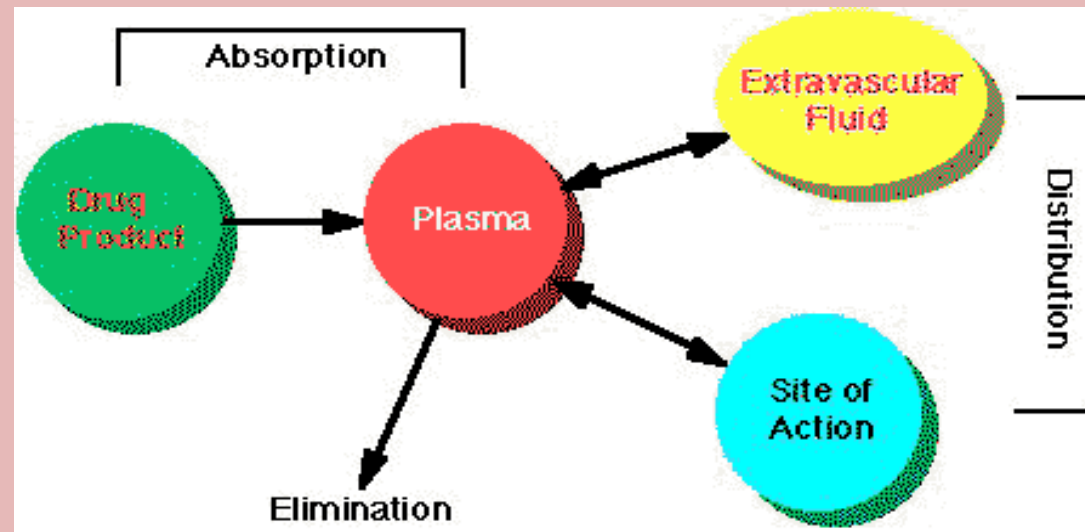# Biopharmaceutics

&

Pharmacokinetics

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

- *Pharmacokinetics* is the science of the <u>kinetics</u> of drug: **absorption**, **distribution**, and **elimination** (ie, **excretion** and **metabolism**).
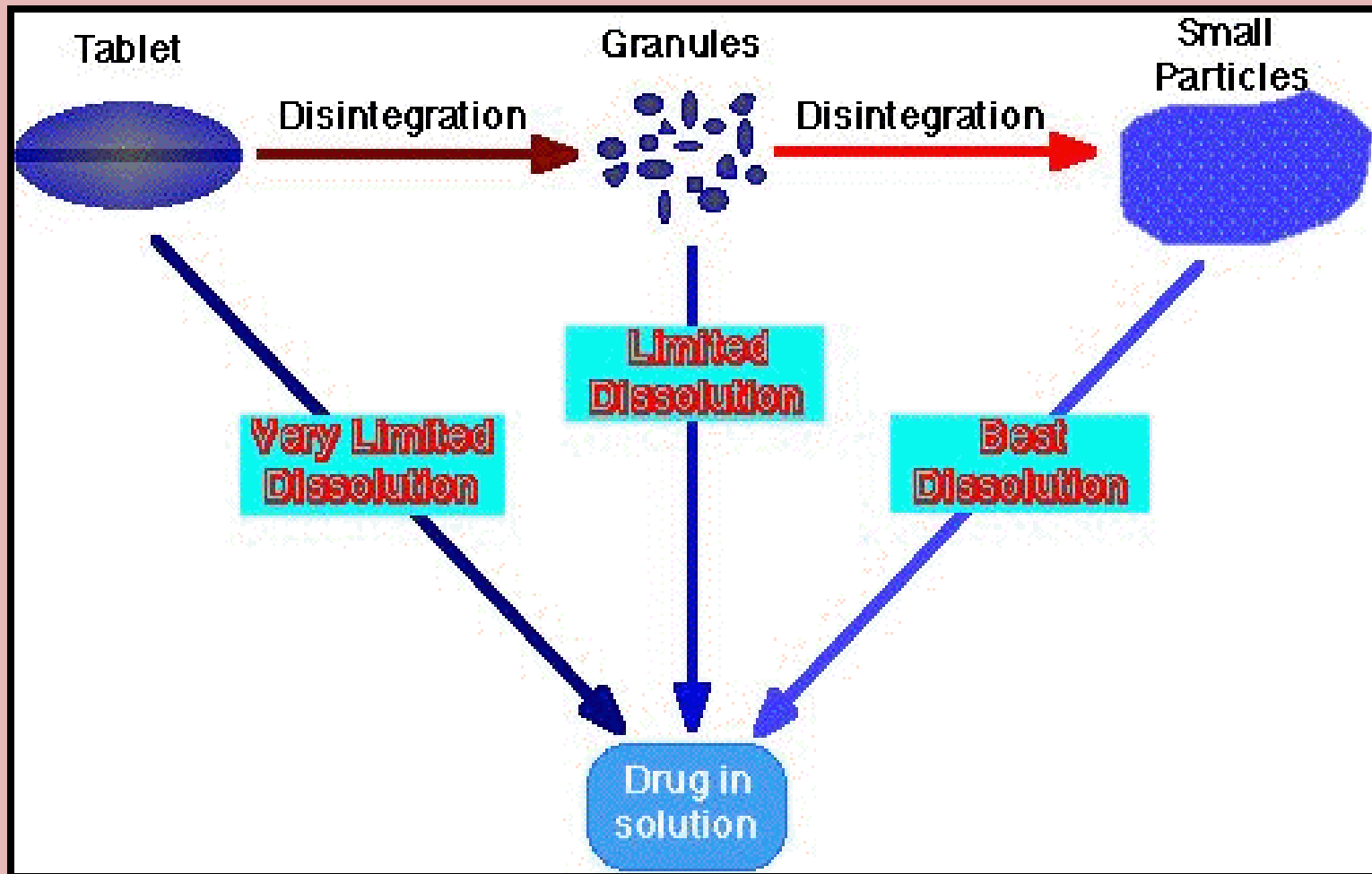
PHARMACODYNAMICS

