# Unit-1
# Industrial Pharmacy-1

## B.Pharma 5th Sem Notes

### Unit: 1

- **Pre-formulation Studies:** Introduction to pre-formulation, goals and objectives, study of physicochemical characteristics of drug substances.
- **Physical properties:** Physical form (crystal & amorphous), particle size, shape, flow properties, solubility profile (pKa, pH, partition coefficient), polymorphism.
- **Chemical Properties:** Hydrolysis, oxidation, reduction, racemization, polymerization.
  **BCS classification of drugs & its significance.**
  Application of pre-formulation considerations in the development of solid, liquid oral and parenteral dosage forms and its impact on stability of dosage forms.

**Pre-formulation Studies:** Introduction to pre-formulation, goals and objectives, study of physicochemical characteristics of drug substances.

### 1. Introduction to Pre-Formulation

Pre-formulation studies are the **systematic investigations carried out before formulation development** to understand the **physicochemical properties of a drug substance**. These studies provide essential information required for the **selection of dosage form, excipients, manufacturing process, and packaging system**.

Pre-formulation acts as a **bridge between drug discovery and formulation development**, ensuring that the drug can be formulated into a **stable, safe, effective, and bioavailable dosage form**.

## Goals:

### Goals and Objectives

The primary goal of pre-formulation is to generate information useful to the formulator in developing a stable and bioavailable dosage form that can be mass-produced.

### Objectives:

- Establish Physicochemical Parameters: To determine the fundamental properties of the new drug molecule.
- Determine Kinetic Rate Profile: To understand the stability of the drug molecule (how fast it degrades).
- establish Compatibility: To ensure the drug does not react negatively with common excipients (binders, fillers, lubricants).
- Optimize Bioavailability: To ensure the drug is absorbed effectively by the body.
- Select the Correct Dosage Form: To decide whether the drug should be a tablet, suspension, or injection based on its solubility and stability.

### Pre-formulation Studies:

Preformulation study is a multidisciplinary approach and involves several aspects of pharmacology, toxicology, clinical pharmacy, biochemistry, medicinal chemistry, and analytical chemistry.

Therefore, the primary objective of preformulation study is to lay down foundation for transforming a new drug entity into a pharmaceutical formulation so that the drug can be administered in a right way, in right amount, and at right target (site).

The secondary objective of preformulation study is to provide longer stability to the developed formulation through proper designing and protecting the drug from environmental condition and to evaluate performance of the prepared formulation.

To improve bioavailability and stability efforts are to be made to optimize a molecule inform of salts, solvates, polymorphs, and importantly prodrug.

**Study of physicochemical characteristics of drug substances:**

- Physicochemical is a fusion of two words, "Physico" and "Chemical", which means physical and chemical. Hence, Physicochemical properties are all the physical and chemical properties of a drug.
- Both of these properties invoke the pharmacological response on the receptor, which can be a biological molecule or system with which it interacts.
- Drugs interact with receptors to form the Drug Receptor Complex, which is responsible for the pharmacological actions of the drug.
- These diversified physicochemical properties of the drug administer the various pharmacological effects of the drugs.

**Salts**

About 50% of the drug molecules being marketed as drug products are available in salt form. Conversion of a molecule into its salt form is widely used approach and the performance of the molecule is also enhanced. This improvement can be achieved in the area such as:

- Performance due to enhanced solubility and bioavailability.
- Increased stability due to improved hydrolytic and thermal stability.
- Improved organoleptic properties due to masking of taste.
- Increased patient compliance due to reduced side effects.
- Modified release dosage form due to change in solubility.

**Prodrug:**

A **prodrug** is a pharmacologically inactive (or significantly less active) chemical derivative of a drug molecule that requires a chemical or enzymatic transformation within the body (in vivo) to release the active drug moiety.

This process is often referred to as **Drug Latentiation**, a term describing the chemical modification of a biologically active compound to form a new compound that releases the parent drug in vivo.

"Note: The prodrug itself does not bind to the receptor or enzyme to produce an effect; it acts as a delivery vehicle that is "unmasked" by metabolism."

