

Biopharmaceutics and Pharmacokinetics

- At the end of the course, students will be able to –
 - 1.Understand the **concept of ADME** of drug in human body
 - 2.Describe pharmacokinetics of drug after **intravenous and oral administration**
 - 3.Explain **development of BA-BE protocol** for various formulation
 - 4.Calculate **pharmacokinetic parameters** of drug by solving numerical
 - 5.Determine various **pharmacokinetic rate constants**
 - 6.Interpret **various regulations** related to BA-BE studies

UNIT I

10 Hours

Introduction to Biopharmaceutics :

Absorption:

Mechanisms of drug absorption through GIT

Factors influencing drug absorption through GIT

Absorption of drug from non-peroral extra-vascular routes.

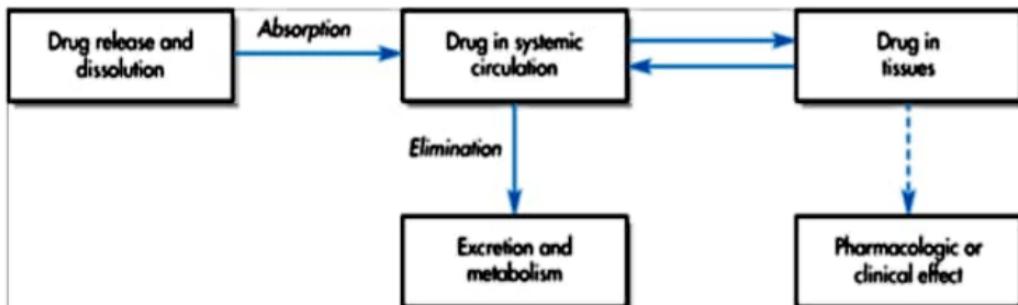
Introduction to Biopharmaceutics :

Distribution:

Tissue permeability of drugs, binding of drugs, apparent, volume of drug distribution, plasma and tissue protein binding of drugs, factors affecting protein-drug binding. Kinetics of protein binding, Clinical significance of protein binding of drugs.

- **Biopharmaceutics:**

- **Biopharmaceutics** considers the interrelationship of the physicochemical properties of the drug, the dosage form in which the drug is given, and the route of administration ,rate and extent of systemic drug absorption.
- it study how the drug get absorbed, distributed, metabolized, and eliminated by the body.
- Biopharmaceutics provides the scientific basis for drug product design and drug product development.



Source: Shargel L, Wu-Pong S, Yu ABC: Applied Biopharmaceutics & Pharmacokinetics, 6th Edition: www.accesspharmacy.com

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Scheme demonstrating the dynamic relationship between the drug, the drug product, and the pharmacologic effect.

- Taken by any route
- Release of drug from dosage form
- Fraction of drug adsorbed to surrounding body
- Drug reaches the site of action
- Pharmacological effect produce when drug concentration reaches the site of action at MEC

- Biopharmaceutics involves factors that influence:

- (1) The design of the drug product
- (2) stability of the drug within the drug product
- (3) The manufacture of the drug product
- (4) The release of the drug from the drug product
- (5) The rate of dissolution/ release of the drug at the absorption site
- (6) Delivery of drug to the site of action, which may involve targeting the drug to a localized area (eg, colon for Crohn disease) for action or for systemic absorption of the drug.

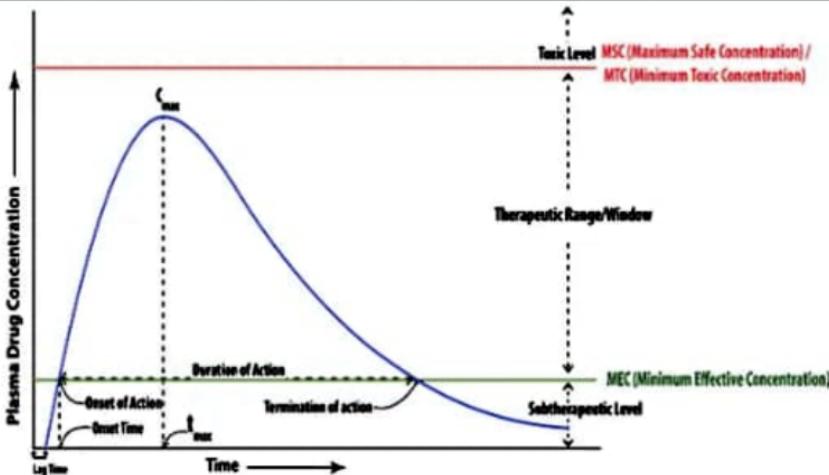
- Studies in biopharmaceutics use both ***in vitro*** and ***in vivo*** methods.
- ***In vitro* methods** are procedures employing test apparatus and equipment without involving laboratory animals or humans.
- ***In vivo* methods** are more complex studies involving human subjects or laboratory animals.



- **PHARMACOKINETICS**

- After a drug is released from its dosage form, the drug is absorbed into the surrounding tissue, the body, or both. The distribution through and elimination of the drug in the body varies for each patient but can be characterized using mathematical models and statistics.
- *Pharmacokinetics* is the science of the kinetics of drug absorption, distribution, and elimination (ie, metabolism and excretion).
- The description of drug distribution and elimination is often termed **drug disposition**.
- Characterization of drug disposition is an important prerequisite for **determination or modification of dosing regimens** for individuals and groups of patients.
- The applications of pharmacokinetic principles in the safe and effective management of individual patient is called as **clinical pharmacokinetics**

- **Pharmacodynamics** is the study of the biochemical and physiological effects of drugs on the body
 - This includes the mechanisms of drug action and the relationship between drug concentration and effect.
 - A typical example of pharmacodynamics is how a drug interacts quantitatively with a drug receptor to produce a response (effect).



- **The plasma drug concentration (level)-time curve** is generated by obtaining the drug concentration in plasma samples taken at various time intervals after a drug product is administered.
- **MEC** : Minimum effective concentration, therapeutic effect starts when concentration of drug reaches the MEC
- **MSC** : Maximum safe concentration
- **Duration of action** : Time for which the plasma drug concentration remains between MEC and MSC

- The ***onset time*** corresponds to the time required for the drug to reach the MEC.
- The ***duration of drug action*** is the difference between the onset time and the time for the drug to decline back to the MEC.
- The ***therapeutic window*** is the concentrations between the MEC and the MTC.
- Drugs with a ***wide therapeutic window*** are generally considered **safer** than drugs with a narrow therapeutic window. Sometimes the term ***therapeutic index*** is used.

- In contrast, the pharmacokineticist can also describe the plasma level-time curve in terms of such pharmacokinetic terms as:
- ***Peak plasma level (Cmax)*** (It is related to the dose, the rate constant for absorption, and the elimination constant of the drug)
- ***Time for peak plasma level (Tmax)*** (marker for average rate of drug absorption)
- ***Area under the curve, or AUC*** The AUC is related to the amount of drug absorbed systemically.

Why Study Pharmacokinetics (PK) and Pharmacodynamics (PD)?

- Individualize patient drug therapy.
- Monitor medications with a narrow therapeutic index.
- Decrease the risk of adverse effects while maximizing pharmacologic response of medications.
- Evaluate PK/PD as a diagnostic tool for underlying disease states.

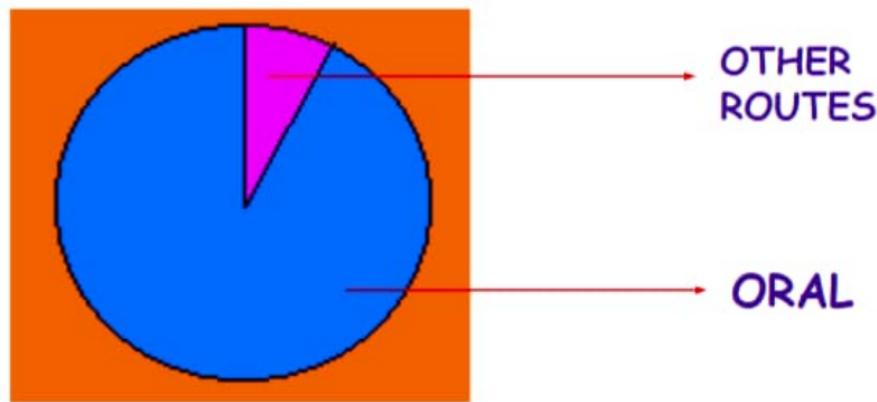
• *Specimens*

- ***Invasive methods*** include sampling blood, spinal fluid, tissue biopsy, or any biological material that requires parenteral or surgical intervention in the patient.
- ***Noninvasive methods*** include sampling of urine, saliva, feces, expired air, or any biologic material that can be obtained without parenteral or surgical intervention.

- If drug I.V. : drug enters directly into systemic circulation and exert pharmacological effect
- Majority of drugs are administered extra vascularly, generally orally.
- To exert effect drug must come in systemic circulation from their site of application and for that absorption is the pre-requisite step.

Absorption

Generally about 80% of drug products are administered through oral route so it is required to study the absorption mechanism in the body.