- *Pharmacodynamics:* relation between **drug conc** at (receptor) and **pharmacologic response**.

The systemic absorption of a drug depend on:

1. **Physicochemical** properties of drug.

2. **Nature** of drug product

3. **Anatomy** and physiology of drug absorption site.

Dissolution

The rate of dissolution:

- **duration** of drug's effect.

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

$$\frac{dW}{dt} = \frac{DA(C_s - C)}{L}$$

- : dw/dt   is the rate of dissolution.
- A is the <u>surface area</u> of the solid.
- C is the concentration of the solid in the bulk dissolution medium.
- C_s is the concentration of the solid in the <u>diffusion</u> layer surrounding the solid.
- D is the diffusion <u>coefficient</u>.
- L is the <u>diffusion layer</u> thickness or called stagnant layer.

- the rate of dissolution may be modified primarily by altering the surface area of the solid. The surface area may be adjusted by altering the particle size (e.g. **micronization**). The rate of dissolution may also be altered by choosing a suitable **polymorph** of a compound. Specifically, crystalline forms dissolve slower than amorphous forms.

- Micronization: is a method of decreasing particle size to increase the surface area of drug available for dissolution medium so increasing dissolution rate.

- Amorphus more soluble than crystalline
- **Stagnant layer:** is concentration of the drug in saturated form.

How to affect dissolution?

- **Micronization: increase dissolution**
- **Polymorph: amorphus type increase dissolution**

- **Coatings decrease dissolution**

Particle

Stagnant layer(diffusion layer)

increase dissolution

Stagnant layer
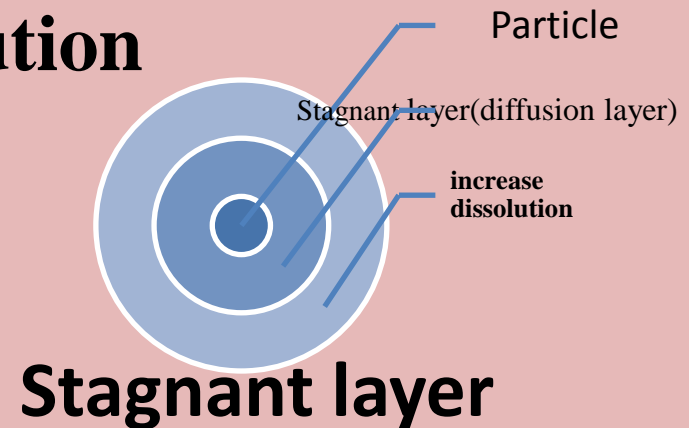
- coatings on a tablet or a pellet may act as a barrier to reduce the rate of dissolution. Coating may also be used to modify where dissolution takes place. For example, **enteric coatings** may be applied to a drug, so that the coating only dissolves in the basic environment of the intestines. This will prevent release of the drug before reaching the intestines.

