

Unit-1

Introduction to Biopharmaceutics

29/1/2020

(a) Pharmacokinetics -

It is defined as study of time course of drug, ADME & their relationship between its therapeutic & toxic effects of the drug.

(b) Biopharmaceutics -

It is defined as the study of the factor affecting the rate & amount of drug that reach the systemic circulation & use of the information to optimize the therapeutic efficacy of drug product.

(c) Absorption -

The process of movement of ^{unchanged} drug from its sites of administration to the systemic circulation is called absorption.

(d) Distribution (Blood distribution) -

The movement of drug between one compartment to another compartment (body organ i.e. lungs, kidney, heart, liver, etc) is called drug distribution.

(e) Elimination -

It is defined as the process that remove the drug from the body & terminate its action.

Elimination are of two process :

- (i) Biotransformation / Metabolism.
- (ii) Excretion - which is responsible for exist of drug / metabolite of drug from the body.

(f) Bioavailability -

It is defined as the rate & amount of drug absorption from the site of administration to the systemic circulation.

(g) Dose Dumping -

(engulfing of drug in solid food)
It is a phenomenon of drug metabolism in which environmental factors can cause the premature & exaggerated release of drug. This can greatly increase the concⁿ of a drug in the body & thereby produce adverse effects or even drug-induced toxicity.

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(h) Clinical Pharmacokinetics -

The use of pharmacokinetic principle in optimizing the drug dosage to use individual patients needs & achieve maximum therapeutic intensity is called as clinical pharmacokinetics.

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Imp. • Vitamin B₁₂ passive & active diffusion
• Facilitation

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Date :

∴ Absorption of Drug -

The drug absorption is defined as the process of movement of unchanged drug from the site of administration to systemic circulation.
(OR)

Absorption can also be defined as the process of movement of unchanged drug from the site of administration (intestine) to the site of measurement (plasma).

∴ Mechanism of Drug absorption -

- (i) Passive diffusion (higher to lower concⁿ)
- (ii) Pore transport
- (iii) Ion pair transport
- (iv) Facilitated or carrier-mediated transport (Active diffusion or Active transport (lower to higher ATP required))
- (v) Endocytosis - Engulf
 - Pinocytosis → for liquid
 - Phagocytosis → for solid

→ Passive Diffusion -

It is also called non-ionic diffusion. It is the major process for absorption of more than 90%.

The driving force of this process is concⁿ gradient. It is defined as the difference in drug concⁿ of either side of the membrane.

The drug movement is a result of the kinetic energy of the molecules.

There is no energy source required in the process is called as Passive diffusion.

Passive diffusion is best expressed by Fick's first law of diffusion -

It states that the drug molecule diffuses from a region of high Conc^n to one of lower Conc^n until the equilibrium is attained and rate of diffusion is directly proportional to the Conc^n gradient across the membrane.

$$\frac{dQ}{dt} = \frac{D A K_{m/w}}{h} (\text{Conc}_{GIT} - C)$$

where, dQ/dt = rate of drug diffusion (amount/time)

D = diffusion coefficient (area/time)

A = surface area of absorbing membrane

$K_{m/w}$ = partition coefficient of drug b/w lipidial membrane & GIT fluids.

$C_{GIT} - C$ = difference in Conc^n of drug in GIT fluid & plasma.

h = thickness of the membrane (GI membrane)

Factors based on Fick's first law of diffusion -

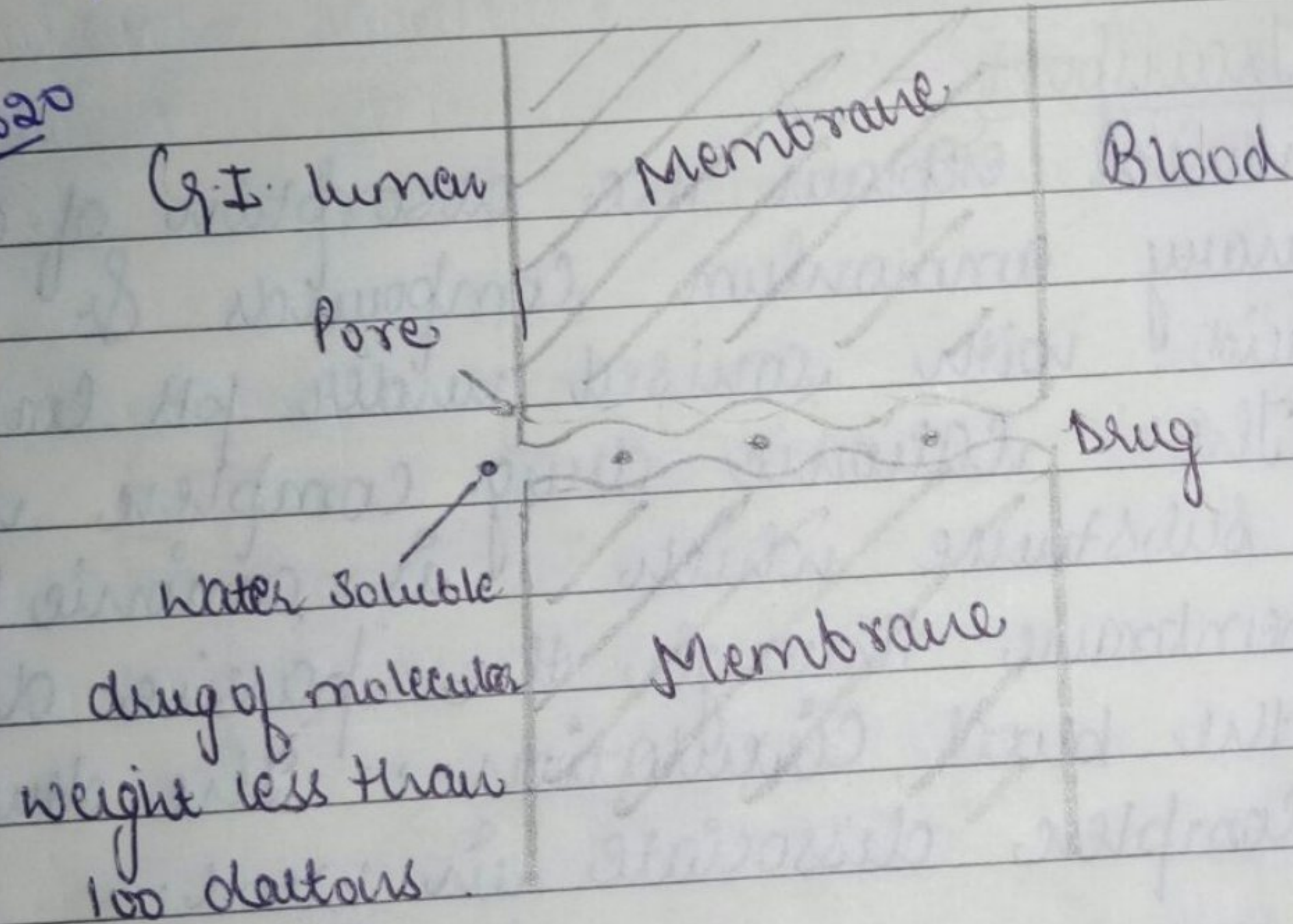
- The drug moves down the Conc^n gradient indicating down line transportation (passive transport/diffusion).
- The process is energy independent.
- Rate of drug transfer is directly proportional to the Conc^n gradient.
- Greater the area ' A ' & lesser the thickness of the membrane, faster the diffusion.
- Drugs which can exist in both ionised & unionised forms. They approach equilibrium firstly.

- by transfer of unionised species.
- The rate of transfer of unionised species 3 to 4 times more than the rate of ionised drugs.
- Greater the partition coefficient of the drug, faster the absorption.
- Drugs having molecular weight b/w 100 to 400 daltons are effectively absorbed passively.

→ Pore transport -

It is also called convective transport, but now this mechanism is responsible for transport of molecules into cell through protein channels present in cell membrane.

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Solvent Drag - [2 marks]

The driving force is constituted by the hydrostatic pressure or the osmotic difference across the membrane, due to which the bulk flow of the water along with small solid molecules occurs through such aqueous channel water flux that promotes such a transport is called as Solvent drag.

The process is important in the absorption of low molecular weight, low molecular size (smaller than the diameter of the pore).

water soluble drug through narrow, aqueous filled channel or pores in the membrane structure.

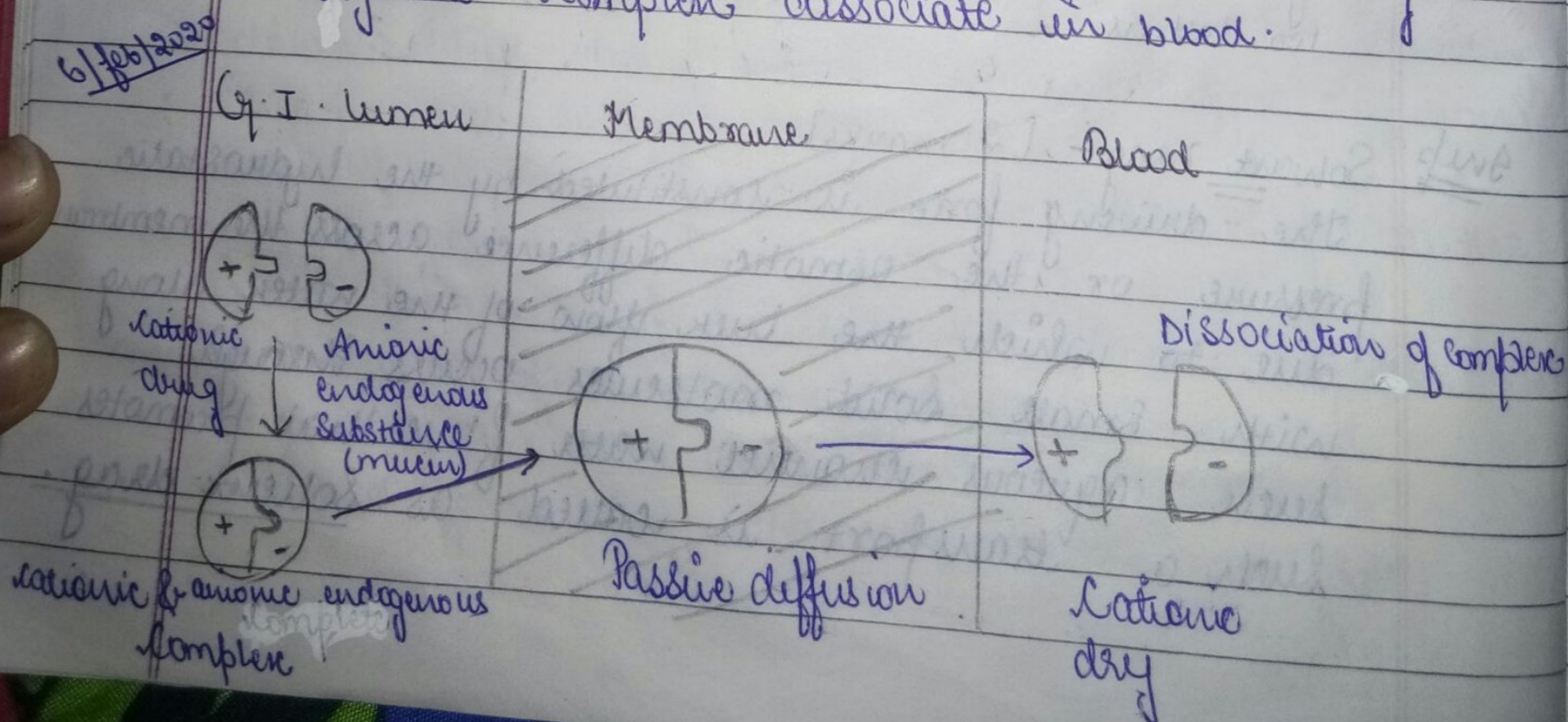
Eg - Urea, water & sugar.

Drug permeation through water filled channel is important in renal excretion removal of drug from the cerebrospinal fluid (CSF) & entry of drug into the liver.

→ Ion Pair Transport -

This mechanism explain the absorption of drug like quaternary ammonium compounds & Sulphonic acid with ionised under pH condition.

The cationic drug complex with endogenous substance which is anionic (mucin). pass the membrane through the passive diffusion & reach the blood circulation. The drug endogenous complex dissociate in blood.



The low oil in water partition coefficient value. Such agent penetrate the membrane by forming reversible neutral complexes with the endogenous ion of the GIT (mucus).

Such neutral complex have both the required lipophilicity as well as aqueous solubility for passive diffusion. Such a phenomenon is called as ion pair transport.

Eg. Propranolol a basic drug that forms an ion pair with citric acid is absorbed by the ion pair transport.

→ Carrier Mediated Transport / Absorption -



Some polar drugs cross the membrane more readily than can be predicted from their concⁿ gradient & partition coefficient value. This suggest presence of specialised transport mechanism without which may

essential for water-soluble nutrient like monosaccharides, amino acids, vitamins will be poorly absorbed.

This mechanism involved a component of a membrane called as carrier that bind reversibly & non-covalently with the solute molecule to be transported.

This carrier-solute complex travels across membrane to the other side where it dissociates & discharge the solute molecule & carrier then return to its original site to complete the cycle by accepting a fresh molecule of solute.

The carriers in membrane are proteins & may be an enzyme or some other component of the membrane.