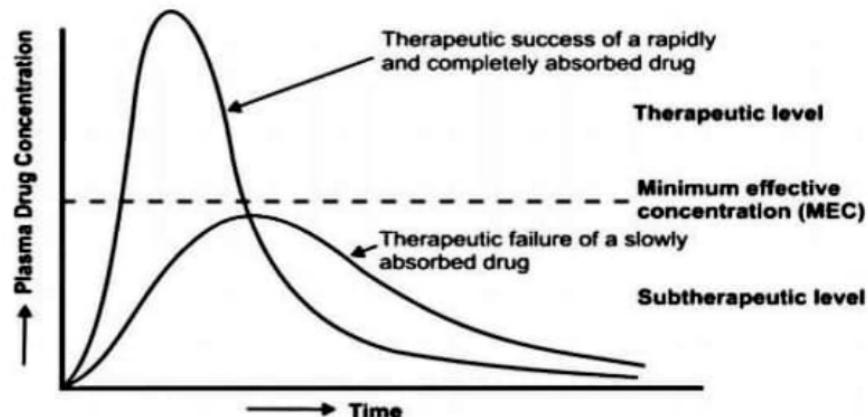


- **Absorption** is simply defined as the process of movement of unchanged drug from the site of administration to the site of action.

- The effectiveness of Absorption can be measured when we measure the drug concentration at the site of action.
- But it is difficult to measure the drug concentration at the site of action. So concentration we measure in **plasma**.
- There is always relationship between the plasma drug concentration and response.

- Absorption defined as the process of movement of unchanged drug from site of administration to site of measurement i.e. plasma

- Not only magnitude of absorption is important but also rate of absorption is also important.
- Slowly and completely – may not give pharmacological effect
- Rapidly absorbed drug – may give effect



- The drug that have to enter the systemic circulation can be administered through three major routes:
- 1. The **enteral route of administration** refers to the delivery of medications or substances through the gastrointestinal (GI) tract. This method involves administering drugs via the mouth, where they are absorbed into the bloodstream through the stomach or intestines.
- Common forms of enteral administration include:
- **Oral (PO)**: The most common method, where the medication is taken by mouth (e.g., tablets, capsules, liquid solutions).
- **Sublingual (SL)**: The medication is placed under the tongue for absorption (e.g., certain tablets like nitroglycerin).
- **Buccal**: The medication is placed in the cheek area and absorbed through the mucous membranes (e.g., lozenges).
- **Rectal**: Medications are introduced into the rectum, where they are absorbed (e.g., suppositories, enemas).

- **2. Parenteral route of administration:**
- **Parenteral drug products include both injection and implanted drug products** that injected through skin or other external boundary tissue or implanted within the body to allow direct administration of active drug into blood vessels, organs, tissues or lesions.

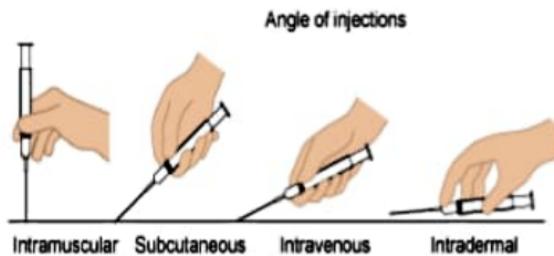
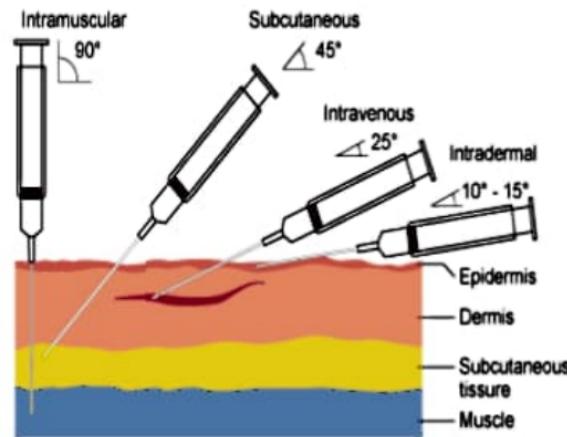
- Routes of administration:

- Primary:

- Intramuscular
- Subcutaneous
- Intradermal
- Intravenous

- Other:

- Intracardial
- Intrathecal (spinal cord)
- Intraarticular (joints for local effect)
- Intrapleural (lungs)



3. The **topical route** is primarily used for treating skin conditions, localized pain, or for delivering medications that need to be absorbed through the skin.

- *Gastrointestinal absorption of drugs*

- **TRANSPORT OF DRUG ACROSS BIOLOGICAL BARRIERS**

- For systemic absorption, a drug must pass from the absorption site through one or more layers of cells to gain access into the general circulation.
- For absorption into the cells, a drug must traverse the cell membrane.

- **Structure of cell membrane:**
- <https://www.youtube.com/watch?v=SsFqmYATM3k>

Transport mechanism across the cell membrane

1) Passive Transport

- a) Diffusion
- b) Facilitated Diffusion
- c) Filtration (Pore Transport)
- d) Osmosis

2) Active Transport

3) Vesicular Transport (Endocytosis and exocytosis)

1) Passive Transport: No energy required, Higher concentration to lower concentration

a) Diffusion(non ionic diffusion) :

- Non ionized drugs can diffuse across the cell membrane.

Thus, drugs that are highly lipid soluble can diffuse rapidly, whereas those that are less lipid soluble will diffuse slowly.

Passive diffusion can be explained by Fick's First law of diffusion:

The drug molecule diffuse from a region of higher concentration to lower concentration until equilibrium is attained and that the rate of diffusion is directly proportional to the concentration gradient across the membrane

$$J = DAK/h(C_G - C)$$

J = Rate of drug diffusion

D= Diffusion coefficient

A= Surface area of absorbing memory for drug diffusion

K = Partition coefficient of drug between lipoidal membrane and aqueous gi fluid

CG- C = Concentration gradient h = Thickness of the membrane

Initially when drug is ingested C_g is much greater than the concentration in plasma and a large concentration gradient exists thereby acting as the driving force for absorption.

As equilibrium approaches the drug diffusion should stop and consequently a large fraction of drug may remain unabsorbed but this is not the case once the passively absorbed drug enters blood it rapidly swept away and distributed into a much larger volume of body fluids hence the concentration of a drug at absorption site is maintained greater than the concentration of drug in plasma such condition is called **sink condition** for the drug absorption

b) Facilitated diffusion

Involves carrier proteins that change shape to move molecules

Passive, no energy required

Highly selective for specific molecules

Glucose transport (GLUT proteins), amino acids, vit B12

Slower (due to conformational changes)

c) Pore transport

Involves channels that form pores for molecules to pass through

Passive, no energy required

Selective but less specific than carriers

Ion channels (e.g., Na^+ , K^+ , Ca^{2+} channels), aquaporins (water)

Faster (direct passage through the pore)

d) Osmosis :

Movement of solvent occur from lower concentration to higher concentration.

Absorption of water to maintain the water level inside the cell (hydration).

In plant also water absorption occur though osmosis

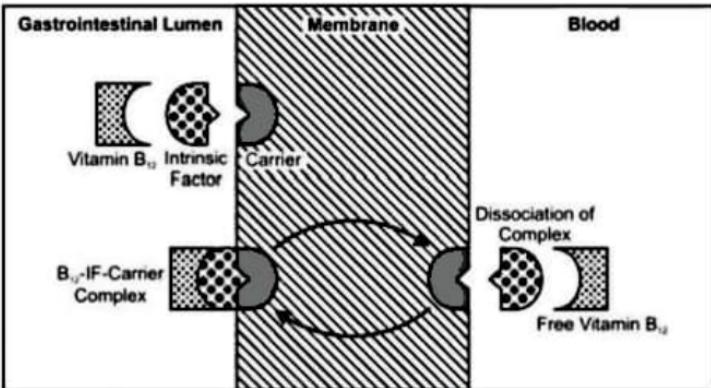


Fig. 2.7. Facilitated diffusion of vitamin B12

Intrinsic factor (IF) is the glycoprotein which produced by the gastric parietal cells forms complex with Vit B12 which is transported across the intestinal membrane by carrier system.

- 2) Active Transport:

- Transport against the concentration gradient
- Require energy in the form of ATP

- **Types of Active Transport:**

- **Primary Active Transport:**

- Direct use of energy (ATP) to transport molecules.

- **Example:**

- **Sodium-potassium pump (Na⁺/K⁺ pump).**

- This pump moves 3 sodium ions (Na⁺) out of the cell and 2 potassium ions (K⁺) into the cell, both against their concentration gradients.

- which helps maintain cellular functions like nerve signaling and osmotic balance.

- **Secondary Active Transport (Cotransport):**

- This uses the **electrochemical gradient created by primary active transport** to move other molecules. For example:

- **Symport:** Both molecules move in the **same direction** (e.g., sodium and glucose are often co-transported into the cell)

- **Antiport:** The molecules move in **opposite directions** (e.g., sodium-calcium exchange, where sodium moves **into** the cell and calcium moves **out**).

