Dosage Form Design

Lecture 7

Dr. Athmar Dhahir Habeeb
PhD in Industrial pharmacy and drug delivery
athmar1978@uomustansiriyah.edu.iq
athmar1978@yahoo.com
athmar.habeeb.12@ucl.ac.uk

GENERAL CONSIDERATIONS IN DOSAGE FORM DESIGN

1. **Drug Consideration In Dosage Form Design**
    - 1.1 Characteristics of Drug Substances
    - 1.2 Drug Stability
    - 1.3 Determining Drug Formulation Stability
    - 1.4 Prevention Against Microbial Contamination
    - 1.5 Appearance and Palatability
2. **Therapeutic Considerations In Dosage Form Design**
    - 2.1 Nature of the disease or illness
    - 2.2 Age of the Patient
3. **Biopharmaceutics Considerations**
    - 3.1 Biopharmaceutics
    - 3.2 Concept of Bioavailability

Biopharmaceutics

- Is the science that study relation of physicochemical properties of drug, dosage form, & route of administration on rate and extent of drug absorption.

pharmacokinetics

- It is the study of the kinetics of absorption, distribution, metabolism, and excretion (ADME) of drugs and their pharmacologic, therapeutic, or toxic effects in animals and man.
- elimination refers to both metabolism and excretion.
- drug in blood exists in equilibrium with drug in tissues.
- **In equilibrium concentration of the drug in blood different (greater or lesser) than the concentration of the drug in tissues. This is due to the physicochemical properties of the drug.**

- The rate of transfer of a drug from one compartment to another is proportional to concentration of the drug in the compartment from which it exits; the greater the concentration, the greater is the amount of drug transfer.

During metabolism a drug substance may be biotransformed into:

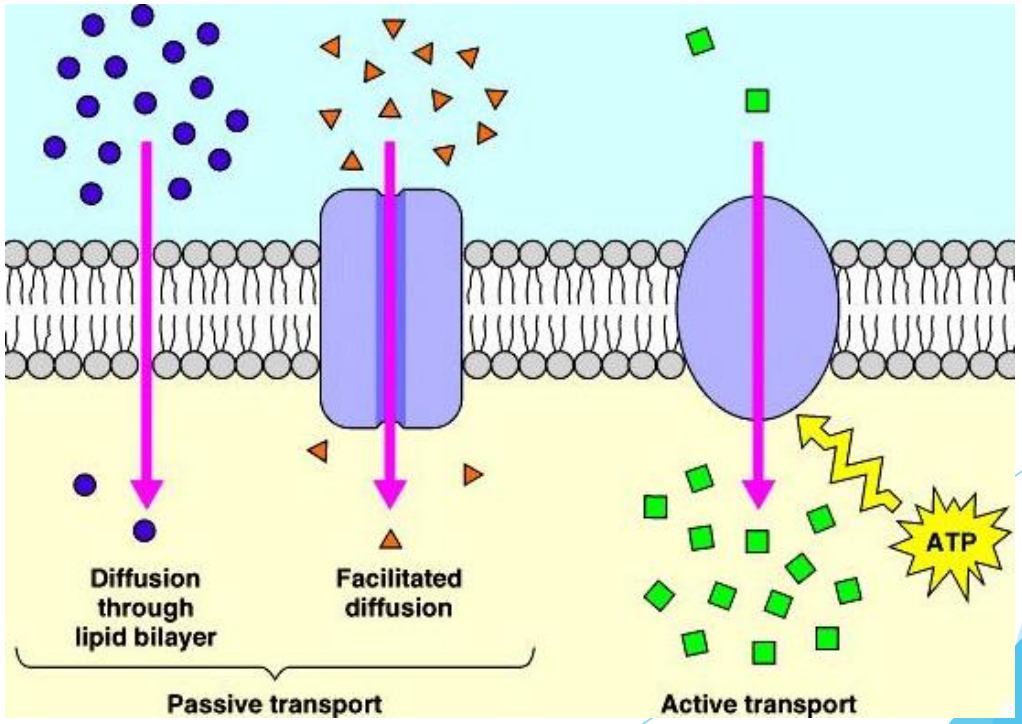
1. **pharmacologically active,**
2. **inactive metabolites,**
3. **or both.**

For example, anticonvulsant drug carbamazepine is metabolized in the liver to active epoxide metabolite.

