INDUSTRIAL PHARMACY - I

UNIT 1 NOTES

PREFORMULATION STUDIES

- Introduction, Goals & Objectives
- Study of Physicochemical Characteristics of Drug Substance
- Physical Properties
- Chemical Properties

IMPERFECT PHARMACY

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PREFORMULATION STUDIES

- Preformulation studies are a critical stage in the development of pharmaceutical products.
- These studies are conducted before the formulation of a drug product and involve the characterization of physical, chemical & mechanical properties of drug substances.
- Preformulation studies help identify potential issues with the drug substance that may affect its performance, stability or manufacturability.

GOALS & Objectives

- Characterization of physicochemical properties of drugs to understand how it behaves.
- Selection of suitable excipients that is compatible with drug To formulate an elegant, safe & effective dosage form with good bioavailibility.
- To formulate new dosage form of already existing drug.
- For Evaluation of drug's stability under various conditions to determine its shelf life & storage requirments.
- Ensuring that the formulation can be manufactured at a larger scale without losing efficacy or stability

Study Of Physicochemical Properties Of Drugs

- The physicochemical properties of drugs are essential characteristics that influence their formulation, stability, bioavailibility & overall therapeutic effectiveness.
- Following are major physicochemical properties of drug substances evaluated in pre formulation research :

Physical Properties

- Physical Form (Crystal & Amorphous)
- Particle Size
- Particle Shape
- Flow Properties
- Solubility Profile (pka, pH, Partition Coefficient)
- Polymorphism

Chemical Properties

- Hydrolysis
- Oxidation
- Reduction
- Racemisation
- Polymerization

PHYSICAL PROPERTIES

- In preformulation studies, the physical properties of a drug substance are critical factors that influence its formulation & manufacturing.
- These properties help determine the appropriate dosage form, improve process efficiency & ensure product stability.
- Here are key physical properties evaluated in preformulation :

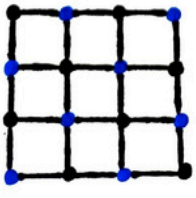
① Physical Form

- In preformulation studies, the physical form of a drug refers to the state or structure in which the drug exists such as its crystalline, amorphous or polymorphic forms.
- The physical form significantly affects the drug's properties, including its solubility, dissolution rate, stability and bioavailibility, which in turn influence formulation decisions.
- Solid dosage form are of generally two types :

(1) Crystalline Solids
(2) Amorphous Solids

Crystalline Solids

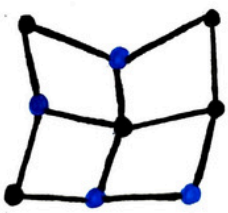
The dosage form that features highly ordered arrangements of their particles (atoms, ions & molecules) in microscopic structure are called crystalline dosage form.



CRYSTALLINE	AMORPHOUS
• Regular arrangement of particles	• Irregular arrangement of particles.
• They are called True Solids	• They are called Pseudo Solids.
• They have sharp melting points.	• They have long range of Melting Point
• They are practically incompressible.	• They are practically compressible.
• They have less aqueous solubility	• They have high aqueous solubility.
• They have high rigidity	• They have less rigidity.

Amorphous Solids

The solids in which the particles are not arranged in any specific order are known as Amorphous Solids.



② Particle Size

- Particle size is a critical parameter in preformulation studies because it significantly affects the drug's physicochemical and biopharmaceutical properties.
- It plays a key role in the drug's solubility, dissolution rate bioavailibility and manufacturing processes.
- Controlling particle size is essential for ensuring consistent drug performance and manufacturability.

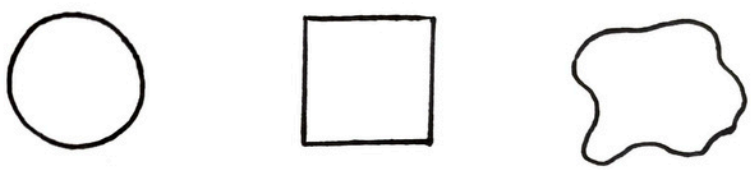
Determination Of Particle Size

Several techniques are employed in preformulation studies to measure particle size & particle size distribution.

