Cocrystals: Screening and Pharmaceutical Applications

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Cocrystals: Screening and Pharmaceutical Applications

• Cocrystals: Some History of Pharmaceutical Applications
  - FDA Approved
  - Tested in Clinic
  - Tested in Animals

• Screening for Cocrystals

• Use of Cocrystals to Enhance Bioavailability
  - Supersaturating Drug Delivery Systems
  - In-vitro/In-vivo Correlations
  - API:Cocrystal Solubility Ratio
  - Dose
  - API Crystallization Rate
  - Dissolution Testing of Cocrystals
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Cocrystals

A crystalline solid that consists of two or more components, where a component is a “constituent part of a system, whose composition, at least in one state of aggregation, does not depend on the concentration of the other parts.”

quote from Kitaigorodsky, A. I. *Mixed Crystals*; Springer-Verlag: Berlin, 1984, p 17
Cocrystals

• This presentation is focused on the use of cocrystals of APIs to overcome poor aqueous solubility
• But remember that cocrystals can be used in many ways
  ➢ Reduce hygroscopicity
  ➢ Alter physical properties like particle size, habit
  ➢ Generate crystalline forms of non-crystalline materials
  ➢ Purification
  ➢ Resolution
  ➢ Stabilization of unstable molecules
Cocrystals: Discovery

• The first cocrystal reported was quinhydrone in 1844
  ➢ Wöhler, F. Annalen Chemie Pharmacie 1844, 51, 145-163

\[
\text{HO-} \begin{array}{c}
\text{O} \\
\text{C} \\
\text{H} \\
\text{H} \\
\text{O}
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\text{O} \\
\text{C} \\
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• The German chemist Paul Pfeiffer published Organische Molekülverbindungen (Organic Molecular Compounds) in 1922
  ➢ The section of the book entitled Rein organische Molekülverbindungen (organic components) lists over 300 known cocrystals
History of Pharmaceutical Applications

• Cocrystals were used as pharmaceuticals by at least 1895 (*Modern Materia Medica*, 4th edition)
  - Cocrystals of the analgesic antipyrine are shown below

![Chemical structures]

- **resopyrine**
- **naphthopyrin**
- **pyrogallopyrine**
- **hypnal**
History of Pharmaceutical Applications

Fig. 5.—The dissolution behavior of anhydrous (N₁), hydrated (H₂), and pentanol solvated (P₁) forms of succinyl sulfathiazole in ∼ 0.001 N sulfuric acid solution at 20°C.

Shefter et al J. Pharm. Sci. 1963, 52, 781
We would like, in particular, to call attention to the possible broader utilization of organic solvates and complexes in dosage form development. Since the apparent free energy change associated with their dissolution in aqueous media can be vastly greater than that exhibited by an unstable polymorph relative to the stable form, much higher temporary solution concentrations and rates of solution can be obtained by their use than from purely crystalline modification. This is because the system utilizes, in effect, the free energy of dilution of the complexing agent to raise the solubility of the drug. Since molecular complexes of this type are readily produced, particularly by relatively insoluble drugs, this approach may often provide the answer for those products which are poorly available because of slow rates of dissolution.

Shefter et al J. Pharm. Sci. 1963, 52, 781
History of Pharmaceutical Applications

Abstract □ The syntheses of 1:1 and 1:2 molecular complexes of caffeine with gentisic acid are described, and their rates of dissolution are reported and compared with that of caffeine. Both complexes were less soluble in water than caffeine, and their rates of dissolution in 0.1 N hydrochloric acid and in a phosphate buffer at pH 7.5 were less than that of caffeine. These complexes thus present a potentially useful way of formulating caffeine in dosage forms such as chewable tablets that are intended to linger in the mouth. Such dosage forms would only release caffeine slowly and should, consequently, have an improved taste factor over ones containing pure caffeine. The rates of dissolution of the complexes

Higuchi et al J. Pharm. Sci. 1973, 62, 55
Cocrystals: FDA Approved

- **Depakote**
  - valproate semisodium (INN) or divalproex sodium (USAN)
  - approved by the FDA in 1996, ER version in 2002
  - treatment of epilepsy and the manic episodes of bipolar disorder
Cocrystals: FDA Approved

• Aminophylline
  - described in Merck as a complex of theophylline and ethylenediamine (2:1)
  - approved by the FDA as a bronchodilator
  - is it a salt or cocrystal?