Henderson–Hasselbalch equation:

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$ **for** acidic drugs

$$pH = pKa + \log \frac{unionized}{ionized}$$ for basic drugs

$$HA + H_2O \rightleftharpoons A^- + H_3O^+$$
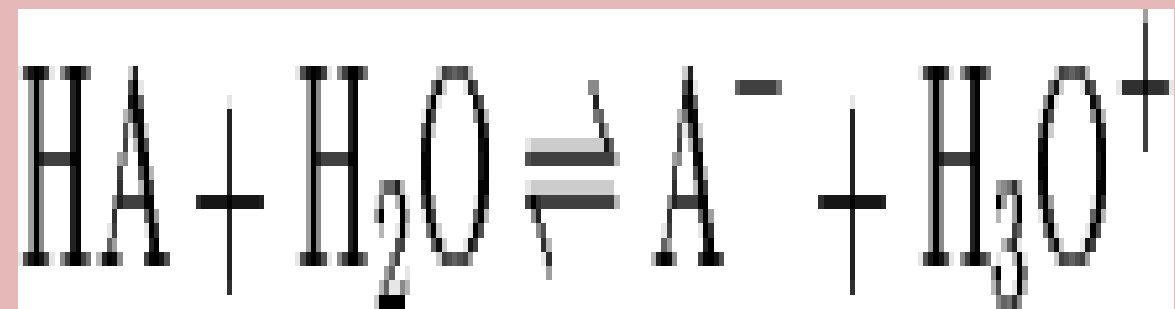
$$pK_a = -\log(K_a) = -\log\left(\frac{[H_3O^+][A^-]}{[HA]}\right)$$

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

- drugs include acids within the pK range 3 to 7.5 and bases in the pK range 7 to **11**

- **Stomach pH: 1-2**

- **Duodenum pH: 2-4**

- **Small intestine pH: 4-6**

- **Large intestine 6-7.8**

Absorption

- **Drug absorption** is the movement of the drug from its site of administration into the bloodstream.

- intravenous therapy, absorption and bioavailability is 100%.

- **Absorption**
- **Main factors affecting oral absorption:**
- Physiological factors
- Physical-chemical factors
- Formulation factors

- **Physiological factors affecting oral absorption**
- **Membrane physiology**
- **Passage of drugs across membranes**
  - Active transport
  - Facilitated diffusion
  - Passive diffusion
  - Pinocytosis
  - Pore transport
  - Ion pair formation
    - » Gastrointestinal physiology
      - Characteristics of GIT physiology and drug absorption
      - Gastric emptying time and motility
      - Effect of food on drug absorption
      - Double peak phenomena
- **Malabsorption**

Mechanisms of Drug Absorption after Oral Administration:

1-Passive Diffusion:

Drugs diffuse across a cell membrane from a region of **high concentration (eg, GI fluids) to one of low concentration (eg, blood).**

Diffusion rate is directly proportional to the **gradient** but also depends on the molecule's **lipid solubility, size, degree of ionization**, and the **area of absorptive surface**. (Primary mechanism for most drugs). Because the cell membrane is lipoid, lipid-soluble drugs diffuse most rapidly. Small molecules tend to penetrate membranes more rapidly than larger ones.

