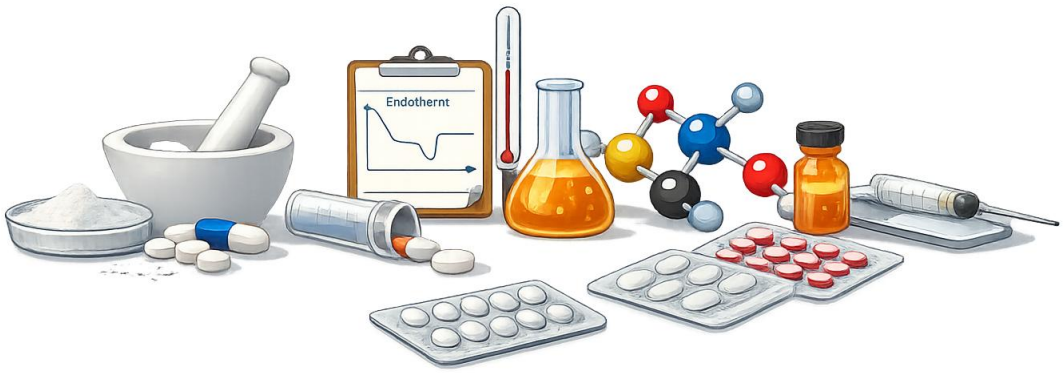
Preformulation Concepts

Preformulation Concepts

Definition

- **Preformulation** is the first stage of pharmaceutical formulation development where the physical and chemical properties of a drug are studied before preparing a dosage form such as tablets, capsules, or injections.



- It helps in designing a stable, safe, and effective dosage form.
- **Purpose of Preformulation:**
  - Understand drug properties
  - Design stable formulations
  - Prevent drug degradation
  - Select suitable excipients
  - Choose appropriate manufacturing methods
- Without preformulation studies, the drug may degrade, lose potency, become toxic, or fail to produce the desired therapeutic effect.

Importance

- **Preformulation helps in:**
  - Improving drug stability
  - Increasing bioavailability
  - Preventing incompatibility
  - Reducing development time
  - Minimizing manufacturing problems

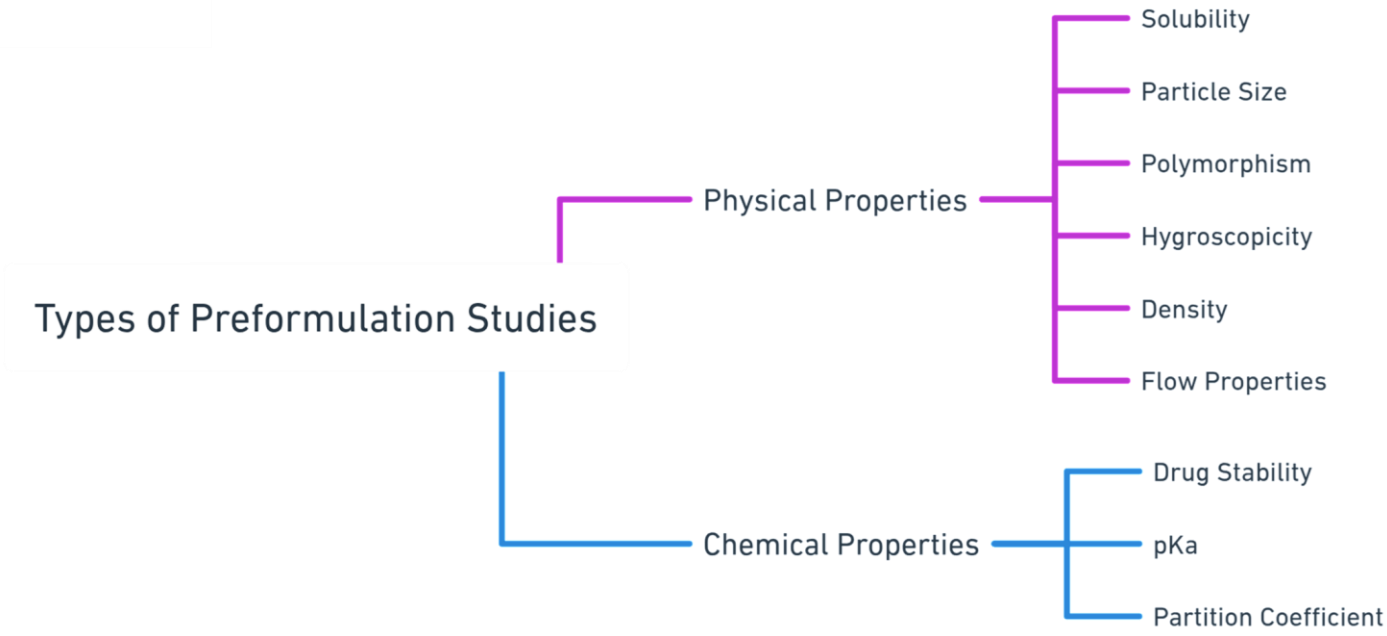
Types of Preformulation Studies

- **Preformulation studies are mainly divided into:**
  - Physical Properties

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- Chemical Properties



1. Physical Properties

Solubility

- Indicates how much drug dissolves in a solvent.
- Types: aqueous solubility, pH solubility, and solubility in organic solvents.

Particle Size

- Affects dissolution rate, bioavailability, and stability.
- Smaller particles dissolve faster.

Polymorphism

- Some drugs exist in different crystal forms with different solubility, stability, and melting points.
- Example: Ritonavir polymorphism issue.

Hygroscopicity

- Some drugs absorb moisture from air, causing degradation or poor stability.

Density

- Influences powder flow and tablet compression.
- Types: true density, bulk density, tapped density.

