-7	Very thick no absorption	-	small	short, typically a few seconds, except for some coated tablets	-
Stomach	1.7-4.5 decompositio n, weak acid unionized	normal	good	small	30 min (liquid) - 120 min (solid food), delayed stomach emptying can reduce intestinal absorption	no
Duodenum	5 - 7	normal	good	very	very short (6"	no

	bile duct, surfactant properties			large	long), window effect	
Small Intestine	6 -7	normal	good	very large 10 - 14 ft, 80 cm^2 /cm	about 3 hours	no
Large Intestine	6.8 - 7	-	good	not very large 4 - 5 ft	long, up to 24 hr	lower colon, rectum yes

FACTORS AFFECTING DRUG ABSORPTION

List of content:--

I.PHARMACEUTICAL FACTORS

A] Chemical factors

B] Physicochemical properties of drug substances

1. Drug solubility & dissolution rate
2. Particles size & effective surface area
3. Polymorphism & amorphism
4. Solvates & hydrates
5. Salt form of drug
6. Ionization state
7. Drug pKa & lipophilicity & GI pH ---pH partition hypothesis.

C] Formulation Factors

1. Disintegration time
2. Manufacturing variables
    a. Method of granulation
    b. Compression force
3. Nature & type of dosage form
4. Pharmaceutical ingredients
5. Product age & storage conditions

II PATIENT RELATED FACTORS

[A] PHYSIOLOGICAL FACTORS

(1) Membrane physiology

A. Nature of cell membrane

B. Transport processes

(2) Gastero-Intestinal motility

- **a.** Gastric emptying rate
- **b.** Intestinal motility
- **c.** Drug stability in GIT
- **d.** pH of GIT
- **e.** Surface area of GIT
- **f.** Intestinal transit
- **g.** Blood flow to GIT.
- **h.** Effect of food

(3) Age

[B] CLINICAL FACTORS

Introduction

Definitions

Pharmacokinetics

• Evaluate the way in which a drug interacts with various barriers within a biological system

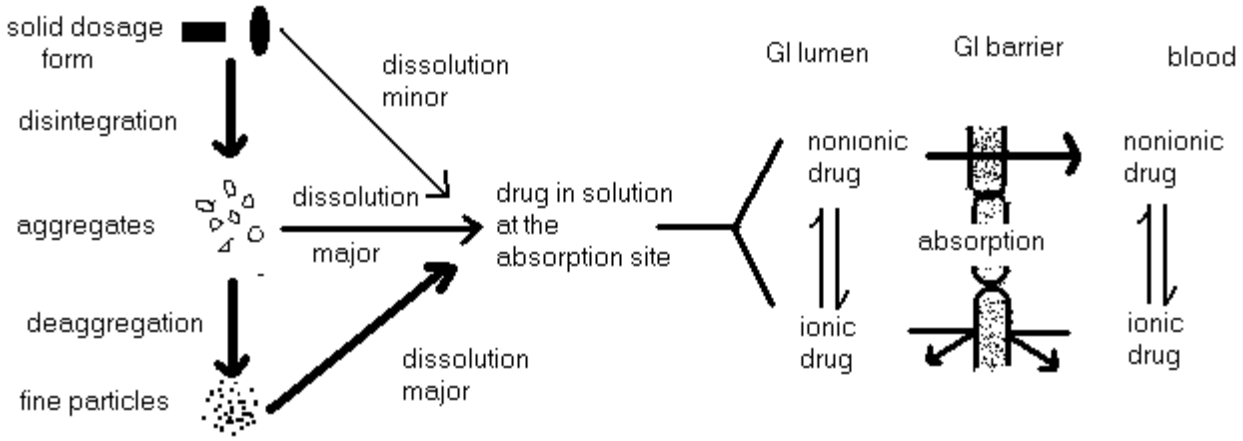
Pharmacodynamics

• Study of the relationship between systemic exposure of a drug and it's biological effects on tissue

 Absorption can be defined as the movement of active drug (or prodrug) from the site of administration across biologic barriers into a site where it is measured in the **blood.** This site of measurement is not specified.

 Bioavailability can be defined as the fraction of administered drug that reaches the **systemic circulation**

 Note the difference in endpoint measurement sites.



seqence of events in the absorption of drugs from orally administered solid dosage form

FACTORS INFLUENCING GI ABSORPTION OF A DRUG FROM IT'S DOSAGE FORM

I PHARMACEUTICAL FACTORS:

It include factors relating to the-

[A] Chemical Factors

 A variety of chemical options can be used to improve the stability and systemic availability of drugs.

 For example, esters can be prepared of both acids and bases to produce more stable derivatives, which hydrolyse to the active parent once absorbed. The stability and solubility of both acids and bases tend to increase when they are in the form of salts.

 Typically, administration of soluble salts of penicillin give rise to higher circulating antibiotic levels than the free acid. When the salt of a weak acid dissolves in the stomach, it generates a diffusion layer of relatively high pH which,in turn, promotes further dissolution. The same argument could theoretically be used for basic drugs.

 However, the pH effect in this case is swamped by the very low pH present in stomach fluids.

 Thus, salts of basic drugs are used primarily for handling and solubility rather than for improved dissolution.

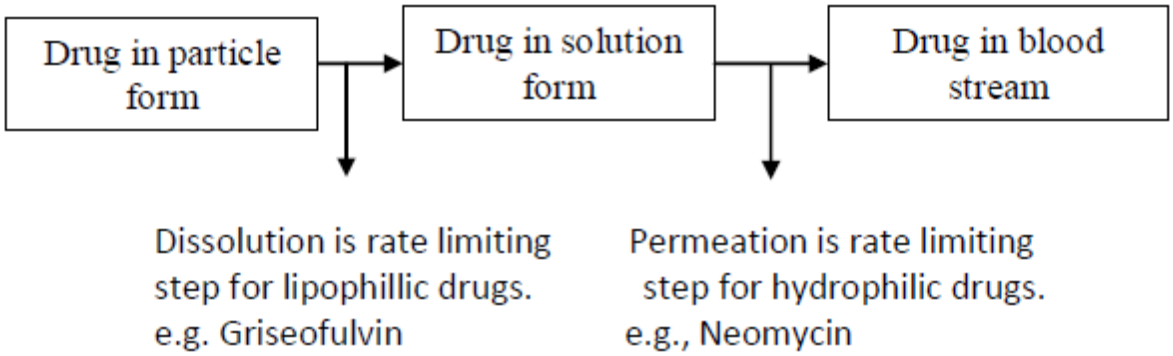
B] Physicochemical properties of drug substances

1.Drug solubility and dissolution rate –

 The rate determining steps in absorption of orally administered drugs are**:**

II.Rate of dissolution

III. Rate of drug permeation through the biomembrane.



 Imp prerequisite for the absorption of a drug is that it must be present in aq solution & this is depends on drug's aq solubility &its dissolution rate.

2. Particle size and effective surface area –

 Smaller the particle size (by micronization) ⇨ greater is the effective surface area ⇨ more intimate contact b/w solid surface and aq solvent ⇨ higher is the dissolution rate ⇨ increase in absorption efficiency

 e.g. poorly aq soluble nonhydrophobic drugs like Griseofulvin, chloramphenicol whose dissolution is rate limited.

 Particle size reduction has been used to increase the absorption of a large number of poorly soluble drugs, such as bishydroxycoumarin, digoxin, griseofulvin, nitrofurantoin,and tolbutamide.

 Griseofulvin has extremely low aqueous solubility, and material of normal particle size gave rise to poor and erratic absorption.

 Microsize particles improve absorption, but it is improved even more when it is formulated in ultramicrosize particles as a monomolecular dispersion in polyethylene glycol.

3. Polymorphism and amorphism –

 When sub exist in different crystalline form i.e. in polymorphic form then diff forms are Many compounds form crystals with different molecular arrangements, or polymorphs. These polymorphs may have different physical properties, such as dissolution rate and solubility.

Stable form	Metastable form
- Lowest energy state - Highest m.pt. - Least aq solubility - Dissolution rate limited	- Less stable form - Highest energy state - Lowest m.pt. - Higher aq solubility - Better absorption and Bioavailability

 e.g The vitamin riboflavin exists in several polymorphic forms, and these have a 20-fold range in aqueous solubility.

 Polymorphs that have no crystal structure, or amorphic forms, have different physical properties from the crystalline forms.

 Absorption of many orally administered drugs is controlled by dissolution rate.

 Amorphous forms generally dissolve faster than crystalline forms because no energy is needed to break up the crystal lattice. For this reason, the amorphous form is often preferred over the crystalline form and several drugs, including hydrocortisone and prednisolone, are marketed in the amorphic form.

 E.g. novobiocin

Amorphous form	Crystalline form
→ More soluble	→ Less soluble
→ Rapidly dissolving	→ Slower dissolving
→ Readily absorbed	→ Not absorbed to significant extent

4. Solvates/hydrates –

 During their preparation, drug crystals may incorporate one or more solvent molecules to form solvates.