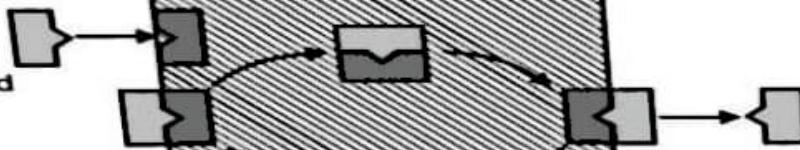
- Active transport is mediated by **specific membrane proteins**, such as pumps, carriers, and channels, which undergo conformational changes that require energy to transport substances. Examples include:
 - **Pumps** (e.g., Na^+/K^+ pump)
 - **Ion channels** (in secondary active transport systems)
 - **Carrier proteins** (facilitating the transport of specific molecules)

- **Examples of Active Transport in Cells:**
- **Sodium-Potassium Pump:** Maintains proper sodium and potassium ion concentrations across the membrane, essential for nerve function, muscle contraction, and maintaining cell volume.
- **Calcium Pump:** Keeps calcium ions at low concentrations inside the cell, which is crucial for processes like **muscle contraction** and **neurotransmitter release**.
- **Proton Pump (H⁺ pump):** Found in the stomach lining cells, helps maintain the acidic environment necessary for digestion by pumping protons (H⁺) into the stomach.

• 3) Bulk Transport (Vesicular Transport)

- This involves the **transport of large molecules, fluids, or particles**, and **requires energy**. It includes processes like:
- **Endocytosis**: The process by which **cells engulf** large particles, liquids, or molecules from outside the cell **by forming vesicles**. Types of endocytosis include:
 - **A) Phagocytosis ("cell eating")**: **Engulfment of solid particles.**
 - **B) Pinocytosis ("cell drinking")**: **Engulfment of extracellular fluid.**
- This Phenomenon is responsible for cellular uptake of macromolecules like fats starch all soluble vitamins like A,D,E, K and drug like insulin
- **Exocytosis**: The process by which cells **expel substances** (such as waste, hormones, or neurotransmitters) in vesicles that fuse with the plasma membrane to release their contents outside the cell.

• Summary of transport mechanisms:

Absorption Mechanism	Drugs Absorbed	GI Lumen	Membrane	Blood
Passive Diffusion	Most drugs having high lipophilicity and MW in the range 100 - 400			
Pore Transport	Water-soluble drugs of MW less than 100			
Ion-Pair Transport	Drugs that ionise at all pH conditions absorbed after complexing with oppositely charged ions			
Carrier-Mediated Transport	Structure-specific drugs with affinity for carriers transported from specific sites			
Endocytosis	Macromolecular nutrients and drugs as solid particles or oily droplets			

- Factors influencing drug absorption through GIT

A. PHARMACEUTICAL FACTORS:

Include factors relating to the physicochemical properties of the drug, and dosage form characteristics and pharmaceutical ingredients

I. Physicochemical Properties of Drug Substances

1. Drug solubility and dissolution rate
2. Particle size and effective surface area
3. Polymorphism and amorphism
4. Pseudopolymorphism (hydrates/solvates)
5. Salt form of the drug
6. Lipophilicity of the drug
7. pKa of the drug and gastrointestinal pH
8. Drug stability
9. Stereochemical nature of the drug

II. Dosage Form Characteristics and Pharmaceutical Ingredients (Pharmaco-technical Factors)

1. Disintegration time (tablets/capsules)
2. Dissolution time
3. Manufacturing variables
4. Pharmaceutical ingredients (excipients/adjuvants)
5. Nature and type of dosage form
6. Product age and storage conditions

B. PATIENT RELATED FACTORS:

Include factors relating to the anatomical , physiological and pathological characteristics of the patient

1. Age
2. Gastric emptying time
3. Intestinal transit time
4. Gastrointestinal pH
5. Disease states
6. Blood flow through the GIT
7. Gastrointestinal contents:
 - a. Other drugs
 - b. Food
 - c. Fluids
 - d. Other normal GI contents
8. Presystemic metabolism by:
 - a. Luminal enzymes
 - b. Gut wall enzymes
 - c. Bacterial enzymes
 - d. Hepatic enzymes

- *Physicochemical Properties of Drug Substances*

- **Solubility and dissolution rate of drug:**

- The two critical slower rate-determining processes in the absorption of orally administered drugs are:
 - 1. Rate of dissolution, and
 - 2. Rate of drug permeation through the biomembrane.
- Dissolution is the RDS for **hydrophobic, poorly aqueous soluble** drugs like griseofulvin and spironolactone; absorption of such drugs is often said to be **dissolution rate-limited**.
- If the drug is **hydrophilic with high aqueous solubility**—for example, cromolyn sodium or neomycin, then dissolution is rapid and RDS in the absorption of such drugs is rate of permeation through the biomembrane. In other words, absorption of such drugs is said to be **permeation rate-limited** or **transmembrane rate-limited**.

- Based on the **intestinal permeability and solubility** of drugs, ***Biopharmaceutics Classification System*** (BCS) which classifies the drugs into 4 groups:

Class I drugs (high solubility/high permeability) :

well absorbed orally since they have neither solubility nor permeability limitation.

Class II drugs (low solubility/high permeability): show variable absorption owing to solubility limitation.

Class III drugs (high solubility/low permeability) also show variable absorption owing to permeability limitation.

Class IV drugs (low solubility/low permeability) are poorly absorbed orally owing to both solubility and permeability limitations.

- An important prerequisite for the absorption of a drug by all mechanisms except endocytosis is that it must be present in aqueous solution. This in turn depends on the drug's aqueous solubility and its dissolution rate.
 - **Absolute or intrinsic solubility** is defined as the maximum amount of solute dissolved in a given solvent under standard conditions of temperature, pressure and pH. It is a static property.
 - **Dissolution rate** is defined as the amount of solid substance that goes into solution per unit time under standard conditions of temperature, pH and solvent composition and constant solid surface area. It is a dynamic process.
-
- **Solubility** determines how much of the drug can dissolve in the GIT fluids, which is the first step in absorption.
 - **Dissolution rate** determines how quickly the drug dissolves and becomes available for absorption.

- There are well known examples of drugs such as **cisapride** which despite their **low aqueous solubility have sufficient oral bioavailability.**
- Two reasons can be attributed to this—
- One, the **rapid rate of dissolution** despite low intrinsic solubility
- Two, the **therapeutic dose of drug may be so small** that the GI transit time is sufficient for adequate dissolution and absorption to occur.
- Thus, in contrast to absolute solubility, the dynamic process of drug dissolution is better related to drug absorption and bioavailability.

- **Theories of Drug Dissolution**

- Dissolution is a process in which a solid substance solubilizes in a given solvent i.e. **mass transfer from the solid surface to the liquid phase.**
- Several theories to explain drug dissolution have been proposed. Some of the important ones are:
 - 1. Diffusion layer model/Film theory,
 - 2. Danckwert's model/Penetration or Surface renewal theory, and
 - 3. Interfacial barrier model/Double-barrier or Limited solvation theory.

- **Diffusion Layer Model/Film Theory**

- This is the simplest and the most common theory for dissolution. Here, the process of dissolution of solid particles in a liquid, in the absence of reactive or chemical forces, consists of two consecutive steps:

- 1. Solution of the solid to form a thin film or layer at the solid/liquid interface called as the **stagnant film** or diffusion layer which is saturated with the drug; this step is usually rapid, and
- 2. Diffusion of the soluble solute from the stagnant layer to the bulk of the solution; this step is slower and is therefore the rate-determining step in drug dissolution. The model is depicted in Fig. 2.16.

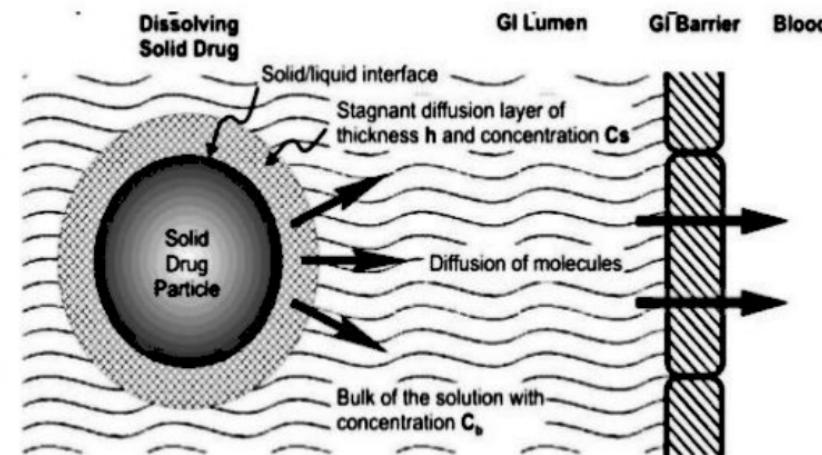


Fig. 2.16. Diffusion layer model for drug dissolution

- The earliest equation to explain the rate of dissolution when the process is diffusion controlled was given by Noyes and Whitney:

$$\bullet \frac{dc}{dt} = k (C_s - C_b) \quad \text{-----(1)}$$

where,

- dC/dt = dissolution rate of the drug,
- k = dissolution rate constant (first order),
- C_s = concentration of drug in the stagnant layer (also called as the saturation or maximum drug solubility), and
- C_b = concentration of drug in the bulk of the solution at time t .

- Nernst and Brunner incorporated Fick's first law of diffusion and modified the Noyes-Whitney's equation to:

- $\frac{dc}{dt} = DAK_{w/o} (C_s - C_b) / Vh$ ----- (2)

- where,

- D = diffusion coefficient (diffusivity) of the drug
- A= surface area of the dissolving solid
- $K_{w/o}$ = water/oil partition coefficient of the drug considering the fact that dissolution body fluids are aqueous. Since the rapidity with which a drug dissolves depends on the $K_{w/o}$, it is also called as the **intrinsic dissolution rate constant**. It is a characteristic of drugs.
- V = volume of dissolution medium.
- h= thickness of the stagnant layer. (can be decreased with increase the agitation)
- $(C_s - C_b)$ = concentration gradient for diffusion of drug.