Cocrystals: Tested in Clinic

- Flavazole
  - Cocrystal of two antibiotics; broad spectrum antiseptic.
  - Clinical trial in the plastic and spinal units of Stoke Mandeville Hospital, UK.
  - Can be used safely as a solution in the conjunctival sac and in any infected cavity as a wound antiseptic.

McIntosh et al Lancet 1945, 246, 97
• Sodium theophylline glycinate
  ➢ “In an eighteen-month clinical trial with sodium theophylline glycinate, W. D. Paul (4) used this dosage form of theophylline in more than 300 patients. It elicited a typical theophylline therapeutic response. It was tolerated without nausea or vomiting in quantities up to 4 Gm. in twenty-four hours; i.e., 2 Gm. of theophylline.”

Cocrystals: Tested in Clinic

- **Digoxin**
  - Digoxin is a naturally-occurring API used to treat heart conditions; it is poorly water soluble.
  - A hydroquinone cocrystal was found.
  - A clinical trial was carried out using 12 people.
  - The cocrystal was not statistically different than digoxin itself.

Cocrystals: Tested in Clinic

- CP-724,714
  - Pfizer API, a reversible, highly selective, oral HER2 tyrosine kinase inhibitor.
  - Clinical phase I trial in patients with advanced solid tumor malignancies that express HER2.
  - The API has acceptable tolerability and safety at 250 mg twice daily.

Cocrystals: Tested in Animals

• Purdue Pharma API
  - API is poorly water soluble with low \textit{in vivo} plasma concentrations
  - Five cocrystals found using Kofler method
  - Glutaric acid cocrystal dissolves 18 times faster than API in water
  - Four-fold AUC increase in dog bioavailability study

Cocrystals: Tested in Animals

- L-883555
  - A potent Merck phosphodiesterase-IV inhibitor with indications for asthma and COPD.
  - Very poor PK properties in rats and rhesus monkeys.
  - Non-stoichiometric cocrystals with L-tartaric acid found.
  - The hemi-tartrate showed a 23 times increase in AUC in rhesus monkeys

Variankaval et al Cryst. Growth Des. 2006, 6, 690
Cocrystals: Tested in Animals

• Carbamazepine/saccharin cocrystal
  - Carbamazepine is an anti-epileptic that is water-insoluble drug and consequently has a high dose requirement.
  - Bioavailability study in dogs showed no statistical difference between a commercial carbamazepine formulation (Tegretol®) and the cocrystal.

Cocrystals: Tested in Animals

• Lamotrigine
  ➢ Lamotrigine is a poorly water soluble anticonvulsant used to treat epilepsy and bipolar disorder.
  ➢ A nicotinamide cocrystal was found that exists as an anhydrate or monohydrate.
  ➢ A PK study in rats using the anhydrate and monohydrate showed a decrease in the serum concentration by about 40% and 68%, respectively, compared to pure lamotrigine.

Cheney et al Cryst. Growth Des. 2010, 10, 394
Cocrystals: Patents

- A search for ‘cocrystals’ on the USPTO website
  - Reveals 10 issued US patents and
  - 25 published US applications

<table>
<thead>
<tr>
<th>Patents</th>
<th>Applications</th>
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<td>7,935,817</td>
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  ➢ API:Cocrystal Solubility Ratio
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Cocrystals: Screening

Break down of techniques used for cocrystallization in open literature

Sheikh *et al* *CrystEngComm* **2009**, 11, 501
Cocrystals: Screening

- Screening methods
  - Phase diagram directed thermodynamic target
  - Stoichiometric slurry conversion/milling
  - Non-stoichiometric and stoichiometric slurry crystallization
  - Kofler screening
  - Large coformer selection based on toxicity and crystal engineering principles.
  - Parallel processing or manual