- **metabolism of drug to inactive products is irreversible process.**
- In some instances, a pharmacologically inactive drug (termed a prodrug) administered for known effects of its active metabolites.
- (k_{el}) : elimination rate constant for drug describe its rate of elimination from body.

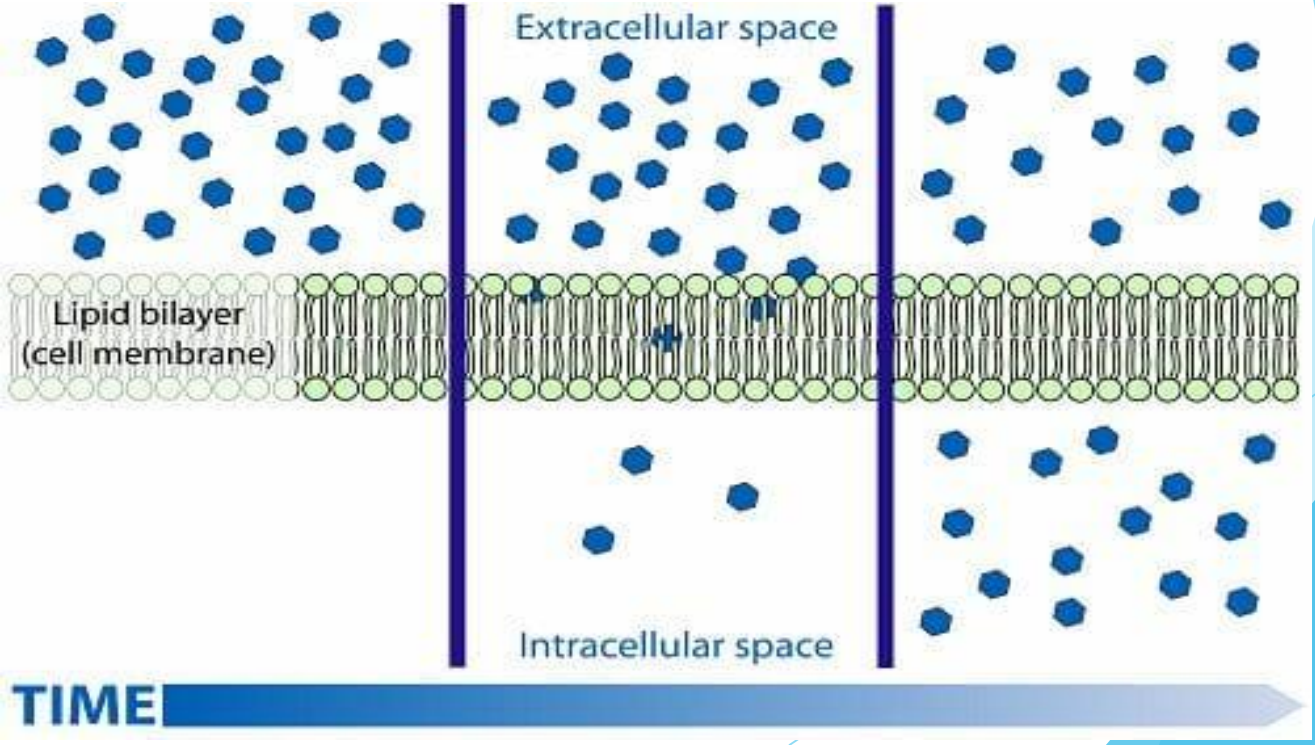
PRINCIPLES OF DRUG ABSORPTION

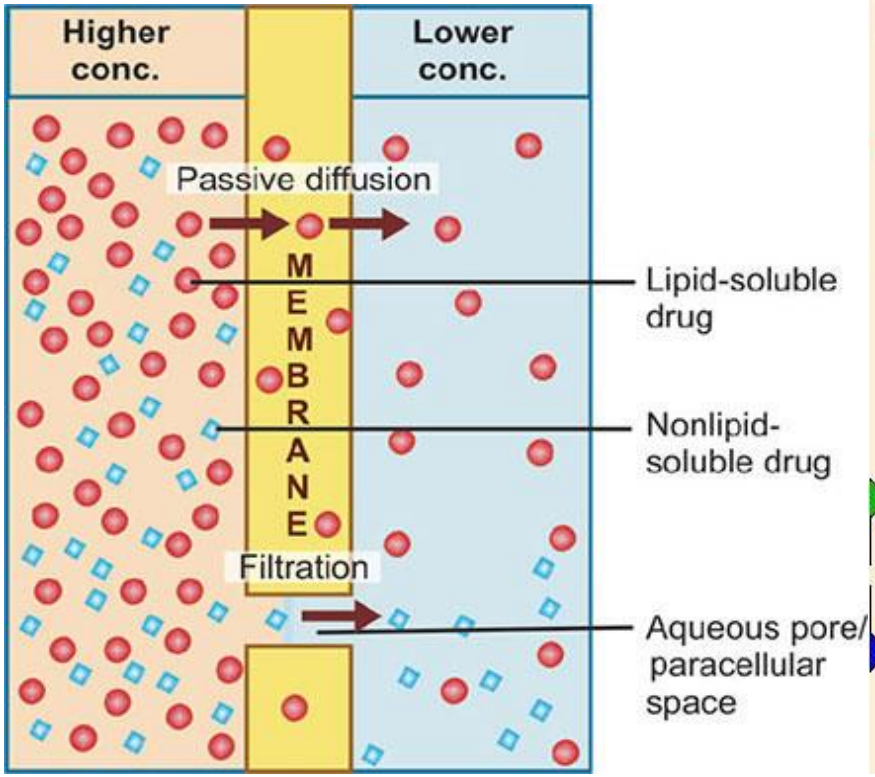
- Passive Diffusion
- Active Transport
- Facilitated Passive Diffusion

