Pharmaceutical Powder Diffraction: Structure Solution from PXRD

How reliable are our structures?

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Direct Methods:

SIR & SHELXS

Maximum Entropy: MICE

Patterson


Lightfoot, Tremayne, Harris & Bruce., *Chem.Comm.* (1992), 1012
SDPD Molecular Materials 93-02

SIRPOW, EXPO, EAGER, OCTOPUS, FOX, DASH, POSSUM, TOPAS, PowderSolve, ESPOIR, PSSP, XLENS, Endeavour


Seaton et al., *Chem Comm.*, (2002), 880

Tedesco et al., *Angew.Chem.* (2000), 39, 4488
Fernandez et al., *J.Pharm.Sci.* (2007), 96, 1192

Chong et al., *Acta Cryst.*.. (2006), B62, 864


Basso et al., *Acta Cryst.*.. (2010), D66, 756
Prednisolone succinate

- 2 molecules in asu; 65 non-H atoms; 25 dof
- Synchrotron data, $d > 1.00\text{Å}$

Genetic Algorithm & Rigid-body refinement: $R_{wp}=8.2\%$

Omit MEM charge density model
$R_{wp}=3.7\%$, refined $R_{wp}=2.9\%$

Dual data refinement with inner angle restraints, $R_{wp}=1.3\%$

"accuracy of structure increased"..."using procedures"..."eliminating model bias during refinement"

**Isotibolone**

Degradation impurity in dosage of tibolone API

- **Genetic Algorithm Laboratory data**

  Gomez, Antonia, Barros de Araujo, Ferreira & Paiva-Santos, *CrystEngComm.*, (2012), 14, 2826

**Naproxen**

Liquid assisted grinding (alcohol/water):
Mg(nap)$_2$.H$_2$O - SXRD
Mg(nap)$_2$.4H$_2$O - PXRD

- **Simulated Annealing Laboratory data**

  Friščić, Halasz, Strobridge, Dinniebier, Stein, Fabian & Curfs, *CrystEngComm.*, (2011), 13, 3125
Molecular Cocrystals (& Salts)

- Crystalline solids containing 2 or more building blocks (solids at rt) in stoichiometric amounts

- Materials that retain the chemical properties of components but display new physical properties

  - melting point
  - stability
  - solubility
  - bioavailability
  - dissolution
  - morphology

- Combination of API with ‘GRAS’ component

  Aakeroy et al., *CrystEngComm.* (2005), 7, 439
  Almarsson et al., *Chem.Comm.* (2004), 1889
... melting point ...

Used to mimic physical property trends...

Thompson, Voguri, Male & Tremayne,
*CrystEngComm*, (2011), *13*, 4188

... or not! ...

Braga et al., *CrystEngComm*. (2010), *12*, 3534
... solubility ...

- Tuned to level of commercial material
- Property rationalised by diacid solubility

Remenar et al., *J.Am.Chem.Soc.*, (2003), 125, 8456

Why Powder Diffraction?

Products showing poor crystal growth resulting from:

- solvent-mediated crystallisation or sonic slurry

Products from solid state synthesis:

- liquid assisted or dry grinding

- alternative stoichiometry

- incompatible solubilities

- solvent-free form

- atypical structural behaviour

Delori, Friscic & Jones., *CrystEngComm.* (2012), 14, 2350

James et al., *Chem.Soc.Rev.* (2012), 41, 413

SDPD of Cocrystals

- Independent components in direct space; greater complexity wrt search surface & parameters

1,2,3-Trihydroxybenzene: HMTA (1:1)
Monte Carlo Laboratory data

Benzquinone: bis-naphthol: anthracene (2:2:1)
Dry grinding; Genetic Algorithm Laboratory data
SDPD of Cocrystals

Gemfibrozil: hydroxybutyramine (1:1)

Genetic Algorithm
Laboratory data
Proton transfer


Theobromine: malonic acid (1:1)

Liquid assisted grinding
Simulated Annealing
Laboratory data

**SDPD of Cocrystals**


Grinding

Synchrotron Simulated Annealing


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<table>
<thead>
<tr>
<th>Table 1. Compounds</th>
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</thead>
<tbody>
<tr>
<td>name</td>
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<tr>
<td>4-hydroxybenzoic acid and 4-phenylpyridine (1:1)</td>
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<tr>
<td>3-hydroxybenzoic acid and 4-phenylpyridine (1:2)</td>
</tr>
<tr>
<td>3-hydroxybenzoic acid and tetramethylpyrazine (2:3)</td>
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<tr>
<td>3-hydroxybenzoic acid and 4,4'-bipyridine (1:1)</td>
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<td>3-hydroxybenzoic acid and 1,2-bis(4-pyridyl)ethane (1:1)</td>
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<tr>
<td>3-hydroxybenzoic acid and <em>trans</em>-1,2-bis(4-pyridyl)ethene (1:1)</td>
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<tr>
<td>4-hydroxybenzoic acid and 1,2-bis(4-pyridine)ethane (2:1)</td>
</tr>
<tr>
<td>3-hydroxyppyridine and isophthalic acid (1:1)</td>
</tr>
<tr>
<td>L-ascorbic acid and nicotinic acid (1:1)</td>
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</tbody>
</table>

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Carbamazepine: indomethacin (1:1)

Dry grinding

Simulated Annealing Laboratory data
SDPD of Cocrystals

Furosemide:nicotinamide (1:1)

Four cocrystal polymorphs
Solvent crystallisation / drying
Parallel Tempering
Laboratory data

Cocrystal/salt from ΔpKa?