Facilitated diffusion (Absorption of vitamin B₁₂, B₁ & B₂) - facilitated

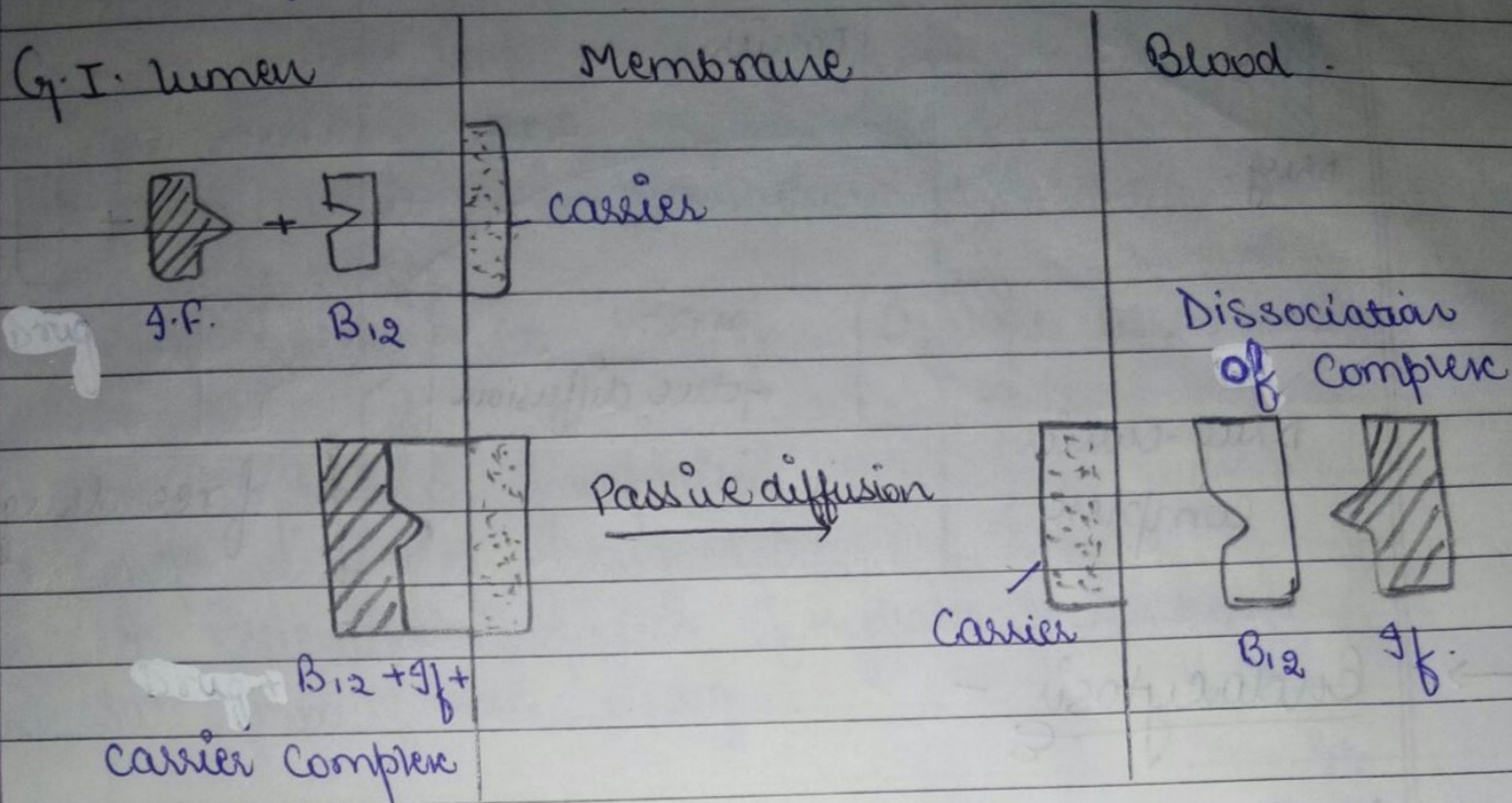
Passive - diffusion is a carrier-mediated transport system that operates down the concⁿ gradient [down the transport].

The driving force is concⁿ gradient so it is passive diffusion & has no energy.

Eg- This transport system include vit. B₁, vit. B₂, vit. B₁₂. A classical example of passive facilitated diffusion G.I. absorption of vit. B₁₂.

An intrinsic factor is a glycoprotein produced by gastric parietal cell which form a complex with vit. B₁₂ which is then transported across the intestinal membrane than transported across the membrane by a

Carrier System.

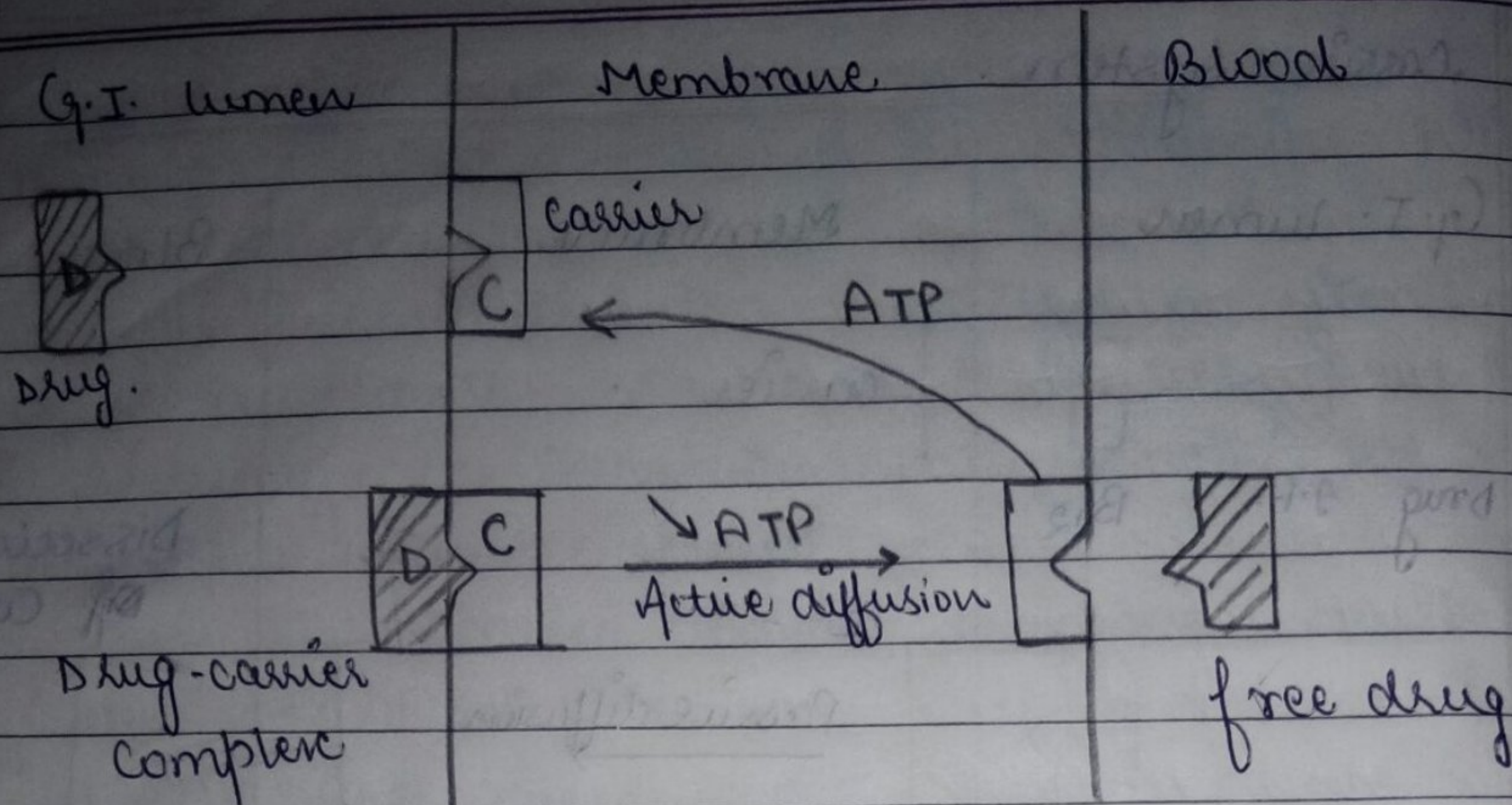


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Active transport -

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- Active transport mechanism require energy in the form of ATP.
- The drug is transported from region of lower to higher concⁿ. i.e. against the concⁿ gradient.
- It is also called up-hill transport.
- This process is faster than the passive diffusion becoz of energy.
- The process is up-hill so energy is required in work done by the carrier.
- Endogenous substances that are transport actively include Ca²⁺, Na⁺, K⁺, Fe, Glucose, certain amino acid & vitamin like niacin, pyridoxin, ascorbic acid.
- Particularly agent used in cancer - 5-fluorouracil, 5-Bromouracil by a actively transport.
- Enalapril work as a carrier.

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→ Endocytosis -

It is minor liquid transport mechanism which involve engulfing extra cellular material within a segment of cell membrane to form a vesicle. This phenomenon is responsible for cellular uptake of macromolecule nutrient such as fat, starch, oil-soluble vitamin like A, B, E, K, water soluble vitamins like vit. B₁₂ & drug-insulin.

These are two types :

(i) Phagocytosis - Absorption uptake of solid
eg - fat & starch

(ii) Pinoctosis - Absorption uptake of fluid solute
eg - polio vaccines, large protein molecules.

Factors Affecting G.I. absorption of drugs

(A) Pharmaceutical factor -

(1) Physiochemical properties of a drug :

(a) Drug solubility & Dissolution rate.

(b) Drug stability.

(c) Particle Size & effective surface area.

(d) G.I. pH.

(e) Polymorphism & Amorphism.

(f) Lipophilicity of Drug.

(g) Pseudopolymorphism [Hydrates & Solvents]

(h) Salt form of the drug.

(2) Doses form factors [Ingredients] :

(a) Disintegration time [solid form].

(b) Dissolution time.

(c) Manufacturing variables.

(d) Pharmaceutical Ingredients [Excipient].

(e) Nature & types of doses form.

(f) Product age & storage condition.

(B) Patient Related factor -

(a) Age.

(b) Gastric emptying time.

(c) Intestinal transit time.

(d) G.I. pH.

(e) Disease state.

(f) Blood flow through G.I.T.

(g) G.I. contents (drugs, fluids, foods, etc).

(h) Contact time with G.I. mucosa [presystemic metabolism by luminal enzymes, Gut wall enzyme, Bacterial & hepatic enzymes, etc].

(A) Pharmaceutical factor -

[1] Physiochemical properties of a Drug

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[A.1.a] Drug Solubility & Dissolution rate :-

- Absolute Solubility is defined as the maximum amount of solute dissolved in a given solvent under standard condition of temperature, pressure, pH.
- Dissolution rate is defined as the amount of solid substance that goes into solution per unit time under standard condition of temperature, pH & solid solvent composition & constant solid surface area.

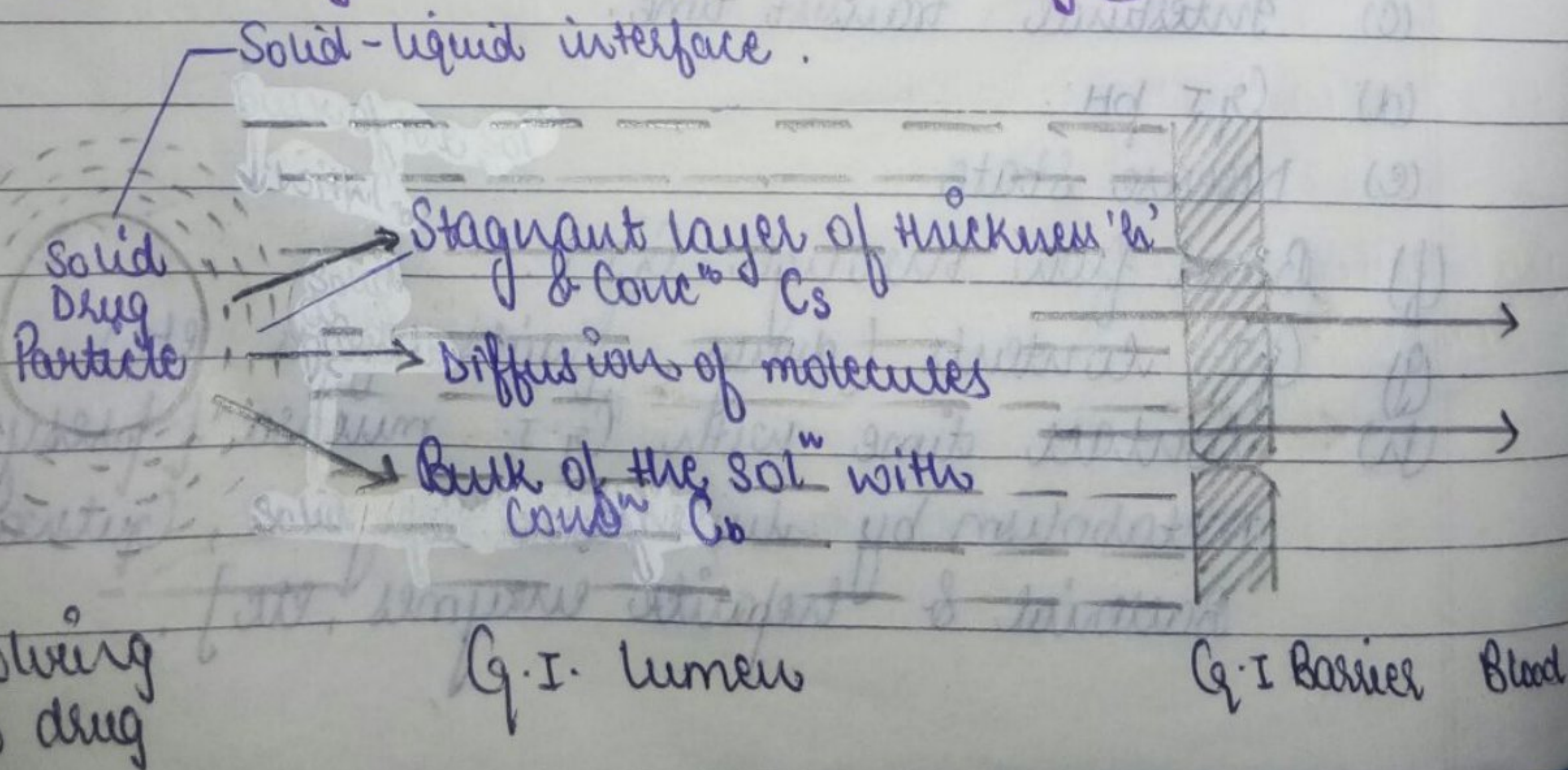
Theories of Drug Dissolution :

Dissolution is a process in which a solid substance solubilized in a given solvent is mass transfer from solid surface to the liquid phase.