2-Facilitated Passive Diffusion:

- Molecules with low lipid solubility (eg, glucose) penetrate membranes more rapidly than expected. One theory is facilitated passive diffusion: A **carrier** molecule in the membrane combines reversibly with the substrate molecule outside the cell membrane, and the carrier-substrate complex diffuses rapidly across the membrane, releasing the substrate at the interior surface. In such cases, the membrane transports only substrates with a relatively **specific molecular configuration**, and the **availability of carriers** limits the process. The process does not require energy expenditure, and transport against a concentration gradient cannot occur.
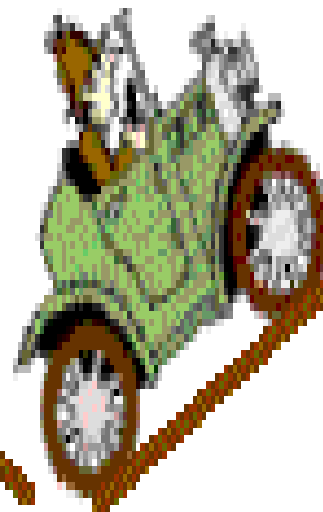
3-Active Transport:

- Moving particles across a <u>biological membrane</u> **against a** <u>concentration gradient</u>. Active transport is **selective**, requires **energy expenditure**, and may involve transport against a concentration gradient. Active transport seems to be limited to drugs structurally similar to endogenous substances (eg, ions, vitamins, sugars, amino acids). These drugs are usually **absorbed from specific sites in the small intestine**.

Passive   Facilitated   Active

Illustration of Different Transport Mechanisms

4-Pinocytosis:

- fluid or particles are engulfed by a cell
- The cell membrane invaginates, encloses the fluid or particles, then fuses again, forming a vesicle that later detaches and moves to the cell interior.
- Energy required.
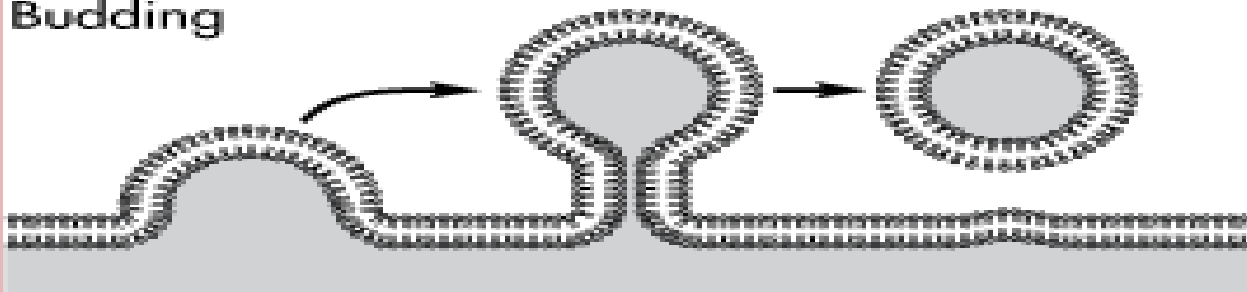- Pinocytosis probably plays a small role in drug transport, except for protein drugs.

Exocytosis
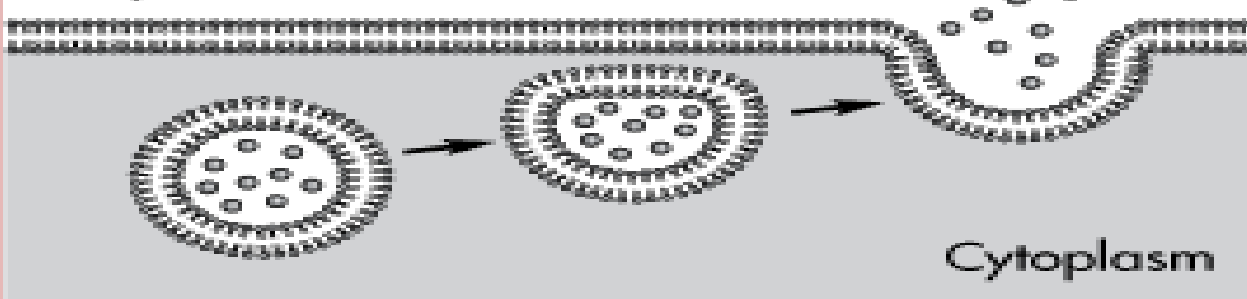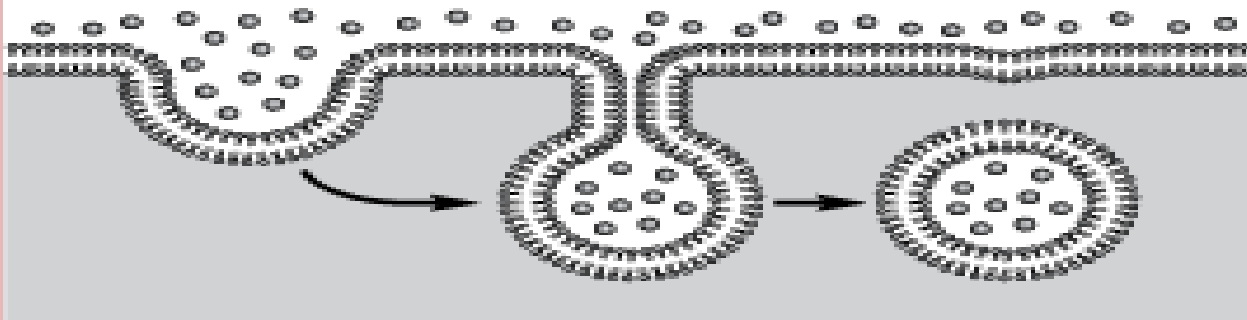
Cytoplasm

