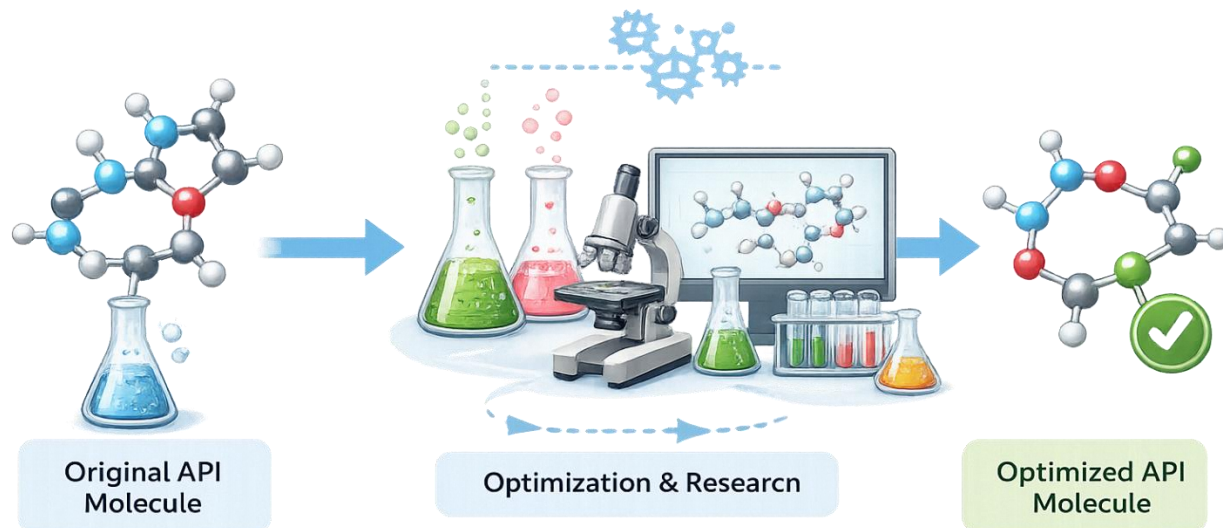


Preformulation Studies

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.



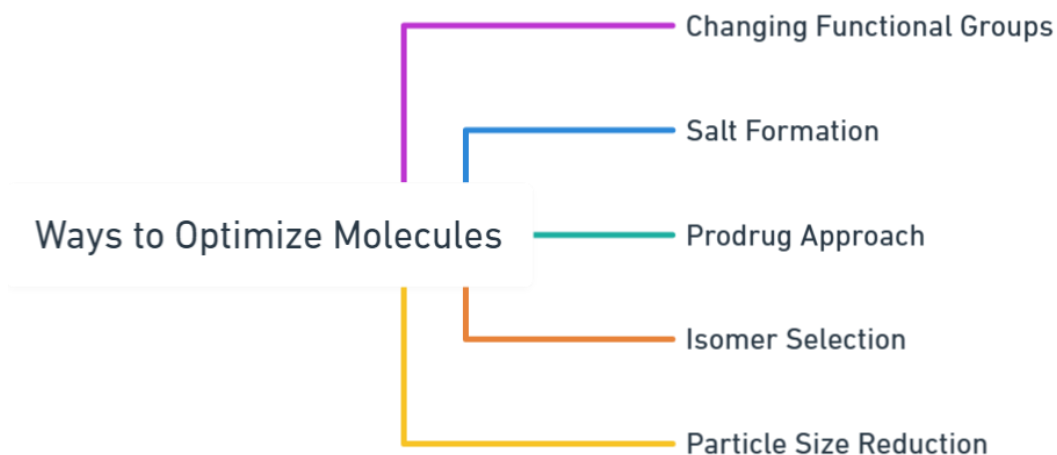
Why it is needed

- 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



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

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.

Crystal Morphology & Variations



Cube



Tetragonal



Hexagonal



Trigonal



Wythohopilit



Nithoutotte



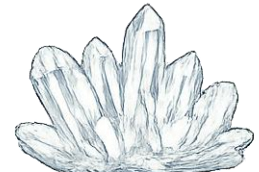
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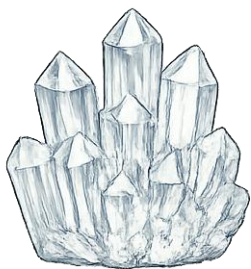
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Akiscoin



Opyrokite



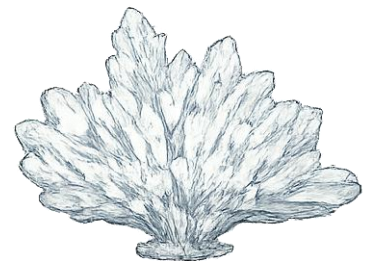
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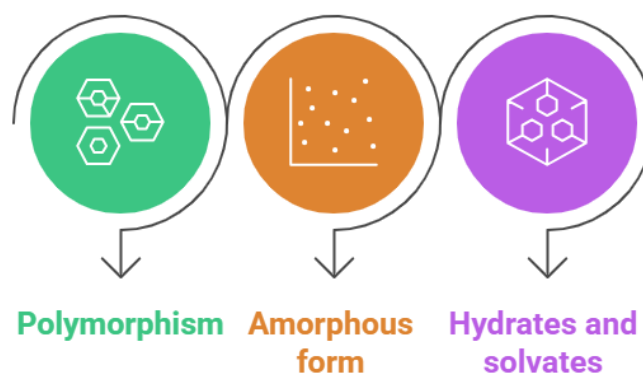


Opyrokite

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

- 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

Methods to Study Crystals

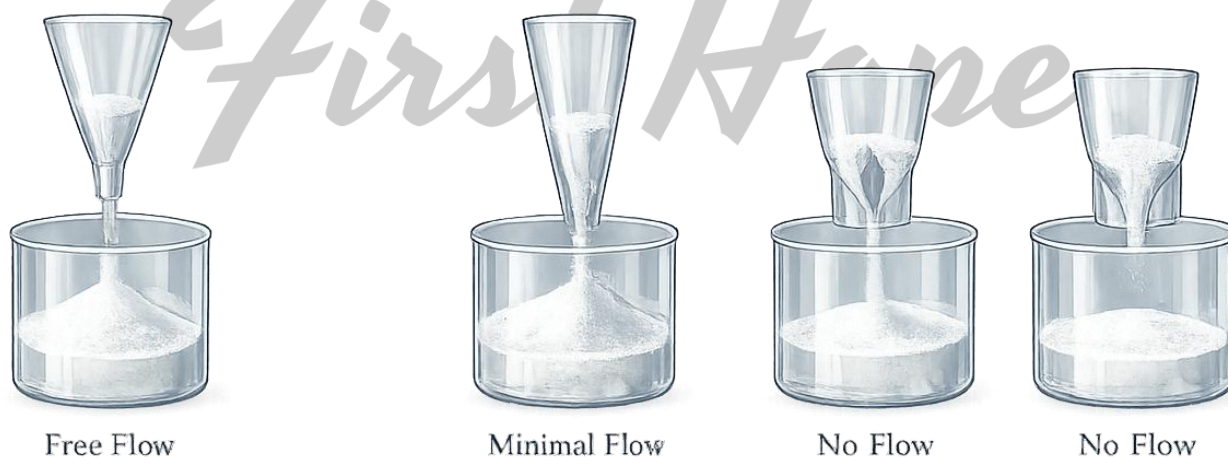
- X-ray diffraction (XRD)
- Microscopy
- Thermal analysis (DSC)

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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