There are mainly 3 theories of drug dissolution:

- (i) Diffusion layer model / Film theory.
- (ii) Danckwerts' model or Surface Renewable theory.
- (iii) Interfacial Barrier model / Double barrier or limited solvation theory.

(1) Diffusion layer model / Film Theory -



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The process of dissolution of solid particles in a liquid, in the absence of reaction or chemical sources consist upto consecutive layers:

- Solution of the solid to form a thin film or layer at the solid-liquid interface. It is called as **Stagnant film** or **Diffusion layer** which is saturated with the drug. This step is usually rapid.
- Diffusion of the soluble solute from the stagnant layer to the bulk of the solution. This step is slower & is therefore, the rate determining step in the dissolution.
- Diffusion layer control equation is **Noyes-Whitney eqⁿ** which is -

$$\frac{dc}{dt} = k [C_s - C_b]$$

Where,

$\frac{dc}{dt}$ = dissolution rate of the drug

k = dissolution rate constant

C_s = concⁿ of the drug in stagnant layer

C_b = concⁿ of drug in the bulk of the solution at time t .

(2) Darckwest's Model / Surface Renewal Theory -

Darckwest did not approve the existence of a stagnant layer & suggested that turbulence in the dissolution medium exist at a solid-liquid interface. As a result, the agitated fluid consisting of macroscopic mass of eddies or packet reach the solid-liquid interface in a random fashion due to eddy

Currents, absorb the solute by diffusion & carry it to the bulk of the solution.

Such solute containing packets are continuously replaced with new packets of fresh solvent due to which the drug concⁿ at the solid-liquid interface never reaches C_s & has a lower limiting value of C_i . Since the solvent packets are exposed to new solid surface each time, the theory is called as **Surface Renewal theory**.

The Danckwert's model is expressed by eqⁿ -

$$V \frac{dc}{dt} = \frac{dm}{dt} = A (C_s - C_b) \cdot \sqrt{rD}$$

where, m = mass of solid dissolved

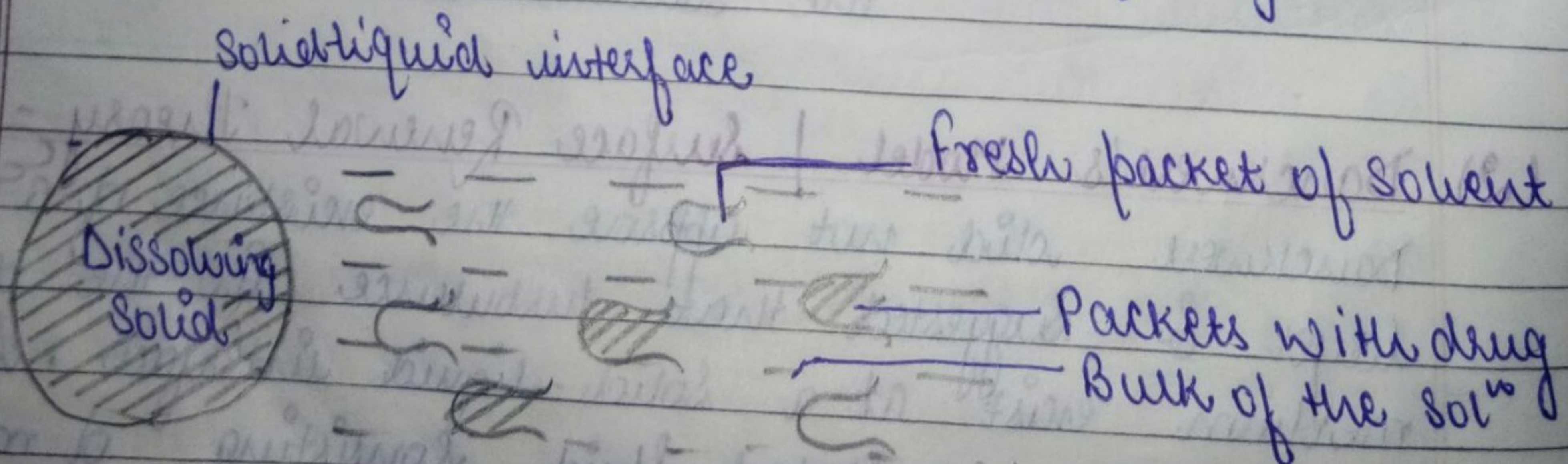
V = Volume

A = Surface area of the dissolving solid

$(C_s - C_b)$ = concⁿ gradient or diffusion of drug

r = Rate of surface renewal or interfacial tension

D = Diffusion coefficient of Drug



- (3) Interfacial Barrier Model / Limited Solution Theory -
The diffusion layer model & the Danckwerts model were based on two assumptions:
- The rate-determining step that controls dissolution is the mass transport.
 - Solid-solution equilibrium is achieved at the solid-liquid interface.

Acc. to the interfacial barrier model, an intermediate concⁿ can exist at the interface as a result of solution mechanism & is a function of solubility rather than diffusion. When considering the dissolution of a crystal, each face of the crystal will have a different interfacial barrier. Such a concept is given by the following eqⁿ:

$$G = K_i (C_s - C_b)$$

where, G = dissolution rate per unit area.
 K_i = effective interfacial transport constant.

In this theory, the diffusivity D may not be independent of saturation concⁿ C_s . The interfacial barrier model can be extended to both diffusion layer model & the Danckwerts model.

[A.1.b] Drug Stability :-

A drug for oral use may destabilize either during its shelf-life or in the G.I.T.
Two major stability problems resulting in poor bioavailability of an orally administered drug are:

- Degradation of the drug into inactive form.
- Interaction with one or more different components either of the dosage form or those present in the GIT to form a complex i.e. poorly soluble.

[A.1.C] Particle Size & effective surface area of the drug

Particle size & surface area of a solid drug are inversely related to each other. Smaller the drug particle, greater the surface area.

Two types of surface area of interest can be defined :

- (i) Absolute surface area which is the total area of solid surface of any particle.
- (ii) Effective surface area which is the area of solid surface exposed to the dissolution medium.

From the modified Noyes-Whitney eqⁿ, it is clear that larger the surface area, higher the dissolution rate.

The surface area increases with decreasing particle size, a decrease in particle size which can be accomplished by micronization will result in higher dissolution rate.

Greater the effective surface area more intimate the contact between the solid surface & aqueous solvent & faster the dissolution.

The absolute surface area of hydrophobic drugs can be converted to their effective surface area by:

- (i) use of surfactant as a wetting agent that decreases the interfacial tension & displace the adsorbed air with the solvent. **Eg- Polysorbate 80, ASI**
- (ii) adding hydrophilic diluents such as **PEG₄, PVP, Dextrose, etc.**

(A.1.d) Drug pKa & Gastrointestinal pH :-

The amount of drug that exist in unionized form is a function of dissociation constant (pK_a) of the drug & pH of the fluid at the absorption site.

The pH range in the GIT from 1 to 8. That of the stomach from 1 to 3 & of the intestine (from duodenum to colon) 5 to 8.

For weak Acids:

- (1) very weak acids ($pK_a > 8$) such as phenytoin, ethosuximide & several barbiturates are essentially unionized at all pH values & therefore, their absorption is rapid & independent of GI pH.
- (2) Acids in the pK_a range 2.5 to 4.5 are greatly affected by changes in pH & therefore their absorption is pH-dependent. **eg- Several NSAIDs like Aspirin, Ibuprofen, phenylbutazone & a no. of penicillin analogs.**

Such drugs are better absorbed from acidic condition of stomach ($pH < pK_a$) where they largely exist in unionized form.

- (3) Stronger acid with ($pK_a < 2.5$) such as cromolyn sodium are ionized in the entire pH range of GIT & therefore remain poorly absorbed.

For weak Bases:

- (1) Very weak bases ($pK_a < 5.0$) such as caffeine, theophylline & a no. of benzodiazepines like diazepam, oxazepam, nitrazepam are essentially unionized at all pH values & therefore their absorption is rapid & pH-independent.
- (2) Bases in the pK_a range 5 to 11.0 are greatly affected by changes in pH & hence their absorption is pH-dependent. eg. several morphine analogs, chloroquine, imipramine & amitriptyline. Such drugs are better absorbed from the relatively alkaline condition of the intestine where they largely exist in unionized form.
- (3) Stronger bases with $pK_a > 11.0$ such as mecamylamine & guanethidine are ionized in the entire pH range of GIT & therefore poorly absorbed.

[A-1.6]

Polymorphism & Amorphism:-

Depending upon the internal structure, a solid can exist either in a crystalline or amorphous form. When a substance exists in more than one crystalline form, the different forms are designated as **polymorphs** & the phenomenon as **polymorphism**.

Polymorphs are of 2 types:

- (i) Enantiotropic polymorph - It is the one which can be reversibly changed into another form by altering the temperature or pressure.
eg. (i) Sulphur.

(ii) 3

polymorphic form of chlorphenicol ABC. [The B form has best availability & used in pharmaceutical].

(iii) Polymorphic form 3 of Riboflavin is 20 times more water soluble than form 1.

(2) Monotropic polymorph - It is the one which is unstable at all temperatures & pressures.
eg- Glycerol Stearates.

Amorphism is having no internal crystal structure. Such drug represent the highest energy state & can be considered as supercooled liquids.

eg - (i) Amorphous form of novobiocin is 10 times more soluble than the crystalline form.

(2) Chloramphenicol palmitate, cortisone acetate & phenobarbital are other examples.

The amorphous form show higher water solubility. The dissolution of different solid forms of drug is -
Amorphous > Metastable > stable.

[A.1.1] Lipophilicity of drug (pH Partition theory) :-

The pH partition theory explain in simple terms, the process of drug absorption from the GIT & its distribution across all biological membrane.

The theory states that for drug compounds of molecular weight greater than 100 daltons which are primarily transported across the biomembrane by passive diffusion.

The process of absorption is governed by :

(a) Dissociation constant (pK_a) of the drug.

(b) Lipid solubility of the unionized drug.

(c) pH at the absorption site.

[A.1.9] Hydrates / Solvates (Pseudopolymorphism) :-

The crystalline form of a drug can either be a polymorph or a molecular adduct or both.

The solvent molecules are incorporated in the crystal lattice of the solid are called as the Solvates, & the trapped solvent as solvent of crystallization.

The solvates can exist in different crystalline forms called as pseudopolymorphs & this phenomenon is called as pseudopolymorphism.

When the solvent in association with drug is water, the solvate is known as a hydrate.

The anhydrous form of a drug has greater aqueous solubility than the hydrates, this is because of hydrates are already in interaction with water.

eg - Anhydrous form of theophylline & ampicillin have higher aqueous solubilities, dissolve at a faster rate.

[A.1.10] Salt form of the drug :-

Most drugs are either weak acids or weak bases. The simplest approach to enhance the solubility & dissolution rate of such drug is to convert them into their salt forms.

Generally, with weakly acidic drugs, a strong base salt is prepared such as the sodium & potassium salts of barbiturates & sulfonamides.

In case of weakly basic drugs, a strong acid salt is prepared such as hydrochloride or sulfate salts of several alkaloidal drugs.

[2] Dose form factors :

[A.2.a] Disintegration time :-

- Rapid disintegration is important to have a rapid absorption so lower disintegration time is required.
- Disintegration time of tablet is directly proportional to amount of binder & compression force.
- Coated tablet especially sugar coated have long disintegration time.
- If larger amount of binder present the disintegration time is longer.

[A.2.b] Dissolution time :-

Dissolution is a process in which a solid substance solubilises in a given solvent i.e. mass transfer from the solid surface to the liquid surface.

Dissolution time is also an important factor which affects the drug absorption.

[A.2.c] Manufacturing Variable :-

The dosage form related factors that influence dissolution & hence absorption of a drug from such formulation are :

- Excipients
- Manufacturing processes.

Several manufacturing processes influence drug dissolution from solid dosage forms are :

- Method of granulation
- Compression force.

(a) Method of Granulation -

- The wet granulation process is the most conventional technique.
- The tablet that dissolve faster than those made by other granulation method.
- The limitation of this method include:
 - (i) Formation of crystal bridge due to the presence of liquid.
 - (ii) The liquid may cause chemical reaction like hydrolysis.
 - (iii) Harmful effects on thermodegradable drugs due to the drying process.
- In granulation, many steps are involved that influence drug dissolution:
 - (i) Method & duration of blending
 - (ii) Method, time & temperature of drying
- The method of direct compression has been utilized to yield tablets that dissolve at a faster rate.
- The recent methods that has resulted in superior product is Agglomerative phase of Communication (APOC).

(b) Compression force -

- The compression force employed in the tableting process influence density, porosity, hardness, disintegration time & dissolution rate of tablets.
- Higher compression forces ↑ the density & hardness of the tablet, ↓ the porosity & hence penetrability of the solvent into the tablet & thus in slowing of dissolution & absorption (fig A)

Dissolution rate

(fig A)

compression force

- on the other hand, higher compression force causes deformation, crushing or fracture of drug particles into smaller ones & causes a large rise in effective surface area. This results in an rise in dissolution rate of tablets. (fig B).

Dissolution rate

(fig. B)

compression force

- A combination of both the curve A & B is also possible as shown in curves C & D.

Dissolution rate

(fig C)

Dissolution rate

(fig D)

compression force

compression force

[A-2d] Pharmaceutical Ingredients :-

more the no. of excipients in the dosage form, more complex it is & greater the potential for absorption & bioavailability problems.