- Solvent mixtures based on solubility values
Cocrystals: Screening

- The cocrystal screening process was optimized and validated by testing many different processes and conditions using a set of 75 known cocrystals of 18 APIs that were selected from the literature.
- The result was a process that consistently produced all 75 known cocrystals with a 100% success rate.
- Our continuous R&D efforts and constant re-evaluation of the process effectiveness has generated improvements that have resulted in increased hit rates.
- In some cases we have been able to compare Triclinic screening results with the screening results from other Pharma groups and CRO’s and the Triclinic process found the same as well as additional cocrystals.
Cocrystals: Screening

• How common is cocrystal formation?
  ➢ A 2007 compilation showed that of 64 compounds that were subjected to cocrystal screening, 39 (61%) formed cocrystals (not hydrates or solvates)
  ➢ 192 cocrystals were found of those 39 compounds


  ➢ Screening in the last 12 months using the Triclinic process afforded cocrystals (not hydrates or solvates) for 24 of 32 APIs tested (75% hit rate).
Cocrystals: Screening

- We reported cocrystals of fluoxetine HCl in 2004
  - The chloride ion is a strong hydrogen bond acceptor
  - In the structure of fluoxetine HCl it is octahedrally coordinated by hydrogen bond donors (2 strong NH donors, 4 weak CH donors)
  - Strong hydrogen bond donors were selected as potential guests
  - Cocrystals with benzoic, fumaric, and succinic acids found

Childs et al. J. Am. Chem. Soc. 2004, 126, 13335
Cocrystals: Screening

Fluoxetine HCl Dissolved (mmol/cm²)

Fluoxetine HCl:Succinic Acid
Fluoxetine HCl:Fumaric Acid
Fluoxetine HCl:Benzoic Acid

Linear (Fluoxetine HCl:Fumaric Acid)
Linear (Fluoxetine HCl:Benzoic Acid)

Fluoxetine HCl Concentration (mM)

Fluoxetine HCl:Succinic Acid
Fluoxetine HCl
Fluoxetine HCl:Fumaric Acid
Fluoxetine HCl:Benzoic Acid

Intrinsic in water at 10 °C

Childs et al. J. Am. Chem. Soc. 2004, 126, 13335

Fluoxetine HCl powder in water at 20 °C

Fluoxetine HCl

 Succinic

–2X

Fumaric

+2X

Benzoic
Cocrystals: Screening

- Fumaric acid and succinic acid cocrystals are isostructural
- Using our current screening process we found a 4-hydroxybenzoic acid cocrystal that is isostructural with the benzoic acid cocrystal
Cocrystals: Screening

• Issues in phase diagram-based solvent screening
  ➢ Estimated component solubilities can be inaccurate
  ➢ Phase diagrams are at equilibrium; slow cocrystal nucleation rates can lead to false negative results
  ➢ Complexation in solution is more common than not in API screens
    • Most often the solubility of a component is higher in a solution of the second component compared to the solubility in solvent alone
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  ➢ Dissolution Testing of Cocrystals
Cocrystals: Bioavailability Enhancement

- Assuming a cocrystal is desired because of low aqueous solubility of an API
- Successful use of a more soluble cocrystal to increase bioavailability depends on
  - Solubility of the cocrystal
  - Solubility of the API
  - Solubility of the coformer
  - Rate of transformation of the cocrystal to the API
Cocrystals: Bioavailability Enhancement

• Drug absorption
  - $J = PC$, where
    - $J$ = flux through gastrointestinal wall
    - $P$ = permeability coefficient
    - $C$ = drug concentration

• Biopharmaceutical classification system

<table>
<thead>
<tr>
<th>I.</th>
<th>high $P$, high $C$</th>
<th>II.</th>
<th>high $P$, low $C$</th>
</tr>
</thead>
<tbody>
<tr>
<td>III.</td>
<td>low $P$, high $C$</td>
<td>IV.</td>
<td>low $P$, low $C$</td>
</tr>
</tbody>
</table>

• Drugs in Class II or IV
  - Maximum achievable concentration may limit absorption
Supersaturating Drug Delivery Systems

• Supersaturating drug delivery systems (SDDS)
  ➢ Designed to create supersaturated concentration of the drug for a time period sufficient for absorption

• Spring and parachute

  • Spring provided by
    ➢ High-energy forms (amorphous, cocrystals, etc.)