Endocytosis

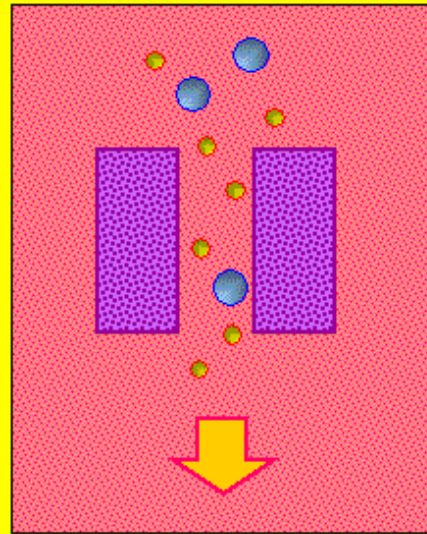Budding

5-Pore Convective Mechanism:

- liquid and gas molecules through a **porous** membrane.

- 'If **pore diameter is large** compared to the molecular diameter, and pressure difference exists across the membrane, bulk or convective flow through pores occurs.

- undesirable because **no separation** of components occur.

- If **concentration or partial pressure differences exist** across the membrane the components will diffuse at different rates through pores, resulting in **some separation**.
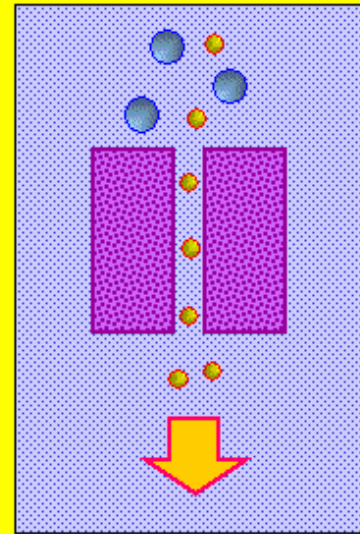
- If pores are **of the order of molecular size**, the diffusion of those components will be **restricted (hindered)**, resulting in separation.
- Molecules of size **larger than the pores** will be **prevented** from diffusing through the pores. This is called **sieving**.
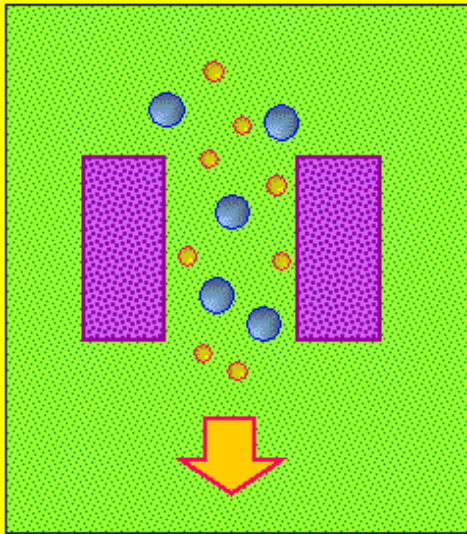
(a) Bulk flow through pores (b) Diffusion through pores (c) Restricted diffusion through pores

Ion-Pair Formation

- Strong electrolyte drugs are highly ionized or charged molecules, such as quaternary nitrogen compounds with **high 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.
- **quinine, which forms ion pair with hexylsalicylate**
- , a basic drug that **forms an ion pair with oleic acid**