Commonly used excipients in various dosage forms are:

(a) Vehicle:

- Rate of absorption depends on its miscibility with biological fluid.
- The 3 vehicles are used:
 - (a) Aqueous vehicle - water & syrup
 - (b) non-Aqueous miscible vehicle - Propylene glycol, glycerol & sorbitol.
 - (c) non-aqueous immiscible vehicle - vegetable oils
- Miscible vehicles causes rapid absorption
- In immiscible vehicle absorption depends on its partitioning from oil phase to aqueous body fluid.

(b) Diluents:

- Hydrophilic diluents (Starch, lactose, microcrystalline solid) imparts absorption.
- Hydrophobic diluents (Dicalcium phosphate [DCP] & tetracycline) retard absorption because of drug-diluent interaction forming insoluble complex.

(c) Binders & Granulating agent:

- Hydrophilic binders imparts to the granule surface which give better dissolution properties. eg - Starch, Gelatin, PVP
- Hydrophobic properties

- More amount of binders increases the hardness of the tablet & retards the absorption.
- eg. PEG-6000 forms a poorly soluble complex with phenobarbital & non-aqueous binders like ethyl cellulose also decrease drug dissolution.

(d) Disintegrants:

- Mostly hydrophilic in nature
- Amount of disintegrant directly affect the bioavailability of drug.
- eg. Microcrystalline cellulose is a good disintegrant but when compression force ↑, drug dissolution ↓

(e) Lubricants:

Commonly hydrophobic in nature therefore inhibits wettability/penetration of water into tablet & their disintegration & dissolution.

(f) Suspending Agents / viscosity agent:

- Stabilized the solid drug particle & thus affect drug absorption.
- Macromolecular gum forms unabsorbable complex with drug. eg - CMC & MC
- Viscosity imparters act as a mechanical barrier to diffusion of drug from its dosage form & retard GI transit of drug.

(g) Surfactant:

- They may enhance or retard drug absorption by interacting with drug or membrane or both.
- eg - Griseofulvin, Steroids.
- It may decrease absorption when it forms the

un-absorbable complex with drug above CMC.

(h) Coating:

- In general, deleterious effect of various coating of the drug dissolution from a tablet dosage form are in the following order:

Enteric coat > Sugar coat > non-enteric coat

- The dissolution profile of certain coating material change on aging. eg - Shellac coated tablets, on prolonged storage, dissolve more slowly in the intestine this can be prevented by incorporating the little PVP in the coating formulation.

(i) Buffers:

- Buffers are sometimes useful in creating the right atmosphere for drug dissolution as was observed for buffered aspirin tablet.
- However, certain buffer system containing potassium cations inhibit the drug absorption as seen with vit. B₁₂ & Sulfamonomide.

(j) Colorants:

- Even a "low concn" of water soluble dye can have an inhibitory effect on dissolution rate.
- They dye molecules get absorbed onto the crystal faces & inhibit the drug dissolution.
- eg - Brilliant blue retards dissolution of Sulfathiazole.

(K) Complexing agent :

Complex formation has been used to alter the physiochemical & biopharmaceutical properties of drug.

eg -

(i) Enhanced dissolution through formation of a soluble complex. eg - ergotamine tartrate - caffeine complex & hydroquinone - digoxin complex.

(ii) Enhanced lipophilicity for better membrane permeability. eg - Caffeine - PABA complex.

[A-2.e] Nature & type of Dosage form :-

• Apart from the proper selection of the drug, clinical success often depends to a great extent on the proper selection of the dosage form of that drug.

• As a general rule, the bioavailability of a drug from various dosage forms decrease in the following order:

Solutions > Emulsions > Suspensions > Capsules > Tablets > Coated tablets > Enteric coated tablets > Sustained Release products.

[A-2.f] Product age & Storage Condition :-

Product aging & storage condition can adversely affect the bio-availability by change in especially the physico-chemical properties of the dosage forms!

eg -

(i) Precipitation of the drug in solution.

(ii) Hardening of tablet.

(iii) Change in particle size of suspension.

[B] Patient Related factors -

[a]

Age :-

- In Infants, the gastric pH is high & intestinal surface & blood flow to the GIT is low results in poor drug absorption in comparison to adults.
- In elderly person, causes of impaired drug absorption include altered gastric emptying, decreased intestinal surface area & GI blood flow, higher incidents of achlorhydria & bacterial overgrowth in small intestine.

[b]

Gastric Emptying :-

Apart from the dissolution of a drug & its permeation through the biomembrane, the passage from stomach to the small intestine called as gastric emptying can also be a rate-limiting step in drug absorption because the major site of drug absorption is intestine.

It is advisable where :

- Rapid onset of action is desired. eg - Sedatives
- Dissolution occurring in the intestine eg - Enteric coated dosage form
- Drugs are not stable in the gastric fluids.
eg - Penicillin G & erythromycin
- Drug is best absorbed from the distal part of the small intestine. eg - Vitamin B₁₂.

Delay in gastric emptying -

- The food promotes drug dissolution & absorption. eg. griseofulvin
- Disintegration & Dissolution of dosage form is promoted by gastric fluids.
- Drugs dissolve slowly. eg. griseofulvin.
- Drugs irritate the gastric mucosa. eg. Aspirin, phenylbutazone
- Drugs are absorbed from the proximal part of the small intestine. eg. Vit. B₂ & Vit. C.

⇒ Gastric emptying is a first-order process. Several parameters are used to quantify gastric emptying:

- Gastric emptying rate:** The speed at which the stomach concⁿ empty into the intestine.
- Gastric emptying time:** The time required for the gastric concⁿ to empty into the small intestine.
- Gastric emptying $t_{1/2}$:** The time taken for half of the contents to empty.

Factors -

- Volume of meal
- Composition of meal
- Physical state & viscosity of meal
- Electrolytes & osmotic pressure
- Temperature of meal
- Gastrointestinal pH
- Disease states

(C) Gastrointestinal pH :-

The GI pH generally increases gradually as one moves down the stomach to the colon & rectum.

GI pH influence in several ways:

- Disintegration:** Disintegration of some dosage forms is pH sensitive, enteric coated tablet dissolve only in alkaline pH

(b) Dissolution : A large no. of drugs either weak acids or weak bases, their solubility is greatly affected by pH.

- weakly acidic drug dissolve rapidly in alkaline pH.
- weakly basic drug dissolve in acidic pH.

(c) Absorption : Depending upon the drug pKa, whether it's an acidic or basic drug, the GI pH influencing drug absorption.

(d) Stability : GI pH influence the chemical stability of drugs. eg - erythromycin

(d) Blood flow to GIT :-

GIT is extensively supplied by blood capillary, about 28% of cardiac output is supplied to GIT portion, most drug reach the systemic circulation by a blood only.

(e) Intestinal Transit :-

Since small intestine is the major site for absorption of most drugs, long intestinal transit time is desirable for complete drug absorption.

Transit time for contents from different regions of Intestine :

Intestinal region	Transit time
Duodenum	5 mins
Jejunum	2 hrs
Ileum	3 to 6 hrs
Cecum	0.5 to 1 hrs
Colon	6 to 12 hrs.

Delayed intestinal transit is desirable for:

- Drugs that dissolve or release slowly from their dosage form. (Sustained release product).
- Drugs that dissolve only in the intestine (enteric coated formulations).
- Drugs absorbed from specific sites in the intestine (Several Vitamin B).

(f) Disease State:-

The 3 major classes of disease states that can influence the bioavailability of a drug are:

(i) Gastrointestinal diseases :

(1) Gastrointestinal diseases & infection -

→ Two of the intestinal disorders related with malabsorption syndrome that influence drug availability are:

- Celiac disease which increased gastric emptying rate & G.I permeability, altered intestinal drug metabolism, steatorrhea, reduced enterohepatic cycling of bile salts.

- Crohn's disease that can alter absorption patterns are altered gut wall microbial flora, decreased gut surface area & intestinal transit rate.

→ G.I infection like shigellosis, gastroenteritis, cholera & food poisoning also result in malabsorption

(2) Gastrointestinal surgery - Gastrectomy can result in drug dumping in the intestine, osmotic diarrhoea & reduced transit time.

(ii) Cardiovascular disease:

Several changes associated with congestive cardiac failure influence bioavailability of a drug viz. edema of the interstium, decreased blood flow to the GIT & gastric emptying rate & altered GI pH, secretion & microbial flora.

(iii) Hepatic Disease:

Disorder such as hepatic cirrhosis, influence bioavailability mainly of drugs that undergo considerable first-pass hepatic metabolism.
eg - Propranolol.

(9) Gastrointestinal Contents :-

A no. of GI contents can influence drug absorption as discussed below:

(i) Food - Drug interaction -

Presence of food may either delay, reduce, increase or may not affect drug absorption.

Influence of food on Drug Absorption			
Delayed	Decreased	Increased	Unaffected
Aspirin	Penicillins	Griseofulvin	Methyldopa
Paracetamol	Erythromycin	Nitrofurantoin	Propylthiouracil
Diclofenac	Ethanol	Diazepam	Sulfasomidine

(ii) Fluid volume -

Administration of a drug with large fluid volume results in better dissolution, rapid gastric emptying & enhanced absorption. eg. erythromycin

(iii) Interaction of drug with normal GI constituents -

The GI contains a no. of normal constituents such as mucin, bile salts & enzyme which influence drug absorption.

(iv) Drug-Drug Interaction in the GI -

These interaction can either be physicochemical or physiological.

(a) Physicochemical interaction are due to :

→ Absorption : antidiarrhoeal prepⁿ containing adsorbents like attapulgite or kaolin-pectin retard absorption of no. of drugs co-administered with them.
eg - Promazine, Erythromycin.

→ Complexation : Antacids or mineral substances containing heavy metals such as Al , Ca^{2+} , Mg^{2+} retard absorption of tetracyclines by forming unabsorbable complexes.

(b) Physiological interaction are due to :

→ Decreased GI transit : Anticholinergics like propantheline retard GI motility & promote absorption of drugs like ranitidine & digoxin & delay absorption of paracetamol & sulfamethoxazole.

→ Increased gastric emptying : metoclopramide promotes GI motility & enhances absorption of tetracycline, pirompicillin & levodopa.

(4) Presystemic Metabolism / First-pass effects :-

The loss of drug through biotransformation by such eliminating organs during its passage to systemic circulation is called as first pass or presystemic metabolism.

The 4 primary system which affect presystemic metabolism of a drug are :

(a) Luminal enzymes - These are the enzymes present in the fluids & include enzymes from intestinal & pancreatic secretion.

The latter contains hydrolases which hydrolyze ester drugs like Chloramphenicol palmitate into active Chloramphenicol & peptidases which split amide linkages & inactivate proteins.

(b) Gut wall enzymes - It is also called mucosal enzyme present in stomach, intestine & colon.

- Alcohol dehydrogenase : enzyme of stomach mucosa inactivates ethanol.

- Intestinal mucosa : contains both phase I & II enzymes . eg:- Sulfation of ethinyl estradiol & isoprenaline

- Colonic mucosa : contains both phase I & II.

(c) Bacterial enzymes - GI microflora is scantily present in stomach & small intestine & is rich in colon.

Colonics generally render a drug more active or toxic on biotransformation.

Sulphasalazine hydrolysis
[drug in ulcerative colitis].

Sulphapyridine &
5-amino salicylic acid

(d) Hepatic enzymes - Several drugs undergo first-pass hepatic metabolism, the highly extracted ones being isoprenaline, propranolol, alprenolol, pentoxifylline, nitroglycerine, diltiazem, nifedipine, lidocaine, morphine, etc.

∴ Absorption of Drugs from Non per oral extravascular Routes -

Non per oral indicate drug administration routes other than the oral route, which bypasses the GIT & enter the systemic circulation.

Some of the non-oral absorption will be discussed here :

(i) Buccal / Sublingual Administration:-

Buccal Route : The medicament is placed b/w cheek & the gum. They are absorbed by passive diffusion.

Sublingual Route : The drug is placed under the tongue & allowed to dissolve. They are absorbed by carrier-mediated transport.

Advantages -

- Rapid absorption.
- No first-pass hepatic metabolism.
- No degradation of drugs.

Disadvantages -

- Limited mucosal surface area.
- Concern for taste & discomfort of the medicament.

Factors -

- Lipophilicity of drugs.
- Salivary Secretion
- pH of the saliva
- Binding to the oral mucosa
- Thickness of oral epithelium.

Examples -

- Antianginals - nitrites & nitrates
- Antihypertensives - nifedipine
- Analgesic - morphine
- Bronchodilators - fenoterol
- Steroids - estradiol
- Peptides - oxytocin.

(2) Rectal Route :-

- The rectal route of administration is still an important route for children & old patients.
- The drug may be administered as solⁿ (microenemas) or suppositories. They are absorbed by passive diffusion.

Advantage -

- Absorption is more rapid.
- Bypasses presystemic hepatic metabolism.

Disadvantage -

- Rectal inflammation occurs.
- Irregular absorption occurs.

Factors -

- Presence of faecal matter
- pH of rectal fluid (around 8)
- Drug Irritability
- Surface area.

Examples -

Aspirin, paracetamol, theophylline & few barbiturates

(3) Topical Administration :-

- It is the largest organ of the body.
- When topically applied drugs are meant to exert their effects systemically, the mode of administration is called as percutaneous or transdermal delivery.
- The principal barrier to the entry of xenobiotics is the most superficial layer of epidermis is called as stratum corneum.
- They are absorbed by passive diffusion.
- Liquid dosage forms such as liniments, lotions, syrup.
- Semisolid like ointments, creams, Pastes, Gels, etc are conventional drug forms for topical drug delivery.

Advantages -

- Drug can be applied easily.
- Protect drug from GI & from first pass metabolism.
- Increased patient compliance by reduced dosing frequency.