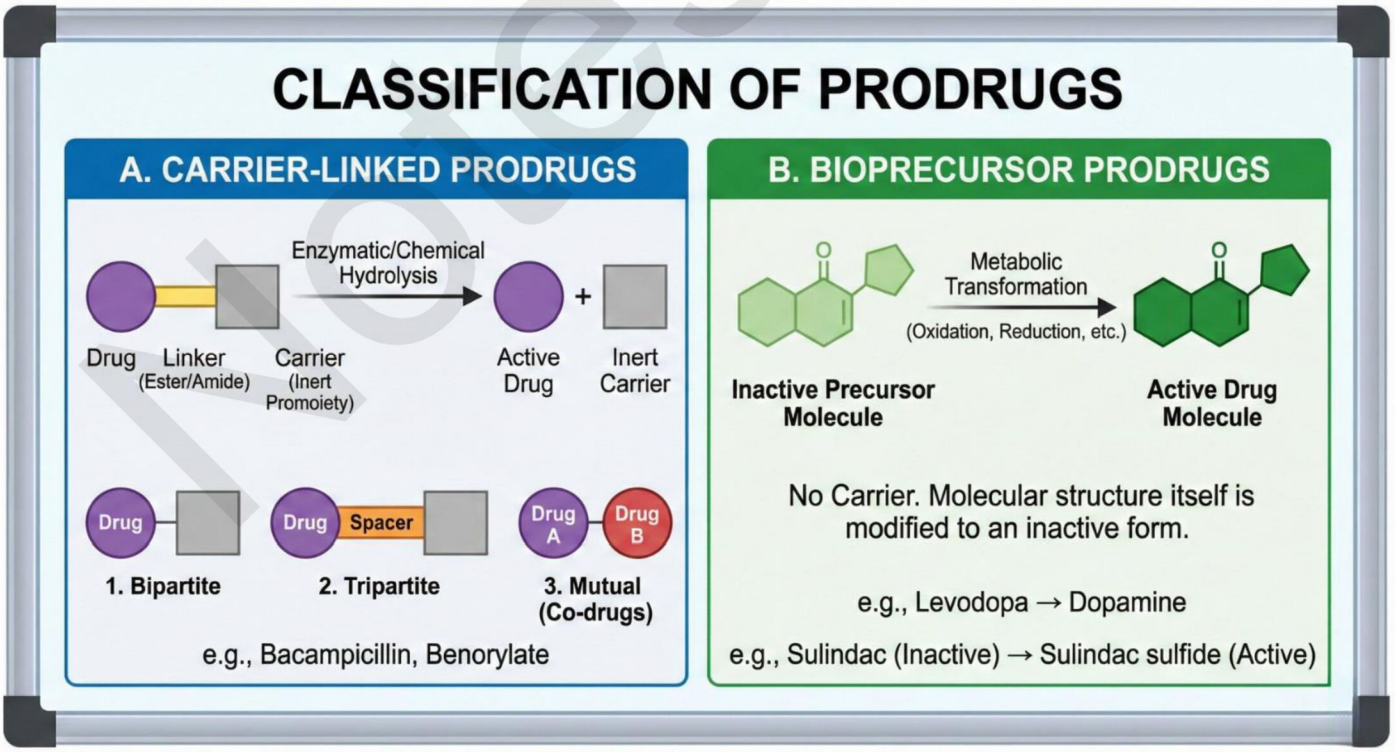
### Objectives of Prodrug Development

- To **improve bioavailability**
- To increase **chemical and metabolic stability**
- To reduce **toxicity and adverse effects**
- To improve **patient compliance**
- To achieve **site-specific drug delivery**
- To improve **pharmacokinetic properties**

### Ideal Characteristics of a Prodrug

- Be **chemically stable** during storage
- Convert rapidly and completely to the active drug in vivo
- Be **non-toxic** before and after conversion
- Have predictable and reproducible activation
- Improve one or more properties of the parent drug
- Not interfere with normal metabolic pathways