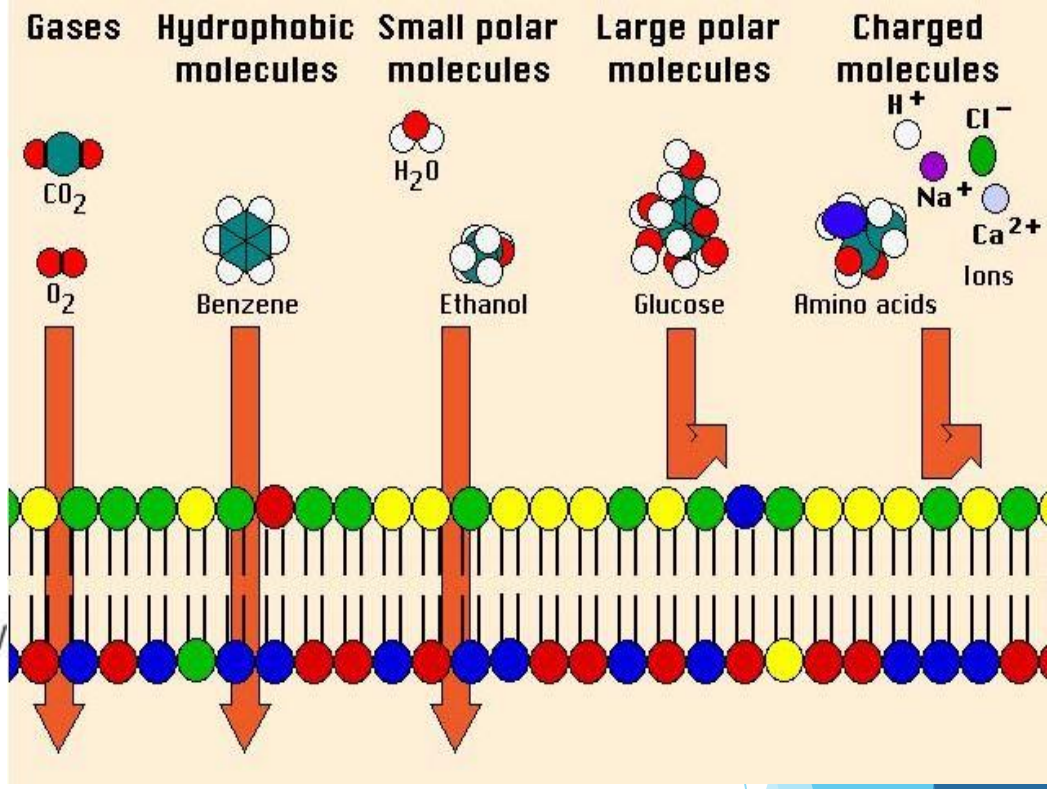


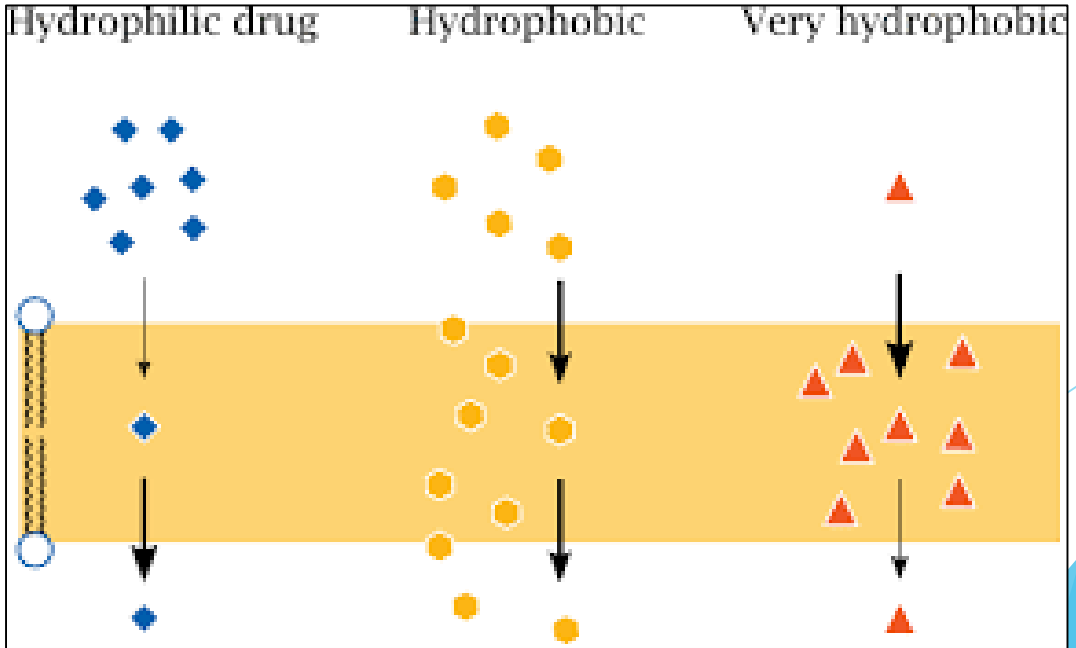
Passive Diffusion

1. From high to low concentration
2. depends on the molecule's lipid solubility, particle size, degree of ionization, and area of absorptive surface.
3. Primary mechanism for most drugs
4. No need for energy or carrier.




Higher conc.
Lower conc.
Passive diffusion
MEMBRANE
Filtration
Lipid-soluble drug
Nonlipid-soluble drug
Aqueous pore/ paracellular space


Gases
Hydrophobic molecules
Small polar molecules
Large polar molecules
Charged molecules
CO_2
O_2
Benzene
H_2O
Ethanol
Glucose
H^+
Cl^-
Na^+
Ca^{2+}
Ions
Amino acids


Hydrophilic drug
Hydrophobic
Very hydrophobic

Fick's law of Absorbtion

drug molecules diffuse from a region of high drug concentration to a region of low drug concentration.

- Where *dQ*/*dt* = rate of diffusion,
- *D* = diffusion coefficient,
- *K* = lipid water partition coefficient
- *A* = surface area of membrane;
- *h* = membrane thickness,
- $C_{GI} - C_p$ = difference between the concentrations of drug in the gastrointestinal tract and in the plasma.

$$\frac{dQ}{dt} = \frac{DAK_{m/w}}{h}\left(C_{GIT} - C_P\right)$$

$$\frac{dQ}{dt} = \frac{DAK_{m/w}}{h}\left(C_{GIT} - C_P\right)$$

- Because *D*, *A*, *K*, and *h* are constants under usual conditions for absorption, a combined constant *P* or permeability coefficient may be defined.