 The most common solvate is water. If water molecules are already present in a crystal structure, the tendency of the crystal to attract additional water to initiate the dissolution process is reduced, and solvated (hydrated) crystals tend to dissolve more slowly than anhydrous forms.

 Significant differences have been reported in the dissolution rate of hydrated and anhydrous forms of ampicillin, caffeine, theophylline, glutethimide, and mercaptopurine

 The clinical significance of these differences has not been examined but is likely to be slight.

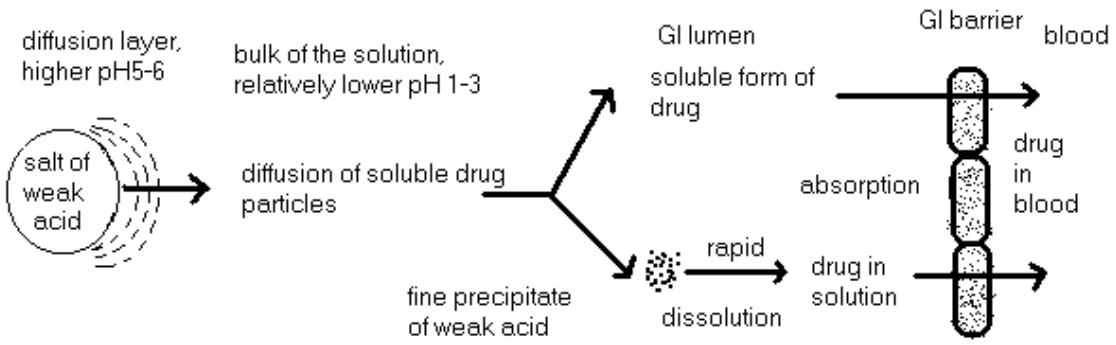
 Solvates have greater solubility than their nonsolvates.e.g. chloroform solvates of Griseofulvin, n-pentanol solvate of fludrocortisone.

5. Salt form of drug: --

 At given pH, the solubility of drug, whether acidic/basic or its salt, is a constant.

 While considering the salt form of drug, pH of the diffusion layer is imp not the pH of the bulk of the solution.

 E.g. of salt of weak acid. ---Which increases the pH of the diffusion layer, which promotes the solubility and dissolution of a weak acid and absorption is bound to be rapid.

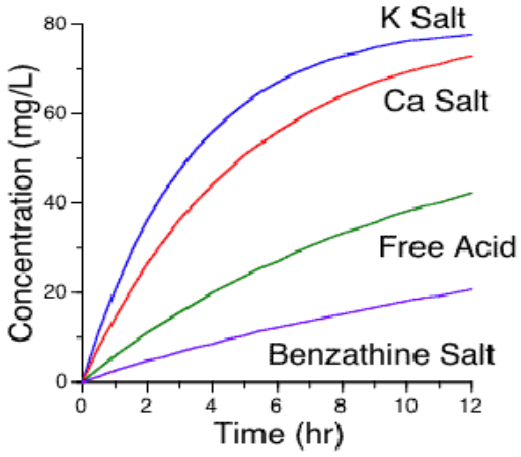


dissolution &absorption of an acidic drug administered in a salt from

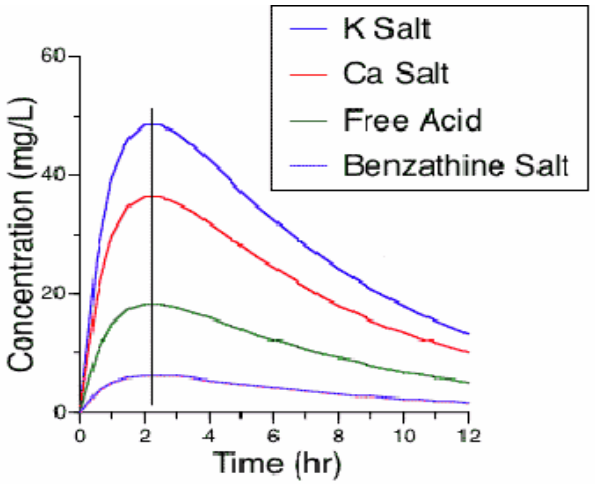
 Reverse in the case of salts of weak bases, it lowers the pH of diffusion layer and the promoted the absorption of basic drugs.

 Other approach to enhance the dissolution and absorption rate of certain drugs is by formation of in – situ salt formation i.e. increasing in pH of microenvironment of drug by incorporating buffer agent.e.g. aspirin, penicillin

 But sometimes more soluble salt form of drug may result in poor absorption.e.g. sodium salt of phenobarbitone and phenobarbitone, tablet of salt of phenobarbitone swelled, it did not get disintegrate thus dissolved slowly and results in poor absorption.



A) It shows the dissolution Profile of various salts



B) It shows the Penicillin plasma Conc. in fasting subjects, after oral Administration of 4 x 10^5 units of Penicillin in different forms.

 Dissolution profile of various salts, where A) shows that potassium salt has the highest solubility B) shows the dissolution profile of various penicillin salts.

6. Ionization state :-

 Unionized state is imp for passive diffusion through membrane so imp for absorption.

 Ionized state is imp for solubility.

7. Drug pKa & lipophilicity & GI pH --- pH partition hypothesis: --

 pH – partition theory states that for drug compounds of molecular weight more than 100, which are primarily transported across the biomembrane by passive diffusion, the process of absorption is governed by

 pKa of drug

 The lipid solubility of the unionized drug

 pH at the absorption site.

a) pKa of drug

 Amount of drug that exist in unionized form and in ionized form is a function of pKa of drug & pH of the fluid at the absorption site and it can be determined by Henderson-hesselbach equation: -

$$pH = pKa + \log \frac{[\text{ionized form}]}{[\text{Unionized form}]} \quad \text{For, Acidic drugs}$$

$$pH = pKa + \log \frac{[\text{unionized form}]}{[\text{Ionized form}]} \quad \text{For, Basic drugs}$$

Drugs	PKa	PH/site of absorption
Very weak acids e.g. pentobarbital Hexobarbital	>8	Unionized at all pH values; Absorbed along the entire length of GIT
Moderately weak acids e.g. aspirin Ibuprofen	2.5 – 7.5	Unionized in gastric pH& ionized in intestinal pH; better absorption from stomach
Stronger acids E.g. disodium cromoglylate	< 2.0	Ionized at all pH values; Poorly absorbed from GIT
Very weak bases e.g. theophylline Caffeine	< 5.0	Unionized at all pH values; Absorbed along entire GIT
Moderately weak bases e.g. codeine	5 – 11	Ionized at gastric pH, unionized at intestinal pH; better absorption from intestine.
Stronger bases e.g. guanethidine	> 11	Ionized at all pH values; Poorly absorbed from GIT

b) Lipophilicity and drug absorption: -

o Ideally for optimum absorption, a drug should have sufficient aq solubility to dissolve in fluids at absorption site and lipid solubility (Ko/w) high enough to facilitate the partitioning of the rug in the lipoidal biomembrane i.e. drug should have perfect HLB for optimum Bioavailability.

o And Ko/w = Distribution of drug in organic phase (octanol)

Distribution of drug in aq phase

o As Ko/w i.e. lipid solubility i.e. partition coefficient increases percentage drug absorbed increases.

[C] Formulation Factors:-

1. Disintegration time: -

 Rapid disintegration is important to have a rapid absorption so lower D.T is required.

 Now D.T of tablet is directly proportional to –amount o f binder

-Compression force.

 And one thing should be remembered that in vitro disintegration test gives no means of a guarantee of drugs B.A. because if the disintegrated drug particles do not dissolve then absorption is not possible.

2. Manufacturing variables: -

a). Method of granulation

 Wet granulation yields a tablet that dissolves faster than those made by other granulating methods. But wet granulation has several limitations like formation of crystal bridge or chemical degradation.