### Classification of Prodrugs:

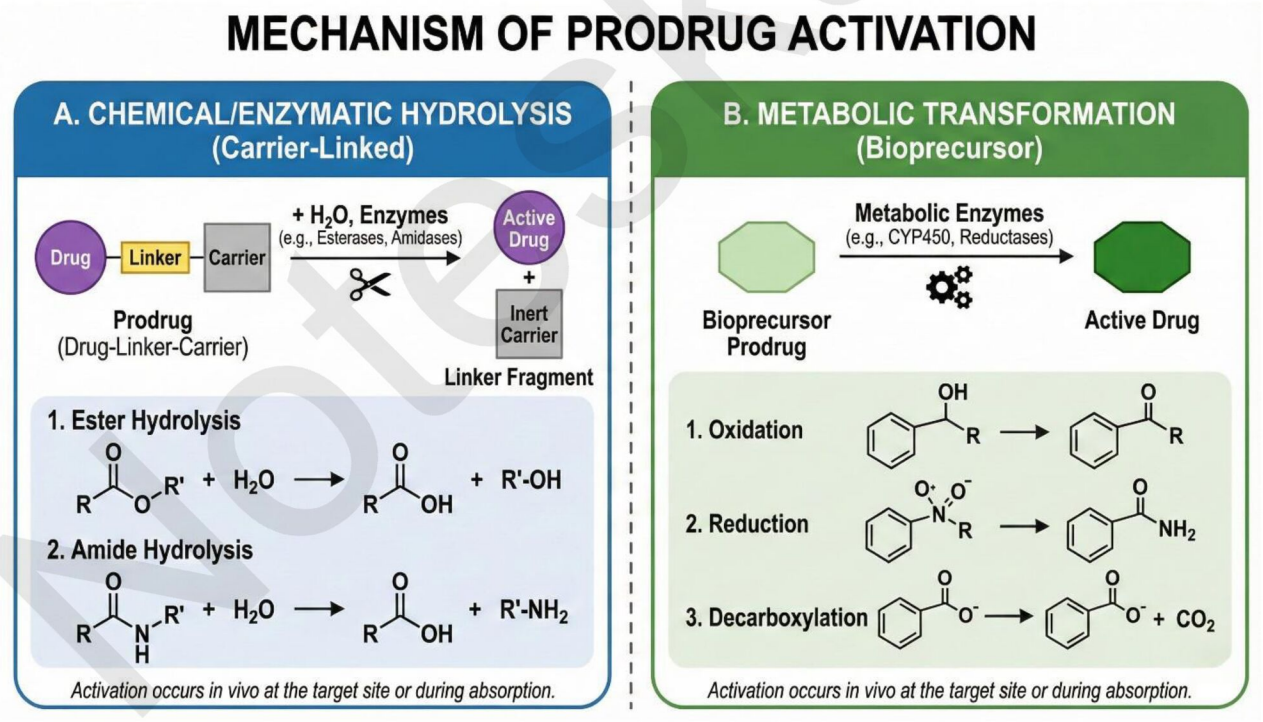


### Advantages of Prodrugs

- Improved **oral absorption**
- Enhanced **solubility**
- Reduced **dose-related toxicity**
- Increased **chemical stability**
- Better **target specificity**
- Improved **therapeutic index**
- Masking of **unpleasant taste or irritation**

### Disadvantages of Prodrugs

- Variable metabolic activation among patients
- Risk of incomplete conversion
- Possibility of toxic intermediates
- Increased development cost
- Complex formulation and regulatory evaluation



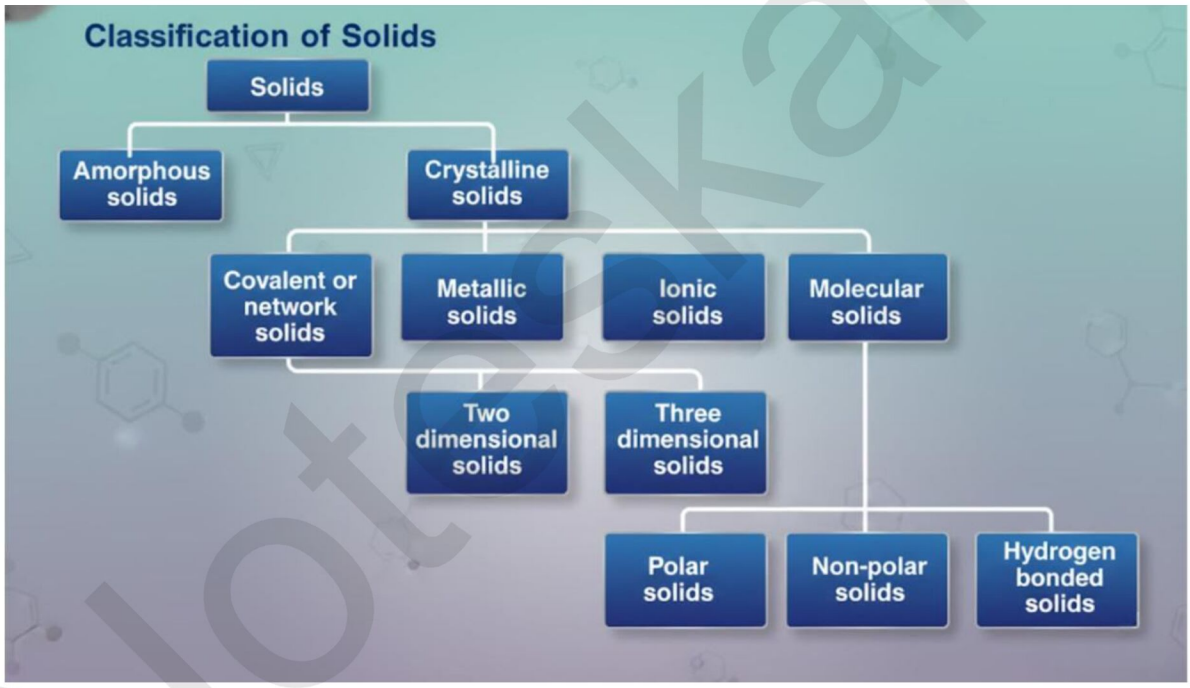
**Physical properties:** Physical form (crystal & amorphous), particle size, shape, flow properties, solubility profile (pKa, pH, partition coefficient), polymorphism.