Disadvantages -

- Skin irritation occurs.
- Improper absorption of certain drugs.
- Ointments have longer duration of action due to sticky & oily texture.

Factors -

- skin condition.
- composition of topical vehicle.
- Application procedure.
- External / environmental factors

Example -

Nitroglycerine, lidocaine, scopolamine, testosterone, betamethasone

(4) Intramuscular Administration :-

Absorption of drugs from I.M. sites is relatively rapid but much slower than I.V. injection.

They are absorbed by passive diffusion, endocytosis & pore transport.

Advantages -

- Uniform absorption occurs.
- Onset of action is fast.
- Mild irritants can be given.
- Prevent first pass metabolism.
- NO GIT-related factors.

Disadvantages -

- Only small quantities of drug can be administered.
- Local pain, abscess, infection may occur.
- Expensive.

Factors -

- Vascularity of the injection site.
- Lipid solubility & Drug ionisation.
- Drug molecular size.
- pH, composition & viscosity of injection vehicle.

- Injection volume & Drug concⁿ.

Examples -

Phenytoin, Digoxin, Several steroids & antibiotics & many other drugs.

(5) Subcutaneous Administration :-

Absorption is slower than I.M. site due to poor perfusion. They are absorbed by passive diffusion.

Advantages -

- Can be self-administered.
- Complete but slow absorption
- Massage / heat: vasoconstriction

Disadvantages -

- Painful
- Irritant drugs cause tissue damage
- Only small quantities of dose (2ml) can be injected.

Factors -

- viscosity of the injection site
- lipid solubility & Drug ionisation
- Drug molecular size
- pH, composition & viscosity of injection vehicle
- Injection volume & Drug concⁿ.

Examples -

Insulin, Heparin, C.R. implants

(6) Pulmonary Administration :-

All drugs intended for systemic effect can be administered by inhalation since the large surface area of the alveoli. They are absorbed by passive diffusion & pore transport.

Advantages -

- Rapid absorption just like exchange of gases b/w the blood & inspired air.
- Lipid-soluble drugs are rapidly absorbed by passive diffusion.
- Polar drugs absorbed by pore transport.

Factors -

- Particle size of drug.
- Properties of propellers such as vapour pressure, toxicity, solvent action.
- Effect of drug & additives on mucous viscosity, mucociliary clearance.

Examples -

Salbutamol, Cromolyn, Beclomethasone.

(7) Intranasal Administration :-

The nasal route is becoming increasingly popular for systemic delivery especially of some peptide & protein drugs. They are absorbed by passive diffusion & pore transport.

Advantages -

- Rapid absorption due to rich vasculature & high permeability.
- Drugs from this route reaches the systemic circulation may cross Blood Brain Barrier.

Factors -

- Required high lipophilic drugs.
- Smaller molecular weight is required.
- pH of nasal secretion.
- Pathological condition.

Examples -

Phenylpropanolamine & antihistamines

(B) Intracocular Administration :-

Topical application of drugs to the eyes is mainly meant for local effects such as mydriasis, miosis, anaesthesia or treatment of infections, glaucoma, etc. They are absorbed by passive diffusion.

Advantages -

- Lipophilic as well as hydrophilic drugs are absorbed.
- pH of lacrimal fluid influence absorption of weak electrolytes.

Factors -

- Rate of blinking shows loss of drug.
- Viscosity of drug also affect on absorption.

Examples -

Atropine, pilocarpine, Adrenaline, antibiotics

(9) Vaginal Administration :-

Drugs meant for intravaginal application are generally intended to act locally in the treatment of bacterial or fungal infection or prevent conception. They are absorbed by passive diffusion.

Advantages -

- Easy administration
- Controlled delivery & termination of drug action when desired with this route

Factors -

- pH of women fluids (4 to 5)
- vaginal secretion.

Examples -

Steroidal drugs & contraceptives, metronidazole, etc.

∴ Distribution of Drugs :-

- Distribution which involves reversible transfer of a drug between compartments. The process is carried out by the circulation of blood, one of the compartments is always the blood or the plasma & other represents extravascular fluids & other body tissues.
- In other words, distribution is reversible transfer of a drug between the blood & the extravascular fluids & tissues.
- Distribution is a passive process (passive diffusion).

Steps in blood distribution :

Distribution of drug present in systemic circulation to extravascular tissues into following 2 steps:

Step 1 :-

Permeation of free or unbound drugs present in the blood through the capillary wall & entry into the extravascular fluid.

Step 2 :-

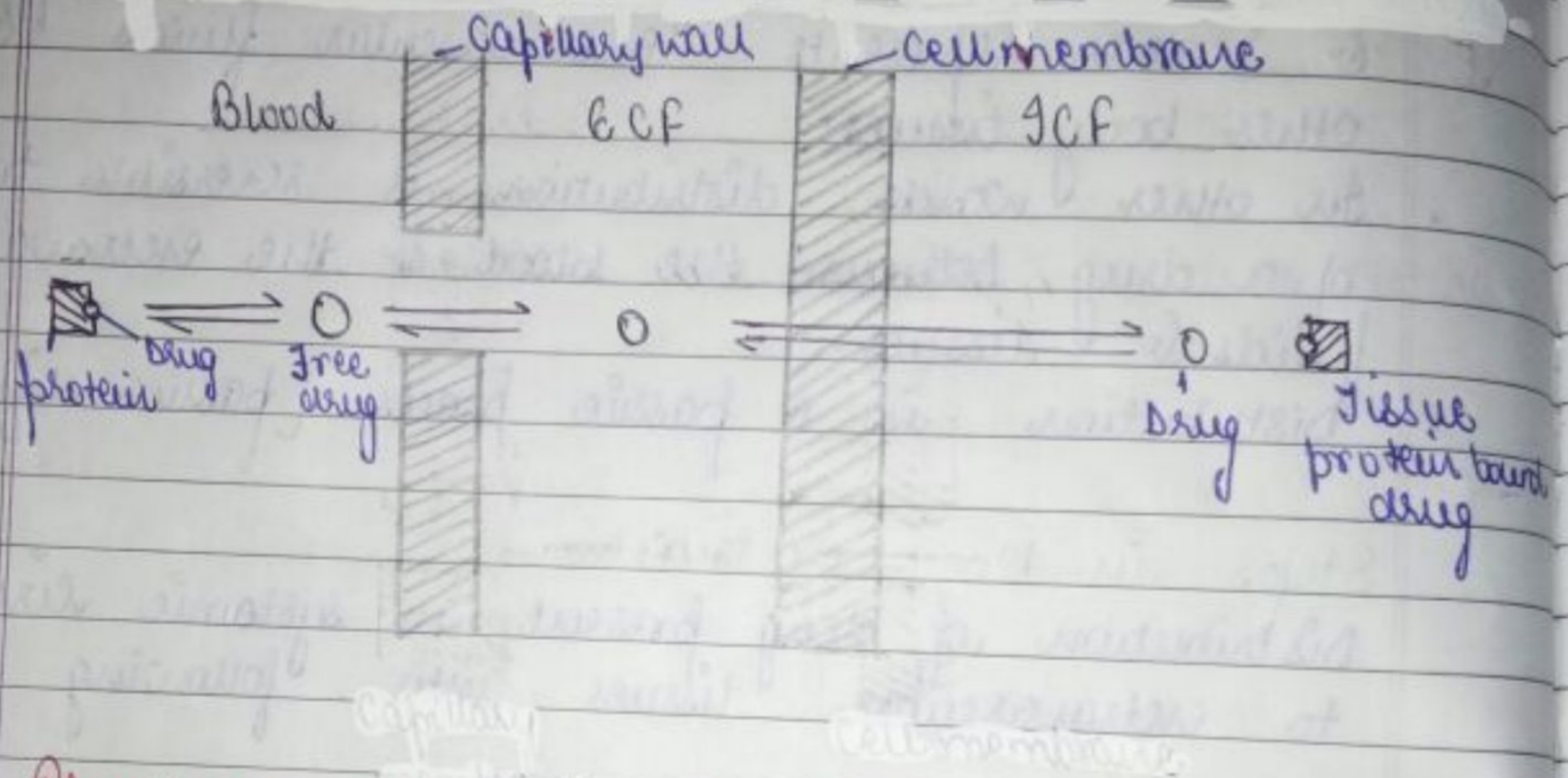
Permeation of drug present in ECF through the membrane of tissue cell & into the ICF.

∴ Tissue Permeability of a Drug :-

The two major rate determining steps in the distribution of drugs are:

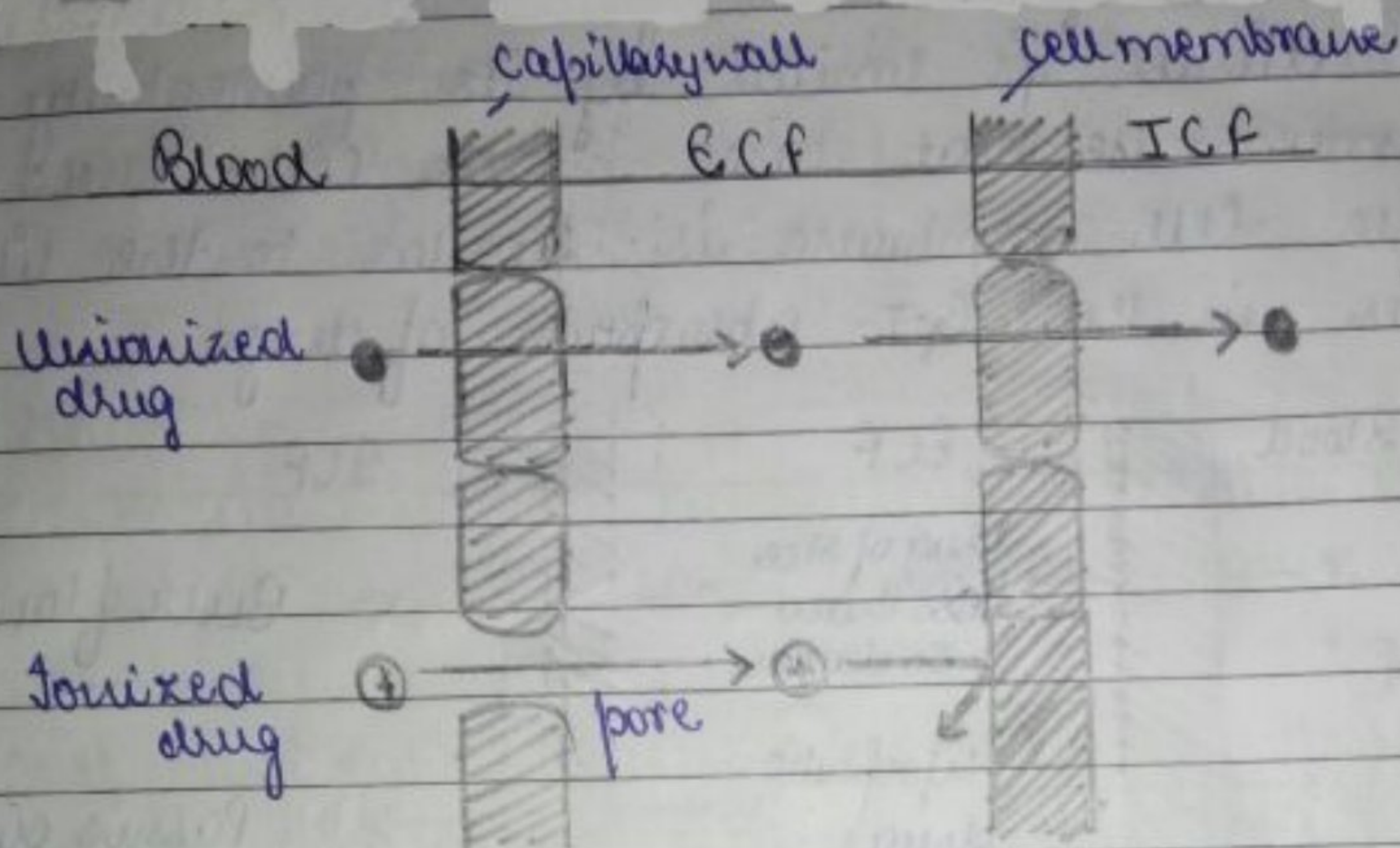
- (1) Rate of tissue permeability.
- (2) Rate of blood perfusion.

The tissue permeability of a drug depends upon the physiochemical properties of a drug as well as the physiological barriers that restricts diffusion of drug into tissues.



- # Physiochemical properties of drug in distribution-
- All drugs having molecular weight less than 500-600 daltons easily cross these capillary membrane to diffused into the extracellular interstitial fluids.
 - Penetration of drugs from the ECF into the cells is a function of molecular size, ionisation constant & lipophilicity of the drug.
 - Only small, water soluble molecules & ions of size below 50 daltons enter the cell through aqueous fluid channels.
 - All drugs that ionised at plasma pH cannot penetrate the lipoidal cell membrane & tissue permeability is the rate-limiting steps in the distribution of drug.

only unionized drugs which are generally lipophilic rapidly cross the cell membrane.
 eg. Thiopental distributes in CSF at a rate 60 times faster than salicylic acid.



Physiological Barriers to Distribution of drug-

Some of the important simple & specialized physiological barriers are:

- (1) Simple capillary endothelial barrier.
- (2) Simple cell membrane barrier.
- (3) Cerebrospinal fluid barrier.
- (4) Placental barrier.
- (5) Blood-testes barrier.
- (6) Blood-Brain Barrier.