Ueto, Takata, Muroyama, Nedu, Sasaki, Tanida & Terada,
Nicotinamide : Oxamic Acid

Crystallisation from MeOH, 1:1 ratio
Solid state IR – salt
GC & EA & NMR – 1:1 stoichiometry

Structure determination from lab PXRD (DE)
2 independent molecules, 14 parameters
210000 Evaluations (1500 Generations), $R_{wp} = 10.38\%$
Restrained Rietveld refinement indicated ‘flip’ of amide group.

DE solution correctly located solution minimum, but amide group incorrect compared to final refined relaxed structure.
Nicotinamide : Oxamate

- Distinct layers of molecular components
- 1:1 salt form
- Bifurcated hetero N(H)...O link
- Amide dimer
- Oxamate amide-amide motif

$R_{wp} = 5.18\%$
Nicotinamide : Oxamate

Structure & syn-conformation confirmed by single crystal

powder(solution)

single crystal

$R_{wp}=5.18\%$
Nicotinamide with ... Succinic Acid

Nicotinamide is a prolific coformer with dicarboxylic acids in stoichiometric variations

Karki, Friscic & Jones., *CrystEngComm*, (2009), 11, 470

<table>
<thead>
<tr>
<th></th>
<th>oxalic</th>
<th>malonic</th>
<th>succinic</th>
<th>glutaric</th>
<th>adipic</th>
<th>pimelic</th>
<th>suberic</th>
<th>azelaic</th>
<th>sebacic</th>
<th>fumaric</th>
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<tr>
<td>1:1</td>
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Amide:Acid Stoichiometry

Athimoolan et al., *Acta Cryst.*, (2007), 63, o263
Orola & Veidis., *CrystEngComm*, (2009), 11, 415
**Nicotinamide : Succinic Acid 2:1**

Crystallisation from MeOH
1:1 ratio
2:1 cocrystal

(Single crystal determination)

- Acid-pyridine & amide-amide motifs
- Anti & syn nicotinamide conformations

Nicotinamide : Succinic Acid 1:1

Crystallisation (MeOH), 1:1 ratio in ‘controlled conditions’
Fine polycrystalline material
Solid state IR – inconclusive
GC & EA & NMR – 1:1 stoichiometry

Simulated from single crystal (2:1)

Structure determination from PXRD (using DE)
2 independent molecules, 16 parameters
More efficient optimisation......

Evolutionary algorithms:
- population of trial structures
- mating, mutation & natural selection until global minimum is found

Traditional DE

Population-managed 'eugenic' DE

$N_p = 300, F = 0.4$
Generations = 1481
Evaluations = 444,300

$N_p = 600/150, F = 0.1/0.5$
Generations = 378
Evaluations = 60,750
Nicotinamide : Succinic Acid 1:1

- Acid-pyridine & amide-acid motifs
- Distinctive supramolecular chain motif (1:1)

\[ \lambda = 1.035\text{Å} \]

Anti nicotinamide & Cis succinic acid conformation?

Not in CSD but isostructural with suberic & fumaric 1:1
<table>
<thead>
<tr>
<th>Conformation</th>
<th>$R_{wp}(%)$</th>
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<th>$R_{wp}(%)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{H}_2\text{N} - \text{CO} - \text{O}$</td>
<td>3.95 (4.37)</td>
<td>$\text{O} - \text{NH}_2$</td>
<td>5.65</td>
</tr>
<tr>
<td>$\text{O} - \text{NH}_2$</td>
<td>4.77 (4.61)</td>
<td>$\text{O} - \text{CO}$</td>
<td>4.14</td>
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<tr>
<td>$\text{H}_2\text{N} - \text{CO} - \text{O}$</td>
<td>5.02 (4.63)</td>
<td>$\text{O} - \text{NH}_2$</td>
<td>6.04</td>
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<tr>
<td>$\text{O} - \text{NH}_2$</td>
<td>5.63 (5.24)</td>
<td>$\text{O} - \text{CO}$</td>
<td>6.38</td>
</tr>
</tbody>
</table>

Is the Conformation Correct?
Tautomer control: adenine adducts

Adenine forms adducts with diacids with reduced melting point

9H cocrystals


1H,9H salt & 7H neutral


1H,9H salt


1H,9H salt

Thompson, Elias, Male & Tremayne, *CG&D*, (2013), 13, 1464

3H,7H salt
SDPD of Tautomers

Fluorescein
- Monte Carlo Synchrotron data
- C-OH & C=O determined by restrained Rietveld

Barbituric Acid
- Simulated Annealing Lab/Synchrotron data
- OCN framework revealed tautomer by Rietveld
New tautomeric polymorph stabilized by Hbonds:
Polymorphs, Salts, and Cocrystals: What’s in a Name?

Is it a Cocrystal or a Salt?

Can hydrogen atom positions be reliably determined from PXRD?


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<tr>
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<th>$R_{wp}$ (%)</th>
<th>Conformation</th>
<th>$R_{wp}$ (%)</th>
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<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
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<td><img src="image2.png" alt="Structure 2" /></td>
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<td>4.04</td>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>5.76</td>
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</table>
Conclusions  .......... and Acknowledgements

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EPSRC  
ICDD

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diamond  
Advantage West Midlands