### Physical Forms of Solids

The physical form of a drug substance describes how its molecules are arranged in the solid state. This arrangement dictates the energy of the solid, which in turn controls properties like **solubility**, **dissolution rate**, **stability**, and **manufacturability**.

There are two primary forms:

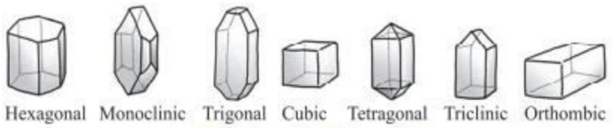
1. **Crystalline Solids** (Internal Order)
2. **Amorphous Solids** (Internal Disorder)




### 1. Crystalline Solids

A crystal is a solid in which the constituent molecules are packed in a highly ordered, repeating, three-dimensional pattern known as a **Crystal Lattice**.

- **Structure:** Long-range order. The position of every molecule is predictable based on the lattice pattern.



Morphological structure of some crystals

- **Binding Forces:** Molecules are held together by specific intermolecular forces (hydrogen bonds, Van der Waals forces) that are uniform throughout the structure.
- **Melting Point:** Because the lattice energy is uniform, crystals have a **sharp, distinct melting point**. At this temperature, the lattice collapses.
- **Stability:** This is the lowest energy state for a solid. It is thermodynamically **stable**, meaning it does not easily change form over time.
- **Properties:**
  - **Anisotropy:** Physical properties (like refractive index or electrical conductivity) can vary depending on the direction of measurement within the crystal.
  - **Lower Solubility:** A high amount of energy (lattice energy) is required to break the crystal structure to let the drug dissolve.
  - **Less Hygroscopic:** The tight packing leaves less space for water vapor to penetrate.

**2. Amorphous Solids**

An amorphous solid (from Greek *a-morphos*, meaning "shapeless") possesses no long-range order.[8] The molecules are arranged randomly, much like they are in a liquid state, but they are "frozen" in place.

- **Structure:** Short-range order only. There is no repeating lattice; the arrangement is chaotic and random. Often referred to as "supercooled liquids."
- **Glass Transition:** They do not have a sharp melting point. Instead, they soften over a range of temperatures. The temperature at which the solid changes from a glassy/brittle state to a rubbery state is called the **Glass Transition Temperature ($T_g$)**
- **Stability:** This is a high-energy, **metastable** state. Because the molecules are not in their preferred lowest-energy positions, amorphous solids have a natural tendency to revert (crystallize) back to the stable crystalline form over time
- **Properties:**
  - **Isotropy:** Physical properties are identical in all directions because the randomness is uniform.
  - **High Solubility:** Since there is no organized lattice to break, the molecules are loosely held and dissolve very rapidly. This is ideal for drugs with poor water solubility.
  - **Hygroscopic:** The disordered structure creates "voids" or free volume where moisture can easily be absorbed.