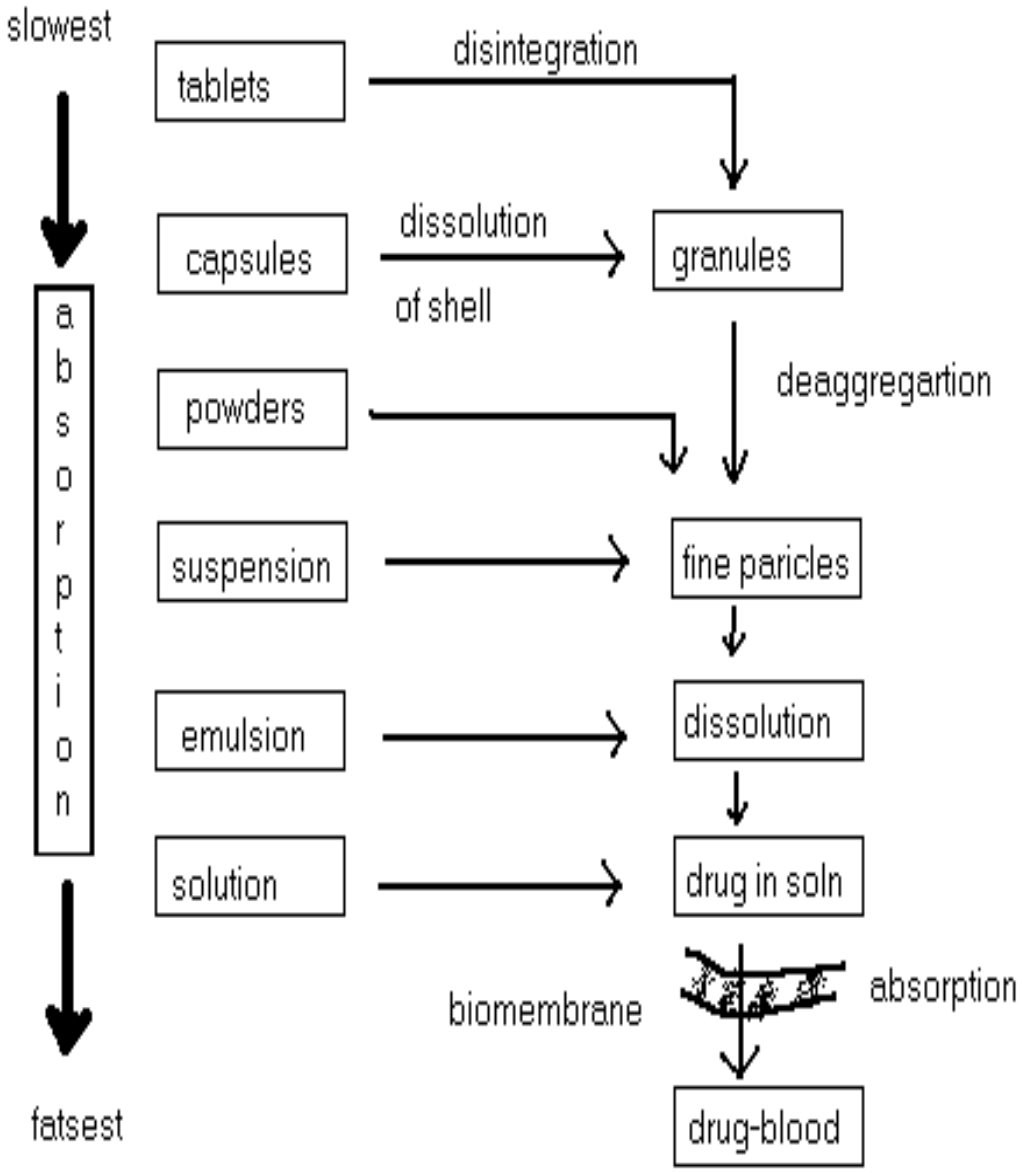
 Other superior recent method named APOC (agglomerative phase of communition) that involves grinding of drug till spontaneous agglomeration and granules are prepared with higher surface area. So tablet made up of this granules have higher dissolution rate.

b) Compression force: -

 Higher compression force yields a tablet with greater hardness and reduced wettability & hence have a long D.T. but on other hand higher compression force cause crushing of drug particles into smaller ones with higher effective surface area which in decrease in D.T.

 So effect of compression force should be thoroughly studied on each formulation.

3. Nature and type of dosage form –



Drug formulations are designed to provide an attractive, stable, and convenient method to use products. Conventional dosage forms may be broadly characterized in order of decreasing dissolution rate as solutions, solid solutions, suspensions, capsules and tablets, coated capsules and tablets, and controlled release formulations.

A.Solutions

 Aqueous solutions, syrups, elixirs, and emulsions do not present a dissolution problem and generally result in fast and often complete absorption as compared to solid dosage forms. Due to their generally good systemic availability, solutions are frequently used as bioavailability standards against which other dosage forms are compared.

B.Solid solutions

 The solid solution is a formulation in which drug is trapped as a solid solution or monomolecular dispersion in a water-soluble matrix. Although the solid solution is an attractive approach to increase drug absorption, only one drug, griseofulvin, is currently marketed in this form.

C. Suspensions

 A drug in a suspension is in solid form, but is finely divided and has a large surface area. Drug particles can diffuse readily between the stomach and small intestine so that absorption is relatively insensitive to stomach emptying rate.

 Adjusting the dose to a patient's needs is easier with solutions and suspensions than with solid dosage forms. Liquid dosage forms, therefore, have several practical advantages besides simple dissolution rate.

 However, they also have some disadvantages, including greater bulk, difficulty in handling, and perhaps reduced stability.

D. Capsules and tablets

 These formulations differ from each other in that material in capsules is less impacted than in compressed tablets. Once a capsule dissolves, the contents generally disperse quickly. The capsule material,

 Although water soluble, can impede drug dissolution by interacting with the drug, but this is uncommon.

 Tablets generally disintegrate in stages, first into granules and then into primary particles. As particle size decreases, dissolution rate increases due to of increased surface area.

 Tablet disintegration was once considered a sufficient criterion to predict in vivo absorption.

As a general rule,the bio-availability of a drug from various dosage forms decrease in the following order:Solutions>Emulsions>Suspensions>Capsules>Tablets>Coated Tablets>Enteric coateds Tablets>Sustained Release Products.

4. Pharmaceutical ingredients/Excipients: -

 More the no. of excepients in dosage form, more complex it is & greater the potential for absorption and Bioavailability problems.

 Changing an excipient from calcium sulfate to lactose and increasing the proportion of magnesium silicate, increases the activity of oral phenytoin.

 Systemic availability of thiamine and riboflavin is reduced by the presence of Fuller's earth.

 Absorption of tetracycline from capsules is reduced by calcium phosphate due to complexation.

 Most of these types of interactions were reported some time ago and are unlikely to occur in the current environment of rigorous testing of new dosage forms and formulations.

a) Vehicle-

 Rate of absorption – depends on its miscibility with biological fluid.

 Miscible vehicles (aq or water miscible vehicle) –rapid absorption e.g. propylene glycol.

 Immiscible vehicles - absorption –depends on its partitioning from oil phase to aq body fluid.

b) Diluents-

 Hydrophilic diluents-form the hydrophilic coat around hydrophobic drug particles –thus promotes dissolution and absorption of poorly soluble hydrophobic drug.

c) Binders & granulating agent -

 Hydrophilic binders – imparts hydrophilic properties to granule surface – better dissolution of poorly wettable drug. e.g. starch, gelatin, PVP.

 More amount of binder – increases hardness of tablet – decrease dissolution & disintegration rate.

d) Disintegrants -

 Mostly hydrophilic in nature.

 Decrease in amount of disintegrants – significantly lowers B.A.

e) Lubricants -

 Commonly hydrophobic in nature – therefore inhibits penetration of water into tablet and thus dissolution and disintegration.

f) Suspending agents/viscosity agent –

 Stabilized the solid drug particles and thus affect drug absorption.

 Macromolecular gum forms unabsorbable complex with drug e.g. Na CMC.

 Viscosity imparters – act as a mechanical barrier to diffusion of drug from its dosage form and retard GI transit of drug.

g) Surfactants –

 May enhance or retards drug absorption by interacting with drug or membrane or both.

 Surfactants have been considered as absorption enhancers, again mostly in animals. Polyoxyethylene ethers have been shown to enhance gastric or rectal absorption of lincomycin,penicillin, cephalosporins, and fosfomycin in rats and rabbits.

 However, in humans, oral polyoxyethylene-20-oleyl ether resulted in poor and variable insulin absorption.

 In general, unionic surfactants have little effect on membrane structure but cationic surfactants have been associated with reversible cell loss and loss of goblet cells.

 Physiologic surfactants – bile salts – promotes absorption – e.g. Griseofulvin, steroids

 It may decrease absorption when it forms the unabsorbable complex with drug above CMC.

h)Bile salts-

 Bile contains conjugates of cholic acid and chenodeoxycholic acid, which emulsify dietary fat, facilitate lipolysis, and transport lipid molecules through the unstirred layer of the intestinal mucosa by micellar solubilization. The ability of bile salts to promote lipid absorption has prompted their investigation as absorption enhancers for drugs, with modest success.

 Absorption of insulin can be increased by bile salts, both in experimental animals and in humans.

i) Colourants

 Even a low concentration of water soluble dye can have an inhibitory effect on dissolution rate of several crystalline drugs.

 The dye molecules get absorbed onto the crystal faces and inhibit the drug dissolution. For example: Brilliant blue retards dissolution of sulfathiazole.

5. Product age and storage conditions –

Product aging and improper storage conditions adversely affect B.A.

E.g. –precipitation of drug in solution
particle size of suspension
& Hardening of tablet

→ decrease rate of Change in drug dissolution & absorption.