- Equation 2 represents first-order dissolution rate process, the driving force for which is the concentration gradient ($C_s - C_b$).
- Under such a situation, dissolution is said to be under non-sink conditions. This is true in case of *in vitro* dissolution in a limited dissolution medium.
- Dissolution in such a situation slows down after sometime due to build-up in the concentration of drug in the bulk of the solution.
- **The *in vivo* dissolution is always rapid than *in vitro* dissolution** because the moment the drug dissolves; it is absorbed into the systemic circulation.
- As a result, $C_b = 0$, and dissolution is at its maximum. Thus, under *in vivo* conditions, there is no concentration build-up in the bulk of the solution and hence no retarding effect on the dissolution rate of the drug i.e. $C_s \gg C_b$ and *sink conditions* are maintained.
- Under sink conditions, if the volume and surface area of solid are kept constant, then equation 2 reduces to:

$$\bullet \frac{dc}{dt} = K \text{ ----- (3)}$$

- where K incorporates all the constants in equation 2
- Equation 3 represents that the dissolution rate is constant under sink conditions and follows zero-order kinetics i.e. yields a linear plot

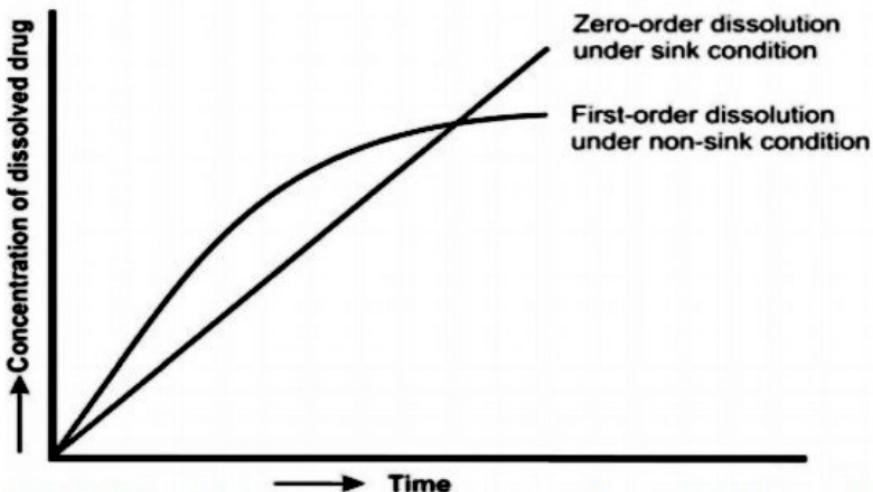


Fig. 2.17. Dissolution rate under non-sink and sink conditions.

- To obtain good in vitro-in vivo dissolution rate correlation, the in vitro dissolution must always be carried under sink conditions.
- This can be achieved in one or more of the following ways:
- Use large the volume of dissolution fluid.
- Removing the dissolved drug by partitioning it from the aqueous phase of the dissolution fluid into an organic phase placed either above or below the dissolution fluid—for example, hexane or chloroform.
- Adding a water miscible solvent such as alcohol to the dissolution fluid or use appropriate solvents or buffers for the drug's solubility
- By adding selected adsorbents to remove the dissolved drug.
- The in vitro sink conditions are so maintained that C_b is always less than 10% of C_s .

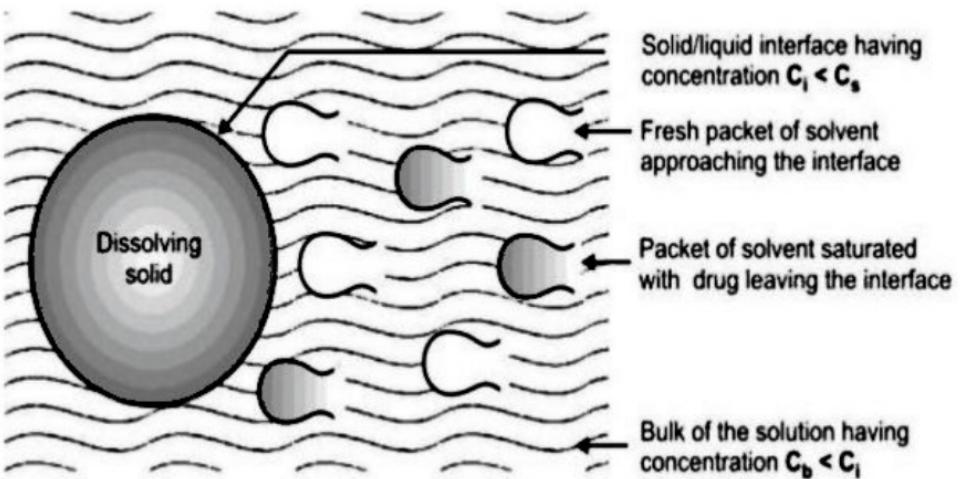
- The Noyes-Whitney's equation assumes that **the surface area of the dissolving solid remains constant during dissolution, which is practically not possible for dissolving particles**
- To account for the particle size decrease and change in surface area accompanying dissolution, **Hixson and Crowell's cubic root law of dissolution** is used:
- $W_0^{1/3} - W^{1/3} = Kt$
- W_0 = original mass of the drug
- W = mass of the drug remaining to dissolve at time t
- K = dissolution rate constant (depend on dissolution rate , surface area, diffusion coefficient)

- **Danckwert's Model (Penetration or Surface Renewal Theory)**

- Danckwert did not approve of the existence of a stagnant layer and suggested that turbulence in the dissolution medium exists at the solid/liquid interface.
- As a result, the agitated fluid consisting of macroscopic mass of packets reach the solid/liquid interface in a random fashion, absorb the solute by diffusion and 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 concentration at the solid/liquid interface never reaches C_s and has a lower limiting value of C_i . ($C_i < C_s$)
- 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 equation:

$$V \frac{dC}{dt} = \frac{dm}{dt} = A C_s - C_b \sqrt{\gamma D}$$

- m = mass of solid dissolved, and
- γ = rate of surface renewal (or the interfacial tension)



- 1. Physicochemical properties of the drug(solubility, particle size, polymorphism, salt form, pseudopolymorphism, complexation, wettability)
- 2. Dosage form factors(several formulation factors and excipients)
 - Affect the dissolution and dissolution rate.
 - Solubility is the prime important factors amongst all.
 - It has been shown that a drug should have a minimum aqueous solubility of 1% to avoid bioavailability problems.

- **Particle Size and Effective Surface Area of the Drug**

- Particle size and 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:
 - 1. **Absolute surface area** which is the total area of solid surface of any particle, and
 - 2. **Effective surface area** which is the area of solid surface exposed to the dissolution medium.

- From the modified Noyes-Whitney equation 2, it is clear that **larger the surface area, higher the dissolution rate.**
- Since the surface area increases with decreasing particle size, a decrease in particle size, which can be accomplished by **micronisation(<0.1micron)**, will result in higher dissolution rates.
- However, it is important to note that it is not the absolute surface area but the **effective surface area that is proportional to the dissolution rate.**
 - Greater the effective surface area, more intimate the contact between the solid surface and the aqueous solvent and faster the dissolution
 - Micronisation of poorly aqueous soluble drugs like griseofulvin, chloramphenicol and several salts of tetracycline(less hydrophobic) results in **superior dissolution rates in comparison to the simple milled form** of these drugs.
 - Micronisation has in fact enabled the formulator to **decrease the dose of certain drugs because of increased absorption efficiency**—for example, the griseofulvin dose was reduced to half and that of spironolactone was decreased 20 times following micronisation.

- However, in case of **hydrophobic drugs** like aspirin, phenacetin and phenobarbital, micronisation actually results in a **decrease in the effective surface area** of such powders and thus, **a fall in the dissolution rate.**
- Reasons have been suggested for such an outcome —
 - 1. The hydrophobic surface of the drug **adsorbs air onto their surface** which **inhibit their wettability.**
 - 2. The particles **re-aggregate to form larger particles due to their high surface free energy,** which either float on the surface or settle at the bottom of the dissolution medium.

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

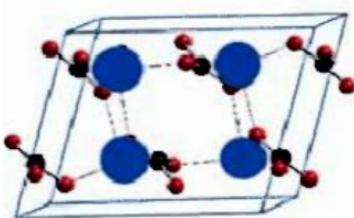
- **1. Use of surfactant as a wetting agent that -**
- Decreases the interfacial tension
- Displaces the adsorbed air with the solvent.

Example: polysorbate 80 increases the bioavailability of phenacetin by promoting its wettability.

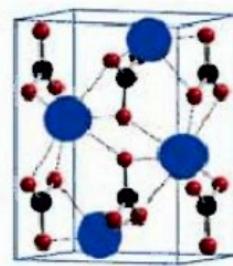
2. Adding hydrophilic diluents such as PEG, PVP, dextrose, etc. which **coat** the surface of hydrophobic drug particles and **render them hydrophilic**.