**Particle Size**
Particle size influences dissolution rate, absorption, and bioavailability. Smaller particles have a larger surface area, which enhances dissolution and improves drug absorption. It also affects content uniformity and stability of dosage forms.

**Particle Shape**
Particle shape affects flowability and packing. Spherical particles show good flow properties, while needle-shaped or plate-like particles exhibit poor flow and may cause processing problems during tableting and capsule filling.

**Flow Properties**
Flow properties determine the ease with which powders move during manufacturing. Good flow is essential for uniform die filling and accurate dosing. It is evaluated using angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio.

**Solubility Profile**

- **pKa:** Indicates the pH at which a drug is 50% ionized. It helps predict drug solubility and absorption.
- **pH:** The solubility of a drug depends on the pH of the medium, especially for weak acids and bases.
- **Partition Coefficient (P):** Represents the ratio of drug concentration in lipid to aqueous phase. It indicates lipophilicity and membrane permeability.

## Polymorphism:

**Definition:**

**Polymorphism** is the ability of a solid drug substance (chemical compound) to exist in two or more different crystalline forms.

- Chemically, these forms are identical.
- Physically, they differ in the internal arrangement of molecules within the crystal lattice.
- These distinct forms are called **Polymorphs**.

Different crystalline forms are called polymorphs.

**Classification Based on Transition (Thermodynamics)**

1. **Enantiotropic Polymorphs:**

- One form can reversibly change into another by varying the temperature or pressure.
- *Example:* Sulfur.

2. **Monotropic Polymorphs:**
   - The change is irreversible. One form is stable at all temperatures, and the other is unstable.
   - *Example:* Glyceryl stearate.

**Effect of Polymorphism on Drug Properties**

1. **Solubility**
   - Metastable polymorphs have higher solubility.
   - Stable polymorphs have lower solubility.
2. **Dissolution Rate**
   - Faster dissolution from metastable forms.
3. **Bioavailability**
   - Higher dissolution → better absorption.
   - Changes in polymorph can cause therapeutic failure.
4. **Stability**
   - Stable polymorph preferred for long-term storage.
5. **Manufacturing**

- Different polymorphs show different:
  - Flow properties
  - Compressibility
  - Compactibility

Chemical properties of **Polymorphism:**

1. **Chemical Stability**

- Different polymorphs show different resistance to chemical degradation.
- Stable polymorph → more chemically stable.
- Metastable polymorph → more reactive, degrades faster.
- Affects:
  - Hydrolysis
  - Oxidation

- Photodegradation

Example:
A metastable form may degrade faster in humid conditions than the stable form.

2. **Reactivity**

- Metastable polymorphs possess higher free energy.
- They show:
  - Higher chemical reactivity
  - Faster interaction with excipients
  - Increased risk of incompatibility

3. **Hygroscopicity**

- Some polymorphs absorb moisture more readily.
- Moisture uptake can cause:
  - Chemical degradation
  - Polymorphic transformation
  - Loss of stability

4. **Solvate and Hydrate Formation**

- Some polymorphs easily form hydrates or solvates.
- This can change:
  - Molecular structure
  - Drug potency
  - Stability

Example:
An anhydrous form may convert into a hydrate in humid air.

5. **Thermodynamic Stability**

- Each polymorph has different:
  - Free energy
  - Enthalpy
  - Entropy

**Stable polymorph:**

- Lower free energy
- Higher thermodynamic stability

Metastable polymorph:

- Higher free energy
- More reactive

6. **Chemical Compatibility with Excipients**

- Different polymorphs interact differently with excipients.
- May affect:
  - Drug-excipient compatibility
  - Shelf life of dosage form

7. **Transformation Kinetics**

- Chemical environment (moisture, temperature, solvents, pH) can cause conversion:
  - Metastable → Stable polymorph
- This conversion can alter drug performance.

8. **Effect on Degradation Pathways**

- Polymorphic form can influence:
  - Type of degradation products
  - Rate of degradation
  - Storage requirements



Chemical Properties: Hydrolysis, oxidation, reduction, racemization, polymerization.

### 1. Hydrolysis

Hydrolysis is the most common cause of drug degradation. It involves the cleavage of chemical bonds by the addition of water. This process is frequently catalyzed by hydrogen ions ($H^+$) or hydroxyl ions ($H^-$), meaning pH plays a vital role in the rate of reaction.