II PATIENT RELATED FACTORS

Physiologic Factors Related to Drug Absorption:

The systemic absorption of a drug is dependent on

(1) the physicochemical properties of the drug,

(2) the nature of the drug product, and

(3) the anatomy and physiology of the drug absorption site.

1) Membrane Physiology

A) Nature of Cell Membrane

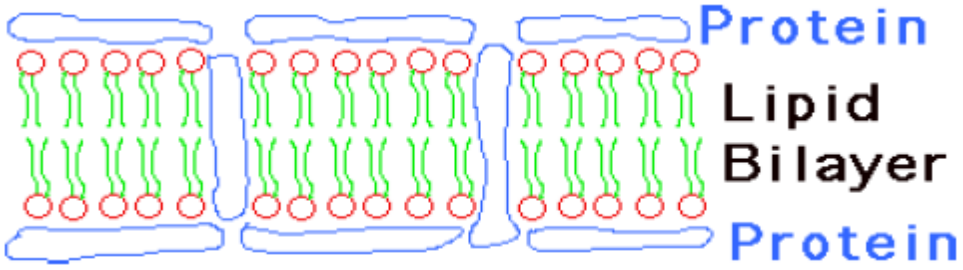


Fig 1.1 Cell Membrane Structure (Fluid Mosaic Model)

 The fluid mosaic model, proposed by , explains the transcellular diffusion of polar molecules.

 According to this model, the cell membrane consists of globular proteins embedded in a dynamic fluid, lipid bilayer matrix ().

 These proteins provide a pathway for the selective transfer of certain polar molecules and charged ions through the lipid barrier.

 As shown in , transmembrane proteins are interdispersed throughout the membrane. Two types of pores of about 10 nm and 50 to 70 nm were inferred to be present in membranes based on capillary membrane

transport studies (). These small pores provide a channel through which water, ions, and dissolved solutes such as urea may move across the membrane.

B) Trasport Processes

Passive Diffusion

 lipophilic drug may pass through the cell or go around it. If the drug has a low molecular weight and is lipophilic, the lipid cell membrane is not a barrier to drug diffusion and absorption.

 Passive diffusion is the process by which molecules spontaneously diffuse from a region of higher concentration to a region of lower concentration. This process is *passive* because no external energy is expended.

Carrier-Mediated Transport

 Theoretically, a lipophilic drug may pass through the cell or go around it. If the drug has a low molecular weight and is lipophilic, the lipid cell membrane is not a barrier to drug diffusion and absorption.

 In the intestine, drugs and other molecules can go through the intestinal epithelial cells by either diffusion or a carrier-mediated mechanism. Numerous specialized carrier-mediated transport systems are present in the body, especially in the intestine for the absorption of ions and nutrients required by the body.

Active Transport

 Active transport is a carrier-mediated transmembrane process that plays an important role in the gastrointestinal absorption and in renal and biliary secretion of many drugs and metabolites.

 A few lipid-insoluble drugs that resemble natural physiologic metabolites (such as 5-fluorouracil) are absorbed from the gastrointestinal tract by this process. Active transport is characterized by the transport of drug against a concentration gradient—that is, from regions of low drug concentrations to regions of high concentrations.

 Therefore, this is an energy-consuming system. In addition, active transport is a specialized process requiring a carrier that binds the drug to form a carrier–drug complex that shuttles the drug across the membrane and then dissociates the drug on the other side of the membrane

Vesicular Transport

 An example of exocytosis is the transport of a protein such as insulin from insulin-producing cells of the pancreas into the extracellular space. The insulin molecules are first packaged into intracellular vesicles, which then fuse with the plasma membrane to release the insulin outside the cell.

Pore (Convective) Transport

 Very small molecules (such as urea, water, and sugars) are able to cross cell membranes rapidly, as if the membrane contained channels or pores. Although such pores have never been directly observed by

microscopy, the model of drug permeation through aqueous pores is used to explain renal excretion of drugs and the uptake of drugs into the liver.

Ion-Pair Formation

 Strong electrolyte drugs are highly ionized or charged molecules, such as quaternary nitrogen compounds with extreme pKa values. Strong electrolyte drugs maintain their charge at all physiologic pH values and penetrate membranes poorly. When the ionized drug is linked up with an oppositely charged ion, an *ion pair* is formed in which the overall charge of the pair is neutral. This neutral drug complex diffuses more easily across the membrane.

 For example, the formation of ion pairs to facilitate drug absorption has been demonstrated for propranolol, a basic drug that forms an ion pair with oleic acid, and quinine, which forms ion pair with hexylsalicylate

2) Gstero-Intestinal Physiology

(A) Gastric emptying rate:-

 Anatomically, a swallowed drug rapidly reaches the stomach.

 Eventually, the stomach empties its contents into the small intestine. Because the duodenum has the greatest capacity for the absorption of drugs from the GI tract, a delay in the gastric emptying time for the drug to reach the duodenum will slow the rate and possibly the extent of drug absorption, thereby prolonging the onset time for the drug.

 Some drugs, such as penicillin, are unstable in acid and decompose if stomach emptying is delayed. Other drugs, such as aspirin, may irritate the gastric mucosa during prolonged contact.

 Gastric emptying rate is faster in case of solution & suspensions than solid & nondisintegrating dosage forms.

Factors that influence gastric emptying rate are: -

a. Volume of meal

b. Composition of meal

c. Physical state and viscosity of meal

d. Temperature of meal

e. Gastrointestinal pH

f. Electrolyte and osmotic pressure

g. Body posture

h. Emotional state

i. Disease state.

(B) Intestinal motility: -

 Normal peristaltic movements mix the contents of the duodenum, bringing the drug particles into intimate contact with the intestinal mucosal cells.

 The drug must have a sufficient time (*residence time*) at the absorption site for optimum absorption. In the case of high motility in the intestinal tract, as in diarrhea, the drug has a very brief residence time and less opportunity for adequate absorption.

(C) Drug stability in GIT: -

 Metabolism or degradation by enzymes or chemical hydrolysis may adversely affect the drug absorption and thus reduces B.A.

 Destruction in gastric acid.

 Generally a problem with orally administered drugs.

(D) Intestinal transit: -

 Long intestinal transit time is desirable for complete absorption of drug e.g. for enteric coated formulation & for drugs absorbed from specific sites in the intestine.

 Peristaltic contraction promotes drug absorption by increasing the drug membrane contact and by enhancing dissolution especially of poorly soluble drugs.

 Influenced by food, disease and drugs. e.g. metoclopramide which promotes intestinal transit &thus enhance absorption of rapidly soluble drugs while anticholinergic retards intestinal transit and promotes the absorption of poorly soluble drugs.

(E) Blood flow to GIT:

 Once the drug is absorbed from the small intestine, it enters via the mesenteric vessels to the hepatic-portal vein and the liver prior to reaching the systemic circulation. Any decrease in mesenteric blood flow, as in the case of congestive heart failure, will decrease the rate of drug removal from the intestinal tract, thereby reducing the rate of drug bioavailability

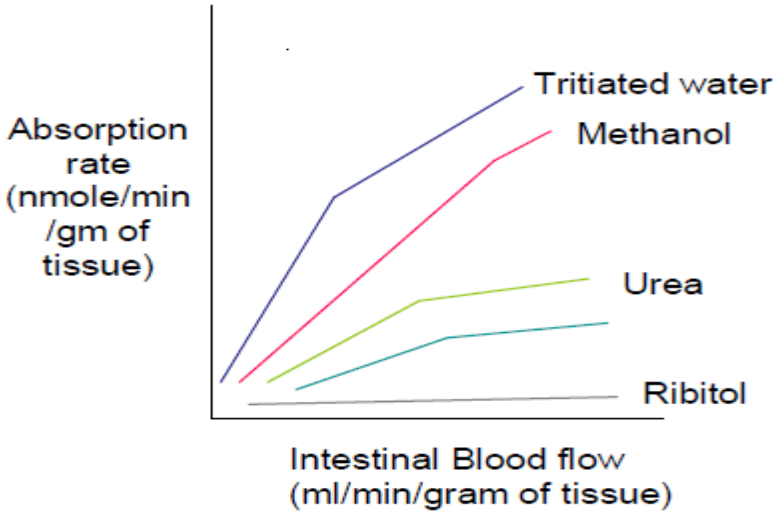
 GIT has higher perfusion rate because it is extensively supplied by blood capillary network.

 Therefore help in maintaining sink conditions &concentration gradient for drug absorption by rapidly removing of drug from site of action.

 Blood flow is imp for actively absorption of drugs.

 Highly permeable drugs or drugs that absorbed through pores –GI perfusion is rate limiting while the drugs with poor permeability GI perfusion is not imp.

 Perfusion increases after meals & persist for few hours but absorption is not affected.



