DRUG ABSORPTION

Occurs by:

→ Intracellular Transport / Transcellular:

Most common pathway for drug transport. Passage of drugs across GI epithelium.

→ Intercellular / Paracellular Transport:

Transport of drugs through junctions betn the GI epithelial cells

eg:- Insulin & cardiac glycosides

→ Vesicular / Corpuscular Transport / Endocytosis / Transcellular

Involve transport of substances within vesicles into a cell. Transport across cell membrance.

Mechanism of Drug Absorption:

① Passive diffusion:

- Drug molecules move frm high conc region to low conc
- for 90% of drugs.
- Non-ionic diffusion.
- Driving force conc / electrochemical gradient
- Drug movement due to KE of molecules.

Fick's first law of diffusion $\frac{dQ}{dt} = \frac{DA K_{m/w} (C_{GIT} - C)}{h}$

- $\frac{dQ}{dt}$ → rate of drug diffusion
- D → Diff co-eff
- A → S.A
- $K_{m/w}$ → Part. co-eff betn lipoidal memb & eg. GI fluid
- $(C_{GIT} - C)$ → conc diff in GIT fluids & plasma
- h → Thickness of memb

- Energy independent
- Rapid over short distances
- Distributed into large vol of body fluids.
- Conc of drug at abs site < GIT is maintained greater than the conc in plasma - Sink Condition

② Pore Transport:

a) Bulk flow / convective transport / filtration.

- Mech through protein channel that in cell membrane.
- Drug permeation through pore transport -
  Renal excretion, removal of drug from CSF & Entry of drug into liver.
- Driving force - osm or hydrostatic pressure differences across the membrane.
  Bulk flow of water along ~~with~~ with small solid molecules through aq. channels. Water flux that promotes such transport is solvent drag.
- Abs of low mol wt < 100 D.
  eg:- Urea, H_2O, sugars.

③ IONIC / ELECTROCHEMICAL DIFFUSION:

If same drug is moving from higher to lower conc, i.e, moving down the electrical gradient, that is electrochemical diffusion.

Rate of permeation.

Unionized molecule > Anions > Cations.

④ Ion-Pair Transport:

Abs of compounds which ionizes at all pH values.
eg:- Quaternary NH_4^+, sulphonic acids.
Ionized moieties form neutral complexes with endogenous ions which have both the req lipophilicity & Aq. solubility for passive diffusion.
eg:- Propranolol.
↳ forms ion pair with oleic acid.

Very weak bases with $pK_a < 5$, are unionized at all pH values.

③ Carrier Mediated Transport: (Mixed order kinetics)

Carrier + Solute molecules → Solute carrier complex
Reversible

- Facilitated → No energy req
  Driving force is conc gradient
  Transport by integral membrane proteins
  Abs of sugars, steroids, a.a, pyrimidines
  frm small intestine
- Active
  - req energy
  - ATP
  - By Na^+ pump, Na^+/K^+ ATPase

- Saturable

④ Primary Active Transport:
- Direct ATP req
- In one direction, Uniport
eg:- Abs of Glucose
ABC (ATP binding cassette) transporters.

⑤ Secondary:
- No direct ATP.
- In both directions
  - Symport (co-transport) Sympoter
    Na^+ glucose
  - Antiport (counter transport)
    Na^+-H^+ ions (kidney)

④ ENDOCYTOSIS (vesicular transport)
- cell absorbs molecules by engulfing them.

occurs by:-

Phagocytosis:- cell eating, Adsorptive uptake of solid particles. Vit A, D, E, K

Pinocytosis:- smaller particles are suspended.
Req. ATP
eg: Polio vaccine, Botulism toxin
☆ to phagocytosis but it is non-specific.
✱ in abs of oil soluble vit & uptake of nutrient.

Transcytosis:- macromolecules are transferred across the cell membr
✱ for transfer of IgA & insulin
captured in vesicles. Endocytic vesicle is transferred frm one extracellular compartment to another.

Absorption factors:

- "Dissl" is rate limiting step for lipophilic drugs.
  eg:- Griseofulvin
- Permeation is rate limiting step for hydrophilic drugs eg:- Neomycin
- The drug should be in solution form for better absorption

- Stable forms have: low energy state
  high m.pt
  least aq. solubility
  Dissln rate limited.

  Metastable forms: high energy,
  low m.pt
  High aq. solubility
  more abs & B.A

- Vit. Riboflavin have 20 fold range in aq. solubility

- Solvates / Hydrates:-
  Drug crystals may incorporate one or more solvent molecules to form solvates.
  eg:- $CHCl_3$ solvate of Griseofulvin
  n-pentanol solvate of fludrocortisone.