- Microscopy
  - Optical microscopy
  - Electron Microscopy
- Sieving
- Sedimentation Techniques
- Coulter Counter

③ Particle Shape

- Particle Shape refers to the geometric form of particles in various contexts.
- In preformulation studies, the shape of particles plays a critical role in determining the physical & chemical properties of drug substances.
- Common shapes include spherical, cubic & irregular.



Spherical Cube Irregular

- Spherical particles typically have better flowability
- Irregular or elongated particles have larger surface area that can enhance the dissolution rate.
- Particles with irregular shapes may pack less efficiently, leading to variation in bulk & tapped density
- Shape can influence how particles compress during tablet formation, irregular shaped particles may deform or fracture under pressure.
- For inhalation formulations, particle shape is crucial in determining aerodynamic properties, irregular or rod shaped particles may affect deposition in the lungs, impacting the drug's absorption & efficacy.

④ Flow Properties

- Flow properties in preformulation studies are essential for understanding how powders and granules behave during manufacturing process like mixing, granulation, compression & filling.
- Poor flow can lead to challenges in ensuring uniformity in drug products, especially in solid dosage forms like tablets & capsules.

Importance of Flow Properties

- Blending: Uniform flow ensures proper mixing of drug & excipient particles
- Filling: Good flow is necessary for accurate filling of tablets & capsules.
- Compression: Poor flow can result in variation in tablet weight hardness & content which affect final product quality.

Factors Influencing Flow Properties

- Larger particles tend to have better flow due to reduced cohesive forces.
- Spherical particles generally flow more easily due to less friction.
- Particles with high moisture content tend to clump or adhere to each others.
- Higher difference between Bulk & Tapped density suggest poor flow & higher compressibility.

Measurment of Flow Properties

Several methods are used to evaluate the flow properties of powders in preformulation studies.

① Bulk & Tapped Density

- Bulk Density is defined as mass per unit volume, including space occupied by particles & voids b/w them.

$$\rho_B = \text{Mass} / \text{Bulk Volume}$$

- Tapped Density is defined as density of material after tapping, which allows the particles to settle more closely together.

$$\rho_T = \text{Mass} / \text{Volume after tapping}$$

- By calculating Carr's Index & Hausner ration, flowability of powder can be detected.

- $$\text{Carr's Index} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

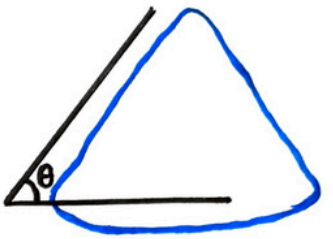
- $$\text{Hausner Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

- Carr's Index $< 15\%$ = Good Flow
  $> 25\%$ = Poor Flow
- Hausner Ratio < 1.25 = Good Flow
  > 1.4 = Poor Flow

Angle of Repose

- Angle formed between horizontal surface & slope of a pile of powder is known as Angle of Repose

$$\tan\theta = \frac{h}{r}$$



- Here θ = angle of repose
  h = height
  r = radius

- Angle of Repose < 30° = Good Flow
- Angle of Repose > 40° = Poor Flow

⑤ Solubility Profile

- The solubility of a drug is defined as maximum amount of drug that can be dissolved in a fixed volume of solvent.
- Solubility is one of the most important parameters in preformulation studies as it directly impacts the bioavailibility, absorption & overall efficacy of a drug.
- Understanding & optimizing solubility is crucial for ensuring that the drug can be absorbed by the body in its active form.

Importance of Solubility in Preformulation

- Bioavailibility: For drugs administered orally, the solubility in GIT fluids is essential for the drug to dissolve & to be absorbed.
- Poor solubility often leads to low bioavailibility.
- Drugs with low solubility may require larger doses to achieve therapeutic affects, which can increase the risk of side effect.
- Poor solubility complicates manufacturing process like granulation compression, affecting the uniformity & quality of final product.
- Solubility helps guide the selection of dosage form.

pH

- pH is one of the major factor that influences solubility of drugs. It is defined as potential or power of hydrogen.
- In case of strong acids/ bases, pH doesn't plays a major role as they are ~~unionl~~ ionizable at all pH.
- In case of weak Acid → Solubility $\propto$ pH.
- In case of weak base → Solubility $\propto$ $^1/_{pH}$.