Graph representing the absorption rate of various drugs affected by intestinal blood flow. 14

(F) Effect of Food

 The presence of food in the GI tract can affect the bioavailability of the drug from an oral drug product (). Digested foods contain amino acids, fatty acids, and many nutrients that may affect intestinal pH and solubility of drugs. The effects of food are not always predictable and can have clinically significant consequences. Some effects of food on the bioavailability of a drug from a drug product include ():

 Delay in gastric emptying

 Stimulation of bile flow

 A change in the pH of the GI tract

 An increase in splanchnic blood flow

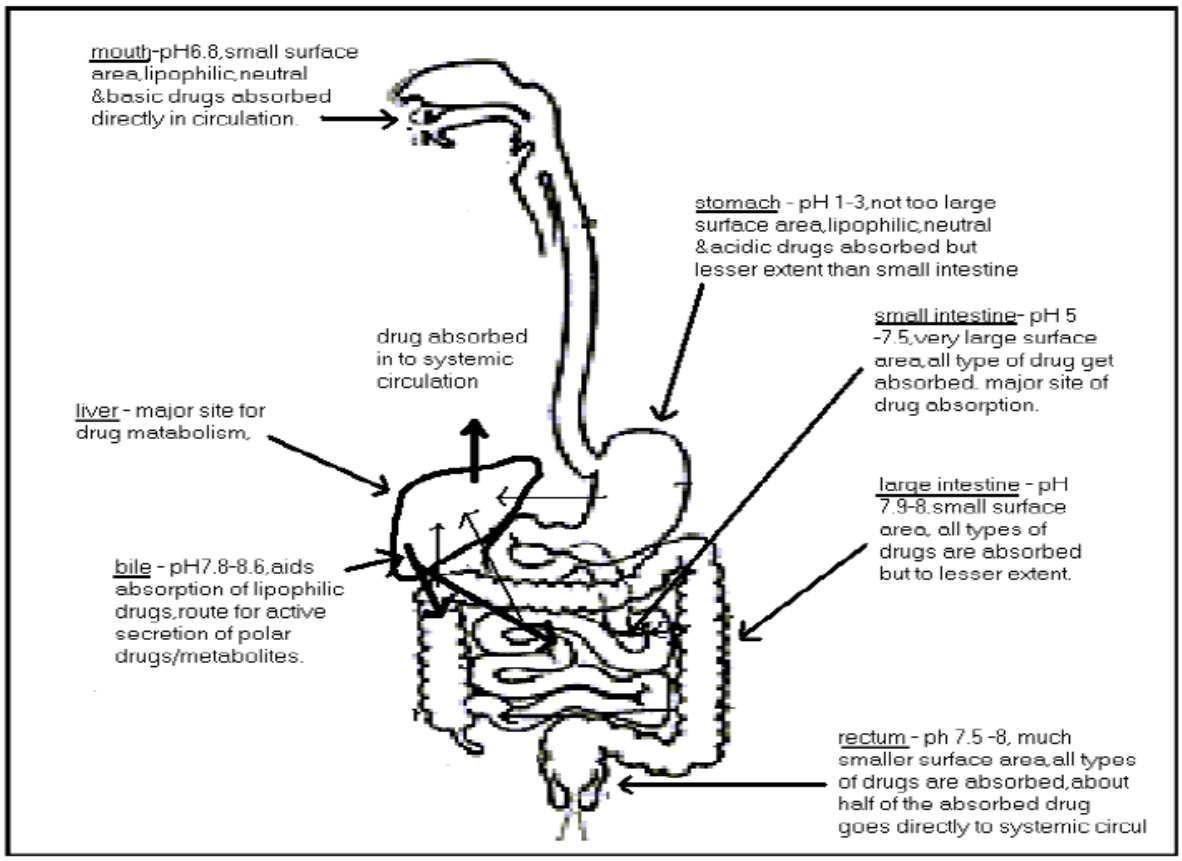
 A change luminal metabolism of the drug substance

 Physical or chemical interaction of the meal with the drug product or drug substance

The absorption of some antibiotics, such as penicillin and tetracycline, is decreased with food; whereas other drugs, particularly lipid-soluble drugs such as griseofulvin and metazalone, are better absorbed when given with food containing a high fat content.

 Propranolol plasma concentrations are larger after food than in fasted subjects. This may be an interaction with the components of food.

(G) pH and surface area of GIT:



3) Age

 In infants, the gastric pH is high and intestinal surface and blood flow to the GIT is low resulting in altered absorption pattern in comparison to adults.

 In elderly persons, causes of impaired drug absorption include altered gastric emptying, decreased intestinal surface area and GI blood flow, higher incidents of achlorhydria and bacterial over growth in small intestine.

cific factors and presence of other drugs: e.g. intrinsic factor of the stomach

Clinical Factors:-

1) Diseases

Parkinson's disease may have difficulty swallowing and greatly diminished gastrointestinal motility. A case was reported in which the patient could not be controlled with regular oral levodopa medication because of poor absorption. Infusion of oral levodopa solution using a j-tube gave adequate control of his symptom.

Patients on tricyclic antidepressants (imiprimine, amitriptyline, and nortriptyline) and **antipsychotic drugs** (phenothiazines) with anticholinergic side effects may have reduced gastrointestinal motility or even intestinal obstructions. Delays in drug absorption, especially with slow-release products, have occurred. 16

Achlorhydricpatients may not have adequate production of acids in the stomach; stomach HCl is essential for solubilizing insoluble free bases. Many weak-base drugs that cannot form soluble salts will remain undissolved in the stomach when there is no hydrochloric acid present and are therefore unabsorbed. Salt forms of these drugs cannot be prepared because the free base readily precipitates out due to the weak basicity.

Dapsone, itraconazole, and ketoconazole may also be less well absorbed in the presence of achlorhydria. In patients with acid reflux disorders, proton pump inhibitors, such as omeprazole, render the stomach achlorhydric, which may also affect drug absorption. Co-administering orange juice, colas, or other acidic beverages can facilitate the absorption of some medications requiring an acidic environment.

HIV-AIDSpatients are prone to a number of gastrointestinal (GI) disturbances, such as increased gastric transit time, diarrhea, and achlorhydria. Rapid gastric transit time and diarrhea can alter the absorption of orally administered drugs. Achlorhydria may or may not decrease absorption, depending on the acidity needed for absorption of a specific drug. Indinavir,

for example, requires a normal acidic environment for absorption. The therapeutic window of indinavir is extremely narrow, so optimal serum concentrations are critical for this drug to be efficacious.

Congestive heart failure (CHF) patients with persistent edema have reduced splanchnic blood flow and develop edema in the bowel wall. In addition, intestinal motility is slowed. The reduced blood flow to the intestine and reduced intestinal motility results in a decrease in drug absorption. For example, furosemide (Lasix), a commonly used loop diuretic, has erratic and reduced oral absorption in patients with CHF and a delay in the onset of action.

Crohn's disease is an inflammatory disease of the distal small intestine and colon. The disease is accompanied by regions of thickening of the bowel wall, overgrowth of anaerobic bacteria, and sometimes obstruction and deterioration of the bowel. The effect on drug absorption is unpredictable, although impaired absorption may potentially occur because of reduced surface area and thicker gut wall for diffusion.

2) Drugs

 Anticholinergic drugs in general may reduce stomach acid secretion. Propantheline bromide is an anticholinergic drug that may slow stomach emptying and motility of the small intestine. Tricyclic antidepressants and phenothiazines also have anticholinergic side effects that may cause slower peristalsis in the GI tract. Slower stomach emptying may cause delay in drug absorption.

 Metoclopramide is a drug that stimulates stomach contraction, relaxes the pyloric sphincter, and, in general, increases intestinal peristalsis, which may reduce the effective time for the absorption of some drugs and thereby reduce the peak drug concentration and the time to reach peak drug concentration. For example, digoxin absorption from a tablet is reduced by metoclopramide but increased by an anticholinergic drug, such as propantheline bromide. Allowing more time in the stomach for the tablet to dissolve generally

helps with the dissolution and absorption of a poorly soluble drug, but would not be helpful for a drug that is not soluble in stomach acid.

 Antacids should not be given with cimetidine, because antacids may reduce drug absorption. Antacids containing aluminum, calcium, or magnesium may complex with drugs such as tetracycline, ciprofloxacin, and indinavir, resulting in a decrease in drug absorption. To avoid this interaction, antacids should be taken 2 hours before or 6 hours after drug administration. As mentioned, proton pump inhibitors, such as omeprazole, render the stomach achlorhydric, which may also affect drug absorption.

 Cholestyramine is a nonabsorbable ion-exchange resin for the treatment of hyperlipemia. Cholestyramine adsorbs warfarin, thyroxine, and loperamide, similar to activated charcoal, thereby reducing absorption of these drugs.

 Absorption of calcium in the duodenum is an active process facilitated by vitamin D, with calcium absorption as much as four times more than that in vitamin D deficiency states. It is believed that a calcium-binding protein, which increases after vitamin D administration, binds calcium in the intestinal cell and transfers it out of the base of the cell to the blood circulation.

