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# Co-crystals: An emerging approach for enhancing properties of pharmaceutical solids

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## Outline

- Importance of solid form selection for drug development process
- Classification of solid-state forms
- Co-crystals as an alternative solid-state form of APIs
  - Design and screening
  - Examples of potential pharmaceutical implications
- Concluding remarks

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## Why is Solid-State Form Important?

■ The solid-state structure of a compound impacts the physicochemical and performance properties, as well as the value/utility of a material

**Solid-State Structure** → **Physicochemical/Performance Properties** → **Value/Utility**

**Performance Properties**

- Thermal
- Mechanical
- Electrical
- Optical
- Solubility
- Dissolution rate
- Hygroscopicity
- Stability
- Flowability
- Compaction

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## Crystallization IS the first formulation step

**MOLECULE** → **CRYSTALLIZATION** → **CRYSTALS** (Purity, physical form, morphology) → **PARTICLES** (Shape, size, surface properties, porosity) → **POWDERS** (Bulk properties and handling issues) → **DOSAGE FORMS** (Processing properties, mechanical integrity, dissolution rate) → **PATIENT** (Clinical performance)

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## Classification of Solid-state Forms

**Single chemical entity**

**Crystalline**  
(Molecules packed in a regularly ordered, repeating pattern)

**Amorphous**  
(Molecules arranged randomly)

**Single-component crystals**

- Polymorph I
- Polymorph II

**Multicomponent crystals**

- Solvate
- Salt
- Co-Crystal

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## Co-crystals: Definition

Crystalline molecular complexes of two or more **neutral** molecules, which are **solid** under ambient conditions

**Guest molecules**

**Caffeine monohydrate:**  
The guest molecule (water) is liquid under ambient conditions

**Caffeine:oxalic acid co-crystal**  
The guest molecule (oxalic acid) is solid under ambient conditions

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## Key Benefits of Co-crystals as an Alternative Solid Form of APIs

- A stable crystalline form (as compared to amorphous solids)
- No need to make or break covalent bonds
- Theoretical capability of all types of API molecules (weakly ionizable / non-ionizable) to form co-crystals
- The existence of numerous potential counter-molecules (food additives, preservatives, pharmaceutical excipients, and other APIs)
- The only solid form that is designable via crystal engineering
- Patentable → expanding IP portfolios
- Can be produced using solid-state synthesis → green technologies → high yield, no solvent or by-products

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## Co-crystal screening: general outline

Much like polymorph or salt screening

**Step 1: DESIGN**

**Step 2: SCREENING**

**Step 3: SELECTION**

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## Co-crystal design

- Evaluation of physico-chemical properties of an API
- Defining the scope of screening
- Selection of co-crystal formers

**Typical selection criteria for co-crystal formers**

- **Pharmaceutically acceptable (preferably, used in commercial drug products)**
- **Nontoxic**
- **The size of the guest molecule relative to the API loading in the potential drug product**

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## Approaches to co-crystal screening

- **Semiempirical approach**
  - examination of number, arrangement and types of functional groups that can participate in H-bonding
  - crystal packing analysis (if single-crystal structure is available)
  - employing molecular modeling tools to select potential co-crystal formers
- **Empirical approach (dominant)**
  - every combination of API and guest molecule is experimentally tested;
  - GRAS and EAFUS lists can be used for selection of potential co-crystal formers

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## Co-crystal screening: experimental techniques

Solvent-based methods	Solid-based techniques*
■ Slurry conversion	■ Crystallization from the melt
■ Solvent evaporation*	■ Net grinding
■ Cooling crystallization	■ Solvent-assisted grinding
■ Precipitation	■ Sonication (applied to either wet or dry solid mixtures)

\* Stoichiometric ratios of components are usually used

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## Co-crystal screening: exploring thermomicroscopy

25 °C      78 °C

85 °C      82 °C

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### Co-crystal Screening: Exploring Solvent-mediated Transformations

Theoretically, the formation of a co-crystal (CC) is the only crystallization pathway in the slurry experiment, providing that a more stable phase for API (D) and co-crystal former (CCF) does not nucleate (Zhang et al., 2005, J Pharm Sci 96:990-995)

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### Co-crystal selection

- Solid-state characterization (structure and composition): single crystal XRD or XRPD, thermal analysis, spectroscopic analysis
- Evaluation of physico-chemical properties
- Stability tests
- Optimal form selection

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### Examples of potential pharmaceutical applications of co-crystals