- **Susceptible Functional Groups:** Esters (e.g., Aspirin), amides (e.g., Penicillin), lactams, and lactones.
- **Mechanism:** Water acts as a nucleophile and attacks the electrophilic carbon of a carbonyl group, leading to the breaking of the bond.
- **Prevention:**
    - Formulating drugs as dry powders for reconstitution.
    - Reducing water activity using non-aqueous solvents (like glycerin or propylene glycol).
    - Adjusting the pH to the point of maximum stability.

### 2. Oxidation

Oxidation involves the loss of electrons or the addition of oxygen (or removal of hydrogen). In pharmaceuticals, this often occurs through **autoxidation**, a free-radical chain reaction involving atmospheric oxygen.

- **Susceptible Functional Groups:** Phenols (e.g., Epinephrine), aldehydes, ethers, and unsaturated fats/oils.
- **Mechanism:** The process occurs in three stages:
    1. **Initiation:** Formation of free radicals (often catalyzed by light, heat, or metal ions).
    2. **Propagation:** Free radicals react with oxygen to form peroxy radicals, which then react with more drug molecules.
    3. **Termination:** Free radicals combine to form stable, non-reactive species.
- **Prevention:**
    - Adding antioxidants (e.g., Ascorbic acid, BHA, BHT).
    - Using chelating agents (e.g., EDTA) to bind metal catalysts.

- Storing products in amber-colored glass to block UV light.

### 3. Reduction

Reduction is the gain of electrons or the addition of hydrogen. While less common than oxidation in ambient storage, it is a significant pathway in biological systems and specific chemical environments.

- **Susceptible Functional Groups:** Silver salts, nitro groups, and double bonds (alkenes).
- **Mechanism:** Often involves the transfer of electrons from a reducing agent or the addition of hydrogen across a multiple bond.
- **Pharmaceutical Context:** Many prodrugs are activated via reduction (e.g., the reduction of a nitro group to an amine).
- **Prevention:** Avoiding contact with reducing agents and controlling the redox potential of the formulation.

### 4. Racemization

Racemization is the process where an optically active compound (a single enantiomer) is converted into an optically inactive mixture of equal parts of both enantiomers (a racemic mixture).

- **Significance:** In many drugs, only one enantiomer is therapeutically active. For example, **L-epinephrine** is significantly more active than **D-epinephrine**. Racemization effectively reduces the potency of the preparation by half.
- **Mechanism:** Typically involves the formation of an intermediate (like a carbanion or carbocation) at a chiral center, which is then attacked from either side with equal probability.
- **Influencing Factors:** Temperature, solvent type, and pH.

### 5. Polymerization

Polymerization is the reaction where two or more identical drug molecules combine to form a larger complex (dimer, trimer, or polymer).

- **Pharmaceutical Examples:**
  - **Ampicillin:** Concentrated solutions of Ampicillin can polymerize, where the amino group of one molecule attacks the lactam ring of another. These polymers are often implicated in allergic reactions.

- **Formaldehyde:** Can polymerize into paraformaldehyde, changing its antiseptic properties.

- **Impact:** Leads to precipitation, loss of activity, and increased toxicity or allergenicity.
- **Prevention:** Proper concentration control and storage at recommended temperatures to slow down molecular collisions.

**BCS classification of drugs & its significance.**

Application of pre-formulation considerations in the development of solid, liquid oral and parenteral dosage forms and its impact on stability of dosage forms.

**Biopharmaceutical Classification System:**

The BCS classifies drugs based on their **aqueous solubility** and **intestinal permeability**. It helps in predicting the in vivo performance of drugs from in vitro data.

The Biopharmaceutical Classification System was first developed by in 1995, by Amidon et al & his colleagues.

The Biopharmaceutics Classification System (BCS) is a fundamental tool in pharmaceutical development that categorizes drug substances based on their aqueous solubility and intestinal permeability.

When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption.

Or

The Biopharmaceutical Classification System is a scientific framework for classifying a drug substance based on its aqueous solubility & intestinal permeability & dissolution rate".

To saved time fast screening is required so drug substances are classified on basis of solubility and permeability. This classification is called Biopharmaceutical Classification System.

