WELCOME

TO

This is an Education Platform

We Provide PDF Notes for Pharmacy Students

Web Site http://www.fdspharmacy.in/

You tube https://www.youtube.com/c/FDSpharmacy

Telegram https://t.me/Fdspharmacy

App https://play.google.com/store/apps/details?id=com.FDSPharmacyMedia.FDSPharmacy

E-mail fdspharmacyinfo@gmail.com

INDUSTRIAL PHARMACY - I

UNIT 1

TOPIC :

- **BCS classification of drugs & its significant**

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

BCS Classification of Drugs

The Biopharmaceutics Classification System divides drugs into four main classes based on the combination of solubility and permeability.

➢ Class I: High Solubility – High Permeability

- Characteristics:
  - Dissolve readily in gastrointestinal fluids.
  - Rapidly permeate the intestinal membrane.
  - Exhibit good bioavailability and predictable absorption.
  - Rate-limiting step: Gastric emptying (not dissolution or permeability).
- Formulation Approach:
  - Simple oral solid dosage forms (tablets, capsules).
  - No need for solubility or permeability enhancement.
- Examples:
  - Propranolol
  - Metoprolol
  - Diltiazem
  - Verapamil
  - Diazepam
  - Theophylline

Summary: Class I drugs are the most ideal for oral drug delivery because of their excellent solubility and permeability.

➢ Class II: Low Solubility – High Permeability

- Characteristics:
  - Permeate intestinal membrane easily but dissolve slowly.
  - Absorption is limited by dissolution rate.
  - Bioavailability depends on formulation design.
- Formulation Approach:
  - Improve solubility or dissolution rate using:
    - Micronization or nanosizing

        - Use of surfactants or solubilizers
        - Solid dispersions or complexation techniques
        - Salt formation
- Examples:
    - Phenytoin
    - Ketoconazole
    - Danazol
    - Carbamazepine
    - Griseofulvin
    - Nifedipine

Summary: Class II drugs are dissolution-rate limited; solubility enhancement is necessary for better absorption.

➢ Class III: High Solubility – Low Permeability

- Characteristics:
    - Dissolve easily but cross the intestinal membrane poorly.
    - Absorption is limited by permeability rather than dissolution.
    - Bioavailability depends on membrane transport processes.
- Formulation Approach:
    - Use permeation enhancers or absorption promoters.
    - Optimize formulation pH to favor unionized form.
    - Use prodrugs or lipid-based systems to improve permeability.
- Examples:
    - Cimetidine
    - Acyclovir
    - Atenolol
    - Metformin
    - Gabapentin

Summary: Class III drugs are permeability-limited; absorption can be improved by modifying membrane transport or formulation strategy.

➢ **Class IV: Low Solubility – Low Permeability**

- Characteristics:
  - Poorly soluble and poorly permeable.
  - Exhibit low and variable bioavailability.
  - Difficult to formulate for oral delivery.
  - Absorption is limited by both dissolution and permeability.
- Formulation Approach:
  - Use advanced formulation technologies:
    - Nanoparticles or liposomes
    - Prodrugs
    - Solid lipid nanoparticles (SLNs)
    - Complexation and self-emulsifying drug delivery systems (SEDDS)
- Examples:
  - Hydrochlorothiazide
  - Furosemide
  - Neomycin
  - Amphotericin B
  - Taxol (Paclitaxel)

Summary: Class IV drugs are the most challenging for oral administration and often require parenteral or targeted delivery systems.

Significance of BCS Classification

1. Prediction of Drug Absorption:
   - Helps to estimate the rate and extent of absorption from oral formulations.
2. Guidance for Formulation Design:
   - Indicates whether to focus on solubility or permeability enhancement.
3. Regulatory Use (Biowaivers):

    - For Class I drugs, in vivo bioequivalence studies can be waived if in vitro dissolution data are satisfactory.
    - Saves time, cost, and animal/human testing.
4. Optimization of Bioavailability:
    - Aids in selecting the most appropriate salt form, particle size, or excipient.
5. Quality Control:
    - Defines suitable in vitro dissolution tests that correlate with in vivo performance (IVIVC).
6. Improved Drug Development Efficiency:
    - Provides a rational approach for early drug screening and development.
7. Helps in Drug Discovery:
    - Assists medicinal chemists in modifying molecules to achieve the desired balance of solubility and permeability.

Applications of BCS

- Used by regulatory bodies (FDA, WHO) for biowaiver approval.
- Guides formulation scientists in selecting excipients and manufacturing methods.
- Supports development of generic drugs by demonstrating bioequivalence.
- Provides the basis for IVIVC (In Vitro–In Vivo Correlation) studies.
- Helps in designing controlled or targeted drug delivery systems.

Application of Preformulation Considerations in the Development of Solid, Liquid Oral, and Parenteral Dosage Forms and Its Impact on Stability

- Preformulation studies are the first and most crucial step in pharmaceutical product development.
- They involve a thorough investigation of the physicochemical and biopharmaceutical properties of a drug substance before formulation.
- The goal of preformulation is to collect essential data that help in:
    - Designing a stable, effective, and safe dosage form.
    - Selecting suitable excipients, formulation methods, and packaging systems.
    - Predicting the stability and compatibility of the final product under various conditions.
- In summary, preformulation studies form the foundation of dosage form design and directly affect the stability, bioavailability, and therapeutic performance of the drug.

Objectives of Preformulation Studies

1. To establish physicochemical properties of drug substances.
2. To identify stability problems such as hydrolysis, oxidation, or photodegradation.
3. To determine compatibility with excipients and packaging materials.
4. To optimize formulation and manufacturing processes.
5. To ensure uniformity, efficacy, and patient safety of the product.
6. To predict the shelf-life and storage conditions.