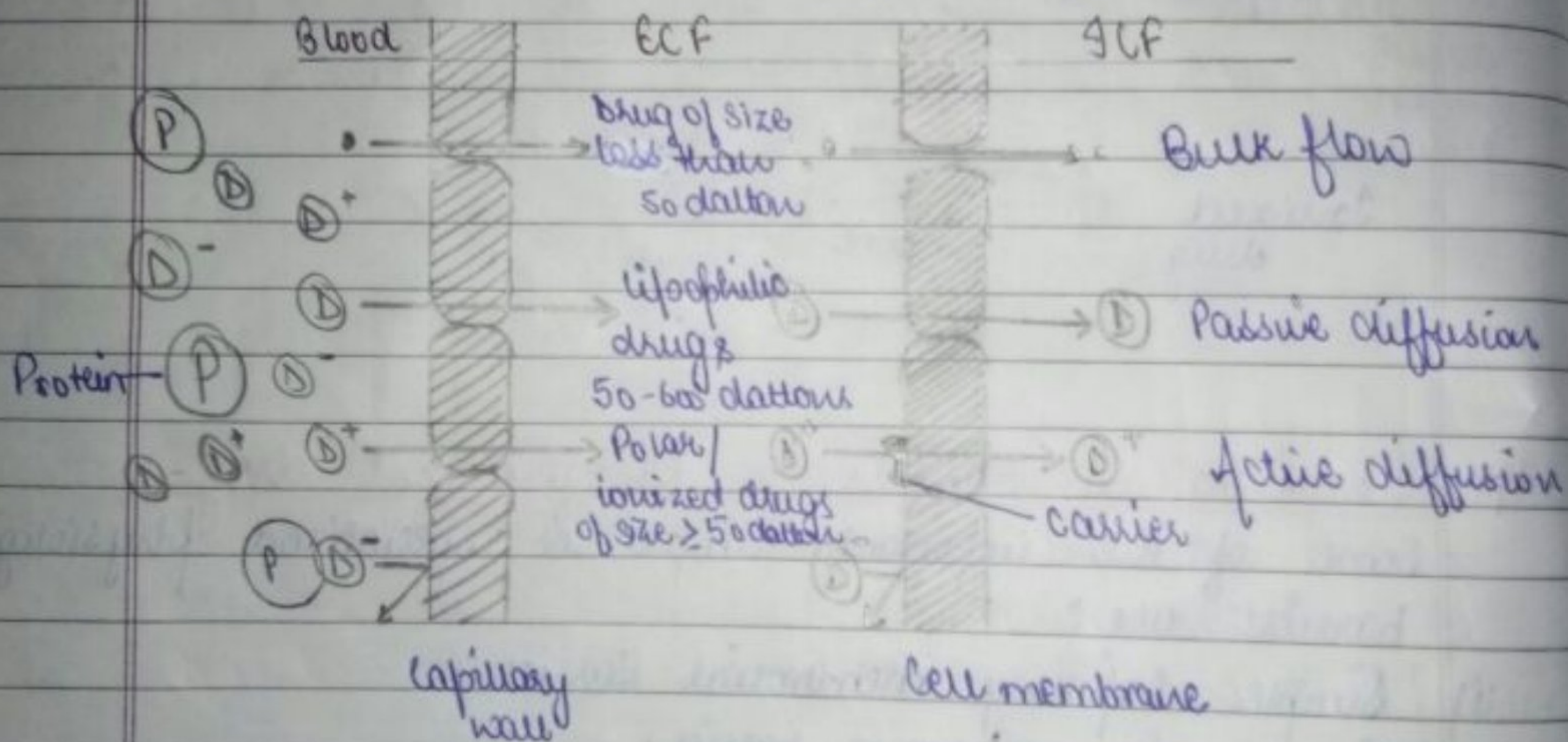
→ Simple capillary endothelial barrier:-

The membrane of capillaries that supply blood to most tissues. All drugs ionized or unionized with a molecular size less than 600 daltons, diffuse through the capillary endothelium & into the interstitial fluid. Only drugs bound to the blood components are

restricted because of the large molecular size of the complex.

→ Simple Cell-membrane Barriers :-

Once a drug diffuses from the capillary wall into extracellular fluid, its further entry into cells of most tissues is limited by its permeability through the membrane that lines such cells. Such a simple cell membrane is similar to the lipoidal barriers in the G.I. absorption of drugs.



Imp

Blood Brain Barriers (BBB) :-

The capillaries found in other parts of the body, the capillaries in the brain are specialized & much less permeable to water soluble drugs. The brain capillaries consist of endothelial cells which are joined to continuous tight intercellular junction comprising which is called as the Blood brain barrier.

The presence of special cells called as parasites / astrocytes which are the elements of the supporting tissue found at the base of endothelial membrane. Mainly the glial cell present in brain nearby extracellular fluids.

A solute pass into the brain by a 2 steps :

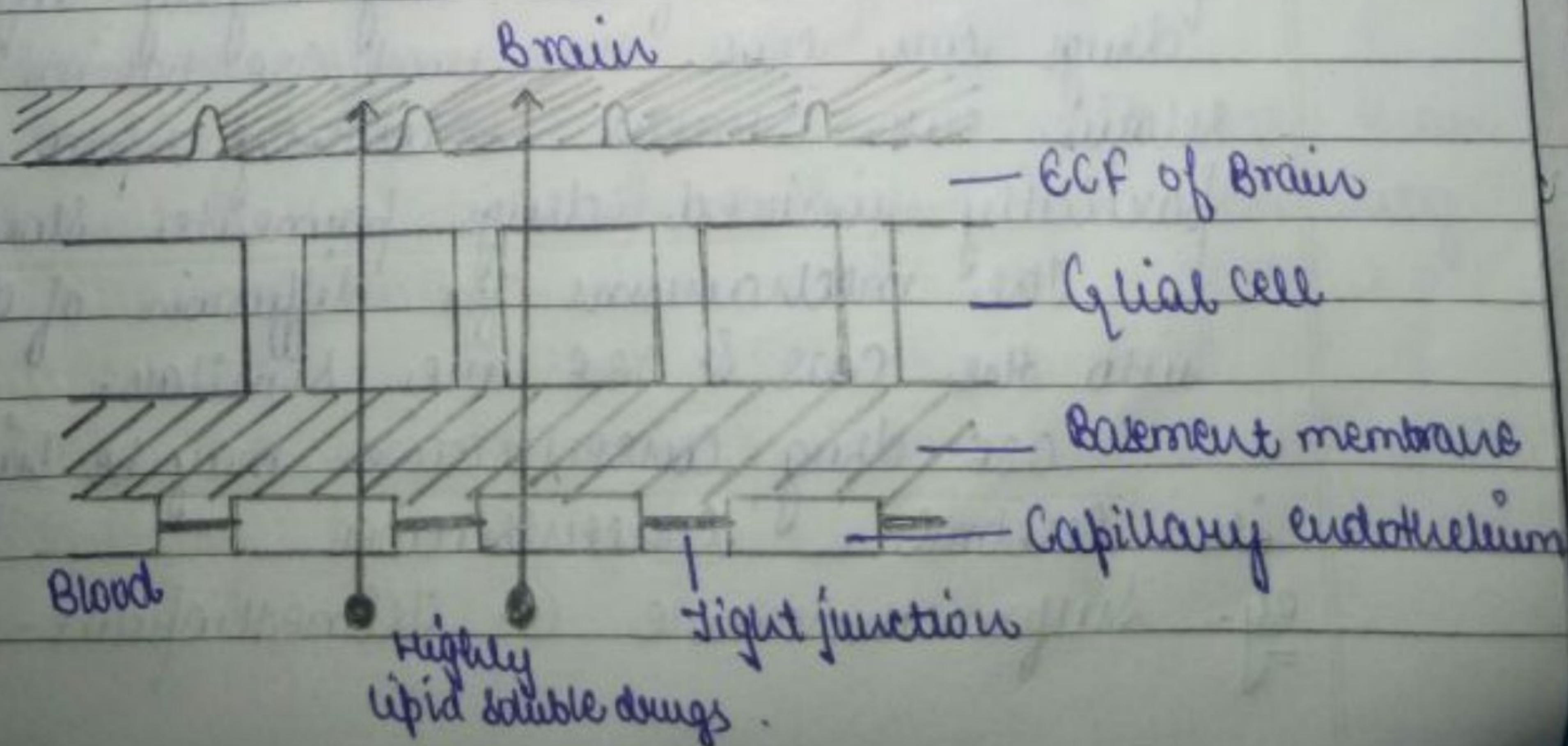
- (i) Passive diffusion through the lipoidal barrier.
- (ii) Active transport of essential nutrients such as sugars & amino acids.

Examples -

(a) Thiopental, a hydrophilic soluble drug that of pentobarbital, & crosses the BBB much more rapidly.

(b) Most antibiotics such as penicillin which are polar, water soluble & ionized at plasma pH do not cross the BBB under normal circumstances.

(c) Parkinson is a disease characterized by depletion of dopamine in the brain cannot be treated by administration of dopamine as it does not cross the BBB. Hence, levodopa which can penetrate the CNS where it is metabolized to dopamine is used in the treatment.

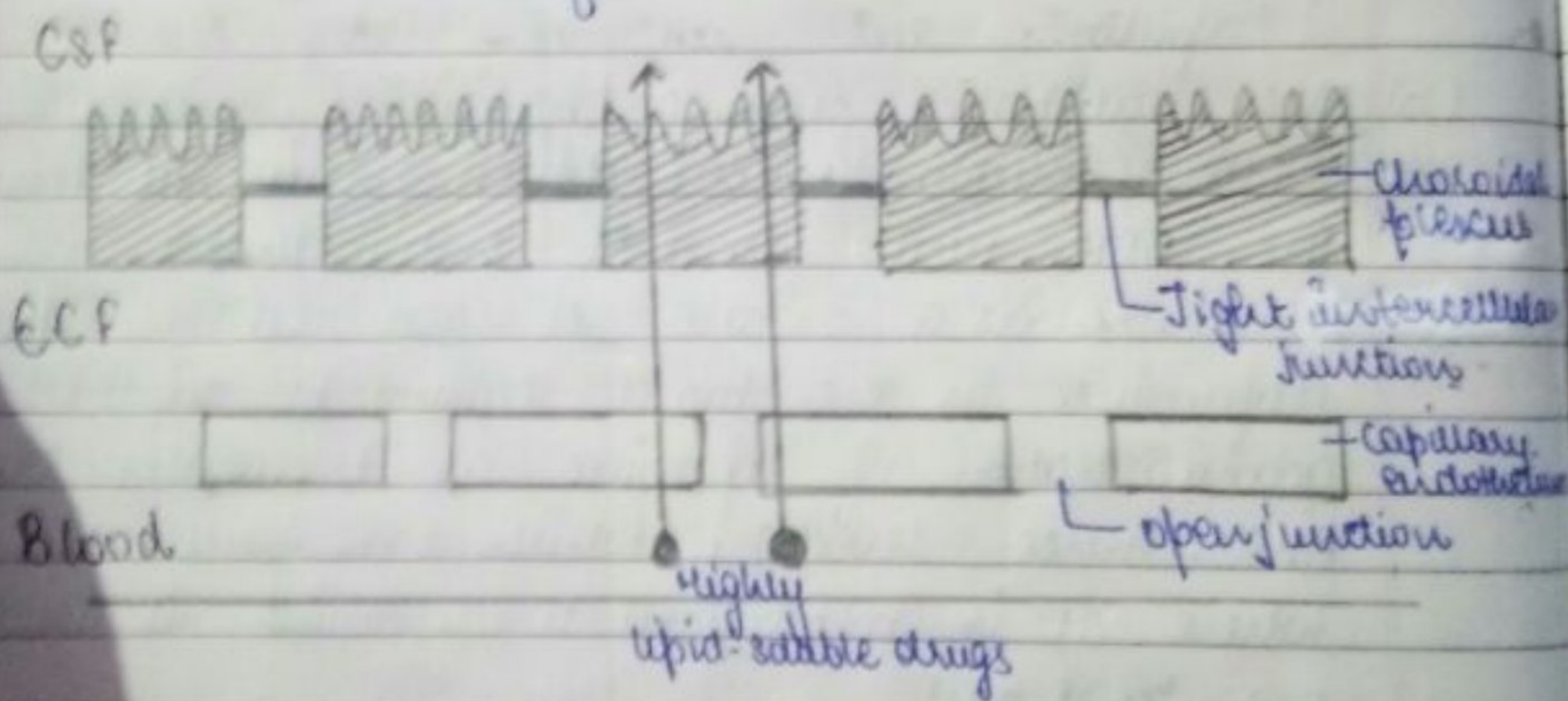


Blood Cerebrospinal Fluid Barrier :-

The cerebrospinal fluid (CSF) is formed mainly by the choroid plexus of the lateral, third & fourth ventricles & is similar in composition to the ECF of brain.

The capillary endothelium have open junctions or gaps & drugs can flow freely into the extracellular space between the capillary wall & the choroidal cell.

The choroidal cells are joined to each other by tight junction forming the blood CSF barrier which has permeability characteristics similar to that of BBB.



As in the case of BBB, only highly lipid soluble drugs can cross the blood CSF barrier with relative ease whereas moderately lipid soluble & partially ionized drugs permeate slowly.

The mechanisms for diffusion of drugs into the CNS & CSF are similar.