**Factor Affecting on BCS:**

The Biopharmaceutical Classification System has been developed to provide a scientific approach to allow for to prediction in vivo pharmacokinetics of oral immediate release (IR) drug product by classifying drug compound based on their,

1. Solubility
2. Permeability
3. Dissolution

1. Solubility:

- The Maximum Amount of solute dissolved in a given solvent under standard conditions of temperature, pressure and pH.
- Solubility is the ability of the drug to be solution after dissolution.
- The higher single unit dose is completely soluble in 250 ml at pH 1-6.8 (37˚C).

2. Permeability

- Permeability of the drug to pass the biological membrane which is the lipophilic.
- Permeability is indirectly based on the extent of absorption of a drug substance.
- Drug substance is considered to be highly permeable, when the extent of absorption in human determined to be 90% or more of administered drug or compare to in vivo reference dose.

3. Dissolution

- It is process in which solid substance solubilises in given solvent i.e mass transfer from solid surface to liquid phase.
- Using USP apparatus I at 100 rpm or USP apparatus II at 50 rpm.
- Dissolution Media [900 ml],
    1. 0.1 N HCl or simulated gastric fluid (pH 1.2) without enzyme.
    2. pH 4.5 buffer & pH 6.8 buffer.
    3. Simulated intestinal fluid without enzyme.

| BCS Class | Solubility | Permeability | Examples |
|---|---|---|---|
| **Class I** | High | High | Paracetamol, Metoprolol |
| **Class II** | Low | High | Ibuprofen, Ketoconazole |
| **Class III** | High | Low | Cimetidine, Acyclovir |
| **Class IV** | Low | Low | Hydrochlorothiazide, Furosemide |

### 1. Class I: High Solubility, High Permeability

These are the "ideal" drug candidates. They dissolve easily and pass through membranes quickly.

- Absorption is very fast and usually only limited by how quickly the stomach empties into the intestine.
- **Formulation:** Simple immediate-release tablets.
- **Examples:** Metoprolol, Propranolol, Paracetamol.

### 2. Class II: Low Solubility, High Permeability

The main problem here is getting the drug to dissolve. Once it dissolves, it enters the blood easily.

- The "dissolution rate" is the bottleneck. If it doesn't dissolve fast enough, it passes through the gut unabsorbed.
- **Formulation Strategy:** We use techniques to increase surface area, like **micronization** (making particles tiny) or adding surfactants (soaps) to help wetting.
- **Examples:** Ibuprofen, Glibenclamide, Ketoconazole.

### 3. Class III: High Solubility, Low Permeability

These drugs dissolve instantly but struggle to get through the "wall" of the intestine.

- They stay in the gut for a long time. Absorption is limited by the surface area of the membrane and the transit time.
- **Formulation Strategy:** We use **permeation enhancers** or prodrugs that are more "lipid-loving" (lipophilic) to help them slip through the membranes.

- **Examples:** Atenolol, Cimetidine, Insulin (which is why it's usually injected).

**4. Class IV: Low Solubility, Low Permeability**

These are the most difficult drugs to work with. They don't dissolve well, and they don't pass through membranes well.

- Very poor oral bioavailability. Small changes in the manufacturing process or even what the patient ate can causes massive changes in how much drug gets into the blood.
- **Formulation Strategy:** Often require complex delivery systems like lipid-based carriers or switching to an intravenous (IV) route.
- **Examples:** Furosemide, Taxol, Hydrochlorothiazide.

**Significance of BCS:**

- Regulatory tool for replacement of certain BE studies.
- It can save both time and money—if the immediate -release, orally administered drug meets specific criteria, the FDA will grant a waiver for expensive and time-consuming bioequivalence studies.
- Valuable tool for formulation scientist for selection of design of formulated drug substance.
- When integrated with other information provide a tremendous tool for efficient drug development.
- Reduces cost and time of approving Scale- up and post approval challenges.
- Applicable in both pre-clinical and clinical drug development process.
- Works as a guiding tool in development of various oral drug delivery systems.

**Pre-formulation consideration in development of dosage forms:**

| Dosage Form | Pre-formulation Focus | Impact on Stability |
|---|---|---|
| **Solid** | Particle size, polymorphism, moisture sensitivity, excipient compatibility | Prevents degradation, ensures uniformity and long shelf life |
| **Liquid Oral** | Solubility, pH stability, preservatives, antioxidants | Controls chemical and microbial instability |
| **Parenteral** | Solubility, pH, isotonicity, sterility, packaging compatibility | Ensures safety, chemical integrity, and physical stability |

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