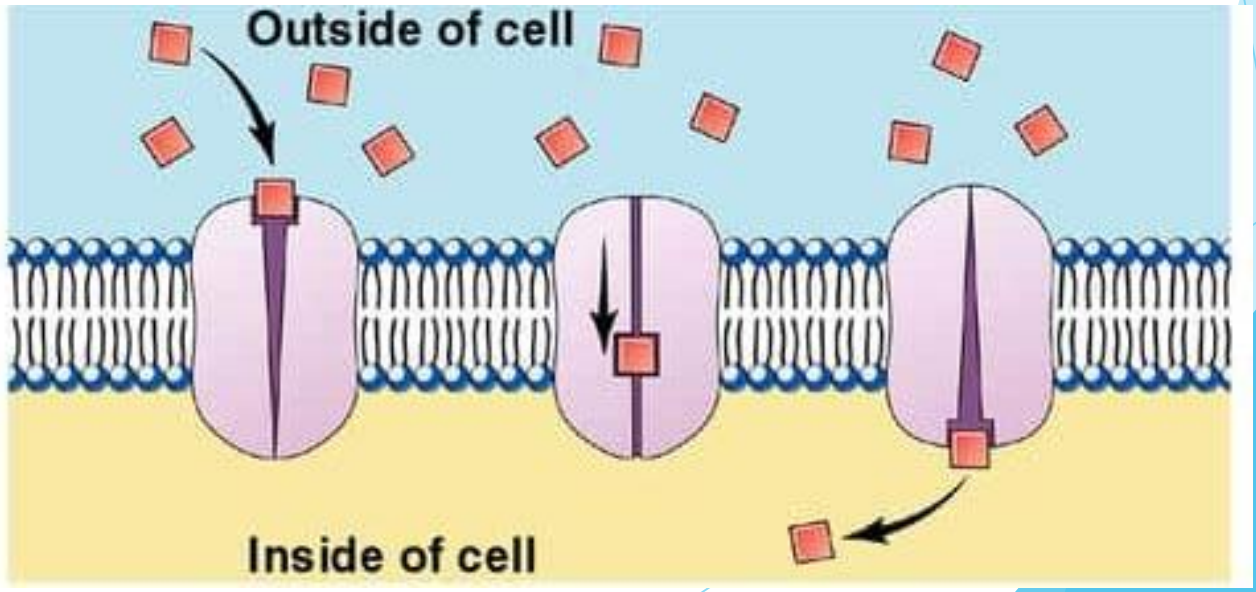
$$P = \frac{DAK}{h}$$

- drug concentration in plasma, *C* p, is extremely small compared to the drug concentration in the gastrointestinal tract, C_{GI}. If *C* p is negligible and *P* is substituted

$$\frac{dQ}{dt} = P(C_{GI})$$

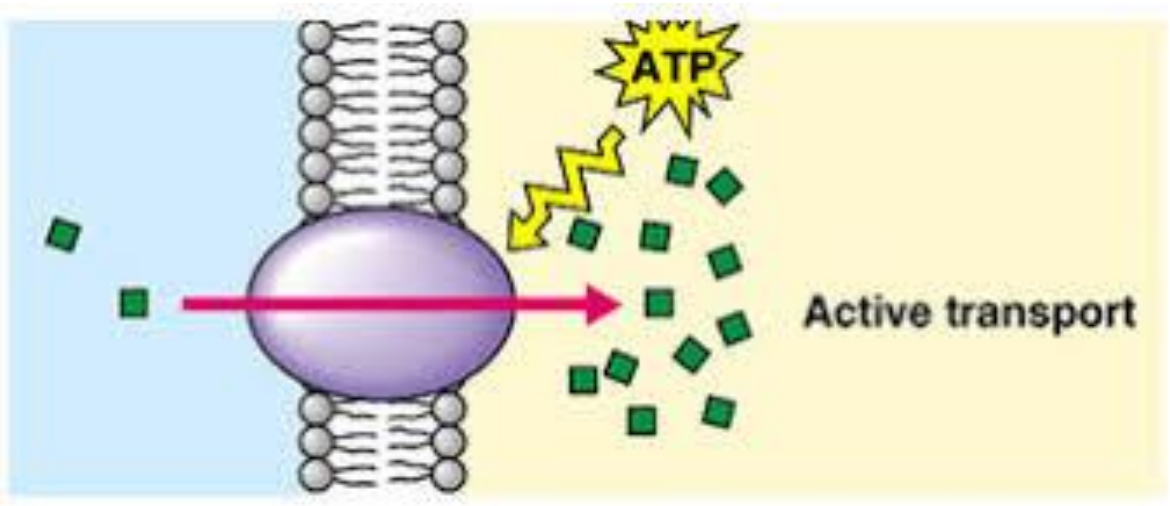
Facilitated Passive Diffusion

1. From high to low concentration
2. Need Carrier in the membrane combines reversibly with the substrate molecule outside the cell membrane
3. No need for energy.
4. specific molecular configuration
5. Limited number of carrier