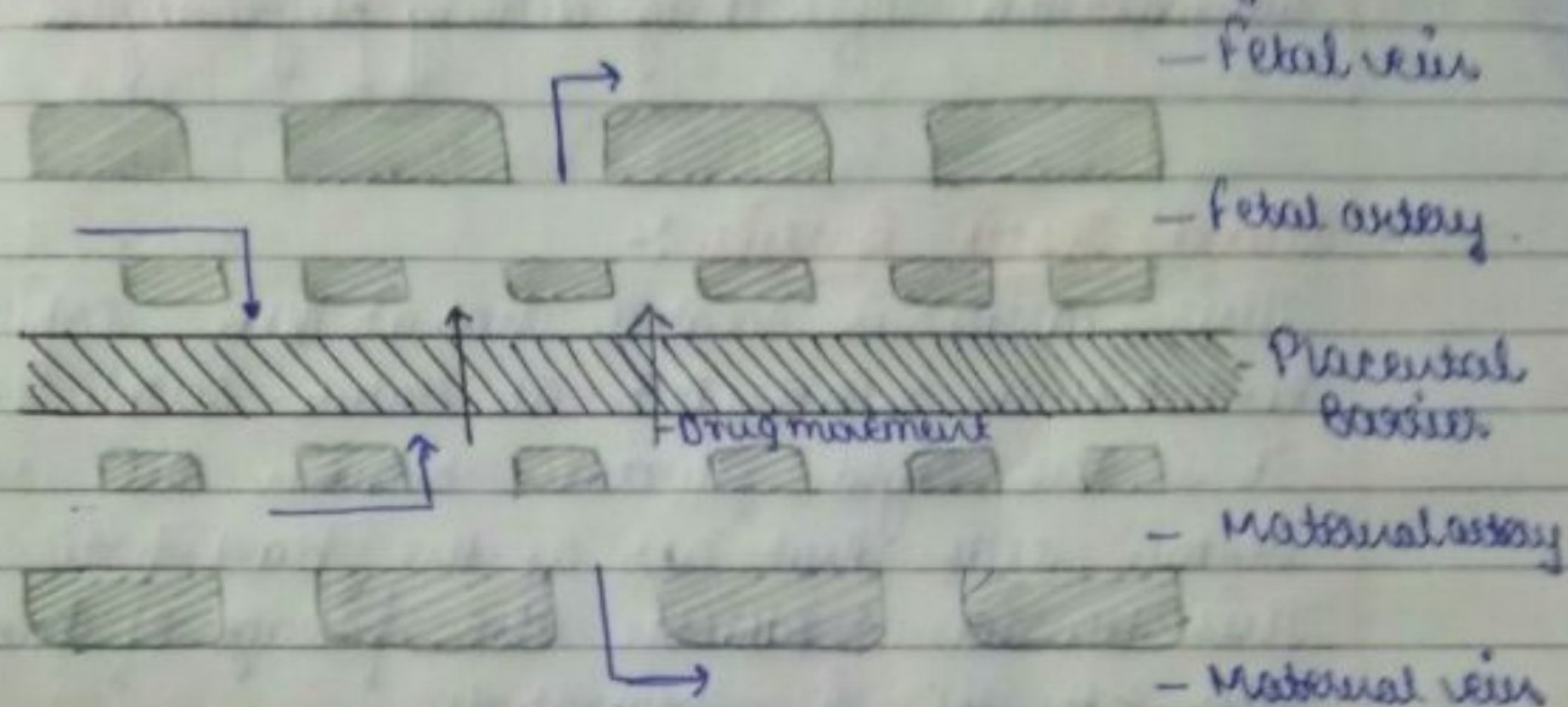
CSF drug concentration may be higher than its cerebral concentration.

Eg. Sulfamethoxazole & Trimethoprim.

Placental Barrier:-

The maternal & the fetal blood vessels are separated by a no. of tissues layers made of fetal trophoblast basement membrane & the endothelium which together constitute the placental barrier.

The flow of blood in the maternal & the fetal blood vessels is shown in diagram:



Placental Barrier are made up of layers i.e. endothelium, connective tissue, trophoblast, syncytium.

The human placental barrier has a mean thickness of 25 microns in early pregnancy that reduces to 2 microns at full term which however does not reduce the effectiveness.

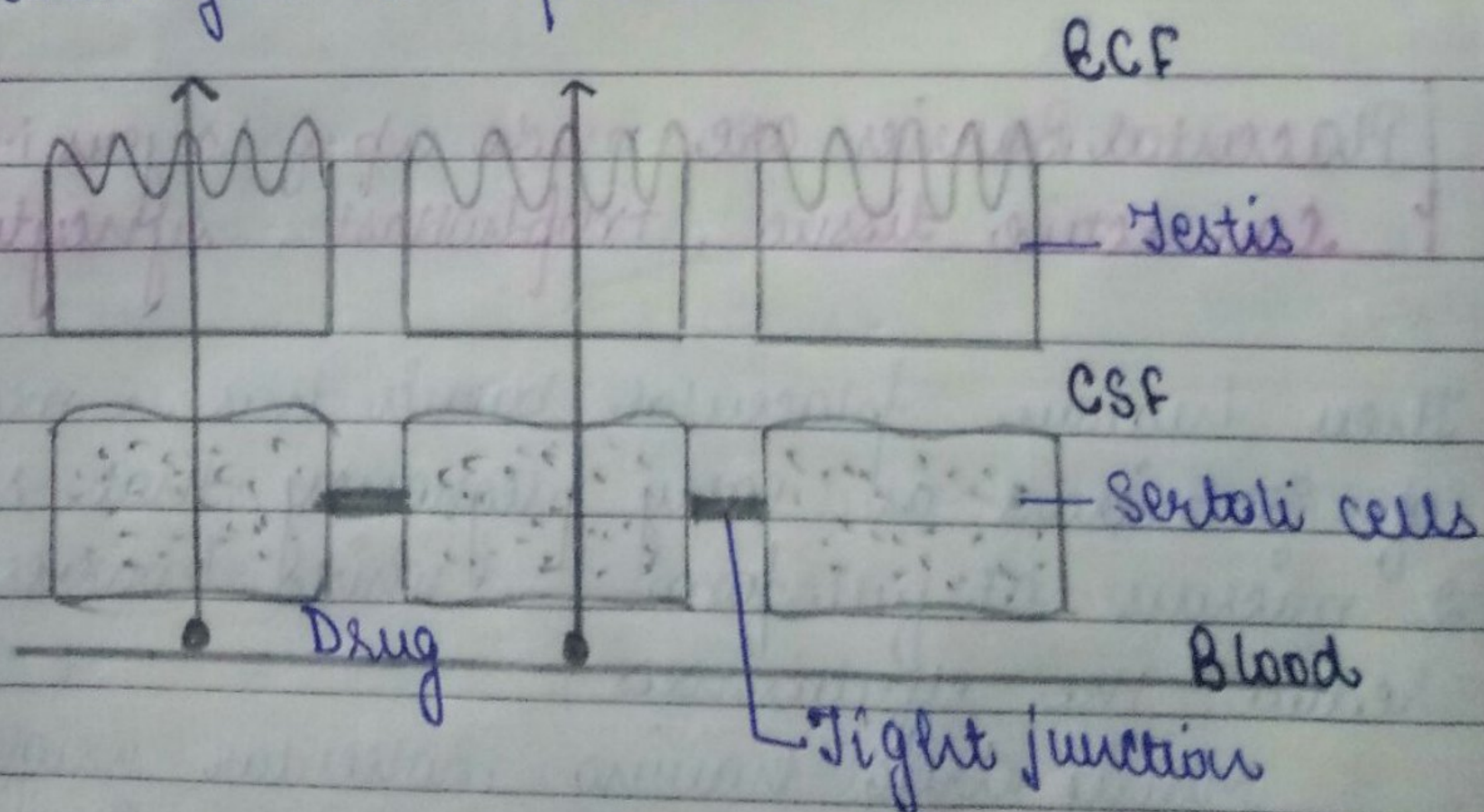
Many drugs having molecular weight less than 100 dalton & moderate to high lipid solubility eg - Ethanol, sulfonamides, barbiturates, gaseous anaesthetics, steroids, narcotic analgesic, anticonvulsants & some antibiotic cross the placental barrier by simple diffusion rapidly.

Sub [• Nutrients essential for the fetal growth are transported by carrier-mediated processes.
Immunoglobulin are transported by endocytosis.

Sub Teratogen is defined as an agent that causes toxic effects on fetal.
Teratogenicity is defined as fetal abnormal caused by administration of drug during pregnancy.

→ Blood-Testis Barrier :-

This barrier is located not at the capillary endothelium level but at Sertoli-Sertoli cell junction. It is the tight junction between the adjacent Sertoli cells that act as the blood-testis barrier. This barrier restricts the passage of drugs to spermatocytes & spermatids.



∴ Binding of Drug -

A drug in the body can bind to several components such as the plasma proteins of blood cells & haemoglobin (blood component) & extravascular proteins & other tissue.

The interacting molecules are generally the molecules such as proteins, DNA or adipose.

The proteins are particularly responsible for such an interaction. The phenomenon of complex formation with protein is called as protein binding of drug.

Binding of drugs mostly 2 types:

- (i) Intracellular binding.
- (ii) Extracellular binding.

→ Intracellular binding: where the drug is bound to a cell protein which may be a drug receptor. These receptors with which drug interact to slow response are called as primary receptors.

→ Extracellular binding: where the drug binds to an extracellular protein. These receptors are called as secondary receptors.

Binding of drugs to protein is generally reversible. It involves weak chemical bonds like H-bonds, hydrophobic bond, ionic bond, vander Waal's forces.

Apparent / volume of drug distribution -
 A drug in circulation distributes to various organs & tissues. When the process of distribution is complete, the different organs & tissues contain varying concentrations of drug which can be determined by the volume of tissues in which the drug is present.

A constant relationship between the concentration of drug in plasma 'C' & the amount of drug in the body 'X'.

$$X \propto C$$

$$X = V_d C$$

$$V_d = \frac{X}{C}$$

Amount of drug in the body is directly proportional to the concentration.

Where, V_d = proportionally constant calling volume of distribution or apparent volume of distribution.

Apparent volume is defined as the hypothetical volume of body fluid into which a drug is dissolved or distributed.

$$\text{Apparent volume of distribution} = \frac{\text{Amount of drug in the body}}{\text{Plasma Drug conc}^n}$$

The real volume of distribution has direct physiological meaning & is related to the body water.

The Plasma volume can be determined by use of substances of high molecular weight or substances that are totally bound to plasma albumin.

Extracellular fluid (ECF) volume can be determined by substances that easily penetrates the capillary membrane & rapidly distribute throughout the ECF.

Total Body water (TBW) volume can be determined by use of substances that distribute equally in all water compartments of the body.

Intracellular fluid (ICF) volume is determined as the difference between TBW & ECF volume.

∴ Plasma & tissue protein Binding Drug-

Many drugs interact with plasma or tissue proteins or with other macromolecules such as melanin & DNA, to form a drug macromolecule complex. The formation of a drug protein complex is called protein binding of drug.

Mechanism of protein drug binding:

Binding of drugs to protein is generally reversible which suggest that it generally involves weak chemical bonds such as H-bond, hydrophobic bond, ionic bond & van der waal's forces.

Irreversible drug binding show a result of covalent binding & reason for the carcinogenicity & tissue toxicity of the drug.

eg- Covalent binding of chloroform & paracetamol metabolites to liver results in hepatotoxicity.

(1) Binding of Drugs to Blood Components :-(a) Plasma protein - Drug Binding -

The entry of a drug into a systemic circulation first thing with which it can interact the blood components like plasma protein, blood cells & haemoglobin.

The order of binding of drugs to various plasma protein is :

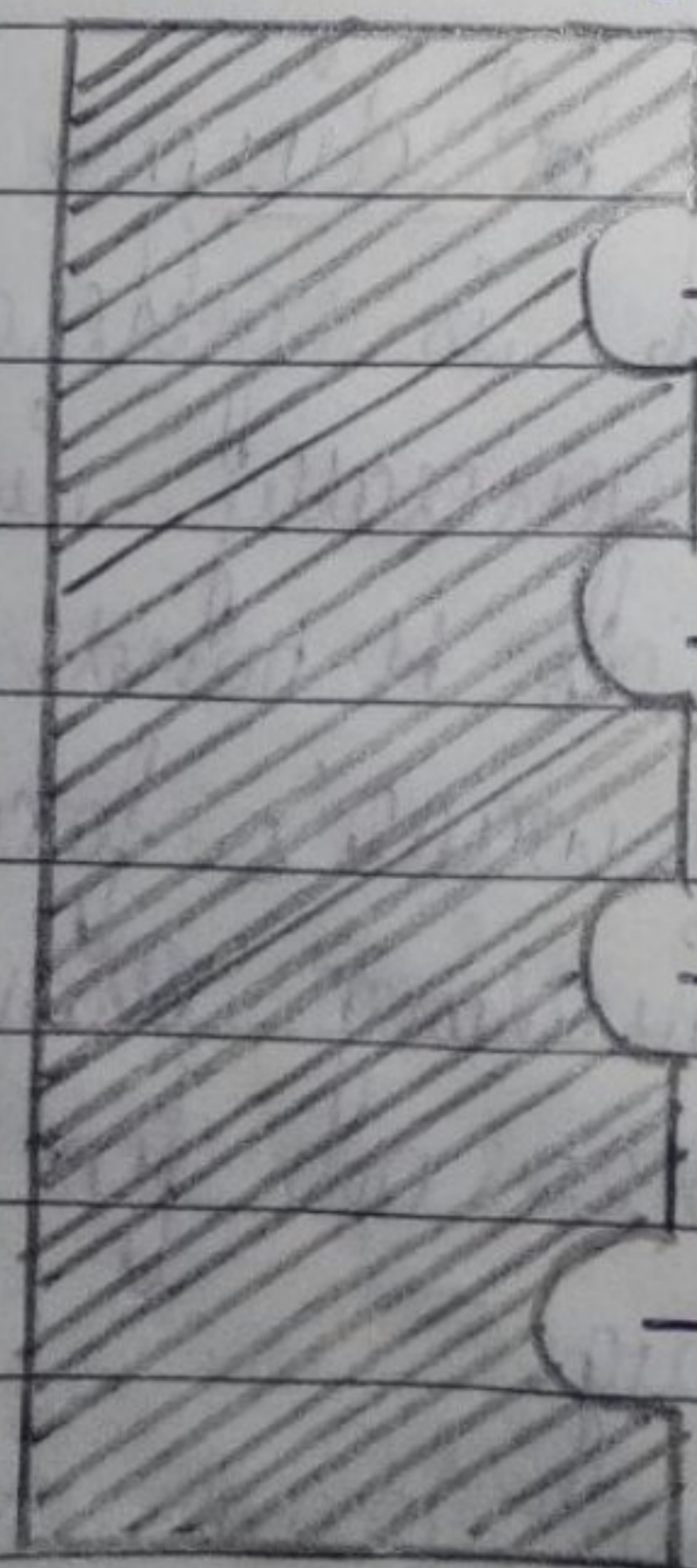
albumin > α_1 -acid glycoprotein > lipoprotein > globulin

Binding of drug to human serum albumin :

The human serum albumin (HSA) having a molecular weight of 65,000 it is most abundant plasma protein with a large drug binding capacity.

