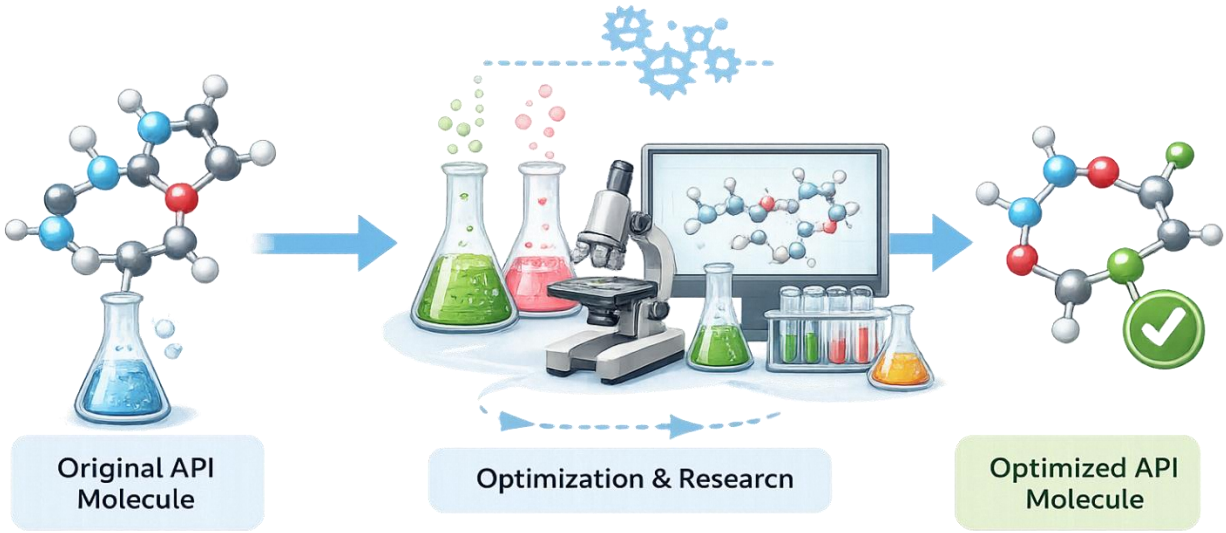
Preformulation Studies

Molecular Optimization of APIs (Drug Substances)

- Molecular optimization means improving the chemical structure of a drug molecule so that it works better in the body and is safe to use.



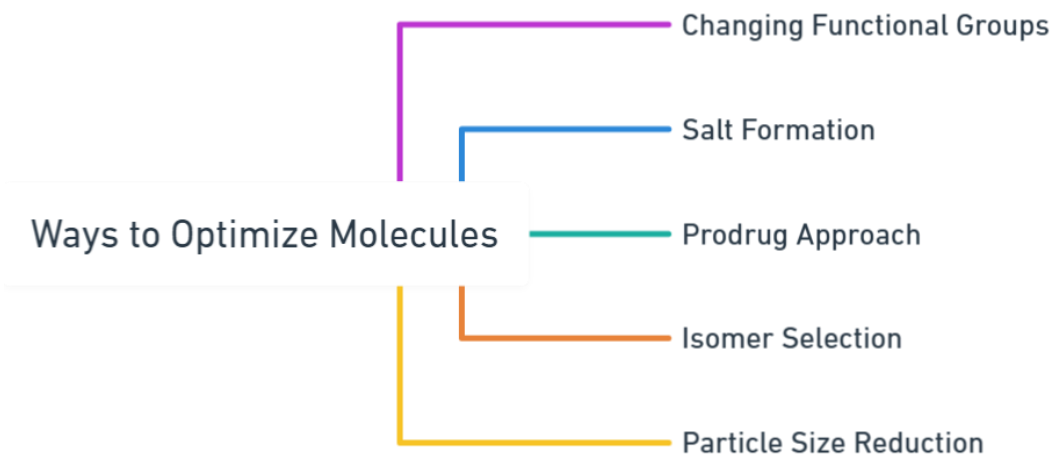
Why it is needed

- A newly discovered drug molecule may not have ideal properties.
- It may be poorly soluble, unstable, toxic, or not absorbed well.
- Optimization helps make it more effective and suitable for formulation.