• Polymorphism and amorphism

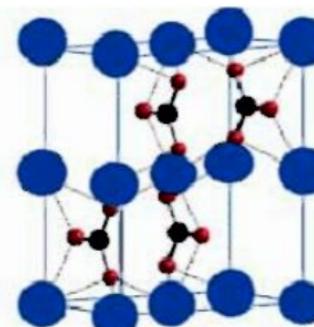
- The occurrence of the same substances in more than one crystalline form is known as polymorphism.
- They have same chemical composition but different arrangement in crystal lattice
- Polymorphs have different stabilities.
- Convert from metastable form to stable form
- They also having different melting point, solubilities, diffraction patterns though they are chemically identical.



Calcite

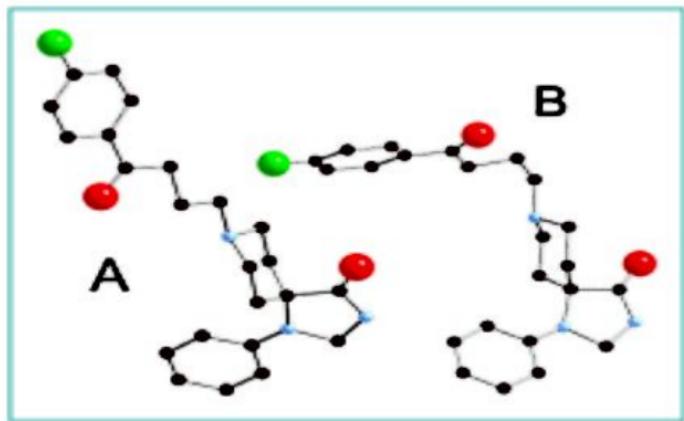
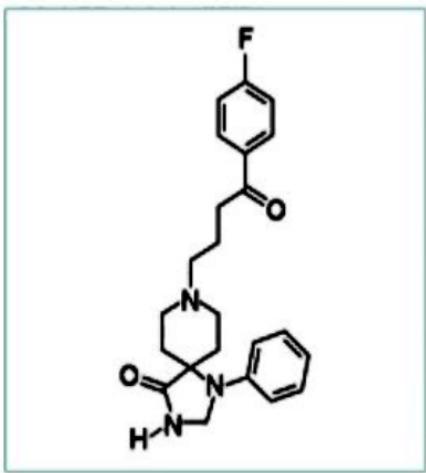


Aragonite



Vaterite





- Polymorphs (I and II) of Spiperone (Antipsychotic)

- Polymorphs have :
- **Unstable form** : They has **higher energy** state and quickly converted to stable form.
- **Metastable form**: It is not the most stable form but can exist in this form for certain period of time. However it eventually **transit into stable form under certain conditions**
- **Stable form** : It is the form that has the **lowest energy state under given conditions** (e.g., temperature and pressure). It is thermodynamically favored, meaning it is less likely to convert into another form over time.

- Many polymorphic forms of drugs are available in market

Different polymorphs have different solubilities. So different dissolution rate so One polymorphs more active therapeutically than other

Examples:

1. Chloramphenicol palmitate (3 polymorphs) alpha beta and gamma form .
Metastable form has faster dissolution and better bioavailability.
2. Sulfamerazine form II is more active than form I
3. Ritonavir (2 forms). Form I is more active and stable than II

- Polymorphism is also **factor in suspension technology**:
- Eg. **Cortisone acetate – five different forms out of which 4 are unstable.**
- These all unstable **form will convert to the stable form so that will lead to the caking problem in suspension**
- So before preparation of suspension must take care of that all four form converted to the stable form

- Some drugs can exist in **amorphous form** (i.e. having no internal crystal structure).
- They have **greater aqueous solubility than the crystalline forms** because the energy required to transfer a molecule from crystal lattice is greater than that required for **non-crystalline (amorphous) solid**
- for example, the **amorphous form of novobiocin is 10 times more soluble than the crystalline form.**
- Chloramphenicol palmitate, cortisone acetate and phenobarbital are other examples where the amorphous forms exhibit higher water solubility.
- Thus, the order for dissolution of different solid forms of drugs is —
 - **Amorphous > Metastable > Stable.**

- Solvates or pseudo polymorphism:

- Solids generally synthesized by crystallization techniques. During crystallization the solvent molecule trapped into the crystalline lattice. This creates co-crystal.
- Crystals contains solvent molecules called solvates. Also called pseudo polymorphs.
- If solvent is water then called hydrates and other than water then called solvates.

- The presence of solvent molecule affect the crystalline structure of molecules.
 - There are difference in **dissolution rate** of solvated and non solvated molecules
 - Eg. Anhydrous form of ampicillin – high dissolution rate than trihydrate – so attain higher blood level in vivo
-
- **The aqueous solubility of solvates are often greater than asolvated form**
 - Eg. Mono ethanol and hemiacetone Solvates of hydrocortisone and prednisolon shows higher absorption than the asolvated form

• Salt Form of the Drug

- Most drugs are either weak acids or weak bases.
- One of the easiest approaches to enhance the solubility and dissolution rate of such drugs is to convert them into their salt forms.
- Generally, with weakly acidic drugs, a strong base salt is prepared such as the sodium and potassium salts of barbiturates and sulphonamides.
- In case of weakly basic drugs, a strong acid salt is prepared like the hydrochloride or sulphate salts of several alkaloidal drugs.

- At a given pH, the solubility of a drug, whether acidic/basic or its salt form is a constant.
- Considering the pH of the diffusion layer and not the pH of the bulk of the solution
- Consider the case of a salt of a **weak acid**.
- At any given pH of the bulk of the solution, **the pH of the diffusion layer (saturation solubility of the drug) of the salt form of a weak acid will be higher than that observable with the free acid form of the drug** (can be practically observed in the laboratory). Owing to the increased pH of the diffusion layer, the solubility and dissolution rate of a weak acid in this layer is promoted; since it is a known fact that **higher pH favours the dissolution of weak acids**. Thus, if dissolution is faster, absorption is bound to be rapid.
- In case of salts of weak bases, **the pH of the diffusion layer will be lower in comparison to that found with the free base form of the drug**. Consequently, the solubility of a basic drug at this *lower pH* is enhanced

- The increase and decrease in pH of the diffusion layer by the salts of weak acids and bases have been attributed to the *buffering action* of strong base cation and strong acid anion respectively.
- A factor that influences the solubility of salt forms of the drug is the **size of the counter ion**. Generally speaking, **smaller the size of the counter ion, greater the solubility of salt**—for example, the bioavailability of novobiocin from its sodium salt, calcium salt and free acid form was found to be in the ratio — 50 : 25 : 1.
- Where the counter ion is very large in **size and/or has poor ionic strength** (as in the case of ester form of drugs), the solubility may be much lower than the free drug itself

- Drug pKa and dissociation constant

- The amount of drug that exists in unionised form is a function of dissociation constant (pKa) of the drug and pH of the fluid at the absorption site.
- The lower the pKa of an acidic drug, stronger the acid i.e. greater the proportion of ionised form at a particular pH.
- Higher the pKa of a basic drug, stronger the base.
- from the knowledge of pKa of drug and pH at the absorption site (or biological fluid), the relative amount of ionised and unionised drug in solution at a particular pH and the percent of drug ionised at this pH can be determined by *Henderson-Hasselbach equations*:

- For weak acids,

- $\text{pH} = \text{pKa} + [\text{ionized drug}] / [\text{unionized drug}]$

- The **pKa** is the pH at which half of the acid is dissociated into its ions.
- When the pH is **lower than the pKa**, the acid will mostly remain in its **unionized** form (HA), since the environment is more acidic.
- When the pH is **higher than the pKa**, the acid will tend to be more **ionized** (H^+ dissociates).

- For weak Bases

- $\text{pH} = \text{pKa} + [\text{unionized drug}] / [\text{ionized drug}]$

- When the concentration of ionised and unionised drug becomes equal, the second term of equations reduces to zero (since $\log 1 = \text{zero}$), and thus $\text{pH} = \text{pKa}$. The pKa is a characteristic of the drug.

- **For Weak Acids:**

- **1. Very weak acids ($pK_a > 8$)** such as phenytoin, ethosuximide and several barbiturates are essentially **unionised at all pH values** and therefore their absorption is rapid and **independent of GI pH.**
- **2. Acids in the pK_a range 2.5 to 7.5** are greatly affected by changes in pH and therefore their **absorption is pH-dependent**; e.g. several NSAIDs like aspirin, ibuprofen, phenylbutazone, and a number of penicillin analogs.
- Such drugs are better absorbed from acidic **conditions of stomach ($pH < pK_a$)** where they largely exist in **unionised form.**
- **3. Stronger acids with $pK_a < 2.5$** such as cromolyn sodium are **ionised in the entire pH range of GIT** and therefore remain poorly absorbed.