Volume of distribution (VD)

The volume of distribution (VD) , also known as apparent volume of distribution, is a pharmacological term used to quantify the distribution of a medication between plasma and the rest of the body after oral or parenteral dosing.

 It is defined as the volume in which the amount of drug would need to be uniformly distributed to produce the observed blood concentration.

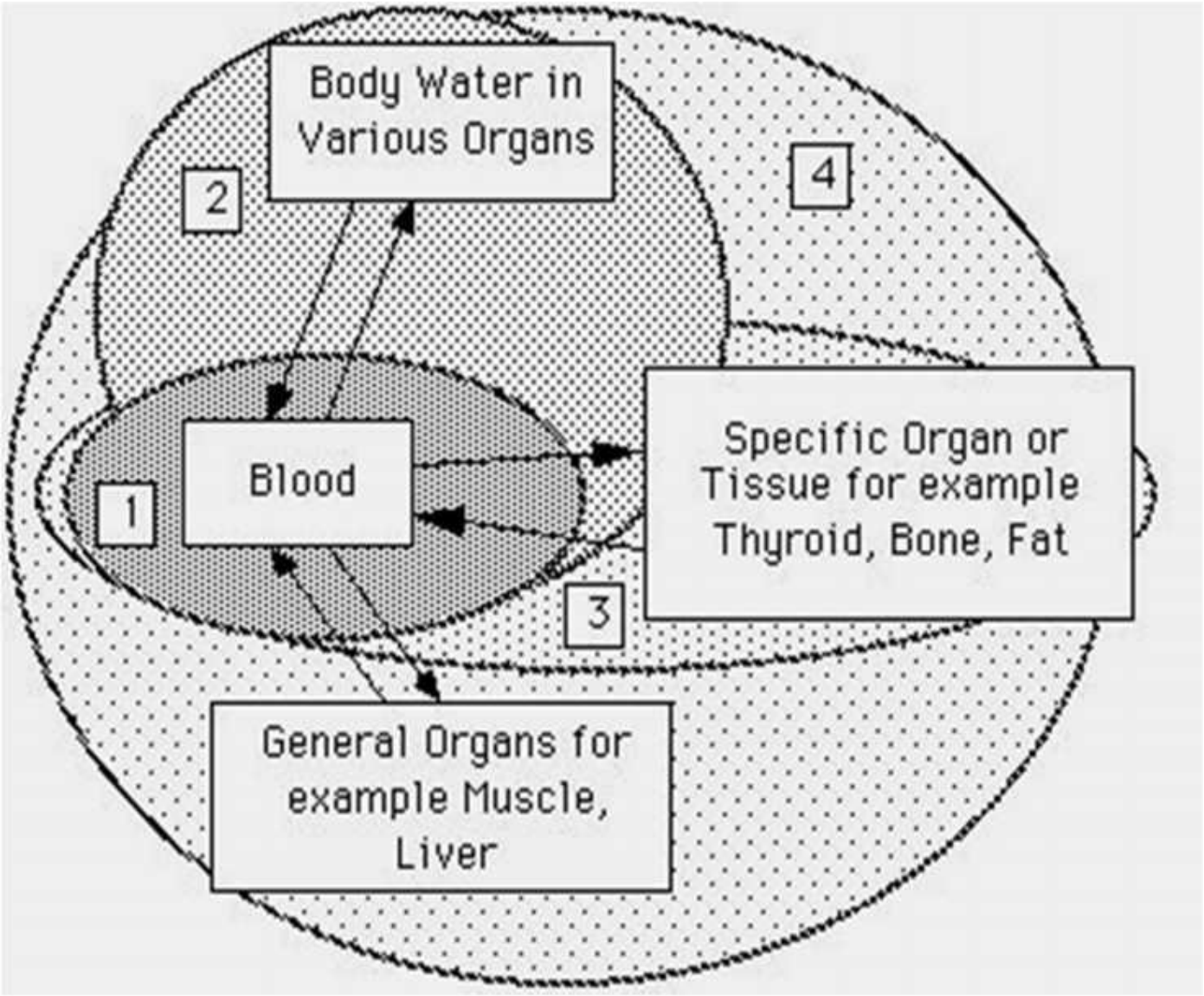
 The volume of distribution is a hypothetical volume of fluid into which a drug is distributed, it’s a useful in predicting amount of drug in the body.

Dose = Cp x VD

Total amount of drug in the body at equilibrium

VD =Plasma Drug concentration

VD = X0/KE.AUC


Body Water in Various Organs
2
4
Blood
1
Specific Organ or Tissue for example Thyroid, Bone, Fat
3
General Organs for example Muscle, Liver

Volumes of body fluids	
Fluid substances	**Volume (liter)**
Extra cellular Fluid	**14**
a) Plasma	**3-4**
b) Interstitial fluid	**10**
Intracellular fluids	**28**
Total body water	**42**

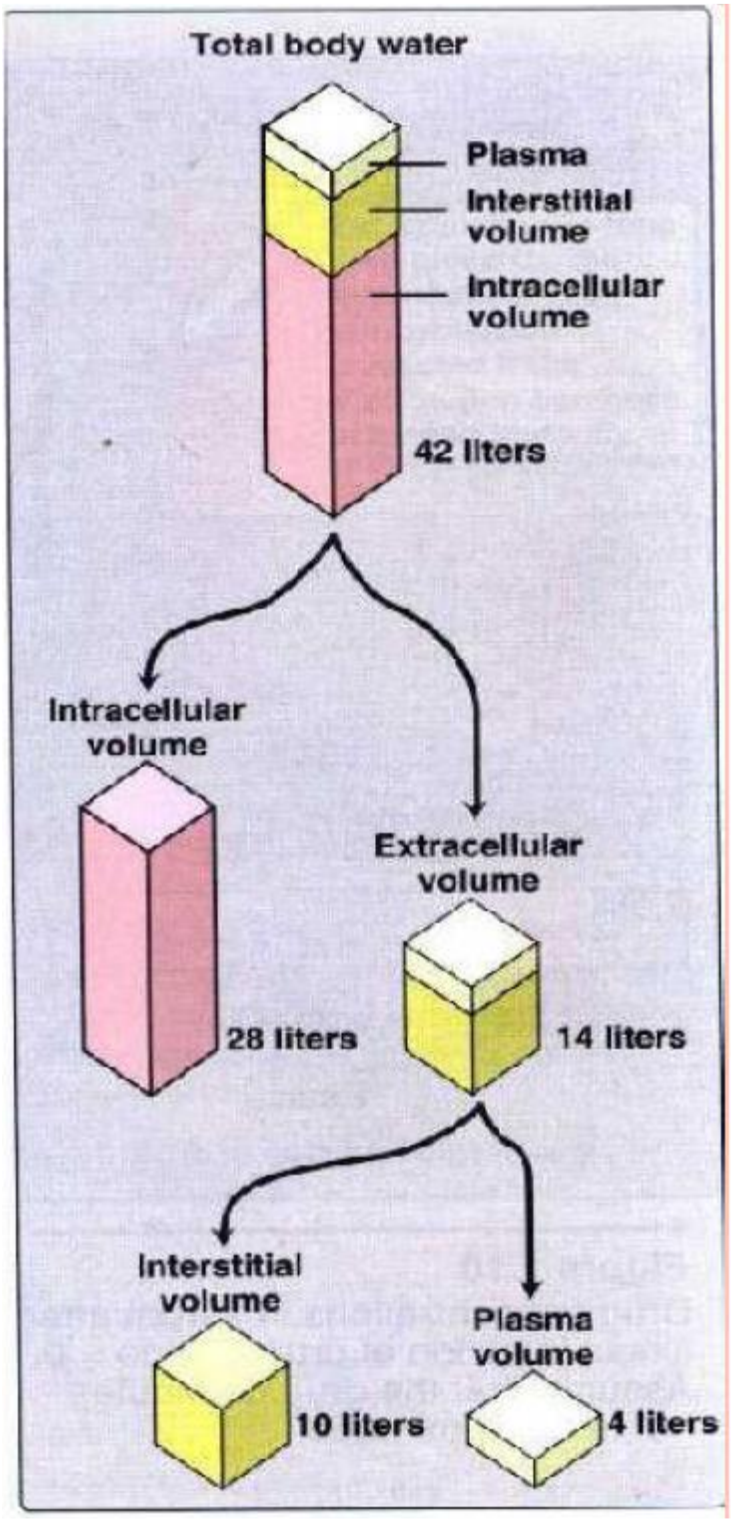
Water compartments of the body:

Once absorbed into the plasma a drug can be distributed to one of three (or all three) distinct fluid compartments.

Plasma compartment (6% body mass).

Extracellular fluid (20% body mass).

Total body water (60% body mass).