The HSA can bind several compounds having varied structures both endogenous compounds such as fatty acids, bilirubin & tryptophan bind to HSA.

Four different sites on HSA have been identified for drug-binding.



→ Site I

(warfarin binding site)

→ Site II

(Diazepam binding site)

→ Site III

(Digitoxin binding site)

→ Site IV

(Tamoxifen binding site)

Site I → Several NSAIDs (phenylbutazone, naproxen, indomethacin), Sulfonamides (sulfadimethoxine, sulfamethizole), phenytoin, sodium valproate & bilirubin.

Site II → Benzodiazepines, ibuprofen, ketoprofen, tryptophan, cloxacillin, probenecid.

A drug can bind more than one site in which case the main binding site is called as the primary site & the other as the secondary site.

Binding of Drugs to α_1 -acid glycoprotein:

It is also called as the orosomucoid. It has a molecular weight of 44,000. It binds to a no. of basic drugs like imipramine, lidocaine, propranolol, quinidine & disopyramide.

Binding of Drugs to lipoproteins:

A drug that binds to lipoprotein by dissolving in the lipid core of the protein & thus its capacity to bind depends upon its lipid content. The molecular weight of lipoproteins vary from 2 lakhs to 34 lakhs.

The 4 classes of lipoproteins are:

- (i) Chylomicron
- (ii) very low density lipoproteins (VLDL)
- (iii) low density lipoproteins (LDL)
- (iv) high density lipoprotein (HDL)

The main physiological role of lipoprotein circulation of lipid tissue through the blood. Similarly, lipoprotein also play an important role in transport of drug to proteins.

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Date :

A no. of acidic drugs (diclofenac), neutral drugs (cyclosporin A) & basic drugs (chlorpromazine) binds to lipoproteins.

Binding of Drugs to Globulin :

Several plasma globulins have been identified & are labelled as α_1 , α_2 , β_1 , β_2 , γ -globulin.

(i) α_1 -globulin - It is also called as transthyretin. It binds a no. of steroidal drugs such as cortisone, prednisone. It also binds to thyroxine & cyanocobalamin.

(ii) α_2 -globulin - It is also called as ceruloplasmin. It binds Vit. A, D, E & K and cupric ions.

(iii) β_1 -globulin - It is also called as transferrin. It binds to ferrous ions.

(iv) β_2 -globulin - It binds to carotinoids.

(v) γ -globulin - It binds to antigen.

(b) Binding of Drugs to Blood cells -

More than 40% of the blood comprises of blood cells of which the major cell component is the RBC. The RBC contributes 95% of the total blood cells.

The RBC comprises of 3 components each of which can bind to drugs :

- Haemoglobin
- Carbonic anhydrase
- Cell membrane

(i) Haemoglobin : 7-8 times the concⁿ of albumin in blood. Drugs like phenytoin, pentobarbital, phenothiazine bind to haemoglobin.

(ii) Carbonic anhydrase : Drugs bind to acetazolamide & chlorothalidone.

(iii) Cell Membrane : Drugs bind to imipramine & chlorpromazine.

(2) Tissue binding of drugs :-

The majority of drugs that bind to extravascular tissue the order of binding is :
liver > kidney > lung > muscle.

Examples of extravascular tissue of binding -

(i) Liver : A no. of halogenated hydrocarbons & paracetamol bind irreversibly to liver tissue resulting in hepatotoxicity.

(ii) Lungs : Basic drugs like imipramine, chlorpromazine & antihistamines accumulate in lungs.

(iii) Kidney : Metallothionein, a protein present in kidneys, binds to heavy metals such as lead, mercury & cadmium & results in their renal accumulation & toxicity.

(iv) Skin : Chloroquine & phenothiazines accumulate in skin by interacting with melanin.

(vi) Eyes: The retinal pigments of the eye is also contains melanin that bind to chloroquine & phenothiazines.

(vii) Hair: Arsenicals, chloroquine & phenothiazine are reported to deposit in hair shafts.

(viii) Bones: Tetracycline is a well known example of a drug that binds to bone & teeth.

(ix) Fats: lipophilic drugs such as thiopental & the pesticide DDT accumulate in adipose tissues.

(x) Nucleic Acids: Molecular components of cells such as DNA interact strongly with drugs like chloroquine & quinacrine.

Sub

Comparison between plasma-protein drug binding & tissue drug binding

Plasma-protein - drug binding	Tissue drug binding
(i) Involves weak bonds & thus reversible.	Involves strong & covalent bonds & thus irreversible.
(ii) Small apparent volume of distribution.	Large apparent volume of distribution.
(iii) Half life is relatively short.	Half life is relatively long.
(iv) Does not result toxicity.	Tissue toxicity is common.
(v) Displacement is responsible by other drugs.	Displacement of drugs generally does not occur.
(vi) Competition b/w drugs for binding to plasma proteins can occur.	Tissue drug binding is generally non-competitive.

Factors affecting protein - Drug binding

(1) Drug Relating Factor :

- Physicochemical characteristic of the drug.
- Concentration of drug in the body.
- Affinity of a drug for a particular binding components.

(2) Protein - Tissue related Factor :

- Physicochemical characteristic of the protein or binding agent.
- Concentration of protein or binding component.
- No. of binding sites on the binding agent.

(3) Drug interaction :

- Competition between drugs for the binding site.
- Competition between drugs & normal body constituents.
- Allosteric changes in protein molecule.

(4) Patient Related Factor :

- Age
- Intersubject variation
- Disease States.

(1.a) Physicochemical characteristic of the Drug :-

- Increase in lipophilicity increases the extent of binding.
- Acidic or ionic drugs such as **penicillin** & **sulfonamides** bind more to HSA, Basic or cationic drugs such as **imipramine** & **aspirin** bind to AAG, neutral or unionized drugs to lipoprotein.

[1.b] Concⁿ of drug in the body :-

- At low concⁿ, most drugs may be bound to proteins.
- At high concⁿ, more free drugs may be present owing to saturation of binding sites on proteins.

[1.c] Drug-Protein/Tissue Affinity :-

- Lidocaine has greater affinity for AAG than for HSA.
- Digoxin has more affinity for protein of cardiac muscles than those of skeletal muscle or plasma.
- Iophenoxic acid, a radiopaque medium, has half-life of 2 1/2 yrs due to high affinity to plasma proteins.

[2.a] Physicochemical properties of protein Binding Component :-

- Lipoprotein & adipose tissue tend to bind lipophilic drugs by dissolving them in their lipid core.
- The physiologic pH determines the presence of active anionic & cationic group on the albumin molecules to bind a variety of drugs.

[2.b] Concⁿ of protein Binding Component :-

The amount of several protein & tissue components available for binding, change during disease state.

[2.c] No. of binding sites on the protein :-

- Albumin has a larger no. of binding sites as compared to other proteins.
- Indomethacin binds to 3 sites on albumin.
- AAG is a protein with limited binding capacity due to low concⁿ & molecular size.
- Lidocaine binds to 2 sites on AAG in presence of HSA.

[3.a]

Competition b/w drugs for the binding site:-
 A drug-drug interaction for the common binding site is called as displacement interaction. The drug which is displaced is called as the displaced drug & drugs as the displacer.
 eg. warfarin & phenylbutazone.

Interaction will result when:

- (1) The displaced drug (warfarin) is more than 95% bound having small volume of distribution, rapid onset of action & also has a narrow therapeutic index.
- (2) The displacer drug (phenylbutazone) has a high degree of affinity & competes for the same binding sites & the drug/protein concⁿ ratio is high.

[3.b]

Competition b/w drugs & normal body constituent:-
 Interaction with free fatty acids level are increased during fasting, diabetes, MI, etc.
 eg. Interaction with salicylate with bilirubin in neonates.

[3.c]

Allosteric changes in protein molecule:-
 It involves alteration of the protein structure by the drug/metabolite modify binding capacity.
 eg. Aspirin acetylation of albumin modify the binding capacity of NSAIDs (increased affinity).

[4.a]

Age:- Neonates - low albumin content, more free drug.
 Young infants - High dose of digoxin due to large renal clearance.
 Elderly - low albumin content, so more free drug.

[4.b]

Intersubject variation:- Due to genetic & environmental factors.

[4.c]

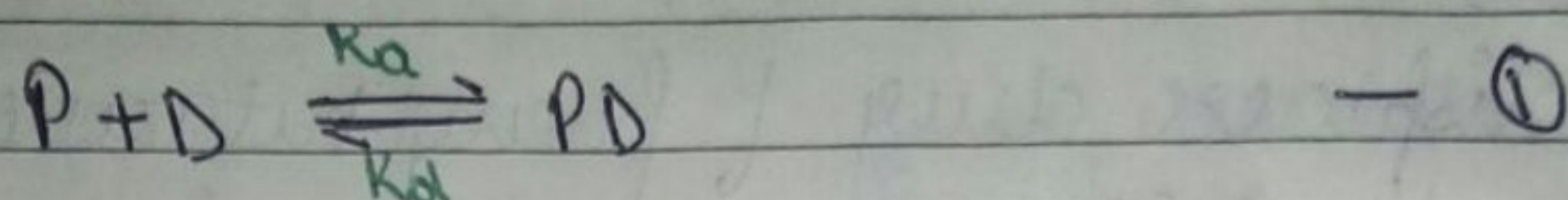
Disease State:-

Disease	Influence on plasma protein	Binding to		
		Acidic	Basic	Neutral
Renal failure	↓ se Albumin content	Decrease	no effect normal or decrease	no effect
Hepatic failure	↓ se Albumin synthesis	Decrease	no effect	no effect
Inflammatory states	↑ se AAG level	no effect	Increase	no effect

M. Sub.

Kinetics of protein-drug binding

In the kinetics of protein-drug binding, if 'P' represent proteins & 'D' represent the drug, then applying law of mass action to reversible protein-drug binding, we can write eqⁿ:



At equilibrium,

$$k_a = \frac{[PD]}{[P][D]} \quad - (2)$$

$$[PD] = k_a [P][D] \quad - (3)$$

where, $[P]$ = concⁿ of free protein

$[D]$ = concⁿ of free drug

$[PD]$ = concⁿ of protein-drug complex.

k_a = association rate constant.

k_d = dissociation rate constant

$k_a > k_d$ i.e. protein-drug binding is favoured.

If P_T is the total concentration of protein present, bound & unbound, the eqⁿ become:

$$P_T = [PD] + [P] \quad - (4)$$

If x is the no. of moles of drug bound to total moles of protein, then eqⁿ become:

$$x = \frac{[PD]}{[P_T]} = \frac{[PD]}{[PD] + [P]} \quad - (5)$$

Substituting the value of $[PD]$ from eqⁿ (3) in eqⁿ (5) we get :

$$x = \frac{k_a [P][D]}{k_a [P][D] + [P]} \quad \text{--- (6)}$$

$$x = \frac{k_a [D]}{k_a [D] + 1} \quad \text{--- (7)}$$

The eqⁿ (7) have only one binding site on the protein & the protein-drug complex is a 1:1 complex. If more than 1 i.e. N no. of binding sites are available per mole of the protein then:

$$x = \frac{N k_a [D]}{k_a [D] + 1} \quad \text{--- (7a)}$$

∴ Clinical Significance of Protein / Tissue binding of Drugs -

(1) Absorption :

The absorption equilibrium is attained by transfer of free drug from the site of administration into the systemic circulation & when the concⁿ in these two compartments become equal.

Binding of the absorbed drug to plasma protein decreases free drug concⁿ & disturbs such an equilibrium.

(2) Systemic Solubility of Drug :

water insoluble drug, neutral endogenous macromolecules such as heparin & several steroids & oil soluble vitamins are circulated

& distributed to tissues by binding especially to lipoprotein which act as a vehicle. (5)

(3) Distribution:

- Plasma protein binding restricts the entry of drugs that have specific affinity for certain tissues.
- This prevents accumulation of a large fraction of drug in such tissues.
- A protein bound drug in particular does not cross the BBB, the placental barrier & the glomerulus. (6)

(4) Apparent volume of distribution & Drug storage:

- A drug i.e. bound to blood component remains confined to blood such a drug has a small volume of distribution.
- A drug that shows extravascular tissue binding has a large volume of distribution. (7)
- The relationship b/w tissue drug binding & apparent volume of distribution as follows:

$$V_d = \frac{X}{C}$$

$$\text{volume of distribution} = \frac{\text{amount of drug in the body} [X]}{\text{Plasma drug conc}^n [C]}$$

(5) Elimination:

Only the unbound or free drug is capable of being eliminated. This is because the drug protein complex can not penetrate into the metabolizing organ (liver).

The large molecular size of complex also prevents glomerular filtration.

- eg - Tetraacycline which is only 65% bound have long elimination half-life.
- Penicillin have short elimination half life.

(6) Displacement Interaction & Toxicity:

Displacement interaction are significant in case of drug which are more than 95% bound. This is explained from the example is a displacement of just 1% of a 99% bound drug results in doubling of the free drug concⁿ i.e. 100% rise.

(7) Diagnosis:

The chlorine atom of chloroquine when replaced with radiolabelled I-131 can be used to visualize melanomas of the eye since chloroquine has a tendency to interact with melanin of eyes.

(8) Therapy & Drug targeting:

The binding of drugs to lipoproteins can be used for site-specific delivery of hydrophobic moieties that is particularly useful in cancer therapy.