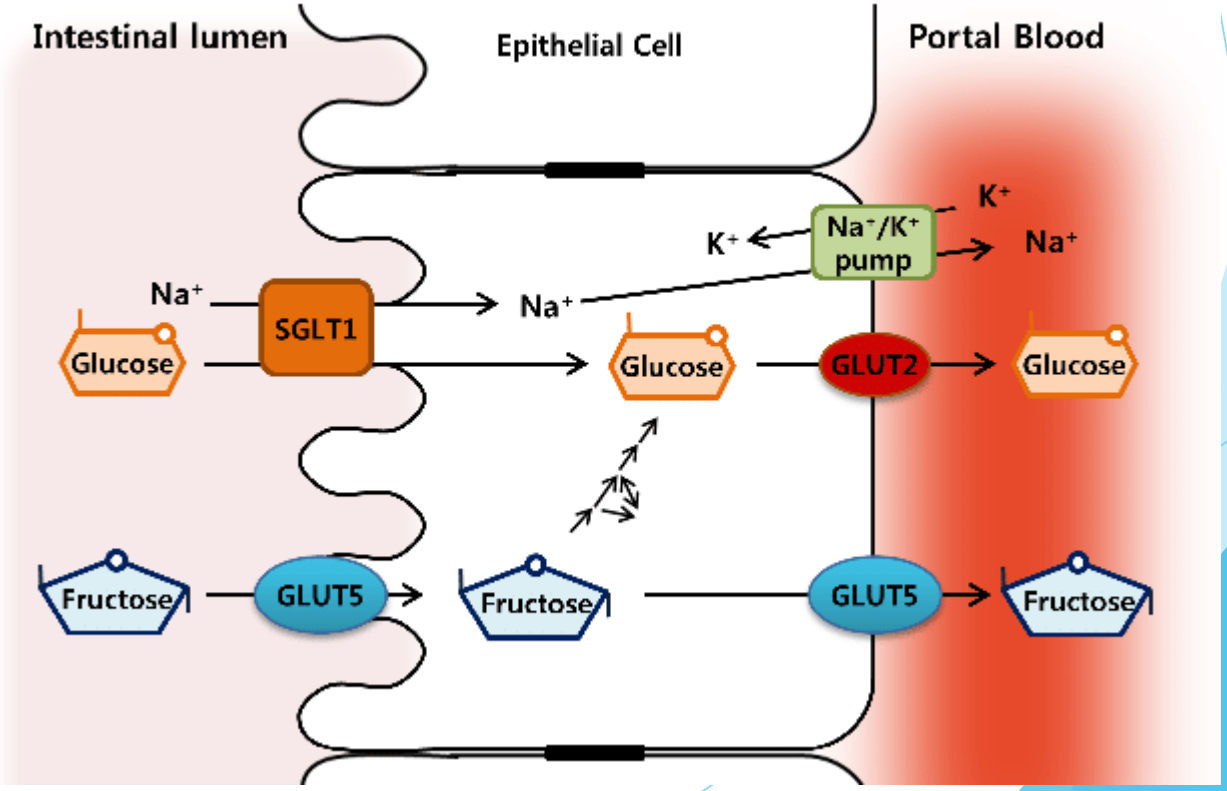


Active Transport

1. Against concentration gradient.
2. selective
3. requires energy
4. limited to drugs structurally similar to endogenous substances (eg, ions, vitamins, sugars, amino acids).
5. These drugs are usually absorbed from specific sites in the small intestine.