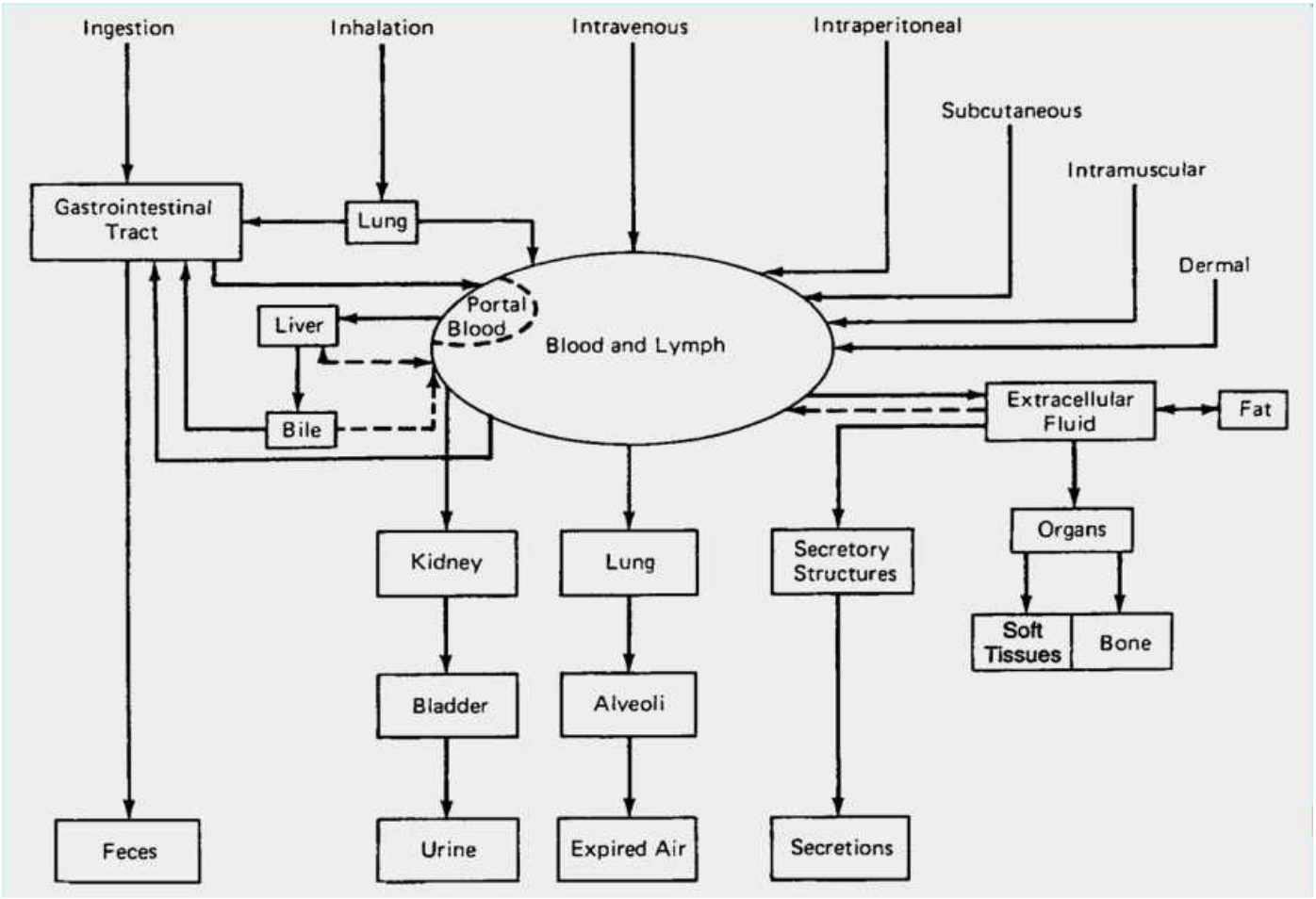
Drug Distribution:

 Distribution is the reversible transfer of a drug between the blood & the extravascular tissues

 Drug distribution is the process by which a drug reversibly leaves the plasma and enters the extracellular fluid to reach cells and tissues.

 This process depends on blood flow, capillary permeability, the degree of drug binding to plasma and tissue proteins and drug solubility.

Disposition of Drugs



PROTEIN BINDING OF DRUGS:

 Extensive plasma protein binding will cause more drug to stay in the central blood compartment.

 Therefore drugs which bind strongly to plasma protein tend to have lower volumes of distribution.

(↑ Protein binding = ↓ VD)

 Although drugs are bound to many macromolecules, binding to plasma protein is the most common. Of these plasma proteins, albumin, which comprises 50 % of the total proteins, binds the widest range of drugs. Drugs bound to plasma proteins are unable to diffuse to active sites. Irreversibly bound drugs are lost, reversibly bound drugs will respond to the concentration gradient in plasma as free drug is sequestered. It is the free drug that is active.

 This binding tends to be non-specific, drugs and endogenous substances can compete for binding sites. Albumin is the major drug binding entity and acts as a reservoir of drug.

Proteins with Potential Binding Sites for Various Drugs		
	Acidic Drugs	**Basic Drugs**
Binding Sites	Albumins/HSA	Globulins, α_1, α_2, β_1, β_2, γ
Example Drugs	**Bilirubin, Bile acids, Fatty Acids, Vitamin C, Salicylates, Sulfonamides, Barbiturates, Phenylbutazone, Penicillins, Tetracyclines, Probenecid**	**Adenisine, Quinacrine, Quinine, Streptomycin, Chloramphenicol, Digitoxin, Ouabain, Coumarin**

 Acidic drugs commonly bind to albumin, while basic drugs often bind to α1-acid glycoproteins and lipoproteins. Many endogenous substances, steroids, vitamins, and metal ions are bound to globulins

 PROTEIN BINDING DETERMINATION:

 Spectral changes

 Gel filtration

 Equilibrium dialysis

 Ultra filtration

The one compartment model assumption is that there is a rapid equilibration in drug concentrations throughout the body, however, this does not mean that the concentration is the same throughout the body. This is illustrated in Figure below….

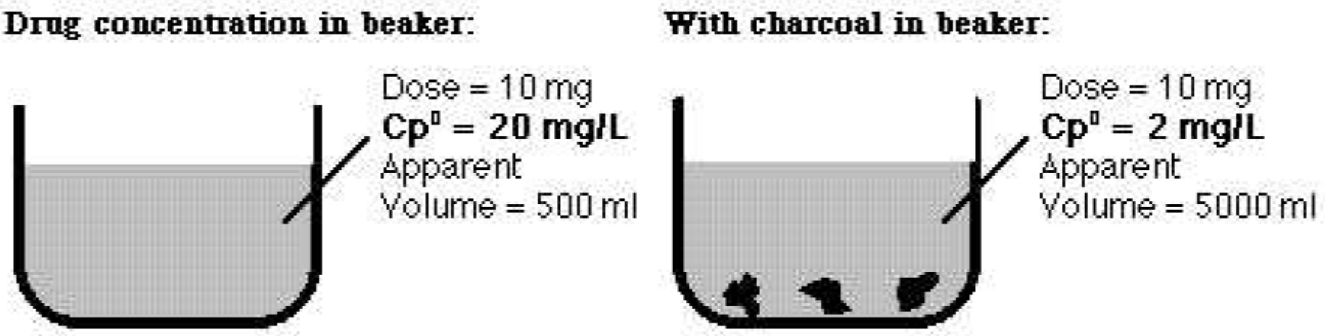
In the first beaker the concentration throughout the beaker is the same and the apparent volume of distribution is the same as the size of the beaker.

In the second beaker after a rapid equilibrium, distribution between the solution (representing plasma) and the charcoal (representing various tissues of the body) may be complete.

However, drug concentrations within the beaker (representing the patient) are not uniform. Much of the drug is held with the charcoal leaving much smaller concentrations in the solution.

After measuring the drug concentration in the solution the apparent volume of the patient is much larger.