Key goals of molecular optimization

- Improve solubility (so it can dissolve in body fluids)
- Increase bioavailability (more drug reaches bloodstream)
- Enhance stability (longer shelf life)
- Reduce toxicity and side effects
- Improve selectivity (acts mainly on target site)

Ways to optimize molecules



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1. **Changing functional groups**
    - Small chemical groups (like -OH, -NH2) are added or replaced
    - This can improve solubility or reduce degradation
2. **Salt formation**
    - Converting drug into salt form (e.g., hydrochloride salt)
    - Improves dissolution and absorption
3. **Prodrug approach**
    - Drug is modified into an inactive form
    - Converts into active drug inside the body
    - Helps improve absorption or reduce irritation
4. **Isomer selection**
    - Some drugs exist in different forms (stereoisomers)
    - One form may be more effective and safer
5. **Particle size reduction**
    - Smaller particles dissolve faster
    - Increases drug absorption

First Hope

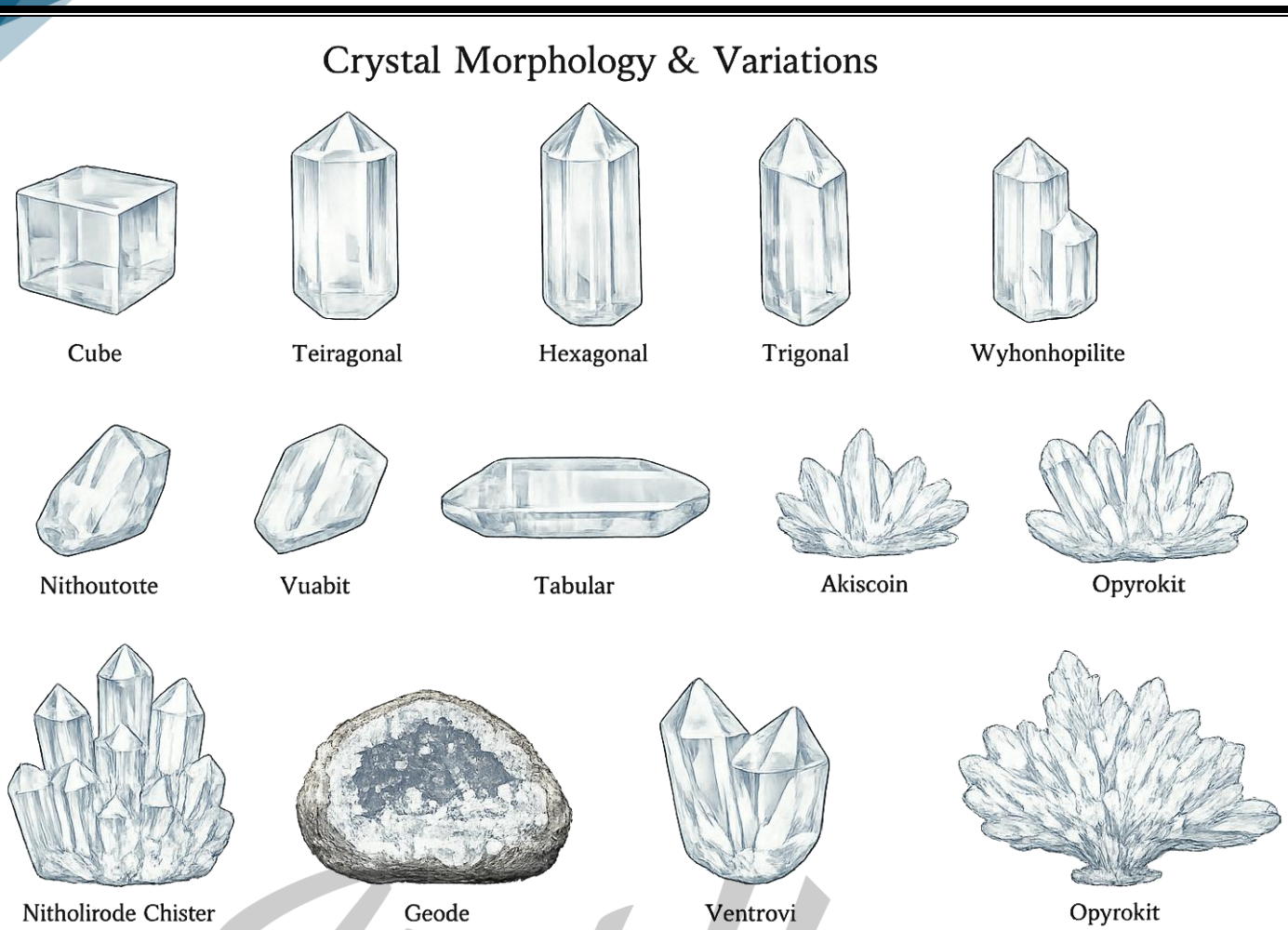
Important considerations

- Changes should not reduce therapeutic effect
- Must remain safe and non-toxic
- Should be easy to manufacture

Crystal Morphology and Variations

- Crystal morphology refers to the **shape and structure of drug crystals**. Variations mean that the same drug can exist in different crystal forms.

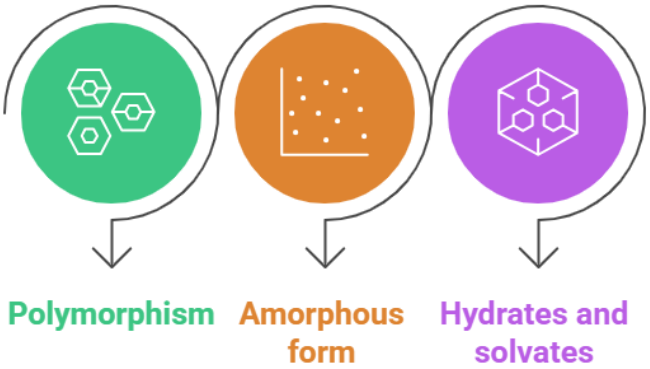
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What is crystal morphology

- It describes the external shape of crystals (needle, plate, cubic, etc.)
- It affects how the drug behaves during manufacturing

Types of crystal variations



1. Polymorphism

- Same drug, different crystal structures
- **Example:** Form I, Form II
- Each form has different properties