Flow Properties

- Important for tablet manufacturing.
- Measured using angle of repose, Carr's index, and Hausner ratio.

2. Chemical Properties

Drug Stability

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- Stability of the drug in water, light, oxygen, and heat.

pKa

- Determines drug ionization and solubility.

Partition Coefficient

- Indicates drug distribution between lipid and water phases.
- Important for drug absorption; lipophilic drugs cross membranes more easily.

Preformulation Process

- **Typical steps include:**
  - Drug characterization
  - Solubility analysis
  - Stability testing
  - Compatibility studies
  - Selection of dosage form
  - Formulation development

Drug–Excipient Interactions

Definition

- **Drug–excipient interaction** refers to physical or chemical reactions between a drug and excipients present in a formulation.
- Excipients are inactive ingredients used in dosage forms.
- **Examples of excipients:**
  - Lactose
  - Starch
  - Magnesium stearate
  - Microcrystalline cellulose
- Although inactive, they may sometimes interact with drugs.

Importance

- **Drug–excipient interactions may cause:**
  - Drug degradation
  - Color change
  - Reduced potency
  - Toxicity

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- Poor stability

- Therefore, interaction studies are essential during formulation development.

Types of Drug – Excipient Interactions

- **There are two main types:**
  - Physical interactions
  - Chemical interactions

1. Physical Interactions

➢ These interactions do not involve chemical reactions.

Adsorption

- Drug molecules attach to the surface of excipients.
- **Example:** Activated charcoal adsorbs drugs.

Complex Formation

- Drug forms a complex with an excipient.
- **Example:** Tetracycline forms complexes with calcium.

Polymorphic Changes

- Excipients may alter the crystal form of a drug.

2. Chemical Interactions

➢ These involve actual chemical reactions.

Hydrolysis

- Drug reacts with water.
- **Example:** Aspirin → Salicylic acid.

Oxidation

- Drug reacts with oxygen.
- **Example:** Vitamin C oxidation.

Maillard Reaction

- Reaction between amine group of a drug and reducing sugars (e.g., lactose).
- Leads to brown color formation.
- **Example:** Ampicillin + lactose.

Photochemical Reactions

- Drug decomposes when exposed to light.
- **Example:** Riboflavin degradation.

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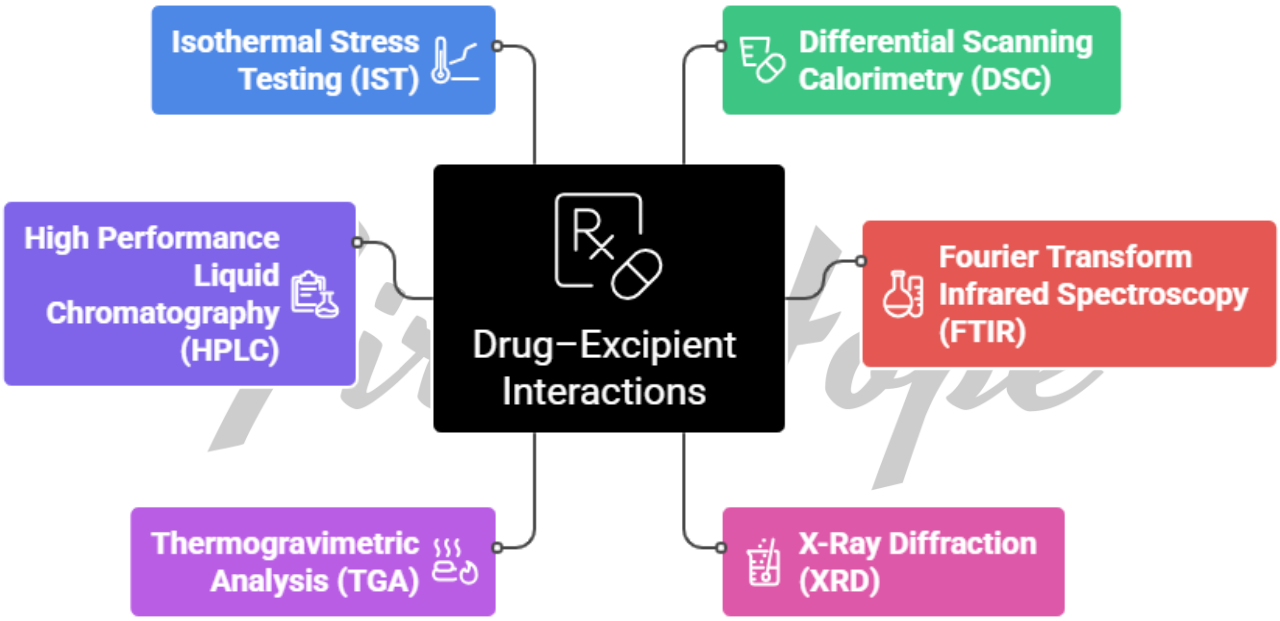
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Factors Affecting Drug–Excipient Interaction

- **Temperature** – Higher temperature increases reaction rate
- **Moisture** – Promotes hydrolysis
- **pH** – Some drugs degrade at certain pH
- **Light** – Causes photodegradation
- **Impurities** – Can accelerate degradation

Methods to Study Drug–Excipient Interactions

Before formulation development, compatibility studies are performed to detect possible drug–excipient interactions using various analytical techniques.



1. Differential Scanning Calorimetry (DSC)

- DSC measures heat flow changes during heating or cooling.
- **Detects**
  - Melting
  - Crystallization
  - Decomposition
- **Principle**
  - Drug–excipient interaction may cause changes or disappearance of the melting peak.
- **Advantages**
  - Fast method
  - Requires small sample

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