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INDUSTRIAL PHARMACY - I

UNIT 1

TOPIC :

- **Preformulation Studies :** Introduction to preformulation, goals and objectives, study of physicochemical characteristics of drug substances.

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

  b. Chemical Properties : Hydrolysis, oxidation, reduction, racemisation, polymerization

Preformulation Studies

- Preformulation is the initial phase of drug development where physicochemical properties of a drug substance are thoroughly investigated before the formulation of dosage forms.
- It is the bridge between drug discovery and formulation development, aiming to gather data that can help design an optimal, stable, safe, and effective dosage form.
- These studies provide critical information about the drug's physical, chemical, and mechanical properties, which influence the choice of excipients, method of formulation, manufacturing process, and storage conditions.

Definition

- Preformulation is defined as the investigation of physical and chemical properties of a drug substance alone and when combined with excipients to design a stable, safe, and effective dosage form.

Need for Preformulation Studies

- To understand the drug's behavior under various conditions.
- To identify stability problems.
- To select the best formulation strategy and delivery system.
- To ensure batch-to-batch consistency in manufacturing.

Goals and Objectives of Preformulation Studies

Goals

1. To establish the physicochemical properties of the drug substance.
2. To determine compatibility with excipients.
3. To predict and improve stability.
4. To develop suitable analytical methods for quality control.
5. To support the development of dosage forms with desired bioavailability.

Objectives

- To determine physical and chemical characteristics of the drug.
- To assess drug-excipient compatibility.
- To select appropriate excipients and formulation design.
- To determine optimum storage conditions and packaging requirements.
- To predict drug performance in vivo, including absorption and bioavailability

Study of Physicochemical Characteristics of Drug Substances

→ The study of physicochemical characteristics of drug substances is a crucial part of preformulation studies, which is the first and most important stage in the development of any pharmaceutical product.

→ It involves a systematic study of the physical and chemical properties of the drug substance before formulating it into a suitable dosage form. These studies help in understanding how the drug will behave under various environmental, physiological, and formulation conditions.

→ The main goal is to ensure that the drug is stable, effective, safe, and compatible with excipients and packaging materials, and that it provides the desired bioavailability when administered.

1. Physical Properties of Drug Substances

a. Physical Form (Crystalline and Amorphous Forms)

- Crystalline Form:
  - Molecules are arranged in a regular, repeating pattern.
  - Has a definite melting point, higher stability, and lower solubility.
  - More resistant to physical and chemical degradation.
  - Common in salts and pure compounds.

    - *Example:* Crystalline penicillin is more stable than its amorphous form.
- Amorphous Form:
    - Molecules are randomly arranged without a definite shape or structure.
    - Higher solubility and dissolution rate, but lower stability.
    - More prone to degradation by moisture or temperature.
    - *Example:* Amorphous novobiocin is more soluble than its crystalline form.

b. Particle Size and Shape

- Particle size plays a key role in influencing:
    - Dissolution rate (smaller particles dissolve faster due to larger surface area).
    - Absorption and bioavailability.
    - Flow properties and compressibility (important in tablet and capsule manufacture).
    - Sedimentation rate in suspensions and content uniformity.
- Shape affects:
    - Flowability and packing of powders.
    - Irregular or needle-like particles often cause poor flow.

Techniques for particle size analysis:

- Sieving method
- Microscopy
- Laser light scattering
- Sedimentation method

Example: Micronization of griseofulvin increases its dissolution rate and oral absorption.

c. Flow Properties

- Good flow properties are essential for uniform mixing, filling, and compression.
- Poor flow leads to weight variation and content uniformity problems.

Parameters used to assess flow:

- Angle of repose: Lower angle indicates better flow.
- Bulk and tapped density: Used to calculate Carr's index and Hausner's ratio.
- Carr's compressibility index: Measures compressibility; lower values indicate good flow.

Example: Lubricants like magnesium stearate are often added to improve flow properties.

d. Solubility Profile

- Solubility is defined as the amount of solute that dissolves in a solvent at a given temperature to form a saturated solution.
- It is one of the most critical factors determining bioavailability.
- Depends on temperature, pH, solvent polarity, and molecular structure.

Methods to improve solubility:

- Salt formation
- Use of surfactants or co-solvents
- Particle size reduction (micronization or nanosizing)
- Complexation with cyclodextrins

Example: Sodium salt of phenytoin is more soluble than the free acid form.

e. pKa and Ionization Constant

- pKa is the pH at which 50% of the drug molecules are ionized and 50% are unionized.
- It helps determine the ionization state of the drug at different pH values.
- Unionized form is more lipid soluble and easily absorbed through biological membranes, while ionized form is more water-soluble.

Importance of pKa:

- Predicts absorption site in GIT.
- Helps in salt selection and buffer optimization.
- Determines stability and solubility at various pH levels.