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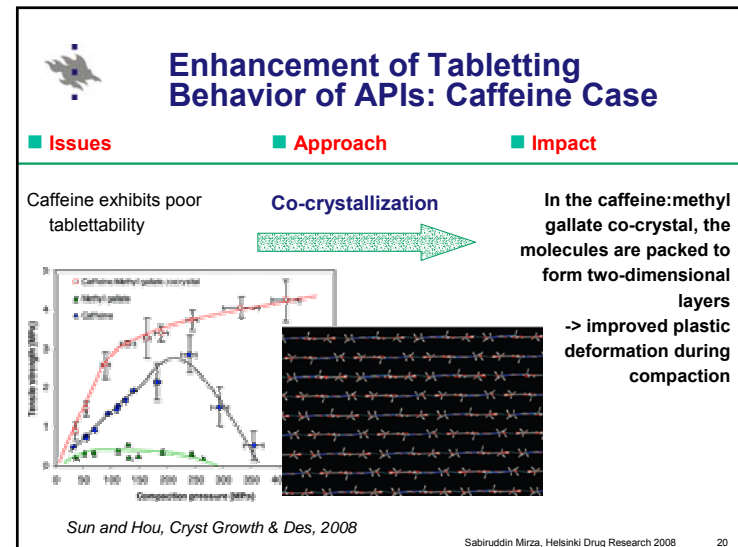
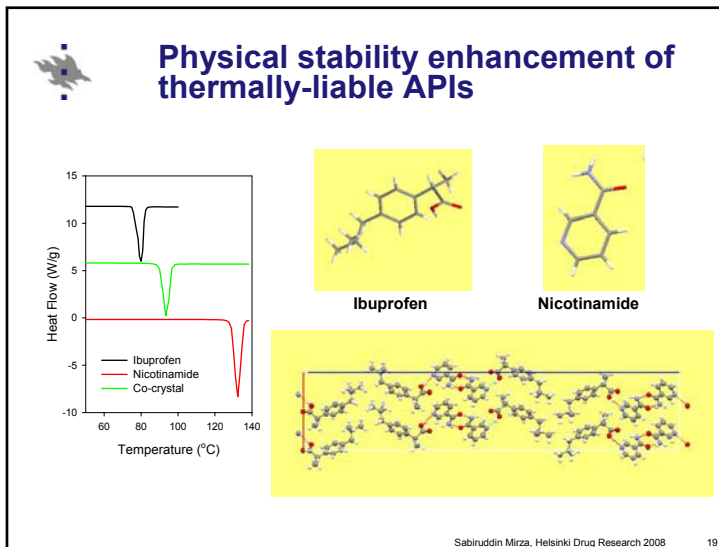
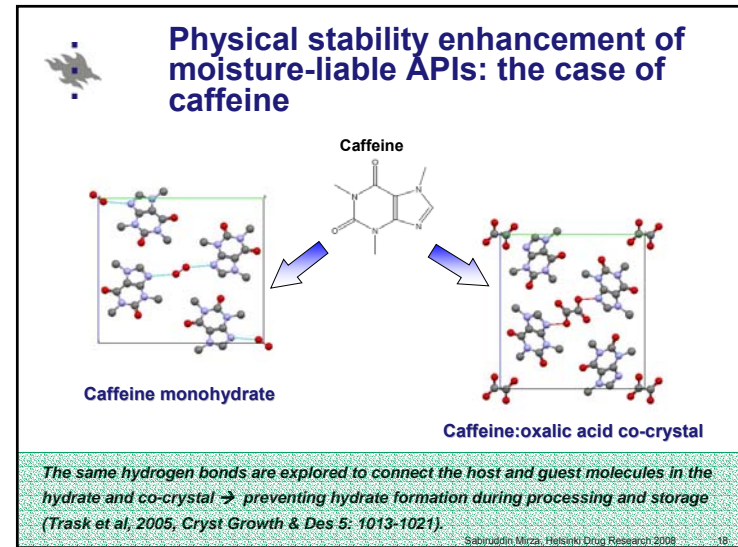
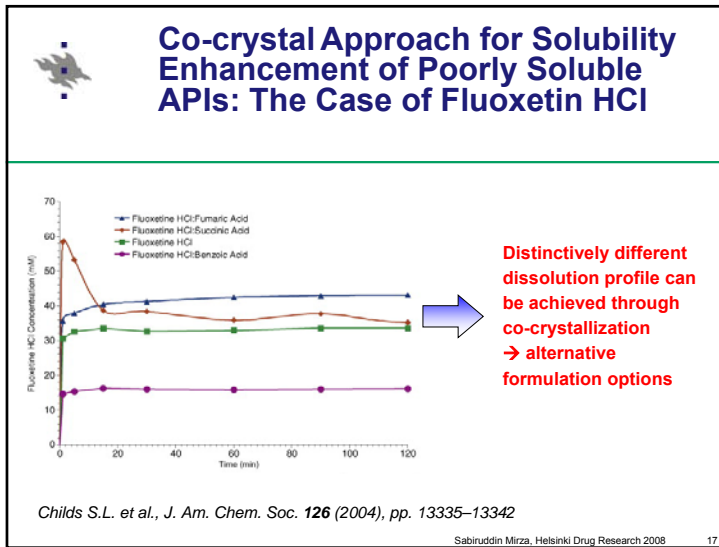
### Co-crystal Approach for Solubility Enhancement of Poorly Soluble APIs: The Case of Itraconazole

■ Issues      ■ Approach      ■ Impact

Extremely water-insoluble antifungal agent      **Co-crystallization**      The dissolution profile of co-crystals with L-malic acid matches that of amorphous cis-itraconazole

Remenar et al, J Am Chem Soc, 2003, 125, 8456-8457

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## Summary

- Co-crystals allow us to significantly **expand the possibilities** for finding a developable solid form of an API
- Co-crystals are **designable** and thus provide means for product line extensions and rescue of APIs that were abandoned due to development problems
- Co-crystals are **patentable** → additional opportunities for the pharmaceutical companies to address intellectual property issues



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