- **For Basic Drugs:**
- **1. Very weak bases ($pK_a < 5.0$)** such as caffeine, theophylline and a number of benzodiazepines like diazepam, oxazepam and nitrazepam are essentially **unionised at all pH values** and therefore their absorption is rapid and **pH-independent**.
- **2. Bases in the pK_a range 5 to 11.0** are greatly affected by changes in pH and hence their **absorption is pH-dependent**; e.g. several morphine analogs, chloroquine, imipramine and amitriptyline.
- Such drugs are better absorbed from the relatively alkaline conditions of the **intestine where they largely exist in unionised form**.
- **3. Stronger bases with $pK_a > 11.0$** like mecamylamine and guanethidine are **ionised in the entire pH range of GIT** and therefore **poorly absorbed**

<i>Drugs</i>	<i>pK_a</i>	<i>pH/site of absorption</i>
Very weak acids ($pK_a > 8.0$)		
Pentobarbital	8.1	Unionised at all pH values; absorbed along the entire length of GIT
Hexobarbital	8.2	
Phenytoin	8.2	
Ethosuximide	9.3	
Moderately weak acids (pK_a 2.5 to 7.5)		
Cloxacillin	2.7	Unionised in gastric pH and ionised in intestinal pH; better absorbed from stomach
Aspirin	3.5	
Ibuprofen	4.4	
Phenylbutazone	4.5	
Stronger acids ($pK_a < 2.5$)		
Disodium cromoglycate	2.0	Ionised at all pH values; poorly absorbed from GIT.
Very weak bases ($pK_a < 5.0$)		
Theophylline	0.7	Unionised at all pH values; absorbed along the entire length of GIT
Caffeine	0.8	
Oxazepam	1.7	
Diazepam	3.7	
Moderately weak bases (pK_a 5 to 11.0)		
Reserpine	6.6	Ionised at gastric pH, relatively unionised at intestinal pH; better absorbed from intestine
Heroin	7.8	
Codeine	8.2	
Amitriptyline	9.4	
Stronger bases ($pK_a > 11.0$)		
Mecamylamine	11.2	Ionised at all pH values; poorly absorbed from GIT
Guanethidine	11.7	

• Lipophilicity and Drug Absorption

- Only the **unionised drug, if sufficiently lipid soluble, is absorbed into the systemic circulation.**
- Thus, even if the drug exists in the unionised form, it will be poorly absorbed if it has poor lipid solubility (or low $K_{o/w}$).
- Ideally, for **optimum absorption**, a drug should have
- **sufficient aqueous solubility to dissolve in the fluids at the absorption site**
- **lipid solubility ($K_{o/w}$) high enough to facilitate the partitioning of the drug in the lipoidal bio membrane and into the systemic circulation.**
- In other words, a **perfect hydrophilic-lipophilic balance (HLB) should be there in the structure of the drug for optimum bioavailability.**

- The **lipid solubility** of a drug is measured by a parameter called as **log P**
- where P is oil/water partition coefficient ($K_{o/w}$ or simply P) value of the drug.
- This value is a measure of the degree of distribution of drug between lipophilic solvents such as n-octanol and an aqueous phase (water or a suitable buffer).
- In general, the octanol/pH 7.4 buffer partition coefficient value in the range of **1 to 2 of a drug is sufficient for passive absorption across lipidal membranes.**

- **Stability of drugs**

- A drug for oral use may destabilize either during its shelf-life or in the GIT.
- **Two major stability problems** resulting in poor bioavailability of an orally administered drug are
- **A) Degradation of the drug into inactive form**
- **B) Interaction with one or more different component(s)** either of the dosage form or those present in the GIT to form a **complex** that is poorly soluble or is unabsorbable.

• Stereochemical Nature of Drug

- Chiral drugs constitute approximately 60% of the drugs in current use.
- Majority of these are marketed as racemic mixtures.
- Although it is well established that optical isomers differ in the potency of pharmacological effect, it is only recently that attention is being paid to influence of chirality on pharmacokinetic processes like absorption, distribution and elimination.
- Enantiomers possess identical physical and chemical properties despite significant differences in spatial configuration. Thus, biological processes which are passive in nature (and thereby depend only upon physical and chemical characteristics of the molecule) do not display selectively for one isomer over another.
- However, biological processes such as protein binding which require interaction of a drug with a macromolecule may exhibit stereoselectivity.
- As majority of drugs are absorbed passively, they do not display stereoselectivity. Conversely, demonstration of stereoselective absorption would be strong evidence that a drug is absorbed by a carrier-mediated process.

- Dosage Form Characteristics and Pharmaceutical Ingredients (Pharmaco-technical Factors)

• Disintegration Time

- Disintegration time (DT) is of particular importance in case of solid dosage forms like tablets and capsules.
- In vitro disintegration test is by no means a guarantee of drug's bioavailability because if the disintegrated drug particles do not dissolve, absorption is not possible.
- However, if a solid dosage form does not conform to the DT, it portends bioavailability problems because the subsequent process of dissolution will be much slower and absorption may be insufficient.
- Coated tablets, especially sugar coated ones have long DT. Rapid disintegration is thus important in the therapeutic success of a solid dosage form.
- **DT of a tablet is directly related to the amount of binder present and the compression force (hardness) of a tablet.**
- **A harder tablet with large amount of binder has a long DT.**
- Disintegration can be aided by incorporating **disintegrants** in suitable amounts during formulation.
- After disintegration of a solid dosage form into granules, the granules must deaggregate into fine particles, as dissolution from such tiny particles is faster than that from granules.

• Manufacturing/Processing Variables

- **Dissolution** is the most important factor in absorption of drug
- The dosage form related factors that influence dissolution are:

Granulation : mixing time, drying time, drying temperature

Compression force : On the one hand, higher compression force increases the density and hardness of tablet, decreases porosity and hence penetrability of the solvent into the tablet, retards wettability by forming a firmer and more effective sealing layer by the lubricant, and in many cases, promotes tighter bonding between the particles, all of which result in slowing of the dissolution rate of tablets

Packing of capsule content:

- **Pharmaceutical Ingredients/Excipients (Formulation factors)**

- Excipients are added to ensure acceptability, physicochemical stability during the shelf-life, uniformity of composition and dosage, and optimum bioavailability and functionality of the drug product.
- Despite their inertness and utility in the dosage form, excipients can influence absorption of drugs.

- **Vehicle:**

- Vehicle or solvent system is the major component of liquid orals and parenterals.
- The 3 categories of vehicles in use are—
- Aqueous vehicles (water, syrup, etc.)
- Nonaqueous water miscible vehicles (propylene glycol, glycerol, sorbitol)
- Nonaqueous water immiscible vehicles (vegetable oils).
- Bioavailability of a drug from vehicles depends to a large extent on its miscibility with biological fluids. Aqueous and water miscible vehicles are **miscible with the body fluids** and drugs from them are rapidly absorbed.
- Quite often, a drug is more soluble in water miscible vehicles like propylene glycol (serving as a *co-solvent*) and show better bioavailability.
- Sometimes dilution of such vehicles with the body fluids results in precipitation of drug as fine particles which, however, dissolve rapidly.
- Solubilisers such as polysorbate 80 are sometimes used to promote solubility of a drug in aqueous vehicles.
- In case of water immiscible vehicles, the rate of drug absorption depends upon it's partitioning from the oil phase to the aqueous body fluids, which could be a rate-limiting step.
- **Viscosity** of the vehicles is another factor in the absorption of drugs. Diffusion into the bulk of GI fluids and thus absorption of a drug from a viscous vehicle may be slower.

- **Diluents (Fillers):**

- To create the bulk for processing
- A diluent may be **organic or inorganic.**
- **Organic diluents:** carbohydrates are very widely used—for example, starch, lactose, microcrystalline cellulose, etc.
- These hydrophilic powders are very useful in promoting the dissolution of poorly water-soluble, hydrophobic drugs like spironolactone and triamterene by forming a coat onto the hydrophobic surface of drug particles and rendering them hydrophilic.
- **Inorganic diluents:** **dicalcium phosphate (DCP)** is most common.
- One classic example of drug-diluent interaction resulting in poor bioavailability is that of **tetracycline** and **DCP**. The cause is formation of divalent calcium-tetracycline complex which is poorly soluble and thus, unabsorbable.

- **Binders and Granulating Agents:**

- Examples:

- polymeric materials (natural, semisynthetic and synthetic) like starch, cellulose derivatives, acacia, PVP, etc. Others include gelatin and sugar solution.

- **Hydrophilic (aqueous) binders show better dissolution profile with poorly wettable drugs like phenacetin** by imparting hydrophilic properties to the granule surface.

- However, the proportion of strong binders in the tablet formulation is very critical. Large amounts of such binders **increase hardness and decrease disintegration/dissolution rates of tablets.**

- PEG 6000 was found to be a deleterious binder for phenobarbital as it forms a poorly soluble complex with the drug.

- **Non-aqueous binders like ethyl cellulose also retard drug dissolution.**

- **Disintegrants:**

- These agents overcome the cohesive strength of tablet and break them up on contact with water which is an important prerequisite to tablet dissolution.
- **Almost all the disintegrants are hydrophilic in nature.**
- A decrease in the amount of disintegrant can significantly lower bioavailability.
- **Adsorbing disintegrants** like bentonite and veegum should be avoided with low dose drugs like digoxin, alkaloids and steroids since a large amount of dose is permanently adsorbed and only a fraction is available for absorption.
- **Microcrystalline cellulose is a very good disintegrant** but at high compression forces, it may retard drug dissolution.

- **Lubricants/Antifrictional Agents:**

- These agents are added to tablet formulations to aid flow of granules, to reduce interparticle friction and sticking or adhesion of particles to dies and punches.
- **The commonly used lubricants are hydrophobic in nature** (several metallic stearates and waxes)
- **Inhibit wettability, penetration of water into tablet and their disintegration and dissolution.**
- This is because the disintegrant gets coated with the lubricant if blended simultaneously which however can be prevented by **adding the lubricant in the final stage.**
- The best alternative is use of soluble lubricants like SLS and carbowaxes(PEG) which promote drug dissolution.