Ionisation Constant (pka)

- Ionisation constant is defined as tendency of ionic compounds to dissociate into ions.
- It is also known as dissociation constant.
- Higher pka value indicates a weak acid, means it dissociates less rapidly.
- Lower pka value indicates a strong acid, means it dissociates more readily into the solution.
- Drugs are usually more soluble in their ionised form, that depends on the pka & pH of medium.
- The degree of ionization also affects membrane permeability, unionized drugs generally permeate biological membrane more easily.

Partition Coefficient

- Partition coefficient find out the distribution / solubility of drugs in two non-miscible solvents.
- It is denoted by k_D.

$$k_D = \frac{\text{Concentration of X in A}}{\text{Concentration of X in B}}$$

- If $k_D > 1$, X is more soluble in A
- If $k_D < 1$, X is more soluble in B

⑥ Polymorphism

- The word Polymorphism is derived from Greek word Poly → Many & Morph → Forms.
- When a substance exist in more than 1 crystalline form & each form has different physical properties, then these types of substances known as polymorphs.
- Polymorphs have same chemical but different physical properties due to different structural arrangement of atoms.
- Example : Carbon, Phosphorus, Sulphur etc.

Types Of Polymorphs

Polymorphs are of usually two types

① Enantiotropic (Reversible)
② Monotropic (Irreversible)

Importance of Polymorphism in Preformulation studies

- Different Polymorphs can exhibit vastly different solubilities, generally less stable form have higher ~~stability~~. Solubility.
- A polymorph with high solubility ensures better absorption & therapeutic effect.
- Different polymorphs have different physical & chemical stability

CHEMICAL PROPERTIES

Study of chemical properties includes studying the factors that cause instability of drug through chemical reactions. Following chemical properties should be evaluated during pre formulation research.

- Hydrolysis
- Oxidation
- Reduction
- Racemisation
- Polymerisation

① Hydrolysis

- Hydrolysis is one of the most common degradation pathway studied in preformulation studies.
- It involves chemical breakdown of a compound due to its reaction with water.
- Understanding hydrolytic stability of drug is essential because it impacts drug's shelf life, efficacy and safety especially in aqueous formulations like solution, suspension or injection.

Prevention

- pH control
- Non- Aqueous Solvents
- Complexation
- Packaging
- Prodrugs.

② Oxidation

- Oxidation is another common degradation pathway studied in preformulation studies.
- It involves loss of electrons by a molecule, often through reaction with oxygen, resulting in chemical instability.
- Oxidation can significantly affect the potency, safety & efficacy of drug.

Prevention

- Antioxidants
- Preventing light exposure
- Inert atmosphere
- Refrigeration

③ Reduction

- Reduction is a less common but significant degradation pathway studied in preformulation studies.
- It involves gain of electrons, leading to decrease in oxidation state.

Prevention

- Avoidance of reducing agents
- Protective Packaging
- Chelating Agents etc.

④ Racemisation

- Racemisation is process in which one enantiomer is converted into its mirror image counterpart, resulting in a mixture of both enantiomers in equal proportions.
- This leads to formation of a recemic mixture, an ophically inactive compound.
- Since enantiomers often exhibit different biological activities, racemization can alter the effectiveness, safety or toxicity of a drug.
- The process can be influenced by factors such as pH, temperature, light & presence of catalysts.
- **Example :** L-Epinephrine is 15-20 times more active than D form, while activity of recemic mixture is half of L form.

Prevention

- pH Control
- Temperature Control
- Solvent Choice
- Stabilizers.

⑤ Polymerisation

- Polymerization is defined as formation of polymers through the combination of monomers.
- It is a critical step in drug formulation, as it can impact the final product's quality
- In pre formulation studies, polymerization is used to :
  - Modify drug release
  - Enhance stability
  - Increase solubility

BCS Classification Of Drugs

- The term BCS stands for Biopharmaceutical classification system.
- It is a scientific framework for classifying drugs based on their solubility & permeability.
- It helps in predicting the drug absorption & bioavailibility, and it is widely used in drug development & regulation.