FIGURE:



FACTORS AFFECTING V_D:

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

Examples of apparent V_D for some drugs:

Drug	L/Kg	L/70 kg
Sulfisoxazole	0.16	11.2
Phenytoin	0.63	44.1
Phenobarbital	0.55	38.5
Diazepam	2.4	168
Digoxin	7	490

Blood Perfusion Rate		
Organ	**Perfusion Rate (mL/min/mL of tissue)**	**Percent of cardiac output (CO)**
Bone	0.02	5
Brain	0.5 - 0.55	14 - 15
Fat	0.01 - 0.03	2 - 4
Heart	0.6 - 0.7	4
Kidneys	4.0 - 4.5	22 - 24
Liver	0.8 - 0.95	25 - 27
Muscle	0.025 - 0.030	15
Skin	0.04 - 0.05	5 - 6
Lungs	10-10.2	100

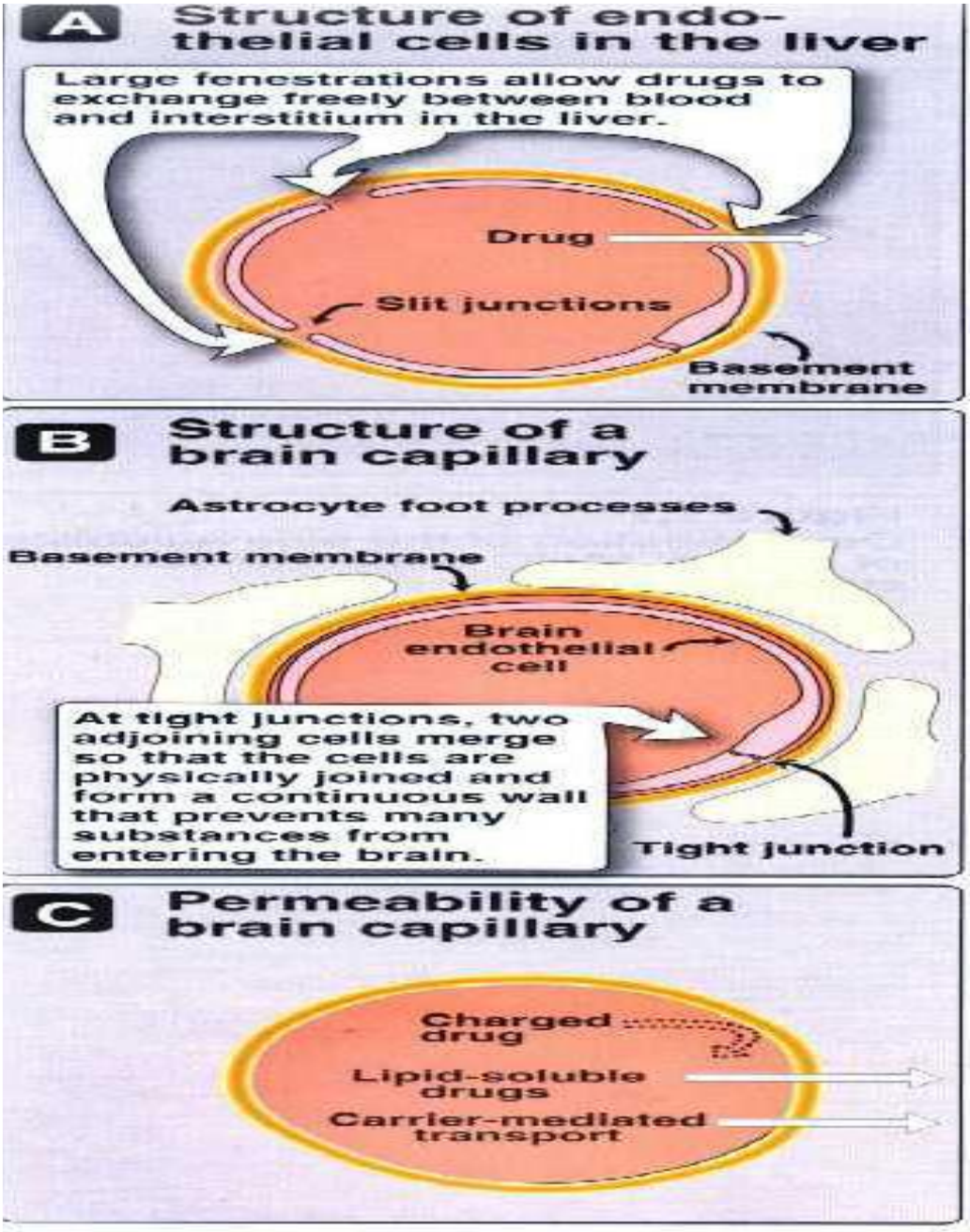
CAPILLARY / MEMBRANE PEMEABILITY:

 Capillary permeability is determined by capillary structure.

 In the liver & spleen large openings between the discontinuous endothelial cells allows even large plasma proteins to pass easily.

 Most capillaries allows large molecules to pass with little impedance, permeability is responsive to both local & systemic factors (inflammation).

 The CNS blood brain barrier is created by tight junctions between endothelial cells and a basement membrane supported by astrocytic foot processes; this presents a formidable barrier to drug penetration. Lipid soluble agents or drugs with specific transport mechanisms can penetrate rapidly.



Blood Perfusion/flow:

 Tissue distribution of a drug is dependent on transport in the bloodstream, high flow tissues (brain, liver & kidney) receive drugs in large volumes prior to muscle & adipose tissue. Some tissues have such low blood flow that drug delivery is a major concern cartilage, connective tissue, abscess).

 Lipid Solubility:

C. Drug structure has a major influence on a drugs ability to penetrate membranes, hydrophobic, nonpolar drugs with uniform electron distribution and no net charge (but still soluble in an aqueous state) move directly through endothelial membranes to reach targets. Polar, hydrophilic, charged molecules must pass through endothelial slit junctions.

Tissue binding of drugs:

 Certain drugs may bind to specific tissues proteins in addition to plasma proteins. they may also bind to other macromolecules such as melanin or DNA.

 The higher the binding of a drug to the tissue/macromolecule decrease in plasma conc. Results in increase in apparent VD.

 Tissue binding of a drug cannot be determined directly. Binding studies are important in understanding the distribution of drugs.

 Order of binding :

liver > kidney > lungs > muscles.

Factors affecting protein binding

 Drug related factors:

1. physicochemical characteristics of the drug
2. Conc. Of the drug in the body
3. Affinity of the drug for binding component

 Protein related factors:

1. physicochemical characteristics of the protein
2. Conc. Of the protein/binding component
3. No. of binding sites on the binding agent

Drug interactions:

1. Competition between drugs for binding site
2. Competition between drugs & normal body constituents
3. Allosteric changes in protein molecule

 Patient related factors:

1. Age
2. Inter subject variation
3. Disease states

Steady state VD :

 Its an estimate of drug distribution independent of elimination process.

 Amount of drug in the body during steady state is given by:

ASS = CSS .VSS

CSS = steady state plasma concentration, which is obtained when drug is introduced in to blood at a constant rate(i.e. iv-infusion)

VSS = steady state volume of distribution. Relation ship between apparent VD & tissue binding of drugs:

Hence VD is directly proportional to the free/ unbound concentration of the drug in plasma.

$$V_D = V_P + V_T \frac{f u}{f u_t}$$

VP = volume of plasma

VT = volume of extravascular tissues.

Relation ship between clearance & VD & elimination t1/2:

 Clearance is defined as the hypothetical volume of body fluids containing drug from which the drug is removed or cleared in a specific period of time.

 It is expressed in "ml/min"

Clt = KE . VD = 0.693 . VD / t1/2

KE = apparent elimination rate constant

Clt = total body clearance

Significance:

 Most of the drugs have an apparent volume of distribution smaller than or equal to, the body mass.

 For some drugs apparent VD will be several times the body mass.

 In i.v administration

VD = Dose iv/ Cp

 For a given dose , a very small Cp may occur in the body due to conc. of drug in peripheral tissues and organs, for this dose small Cp large VD

 Drugs with large apparent VD more concentrated in extravascular tissues & less concentrated intravascularly.

 If a drug is highly bound to plasma proteins or remains in vascular region then Cp will be higher resulting in a smaller apparent VD

 VD is a volume term can be expressed in simple volume in liters % body weight

 If VD is large number i.e. > 100 % of body weight then it may be assumed that the drug is more concentrated in certain tissue compartments. Thus the apparent VD is a useful parameter in considering the relative amounts of drug in the vascular & in the extravascular tissues. apparent VD for a particular drug is known , the total amount of drugs in the body at any time after administration of the drug may be determined by measurement of drug conc. in the plasma.

 Apparent VD is a constant, for each drug. But in certain pathologic cases, the apparent VD for the drug may be altered, if the distribution of the drug is changed.

 example: In edematous condition total body water + total extracellular water increases , this is reflected in a large apparent VD for a drug that is highly water soluble.

 Similarly changes in total body weight , lean body mass may also affect the apparent VD .

 Vd is useful in determining an appropriate dose to obtain a particular plasma level, therapeutic levels are measured and referenced to plasma levels.

 A large Vd has an important influence on the half-life of a drug because elimination usually depends on the amount of free drug delivered to the liver or kidney, with a large volume of distribution much/most of a drug will be extravascular or protein bound and not readily available to excretory organs.

 Clt = KE . VD = 0.693 . VD / t1/2

QUESTIONS

Ten mark question –

1. What is absorption? How pharmaceutical parameters affect the absorption of drugs?

2. Enlist the factors affecting drug absorption. Write in detail about the factors that are related to the physiological conditions and formulation of dosage form.

3. Write in brief about factors affecting drug absorption.(2003)

4. Discuss Physiological & Clinical factors Affecting drug absorption.(2007)

One-mark` questions –

1. What is important of pKa of drug in absorption?

2. Does food have any effect on drug absorption? How it affects it?

3. What is the relation between drug absorption & gastric emptying rate?