Combining Crystal Structure and Interaction Topology for Interpreting Functional Molecular Solids: A Study of Theophylline Co-Crystals
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**Background**
- How molecules arrange in space (crystal structure) directly impacts a broad variety of pharmaceutical functions.
- A co-crystal is the combination of a drug and inert coformer, in a defined stoichiometry, all assembled into the same crystal.
- Co-crystal physical structures may fall into two broad categories: flat-layered structures and columnar structures.

**Objectives**
- Determine how the organization of molecules in space impacts their function as pharmaceutical products.
- Identify which co-crystal (and crystal structure) best promotes tabletting performance.
- Show how co-crystallization of a molecule with theophylline improves its tabletability.
- Prove that flat-layered structures are superior to columns in terms of tabletting performance.

**Methods**

**Co-Crystal Preparation**
- Preparation of THY-FNBA Co-crystal: Liquid assisted grinding was used to generate the bulk form of this co-crystal.
- Preparation of THY-APAP Co-crystal: The THY-APAP co-crystal was prepared using solution mediated phase transformation; a slurry containing equimolar quantities of THY and APAP in acetonitrile was stirred overnight.
- Preparation of THY-PABA Co-crystal: The THY-PABA co-crystal was synthesized using liquid assisted grinding.

**Analysis**
- Did we make a co-crystal (a new material)?
- Differential Scanning Calorimetry
- Powder X-Ray Diffraction
- How did the material perform?
- Powder Compaction
- Did the tabletability change? Why?
- Single-Crystal X-Ray Diffraction
- Powder Brillouin Light Scattering (p-BLS)

**Results**

**Compressibility**
- With increasing pressure, the tablets became more dense and displayed a lower porosity.
- The compressibility of THY was increased when crystallized with either FNBA or APAP.
- The more dense a tablet was, the more compressibility it exhibited, and the better tablets it formed.
- Regarding the two columnar crystal structures, THY-PABA was less compressible than THY alone.
  - The interdigitated columns of THY-PABA resisted compression.

**Compactability**
- THY showed intermediate compactability to the two layered structures (THY-FNBA and THY-APAP).
- At lower pressure and higher porosity, THY-FNBA was the most compactable and compressible.
  - If a tablet is both compactable and compressible, then a strong tablet will likely form.

**Tabletability**
- The two layered structures, THY-FNBA and THY-APAP, formed superior tablets compared to THY by itself.
- The two columnar structures, THY and THY-PABA, displayed approximately the same performance.

**Mechanical Properties**
- THY-FNBA was found to have the lowest Young’s modulus and lowest shear modulus.

**Sound Velocities and Intermolecular Interactions**
- The two layered structures had low velocity sound waves; there are directions within these materials with very weak intermolecular interactions.

**Discussion and Conclusions**
- How molecules arrange in space directly influences the function of the material.
- Co-crystals are one way to deliberately modify this organization to target an improved material performance.
- THY-FNBA and THY-APAP co-crystals (both layered structures) made better tablets than THY alone (columnar structure).
- Two materials may be structurally similar, yet they may not necessarily display the same properties. The differences depend on the intermolecular interactions.
- When designing new materials, you need to look at both crystal structure and interaction topology.