Class	Solubility	Permeability	Absorption	Example
I	High	High	Good	Metaprolol
II	Low	High	Variable	Nifedipine
III	High	Low	Variable	Cimetidine
IV	Low	Low	Poor	Furosemide

① Class I

- Drug in this class are highly soluble in nature & can easily permeate inteshinal membrane.
- They rapidly absorbed after oral administration
- Exhibit good bioavailibility.
- Drugs in this category are often considered ideal for oral delivery.
- Examples : Metaprolol, Propranolol.

Class II

- These drugs have poor solubility but can easily permeate the intestinal membrane.
- The bioavailibility of these drugs can be improved by formulations that enhance solubility.
- These drugs are also suitable for controlled release developments.
- Examples : ketaconazole, Ibuprofen, Phenytoin.

Class III

- Drug in these class have good solubility but having difficulty in permeating intestinal membrane.
- Changes in the integrity of gastrointestinal membrane, such as from disease or drug interactions, may affect bioavailibility.
- Presence of food can alter absorption process.
- Example : Cimetidine, Atenolol, Acyclovir.

Class III

- Drugs in these class have poor solubility & permeability.
- They have poor absorption & bioavailibility.
- These drugs may require novel drug delivery system.
- Drug development in this category is a challenging process.
- Example : Furosemide.

Application Of Preformulation Considerations In Dosage Form

- Preformulation is a critical stage in drug development where the physical, chemical & mechanical properties of drug substance are evaluated to develop a stable, effective and safe dosage form.
- The primary goal of preformulation is to gather information that helps in the formulation of drug product.
- Here's how preformulation considerations apply in the development of solid, liquid and parenteral dosage forms :-

Solid Dosage Forms

Solubility : For solid dosage forms, drug solubility in aqueous and non-aqueous solvents is a major considerations. Poor solubility can lead to low bioavailibility, so techniques like salt formation, use of surfactants or particle size reduction may be explose to enhance solubility.

Particle Size : The size and distribution of drug particles affect the drug's dissolution rate & bioavailibility Micronization & other size reduction techniques can be applied to achieve optimal particle size.

Polymorphism : Drug can exist in multiple crystalline forms, which can affect stability, dissolution & bioavailibility Identifying & selecting the most stable polymorph is critical for solid dosage forms.

Hygroscopicity : Some drug substances absorb moisture from air, which can lead to changes in drug's properties. Preformulation helps determine the need for moisture protection.

Flow Properties : The ability of the drug to flow is important in tablet and capsule production, as poor flow can result in weight variation and poor content uniformity.
Flow enhancers or granulation processes can be utilized to improve flow.

Liquid Dosage Forms

Solubility : Solubility is crucial for liquid formulations. Drugs with poor solubility require solubilization techniques such as pH adjustment, cosolvency, use of surfactants etc.

Viscosity : Liquid formulations should have appropriate viscosity to ensure ease of pouring, accurate dosing & palatability for oral drugs.
Viscosity enhancers like gums or polymers can be added for suspensions or syrups.

Stability : Chemical stability of the drug in solution, including hydrolysis, oxidation and photodegradation, must be assessed.
Antioxidants, Preservatives or appropriate packaging may be needed.

pH : The pH of liquid is crucial for both stability & solubility.
Buffers may be added to maintain the drug at a stable pH throughout its shelf life.

Suspension Stability : For suspensions, particle size & distribution as well as sedimentation rate, are important to maintain the drug's uniformity in the formulation.
Suspending agents are added to improve stability.

Taste Masking: Oral liquids often require taste-masking agents to make them palatable. sweeteners, flavouring agents may be used.

PARENTERAL DOSAGE FORM

Sterility : Parenteral products must be sterile, Preformulation identifies the appropriate sterilization methods.

Solubility : For parenterals, solubility is critical since the drug is administered directly into systemic circulation.

Isotonicity : Parenteral formulations must be isotonic with body fluids to avoid irritation or tissue damage.

pH : The pH of parenteral formulations must be within a range that is physiologically acceptable & that ensures drug's stability.

Stability : Parenterals are often aqueous solutions, so drug stability against hydrolysis or oxidation must be evaluated.

Solvent Selection : For drugs that are poorly soluble in water non aqueous solvents like propylene glycol, polyethylene glycols or oils may be used in parenteral formulations.

Particle Size : In parenteral suspensions, particle size affects injectability & distribution in body.

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