  • Parachute provided by
    ➢ Precipitation inhibitors

Brouwers et al J. Pharm. Sci. 2009, 98, 2549
Supersaturating Drug Delivery Systems

• What affects the metastable zone lifetime?
  ➢ The higher the supersaturation level, the more drive for API precipitation, the shorter the lifetime
  ➢ The faster the API precipitation rate relative to the dissolution rate of the high-energy form, the shorter the lifetime

• Dissolution experiments designed to evaluate the effect of an SDDS must be done carefully
  ➢ Always under non-sink conditions

• Remember there is not always correlation between in-vitro dissolution results and in-vivo bioavailability results
In-vitro/In-vivo Correlations

- AZD0865 (BCS class II)
  - Theoretical predictions and in-vivo dissolution studies indicated rapid precipitation would occur from supersaturated solutions

Carlet *et al* Pharm. Res. **2010**, 27, 2119
**In-vitro/In-vivo Correlations**

- No evidence of precipitation in-vivo in humans
  - API delivered in solution
  - Plasma levels correlated with dose

*Carlet et al Pharm. Res. 2010, 27, 2119*
API:Cocrystal Solubility Ratio

- The solubility of a cocrystal is related to the solubility of the coformer
  - More soluble coformers will result in more soluble cocrystals
  - The relationship is not always linear
- Rule of 10
  - In general, if the coformer solubility is >10 times the API solubility, the cocrystal solubility will be very high and the conversion rate from cocrystal to API will be rapid.
The cocrystal:API solubility ratio affects supersaturation level and API precipitation rate.
API:Cocrystal Solubility Ratio

- Effect on dissolution profile of API solubility enhancer (SLS)
  - Tablets containing ~1 mg API and various amounts of SLS
  - Medium is 30 mL phosphate buffer at 37 °C

<table>
<thead>
<tr>
<th></th>
<th>API 10 mg SLS</th>
<th>API 20 mg SLS</th>
<th>Cocrystal 10 mg SLS</th>
<th>Cocrystal 20 mg SLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration (mg/mL)</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>Time (minutes)</td>
<td>0</td>
<td>10</td>
<td>20</td>
<td>30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>API 10 mg SLS</th>
<th>API 20 mg SLS</th>
<th>Cocrystal 10 mg SLS</th>
<th>Cocrystal 20 mg SLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>amount SLS (mg)</td>
<td>10</td>
<td>20</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>supersaturation level achieved</td>
<td>—</td>
<td>2.4</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>amount dissolved at max (mg)</td>
<td>0.087</td>
<td>0.21</td>
<td>0.44</td>
<td>1.2</td>
</tr>
<tr>
<td>area under curve at 30 min</td>
<td>0.038</td>
<td>0.083</td>
<td>0.38</td>
<td>1.1</td>
</tr>
</tbody>
</table>
Dose

- The amount of API relative to the solubility level is a key variable
  - Solid lines: larger dose
  - Dashed lines: smaller dose
Dose

- Effect on dissolution profile of different drug loadings in identical media volumes
  - API solubility is ≈ 0.0004 mg/mL
  - Medium is 15 mL of FaSSIF buffer (pH 6.5) plus TPGS at 37 °C

<table>
<thead>
<tr>
<th>Amount (mg)</th>
<th>API</th>
<th>Cocystal</th>
<th>Cocystal</th>
<th>Cocystal</th>
</tr>
</thead>
<tbody>
<tr>
<td>loading level (ratio to API solubility)</td>
<td>167</td>
<td>83</td>
<td>167</td>
<td>333</td>
</tr>
<tr>
<td>supersaturation level achieved</td>
<td>—</td>
<td>12</td>
<td>19</td>
<td>24</td>
</tr>
<tr>
<td>Amount dissolved at max (mg)</td>
<td>0.0060</td>
<td>0.073</td>
<td>0.12</td>
<td>0.14</td>
</tr>
<tr>
<td>Area under curve at 30 min</td>
<td>0.0045</td>
<td>0.066</td>
<td>0.095</td>
<td>0.051</td>
</tr>
</tbody>
</table>
API Crystallization Rate

If the API crystallization rate is slow relative to the dissolution rate of the cocrystal, the metastable state will persist for a longer time.