- **Suspending Agents/Viscosity Imparters:**
- Popular suspending agents are:
- Hydrophilic polymers like vegetable gums (acacia, tragacanth, etc.)
- Semisynthetic gums (CMC, MC)
- Synthetic gums
- primarily stabilize the solid drug particles by **reducing their rate of settling through an increase in the viscosity of the medium.**
- The macromolecular gums often form unabsorbable complexes with drug
- for example, sodium CMC forms a poorly soluble complex with amphetamine. An increase in viscosity by these agents acts as a mechanical barrier to the diffusion of drug from the dosage form into the bulk of GI fluids and from GI fluids to the mucosal lining by forming a viscid layer on the GI mucosa. They also retard the GI transit of drugs.

- **Complexing Agents:**

- Complex formation has been used to alter the physicochemical and biopharmaceutical properties of a drug. A complexed drug may have altered stability, solubility, molecular size, partition coefficient and diffusion coefficient. Basically, such complexes are pharmacologically inert and must dissociate either at the absorption site or following absorption into the systemic circulation.

- Several examples where complexation has been used to **enhance drug bioavailability** are:

- 1. Enhanced dissolution through formation of a soluble complex e.g. ergotamine tartarate-caffeine complex and hydroquinone-digoxin complex.
- 2. Enhanced lipophilicity for better membrane permeability e.g. caffeine-PABA complex.
- Complexation can be **deleterious to drug absorption due to formation of poorly soluble** or poorly absorbable complex e.g. complexation of tetracycline with divalent and trivalent cations like calcium (milk, antacids), iron (haematinics), magnesium (antacids) and aluminium (antacids).

- **Nature and Type of Dosage Form**

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

• Product Age and Storage Conditions

- A number of changes, especially in the physicochemical properties of a drug in dosage form, can result due to aging and alterations in storage conditions which can adversely affect bioavailability.
- With **solution** dosage form, precipitation of drug due to altered solubility, especially due to conversion of metastable into poorly soluble, stable polymorph can occur during the shelf-life of the product.
- Changes in particle size distribution have been observed with a number of **suspension dosage forms** resulting in decreased rate of drug dissolution and absorption.
- In case of **solid dosage forms**, especially tablets, disintegration and dissolution rates are greatly affected due to aging and storage conditions. An increase in these parameters of tablets has been attributed to excipients that harden on storage (e.g. PVP, acacia, etc.) while the decrease is mainly due to softening/crumbling of the binder during storage (e.g. CMC).

- Patient related factors

- Age
- **Gastric emptying time:**
- *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.
- Thus, generally speaking, rapid gastric emptying increases bioavailability of a drug.
- **Rapid gastric emptying is advisable where:**

A rapid onset of action is desired e.g. sedatives.

Dissolution of drug occurs in the intestine e.g. enteric-coated dosage forms.

The drugs are not stable in the gastric fluids e.g. penicillin G and erythromycin.

The drug is best absorbed from the distal part of the small intestine e.g. vitamin B12.

- Delay in gastric emptying is recommended in particular where:
 - 1. The food promotes drug dissolution and absorption e.g. griseofulvin.
 - 2. Disintegration and dissolution of dosage form is promoted by gastric fluids.
 - 3. The drugs dissolve slowly e.g. griseofulvin.
 - 4. The drugs are absorbed from the proximal part of the small intestine and prolonged drug-absorption site contact is desired e.g. vitamin B2 and vitamin C

- A large number of factors influence gastric emptying as discussed below.
- 1. Volume of meal
 - 2. Composition of meal: Predictably, the rate of gastric emptying for various food materials is in the following order: carbohydrates > proteins > fats. Fats promote secretion of bile which too has an inhibitory effect on gastric emptying. Delayed gastric emptying as observed with fatty meals, is beneficial for the absorption of poorly soluble drugs like griseofulvin.
 - 3. Physical state and viscosity of meal: Liquid meals take less than an hour to empty whereas a solid meal may take as long as 6 to 7 hours. Viscous materials empty at a slow rate in comparison to less viscous materials.
 - 4. Temperature of the meal: High or low temperature of the ingested fluid (in comparison to body temperature) reduce the gastric emptying rate.
 - 5. Gastrointestinal pH:
 - 6. Electrolytes and osmotic pressure: Water, isotonic solutions, and solutions of low salt concentration empty the stomach rapidly whereas a higher electrolyte concentration decreases gastric emptying rate.
 - 7. Emotional state: Stress and anxiety promote gastric motility whereas depression retards it.
 - 8. Disease states: Diseases like gastroenteritis, gastric ulcer, pyloric stenosis, diabetes and hypothyroidism retard gastric emptying. Partial or total gastrectomy, duodenal ulcer and hyperthyroidism promote gastric emptying rate.
 - 9. Drugs: Drugs that retard gastric emptying include poorly soluble antacids (aluminium hydroxide), anticholinergics (atropine, propantheline), narcotic analgesics (morphine) and tricyclic antidepressants (imipramine, amitriptyline). Metoclopramide, dom-peridone and cisapride (prokinetic agents) stimulate gastric emptying.

- **Intestinal Transit**

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

- **Delayed intestinal transit is desirable for:**

- 1. Drugs that dissolve or release slowly from their dosage form (sustained-release products) or when the ratio of dose to solubility is high e.g. chlorothiazide.
- 2. Drugs that dissolve only in the intestine (enteric-coated formulations).
- 3. Drugs which are absorbed from specific sites in the intestine (several B vitamins, lithium carbonate, etc.).
- 4. When the drug penetrates the intestinal mucosa very slowly e.g. acyclovir

- **GI pH:**

- A tremendous 10^7 fold difference in the hydrogen ion concentration is observed between the gastric and colon fluids.
- **Disintegration** is pH sensitive – enteric coated dosage forms
- **Dissolution:** A large number of drugs are either weak acids or weak bases whose solubility is greatly affected by pH.
- **Stability:** GI pH also influences the chemical stability of drugs. The acidic stomach pH is known to affect degradation of penicillin G and erythromycin.

• 5. Disease States

- Several disease states can influence the rate and extent of drug absorption.
- The 3 major classes of disease states that can influence the bioavailability of a drug are:
 - 1. Gastrointestinal diseases,
 - 2. Cardiovascular diseases, and
 - 3. Hepatic diseases.

- **Cardiovascular diseases:** Several changes associated with congestive cardiac failure influence bioavailability of a drug viz. **edema of the intestine, decreased blood flow to the GIT and gastric emptying rate and altered GI pH, secretions and microbial flora.**
- **Hepatic diseases:** Disorders such as hepatic cirrhosis influence bioavailability mainly of drugs that undergo considerable first-pass hepatic metabolism e.g. propranolol
- **Enhanced bioavailability is observed in such cases.**

- **Degradation by the GIT and Liver: drug has to pass through GIT and liver**
- Luminal enzymes – the metabolism by these enzymes are further categorised into two –
 - (a) Digestive enzymes, and
 - (b) Bacterial enzymes.
- 2. Gut wall enzymes/mucosal enzymes.
- 3. Hepatic enzymes.

First pass effect:

Process of first pass metabolism:

Absorption: After oral ingestion, the drug is absorbed through the lining of the stomach or small intestine and enters the portal vein, which carries blood directly to the liver.

Liver Metabolism: Once the drug reaches the liver, it is metabolized by liver enzymes, particularly cytochrome P450 enzymes. These enzymes can chemically alter the drug, either activating it, deactivating it, or converting it into a form that is easier for the body to excrete.

Excretion or Circulation: After the liver metabolizes the drug, a fraction of the drug may be excreted in bile or urine, while the remaining portion enters the systemic circulation (the bloodstream) and is distributed to the rest of the body.

Absorption of drug from non-peroral extra-vascular routes

- The term **per-oral** (often abbreviated as **PO**) refers to a method of **administering medication or substances through the mouth**, where the substance is swallowed and absorbed in the gastrointestinal tract.
- In medical contexts, "per-oral" typically implies that the substance is taken by mouth, rather than through injections, topically, or other methods.
- Non-peroral extravascular routes refer to methods of administering medications or substances to the body that do not involve the mouth (per-oral) and are outside of the gastrointestinal tract (extravascular). These routes allow the substance to enter the bloodstream or body tissues directly, bypassing the digestive system.