Key Preformulation Parameters

Some of the most important preformulation studies include:

- Physical form (crystalline/amorphous)
- Particle size, shape, and flow properties
- Solubility and pKa determination
- Partition coefficient
- Polymorphism
- Stability to heat, light, and moisture
- Compatibility with excipients and solvents

The data obtained from these studies guide the design of different dosage forms—solid, liquid oral, and parenteral.

1. Application in the Development of Solid Dosage Forms

Solid dosage forms include tablets, capsules, powders, and granules.

a. Role of Preformulation in Solid Dosage Forms

1. Particle Size and Shape:
    - Affect flowability, compressibility, and content uniformity.
    - Smaller particle size increases surface area → improves dissolution rate and bioavailability.
    - Irregular shape can cause poor flow and non-uniform filling.
2. Polymorphism:
    - Different crystal forms show variations in solubility, melting point, and stability.
    - The most thermodynamically stable polymorph is preferred.
    - Unstable polymorphs may convert during manufacturing, causing instability.
3. Moisture Content and Hygroscopicity:
    - Moisture-sensitive drugs (e.g., aspirin, vitamin C) may degrade by hydrolysis.
    - Controlled by dry granulation, desiccants, and protective coatings.

4. Flow Properties:
    - Critical for uniform filling in tablet dies or capsule shells.
    - Improved using glidants (e.g., talc, colloidal silica).
5. Compressibility:
    - Determines tablet hardness and mechanical strength.
    - Affected by particle size, moisture, and crystalline form.
6. Drug-Excipient Compatibility:
    - Incompatible excipients can cause degradation or discoloration.
    - Compatibility studies are performed using DSC, FTIR, or TLC.
7. Stability:
    - Assessed under different temperature and humidity conditions.
    - Helps choose appropriate coating, storage, and packaging.

b. Impact on Stability

- Moisture-sensitive drugs are stabilized by coatings and desiccants.
- Light-sensitive drugs (e.g., riboflavin) are protected by amber packaging.
- Oxidation-prone drugs (e.g., vitamin C) are stabilized with antioxidants.
- Selection of the proper polymorph enhances chemical and physical stability.

2. Application in the Development of Liquid Oral Dosage Forms

Liquid oral dosage forms include solutions, syrups, suspensions, and emulsions.

a. Role of Preformulation in Liquid Oral Formulation

1. Solubility Studies:
    - Essential for determining whether the drug can be formulated as a true solution or must be prepared as a suspension.

    - If poorly soluble, solubility enhancement techniques (cosolvency, pH adjustment, or complexation) are applied.
2. pKa and pH Stability Profile:
    - Helps determine the pH range for maximum drug stability and solubility.
    - Buffers are selected based on pKa values.
3. Choice of Solvent System:
    - Water, alcohol, glycerin, propylene glycol, or polyethylene glycol may be used depending on solubility.
    - Solvent must be non-toxic, compatible, and stable.
4. Viscosity and Rheology:
    - Controlled using viscosity modifiers like sucrose, glycerol, or carboxymethylcellulose to improve mouthfeel and stability.
5. Surface Activity:
    - Surfactants improve wetting and uniform dispersion of insoluble drugs.
6. Preservatives:
    - Used to prevent microbial contamination.
    - Selection depends on pH and solubility of preservative (e.g., parabens, benzoic acid).
7. Flavoring and Coloring Agents:
    - Should be chemically compatible and stable with the formulation.

b. Impact on Stability

- pH optimization prevents hydrolysis or degradation.
- Use of antioxidants (e.g., ascorbic acid) prevents oxidation.
- Proper choice of solvent and preservative ensures microbial and chemical stability.
- Surfactant concentration is optimized to avoid phase separation.

Example: Paracetamol syrup formulation stability depends on maintaining pH around 5–6 and preventing oxidation.

3. Application in the Development of Parenteral Dosage Forms

Parenteral dosage forms include injections, infusions, and sterile preparations, which are administered directly into the bloodstream or tissues.

a. Role of Preformulation in Parenteral Formulation

1. Solubility and Solvent Selection:
    - Drugs must be completely soluble in the vehicle to avoid precipitation after injection.
    - Solvents used include water for injection, glycerin, PEG, ethanol, or propylene glycol.
2. Isotonicity:
    - Formulations must be isotonic with body fluids to prevent tissue irritation.
    - Adjusted using sodium chloride, dextrose, or mannitol.
3. pH and Buffer Capacity:
    - pH is adjusted to enhance stability and minimize irritation.
    - Buffers such as phosphate or citrate are used.
4. Sterility and Pyrogen Control:
    - Preformulation studies identify suitable sterilization methods (autoclaving, filtration, or dry heat).
    - Pyrogen-free water and equipment are essential.
5. Solvent–Drug Compatibility:
    - Drug must remain stable in solvent during storage.
    - Incompatibilities may cause precipitation or degradation.
6. Container Compatibility:
    - Containers (glass or plastic) should not react with the drug.
    - Adsorption or leaching studies are done.
7. Antioxidants and Stabilizers:

- Antioxidants (e.g., sodium metabisulfite, ascorbic acid) and chelating agents (EDTA) are added to enhance stability.

b. Impact on Stability

- Maintaining pH and isotonicity prevents precipitation or irritation.
- Proper sterilization ensures microbial stability.
- Antioxidants and buffers increase chemical stability.
- Correct container selection prevents contamination and adsorption.

Example: Vitamin C injection is stabilized by using nitrogen-filled ampoules and adding antioxidants.