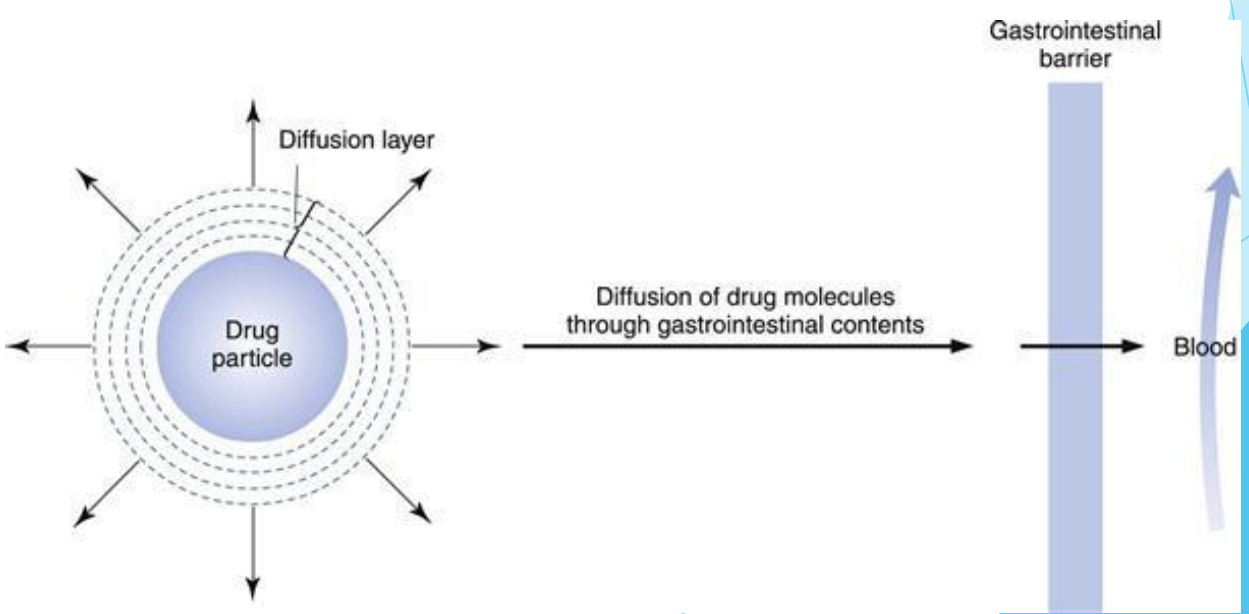


- Many body nutrients, such as sugars and amino acids, are transported across the membranes of the gastrointestinal tract by carrier processes.
- Certain vitamins, such as thiamine, niacin, riboflavin, and pyridoxine, and drug substances, such as methyldopa and 5-fluorouracil, require active transport mechanisms for their absorption.

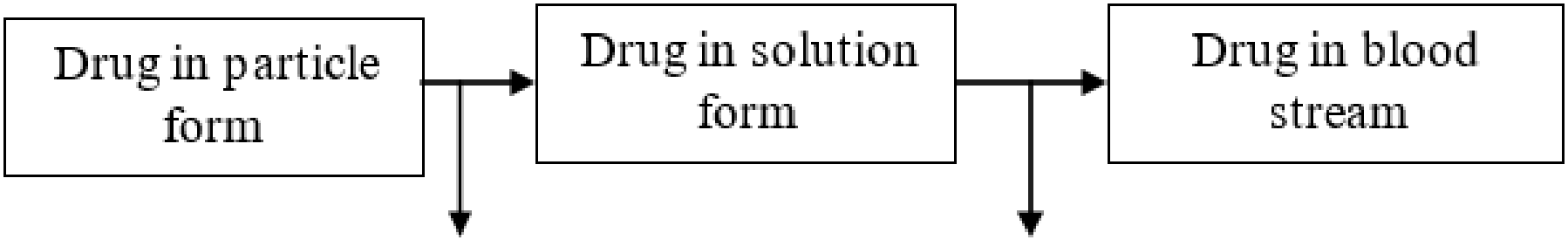


DISSOLUTION

- The process by which a drug particle dissolves.
- For a drug to be absorbed, it must first dissolved in the fluid at absorption site.
- As a drug particle undergoes dissolution, the drug molecules on the surface are the first to enter into solution, creating a saturated layer of drug solution that envelops the surface of the solid drug particle. This layer of solution is the diffusion layer.
- From diffusion layer the drug molecules pass throughout the dissolving fluid and make contact with biologic membranes, and absorption ensues.



- If dissolution is rapid or if the drug is administered as a solution the rate at which the drug becomes absorbed depends mainly on its ability to traverse the membrane barrier.
- If dissolution slow because of the physicochemical characteristics of the drug substance or dosage form, dissolution is a rate-limiting step in absorption.



Dissolution is rate limiting Step for lipophilic drugs. E.g. Griseofulvin

Permeation is rate limiting Step for hydrophilic drugs. e.g., Neomycin

- Drug remain in stomach (2 to 4 hours) and in small intestine (4 to 10 hours).
- The gastric emptying time for a drug is rapid with fasting stomach and slower as food content is increased.

Changes in gastric emptying time or intestinal motility can affect drug transit time and thus opportunity for drug dissolution and absorption.