- **Buccal/Sublingual Administration**

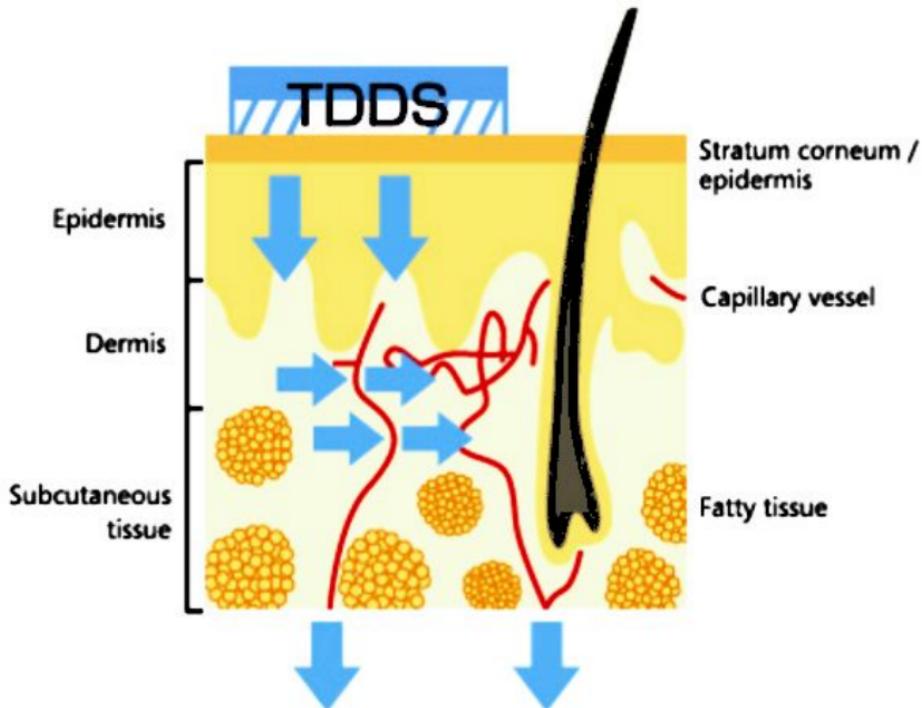
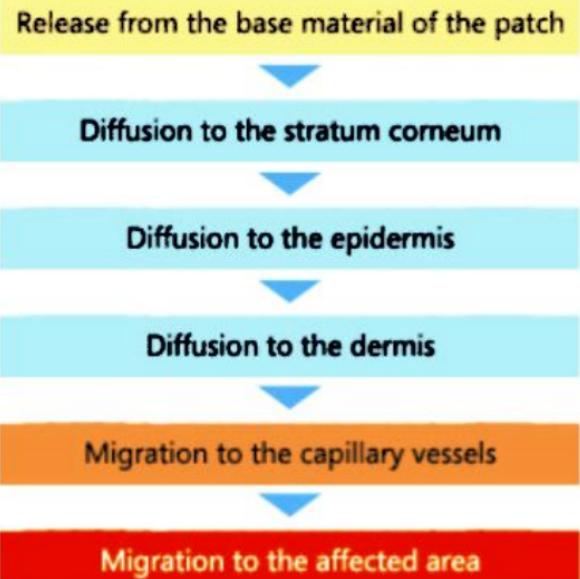
- **Advantages:**
 - **Rapid absorption** and higher blood levels due to **high vascularization** of the region and therefore particularly useful for administration of anti-anginal drugs.
 - **2. No first-pass hepatic metabolism** and **No degradation of drugs** such as that encountered in the GIT
- **Disadvantages:**
 - limited mucosal surface area (thus only a small dose can be administered)
 - Concern for taste of the medicament and discomfort

- **Factors affecting drug absorption:**

- **Lipophilicity of drug:** Slightly higher lipid solubility than that required for GI absorption is necessary for passive permeation.
- **2. Salivary secretion:** In addition to high lipid solubility, the drug should be soluble in aqueous buccal fluids i.e. biphasic solubility of drug is necessary for absorption; absorption is delayed if the mouth is dry.
- **3. pH of the saliva:** Usually around 6, the buccal pH favours absorption of drugs which remain unionised.
- **6. Thickness of oral epithelium:** Sublingual absorption is faster than buccal since the epithelium of former region is thinner and immersed in a larger volume of saliva.

- Topical Administration

- It is the largest organ of the body weighing approximately 2 Kg and 2 m² in area and receives about 1/3rd of total blood circulating through the body.
- Majority of drugs applied topically are meant to exert their **effect locally**.
- *When topically applied drugs are meant to exert their effects systemically, the mode of administration is called as percutaneous or transdermal delivery.*
- Percutaneous absorption occurs only if the **topically applied drug permeates the dermal capillaries and enters the blood stream.**



- Factors affecting percutaneous penetration in skin

1. Physicochemical properties of permeant:

- Drug solubility (soluble form increases drug penetration)
- Particle size, molecular weight of drug (**<400 Dalton**)
- Wettability
- Partition co-efficient (1-4)

2. Thickness of stratum corneum:

- Absorption is less in foot and palm

3. Presence of hair follicle :

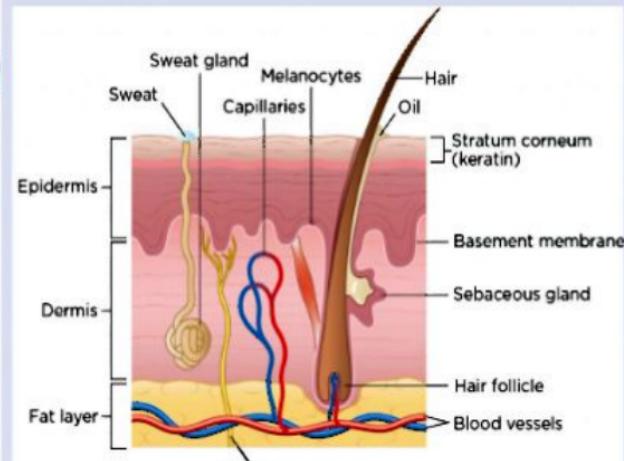
- Absorption is rapid in the region where numerous hair follicles are present

4. Hydration state of stratum corneum: (hydration of skin increases the penetration of drug

5. Environmental humidity and temp:

- Greater humidity and temp. increases rate of hydration and local blood flow and hence increase drug absorption

Fig 1. Cross-section through the skin



6) Exposure to chemicals:

- Exposure to the solvent will lead to the peeling of epidermal cells and thereby increases absorption

7) Vehicle used :

- Use vehicle in which drug get dissolved rather dispersed

8) Use of permeation enhancers :

- Poorly penetrating drug – use permeation enhancers like dimethyl formamide , dimethyl sulfoxide, PG and surfactants

9) Condition of skin:

- Cuts, rashes, mild burns, inflammation in which stratum coronium is destroyed promote drug absorption

- **Intramuscular Administration**

- Absorption of drugs from i.m. sites is relatively rapid but much slower in comparison to i.v. injections. Factors that determine rate of drug absorption from i.m. sites are:
- **1. Vascularity of the injection site:** the decreasing order of blood flow rate to muscular tissues in which drugs are usually injected is:
 - Arm (deltoid) > Thigh (vastus lateralis) > Buttocks (gluteus maximus).
- Since blood flow rate is often the rate-limiting step in absorption of drugs from i.m. sites, most rapid absorption is from deltoid muscles and slowest from gluteal region. The absorption rate decreases in circulatory disorders such as hypotension.
- **2. Lipid solubility and ionization of drug:** highly lipophilic drugs are absorbed rapidly by passive diffusion whereas hydrophilic and ionised drugs are slowly absorbed through capillary pores.

- **3. Molecular size of the drug:** **Molecular size:** Smaller molecules are usually absorbed more quickly compared to larger molecules..
- **4. Type of dosage form :** solution or suspension
- **5. pH, composition and viscosity of injection vehicle:**
 - Aqueous solution – faster rate of absorption
 - Non aqueous – drug is dissolved in oil (sesame oil, cotton seed oil etc..) when injected the drug get precipitated out and give depot formulation design to release drug slowly.

Naso- pulmonary administration:

• Factors Related to Formulation

- 1) Physicochemical Properties of the Formulation:
 - a) pH and Mucosal Irritancy : pH of nasal mucosa is 5 to 7
 - The pH of the formulation, as well as that of nasal surface, can affect a drug's permeation.
 - To avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5–6.5
 - pH of the formulation should be selected such it will achieve greatest stability and drug will remain in unionized form

- b) **Osmolarity:** isotonic solutions are preferred

- c) **Viscosity :**

- A higher viscosity of the formulation increases contact time between the drug and the nasal mucosa thereby increasing the time for permeation. At the same time, highly viscous formulations interfere with the normal functions like ciliary beating or mucociliary clearance and thus alter the permeability of the drug

- D) **Particle size of drug or formulation :**

- **Particle size :**

- Mouth and nose : 10-30 μm

- bronchus (right and left) , bronchioles – 2-10 μm

- Alveoli - < 2 μm

- <https://www.youtube.com/watch?v=HMdrhwEnY6M> – muco ciliary clearance

- **Physiological Factors:**

- **Pathological condition of nose:**

- Allergic rhinitis, common cold influence the drug absorption.
- Most of the pathological condition lead to excessive secretion of mucus which will wash away a nasally administered drug before it can be absorbed.

- **pH of the nasal cavity**

- **Mucociliary clearance :** Defense mechanism of nasal cavity. It will clear the mucus and substances like dust and micro-organism adhered to it to the nasopharynx for eventual discharge into the GI tract.

- **Enzymes present into nasal cavity:**

- Nasal route is selected to avoid enzymatic degradation of GIT.
- However the nasal cavity itself contain group of enzymes like
- Oxidative enzyme , non oxidative enzymes , proteolytic enzymes such as endo-peptidase
- The activity of nasal enzymes seems to be lower than the enzymes present in GIT

Ophthalmic or intraocular administration

- **pH:** equivalent to tear fluid 7.4
- Eye can tolerate pH 3-8.6
- **Osmolality:** eye can tolerate tonicity 0.5-5% of NaCl solution
- Hypotonic solution are more tolerated than hypertonic solution
- **Particulate matter test**
- **Sterility test**
- **Viscosity :** 15-25cps
- **Drop size:** 20-70 μ L
- **For Suspension: particle size is recommended <10 μ m**
- Ophthalmic suspension available are anti-inflammatory steroids like prednisolone acetate, hydrocortisone