2. Amorphous form

- No definite crystal structure

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- More disordered arrangement
- Usually dissolves faster but less stable

3. Hydrates and solvates

- Crystals contain water (hydrate) or solvent (solvate)
- Example: drug + water molecules inside crystal

Why Crystal Form Matters

A. Solubility

- Some crystal forms dissolve faster than others

B. Stability

- Certain forms are more stable during storage

C. Bioavailability

- Faster dissolution leads to better absorption

D. Processing properties

- Affects compression, flow, and mixing

Example

- One polymorph may dissolve quickly (better absorption)
- Another may be stable but poorly soluble

Crystal Shape (Morphology)

- Needle-shaped
- Plate-shaped
- Cubic
- Irregular

Effects of Shape

- Needle-shaped → poor flow, difficult processing
- Spherical → better flow and uniform mixing

Factors Affecting Crystal Formation

- Temperature
- Solvent used
- Rate of cooling
- Presence of impurities

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Methods to Study Crystals

- X-ray diffraction (XRD)
- Microscopy
- Thermal analysis (DSC)

Control of crystal form

- Controlled during crystallization process
- **Factors:**
  - Temperature
  - Solvent used
  - Rate of cooling
  - Stirring conditions

Powder Flow

- Powder flow refers to how easily drug particles move or flow during manufacturing processes.



Why Powder Flow is Important

- Ensure uniform dose in each tablet/capsule
- Prevents manufacturing problems (blockage, uneven filling)
- Improves production speed and efficiency

Factors affecting powder flow

1. **Particle size**
   - ➢ Larger particles → better flow
   - ➢ Very fine particles → poor flow (stick together)
2. **Particle shape**

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