- For more than 100 (M.W), which abs by passive diffusion,
  pK_a → Amt of drug existed in unionized form.
  pH of fluid at abs site by Henderson-Hasselbach eq.

$$pH = pK_a + \log \frac{(ionized)}{(unionized)}$$ for acidic

Base
W A

$$pH = pK_a + \log \frac{(unionized)}{(ionized)}$$ for basic.

Conj Acid
W B

$$K_{o/w} = \frac{\text{Distribution of drug in org. phase}}{\text{" " " in aq. phase}}$$

- Disintegration time is directly proportional to amount of binder & compression force.
- Limitation of wet granulation - form" of crystal bridge or chemical degradation.
- APOC - Agglomerative phase of comminution - grinding of drug till spontaneous agglomeration & granules are prepared & higher SA.

- Surfactants - Absorption enhancers.
  (Poly Oxyethylene ethers enhance gastric & rectal abs of Vancomycin, penicillin)
  eg:- Bile salts.
  ↳ conjugation of cholic acid & chenodeoxycholic acid

- Brilliant Blue retards dissln of sulfathiazole.
- Gastric emptying - passage frm stomach to small intestine.
- Vit B_{12} - abs frm distal part of intestine
  Vit B&C - " " proximal " " small intestine.
- Gastric Emptying Rate: Carbs > Proteins > Fats.
- 28% of Cardiac ouput is supplied to GIT portion

Drug-Drug Interactions in GIT:

- Anti-diarrhoeal prep like kaolin prevents abs of many co-administered drugs ⊗
- Complexation like Ca, Al ↓ Tetracycline.
- Anticholinergics like propanthelin ↓ GI Transit & ↑ abs of ranitidine & Digoxin.
- Metaclopramide ↑ GI motility & ↑ GI Abs of Tetracycline, levodopa.
- Erythromycin ↑ efficacy of Digoxin.
  ↳ Not stable in gastric fluid

Affecting first pass metabolism

- Luminal Enz: Enz in gut fluids, cum intestinal & pancreatic secretions
  eg: Hydrolases
- Gut Wall Enz: (Mucosal enz) in gut & intestine, Colon.
  eg: - Alc. dehydrogenase.

- Antiemetic - Scopolamine - TD route.

DRUG DISTRIBUTION - Det chiefly by rate of blood flow to tissues.

- Reversible transfer of drug betn the blood & extra vascular fluids & tissues of the body.

Factors affecting drug distribution:

① Tissue permeability of the drug:
- Rate of Tissue permeability - Depends of physicochemical prop.
- Rate of Blood perfusion.

② Physico chemical properties of drugs:-

- Molecular size:- MW < 500-600 D easily pass capillary memb to ECF.
  From ECF to cross cell memb - particle size < 50 D.
- pK_a - Degree of Ionisation:-
  pH at which half of drug is ionized
- o/w permeability:-
  less ionized more permeability.

(b) Physiological Barriers:

→ Simple capillary endothelial barrier:-
< 600 D drugs diffuse through capillary endothelium.

→ Simple cell membrane barrier:-

capillary → ECF → cell memb

lipophilic drugs ≥ 50-600 D
Hydrophilic " ≤ 50 D will pass through the membrane

→ Blood brain barrier:-

- Brain capillaries consist of endothelial cells which are joined to one another by cont intercellular junction.
- lipoidal barrier, max permeable to CO_2.
- Allows ≥ high o/w part. co-eff to diffuse passively.

eg:- Use of permeation enhancers
(Dimethyl sulfoxide)
- Osmotic disruption of BBB by infusing internal carotid artery with mannitol.
- Dihydropyridine redox system as drug carrier (Active Transport)
DHP redox

→ Blood-CSF Barrier:
CSF - choroid plexus of lateral, 3rd & 4th Ventricles.
eg:- Sulphamethoxazole & Trimethoprim

→ Placental Barrier:-
MW < 1000 D

→ Blood-Testis Barrier:
Sertoli-sertoli junction - restricts the passage of drugs to spermatocytes & spermatids.

Perfusion rate:-
Vol of blood that flows per unit time per unit volume of tissue ml/min/ml

VoD:

- Apparent VoD - to quantify the distribution of drug betn plasma & the rest of the body after oral or parenteral dosing.

- loading dose of a drug is dependent on VoD

$$X = V_d \cdot C$$

$$V_d = \frac{X}{C} \quad \frac{(\text{Amt of drug in the body})}{(\text{plasma drug conc})}$$

litres/kg B.W.

∝ conc of drug in plasma.

large V.d — more conc in extra vascular tissues & less conc in intravascular tissues