![Graph showing API Crystallization Rate]

- **Slow API growth**
- **Fast API growth**
- **API**
API Crystallization Rate

- If the API precipitation rate is slow relative to the dissolution rate of the cocrystal, bioavailability can improve.
- Cocrystal of Purdue Pharma compound

API Crystallization Rate

Intrinsic Dissolution (37 °C in water)
cocrystal dissolves 18× faster than API

Bioavailability study (dogs)
~4X AUC increase

API Crystallization Rate

• If the API crystallization rate is fast relative to the dissolution rate of the cocrystal, coating can prevent cocrystal dissolution
  ➢ Can be difficult to detect
API Crystallization Rate

- Carbamazepine
- Glutaric acid

**Aqueous solubilities**

- Carbamazepine: 0.12 mg/mL
  (Chen et al Pharm. Res. 2004, 21, 1758)

- Glutaric acid: 639 mg/mL
  (Seidell Solubilities of Inorganic and Organic Compounds, 2nd edition, 1919, p 307)
API Crystallization Rate

Intrinsic dissolution of carbamazepine anhydrate and carbamazepine:glutaric acid cocrystal

- Raman spectrum of tablet taken every 20 seconds
  - Laser penetrates about 0.4 mm
  - Conversion to dihydrate took 1-2 minutes

- UV spectra of solution
  - Cocrystal converts to dihydrate more quickly than carbamazepine anhydrate does
  - Layer of dihydrate forms immediately
API Crystallization Rate

- Crystallization inhibitors can be added to the formulation to slow the rate of API crystallization
- Inhibitors can work by:
  - reducing the degree of supersaturation by increasing the API solubility
  - Increasing viscosity, resulting in reduced molecular mobility (decreased nucleation rate) and diffusion coefficient (decreased growth rate)
  - Increasing the cluster–liquid interfacial energy (decreased nucleation rate)
  - Changing the adsorption layer at the crystal–liquid interface by adsorbing onto the crystal surface (decreased growth rate)
  - Changing the level of solvation at the crystal–liquid interface, thereby affecting the integration of drug molecules into the crystal.
API Crystallization Rate

- Itraconazole dissolution profiles
  - Amorphous vs. crystalline
  - In the presence of 2-hydroxypropyl-β-cyclodextrin (top)
  - In the presence of dimethyl-β-cyclodextrin (bottom)

![Graph showing dissolution profiles](image)

*Figure 5. Concentration–time profiles for itraconazole starting from crystalline (○) or amorphous (●) drug substance in the presence of HPβCD (panel A) or DMβCD (panel B). Adapted from Brewster et al.*

API Crystallization Rate

- Effect on dissolution profile of crystallization inhibitor (HPMC) in tablet
  - API solubility is ≈ 0.003 mg/mL
  - Medium is 15 mL of FaSSIF buffer (pH 6.5) plus TPGS at 37 °C
Dissolution Testing of Cocrystals

• To determine if a cocrystal will enhance dissolution rate and maintain a supersaturated condition:
  • Test under non-sink conditions
  • Use a biorelevant medium
  • Know cocrystal solubility
    • Estimate (rule of 10)
    • Determine (Good et al Cryst. Growth Des. 2009, 9, 2252)
  • Use excipients to alter API:cocrystal solubility ratio
  • Use excipients to inhibit API crystallization
  • Test excipients for ability to maintain a supersaturated condition

• Whether a cocrystal will enhance dissolution rate and maintain a supersaturated condition is compound dependent
  • Use an empirical approach

• We have seen cocrystals dismissed as potential solutions to poor API solubility based on flawed dissolution testing
Thank you for your attention

Questions welcome

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