Example: Aspirin (weak acid) is absorbed in the stomach; morphine (weak base) is absorbed in the intestine.

f. Partition Coefficient (P or log P)

- The partition coefficient measures the drug's distribution between a lipid phase (usually n-octanol) and an aqueous phase (water).

$$P = \frac{C_{lipid}}{C_{aqueous}}$$

Indicates the lipophilicity or hydrophilicity of a compound.

- High P = lipophilic = better membrane permeability but poor solubility.
- Low P = hydrophilic = better solubility but poor permeability.

Applications:

- Predicts drug absorption and distribution.
- Affects CNS penetration and protein binding.
- Useful in designing prodrugs.

Example: Lipophilic barbiturates cross the blood-brain barrier quickly and act as CNS depressants.

g. Polymorphism

- Polymorphism refers to the ability of a drug to exist in more than one crystalline form.
- Different polymorphs have different melting points, solubility, and dissolution rates.
- The polymorph with the lowest free energy is the most thermodynamically stable form.

Detection techniques:

- X-ray diffraction (XRD)
- Differential scanning calorimetry (DSC)
- Infrared spectroscopy (IR)

Example: Ritonavir showed formulation failure due to formation of a less soluble polymorphic form.

2. Chemical Properties of Drug Substances

a. Hydrolysis

- Hydrolysis involves decomposition of the drug by reaction with water.
- Common in esters, amides, and lactones.
- Accelerated by moisture, temperature, and pH extremes.

Prevention:

- Store in dry conditions.
- Use anhydrous solvents and buffer pH optimization.
- Encapsulation or coating to protect from moisture.

Example: Aspirin hydrolyzes to acetic acid and salicylic acid.

b. Oxidation

- Oxidation is a reaction involving addition of oxygen or removal of hydrogen or electrons.
- Common in phenols, aldehydes, and unsaturated compounds.
- Catalyzed by light, heat, and metal ions.

Prevention:

- Use antioxidants like ascorbic acid or sodium metabisulfite.
- Add chelating agents like EDTA to remove metal catalysts.
- Use amber-colored containers or nitrogen flushing.

Example: Adrenaline oxidizes to adrenochrome on exposure to light and air.

c. Reduction

- The gain of electrons or removal of oxygen.
- Occurs less commonly than oxidation.
- Can change drug potency or produce toxic products.
- Controlled by oxygen-free environment or inert atmosphere packaging.

Example: Nitro compounds can be reduced to amines.

d. Racemization

- Conversion of an optically active (chiral) compound into an inactive racemic mixture containing both enantiomers.
- Affects biological activity and potency.
- Influenced by temperature, pH, and solvent polarity.

Example: L-epinephrine racemizes to D-epinephrine, reducing its activity.

e. Polymerization

- Process where smaller molecules combine to form larger polymer chains.
- May lead to discoloration, loss of potency, or precipitation.
- Promoted by heat, light, or high concentration.

Prevention:

- Use of stabilizers, antioxidants, and cool storage conditions.

Example: Formaldehyde tends to polymerize during storage.

Biopharmaceutics Classification System (BCS) and Its Significance

- The Biopharmaceutics Classification System (BCS) is a scientific framework that classifies drug substances based on their aqueous solubility and intestinal permeability.
- This system was developed by Amidon et al. (1995) and is widely used by regulatory agencies such as the U.S. FDA (Food and Drug Administration) and EMA (European Medicines Agency) to predict oral drug absorption, bioavailability, and the possibility of granting a biowaiver for in vivo bioequivalence studies.
- It provides a scientific basis for designing formulations and helps in predicting the rate and extent of drug absorption from oral dosage forms.

Need for BCS Classification

- Different drugs show different absorption characteristics after oral administration.
- The extent of absorption depends mainly on:
    1. Solubility – how easily the drug dissolves in gastrointestinal fluids.
    2. Permeability – how easily the dissolved drug crosses the intestinal membrane.

    By evaluating these two parameters, BCS helps in predicting the in vivo performance of drugs based on in vitro (laboratory) data, thus reducing the need for animal or human studies.

Parameters Used in BCS Classification

1. Solubility

- A drug is considered highly soluble when the highest dose strength is completely soluble in 250 mL or less of aqueous media over the pH range 1.0 to 7.5 at 37°C.
- Solubility depends on:
  - pH of the solution
  - Temperature
  - Drug's ionization constant (pKa)
  - Molecular structure and crystalline nature

  Importance:
  Solubility affects the rate of dissolution, which in turn influences bioavailability.

2. Permeability

- A drug is considered highly permeable when ≥ 90% of the administered dose is absorbed through the intestinal membrane.
- Determined by:
  - Human intestinal absorption studies
  - In situ intestinal perfusion studies
  - Caco-2 cell models (in vitro studies using human epithelial cells)

  Importance:
  Permeability affects the rate and extent of absorption, thus influencing the onset and intensity of pharmacological action.

3. Dissolution

Although not a direct classification parameter, dissolution rate plays an important role in oral absorption:

- A drug must dissolve before it can be absorbed.
- BCS also helps define dissolution testing criteria for predicting bioavailability.