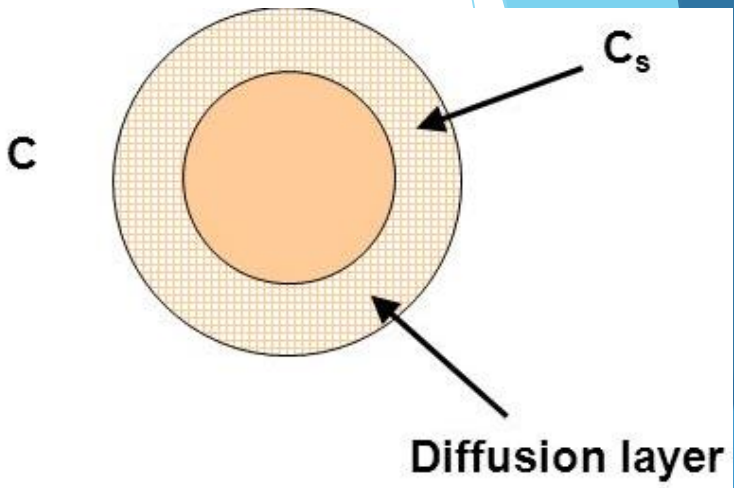
a. anticholinergic drug, slows gastric emptying. Which increases drugs absorption from stomach and reduce drugs absorption from small intestine.
b. drugs that enhance gastric motility, for example, laxatives, reduce amount of drug absorbed.
c. Aging decrease absorption (geriatrics)

decrease in gastric emptying time is advantageous for drugs absorbed from stomach but disadvantage for drugs prone to acid degradation, like penicillins and erythromycin, or inactivated by stomach enzymes, like L-dopa.

The rate of dissolution

- Rate of dissolution described by **Noyes-Whitney equation** :

$$\frac{dC}{dt} = \frac{D \cdot A(C_S - C)}{h}$$



dC/dt: the rate of dissolution of the drug particles

D: the diffusion coefficient of the drug in solution in the gastrointestinal fluids

A: the effective surface area of the drug particles in contact with the gastrointestinal fluids

h: the thickness of the diffusion layer around each drug particle

Cs: the saturation solubility of the drug in solution in the diffusion layer

C: the concentration of the drug in the gastrointestinal fluids

- rate of dissolution governed by rate of diffusion of solute through diffusion layer. Dissolution rate increased by:

1. increasing surface area (reducing the particle size),
2. by increasing the solubility of drug in diffusion layer, by factors embodied in dissolution rate constant, D, including the intensity of agitation of the solvent and diffusion coefficient of dissolving drug.
3. Increasing rate of agitation of the dissolving medium will increase the rate of dissolution.
4. reduction in the viscosity of solvent enhance dissolution rate of a drug.
5. Changes in pH or nature of solvent that influence the solubility of the drug may be used to increase dissolution rate.

Henderson–Hasselbalch equation

- Drug movement **not always affected by pH.**
- Very weak acids and bases completely **non ionized** at physiological pH ,their transfer rapid and independent of pH.
- Strong acids and bases are completely ionized and so their transfer is usually slow and pH-independent.

Surface area

When a drug particle is broken up, surface area increased. For drug substances that are poorly or slowly soluble, this generally results in increase in the rate of dissolution.

To increase surface area, use **micronized** powders in their solid products. micronized powders consist of drug particles reduced in size to about **5 µm** and smaller

Crystal or Amorphous Drug form

- Solid drug materials may occur as crystalline or amorphous.
- Amorphous usually more soluble than crystalline form, different extents of drug absorption :
- **antibiotic chloramphenicol** palmitate, are inactive when administered in crystalline, but when administered **amorphous**, absorption from GIT rapidly, with good therapeutic response.
- **In other instances:** crystalline forms of drugs may be used because of greater stability than amorphous forms.

For example, **the crystalline forms of penicillin G** as potassium salt or sodium salt are **more stable than amorphous forms**. Thus, in formulation work on penicillin G, the **crystalline forms are preferred** and result in excellent therapeutic response.

Polymorphism

- The dissolution rate of a salt of a drug is different from that of the parent compound.
- Sodium and potassium salts of weak organic acids and hydrochloride salts of weak organic bases dissolve more than free acids or bases.
- The state of hydration of a drug molecule can affect its solubility and pattern of absorption.
- Usually, the anhydrous form of an organic molecule is more readily soluble than the hydrated form.
- This characteristic was demonstrated with the drug ampicillin. The rate of absorption for the anhydrous form was greater than that for the trihydrate form of the drug.

A drug's solubility in GIT can be affected by **food**. A drug may interact with agents present to form a **chemical complex** that result in reduced drug solubility and decreased absorption.

The classic example of this **complexation: between tetracycline and calcium, magnesium, and aluminum**, resulting in non absorbable complex so decreased absorption of the tetracycline

Reference

Ansel's pharmaceutical dosage forms and drug delivery systems , tenth edition