Pharmaceutical Cocrystals to Modify Physico-Chemical and Dissolution Profile of APIs

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Talk plan

• Crystal Engineering
  – Heterosynthons in cocrystal design
  – New cocrystals of Acid and Amide APIs
  – Cocrystals of Temozolomide, Fluoroquinolones, SNRI

• Modify PC and PK drug profile
  – Stability improvement in Temodar
  – Solubility enhancement in Norflox/ Ciproflox
  – Amorphous salt of Olanzapine
  – Stability and Dissolution studies

• IP and Biz Potential in Pharma formulation
Acknowledgments

• University of Hyderabad
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  – DST
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  – UGC
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Different Crystalline States

Polymorphs of API

Polymorphs of solvate/hydrate

API salt

API cocystal
Cocrystal 101 (Co-crystal)

• … the term cocrystal should encompass all multi-component solid-state assemblies of two or more molecules held together by any type or combination of intermolecular interactions. Nangia, *Mol. Pharma.* **2007** 417.

\[
\begin{align*}
A(s) + B(s) \\
A(s) + B(l) \\
A(s) + B(g) \\
A(l) + B(l) \\
\vdots
\end{align*}
\rightarrow A \cdot B
\]

• … a (pharmaceutical) co-crystal is a multi-component crystal in which two or more molecules that are solids under ambient conditions coexist through a hydrogen bond. Almarsson, Zaworotko, *Chem. Commun.* **2004** 1889.
Supramolecular Synthons
Homo- and Heterosynthons

Desiraju, Angew. Chem. IE 1995 34 2311-2327
Crystal Structure Organization and Stabilization

*New Scientist* 1991, 13 July

Chem. Mater. 1994, August

A hydrogen bond is like the attraction of a hummingbird to a flower...

...strong and directional, and also, lovely

—Margaret C. Etter
**Organization and Stabilization**

Crystal structure total energy = $U_{\text{lat}}$ is make up of electrostatics, H bonding and van der Waals

H bonding typical contributes 15-20% of energy

Balance 80% is van der Waals and packing

20% energy controls 80% of the structure motif

Therefore justified to use a H bonding design

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**Table 4. Lattice energies [$U_{\text{lat}}$ kcal mol$^{-1}$] of forms A–D computed in Cerius$^2$, corrected to per molecule of 1.**

<table>
<thead>
<tr>
<th></th>
<th>Form A</th>
<th>Form B</th>
<th>Form C</th>
<th>Form D</th>
</tr>
</thead>
<tbody>
<tr>
<td>$U_{\text{lat}}$</td>
<td>COMPASS</td>
<td>DREIDING 2.21</td>
<td>COMPASS</td>
<td>DREIDING 2.21</td>
</tr>
<tr>
<td>hydrogen bond[a]</td>
<td>–1.84</td>
<td>–2.01</td>
<td>–1.99</td>
<td>–2.74</td>
</tr>
</tbody>
</table>

[a] The hydrogen bond energy is partitioned in the DREIDING 2.21 force field but it is part of the coulombic component in the COMPASS force field.
Cis,cis-1,3,5-CTA – Bipy-ethyl

Two-component cocrystal
[CTA–Bipy-bu–Bipy-et]–Guest

3 component host lattice

4 component cocrystal

Self-assembly model
Hexagonal and Square nets

Acid, Amide, Py synthons
Supramolecular isomerism

\[ \text{α,ω-alkanedicarboxylic acid + isonicotinamide} \]

1:2 co-crystal

\[ n = 2, 3, 4, 5, 6 \]

1:1 co-crystal

\[ n = 5, 6 \]

**Cryst. Growth Des. 2003 3 783-790**
Acid–Pyrimidinone dimer

1,3cis,5cis-cyclohexane-tricarboxylic acid, H$_3$CTA

4(3H)-Pyrimidinone, 3H-pyr

3H-pyr N-H...O dimer

3H-pyr N-H...O + C-H...O dimer

4,4’-Bipyridine

*CrystEngComm* 2008, 10th anniversary issue, 1735-1738
Crystal engineering of the composition of pharmaceutical phases


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b Department of Pharmaceutical Sciences, College of Pharmacy, University of Michigan, Ann Arbor, MI 48109-1065, USA

Ibuprofen and its cocrystal

Aspirin and its cocrystal
Structure of a 1:1 complex between the anthelmintic drug mebendazole and propionic acid

Mino R. Caira,*(1) Theo G. Dekker,(2) and Wilna Liebenberg(2)

J Chem Cryst 1998, 11

Molecular complexes of sulfonamides. 3. Structure of 5-methoxysulfadiazine (Form II) and its 1:1 complex with acetylsalicylic acid

Mino R. Caira(1)

J Chem Cryst 1994, 695

Selective formation of hydrogen bonded cocrystals between a sulfonamide and aromatic carboxylic acids in the solid state

Mino R. Caira,* Luigi R. Nassimbeni and Alexander F. Wildervanck

Department of Chemistry, University of Cape Town, Rondebosch 7700, South Africa

Temozolomide

- 8-Carbamoyl-3-methylimidazo[5,1-d]-1,2,3,5-tetrazin-4(3H)-one (TMZ)
- Anti-tumor drug. Clinically active against malignant melanoma
- One crystal structure in the CSD
- Structural origins of polymorphism in TMZ are not known. Polymorphic forms were characterized by PXRD and IR spectroscopy
- No cocrystals
- Co-crystallized TMZ and 4,4'-bipyridine-N,N'-dioxide (BPNO) and COOH partners
TMZ Cocrystals
Experiments planned

TMZ

API

Coformer

BCS class II/IV

GRAS chemicals

New COM that is Patentable

Cocrystal
**TMZ : BPNO 1:0.5**
Form I (MeCN/EtOH)

*TMZ* syn N–H⋯O amide, anti N–H⋯N dimer, C–H⋯O dimer

*BPNO* C–H⋯O dimer, Weak TMZ–BPNO C–H⋯O interaction
TMZ : BPNO 2:1
From II (MeOH, US or DMSO)

**TMZ** syn N–H⋯O N-oxide, C–H⋯O dimer
anti N–H is not intermolecularly bonded
Enantiotropic system

Non-bonded N-H (metastable) form 2 $\rightarrow$ N-H⋯N (stable) form 1

<table>
<thead>
<tr>
<th>Crystal structure</th>
<th>Stoichiometry</th>
<th>Predominant Synthon</th>
<th>Conformer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydrolyzed TMZ</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hydrolyzed TMZ · H$_2$O</td>
<td>1:1</td>
<td>Amide–water (X)</td>
<td>A</td>
</tr>
<tr>
<td>TMZ · Methanolyzed TMZ</td>
<td>1:1</td>
<td>Amide–tetrazinone VI</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amide catemer (II)</td>
<td></td>
</tr>
<tr>
<td>Ethanoloyzed TMZ</td>
<td></td>
<td>Amide–imidazole (V)</td>
<td></td>
</tr>
<tr>
<td><strong>TMZ solvates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMZ · H$_2$O</td>
<td>1:1</td>
<td>Amide–tetrazinone (VI)</td>
<td>A</td>
</tr>
<tr>
<td>TMZ · MeNO$_2$</td>
<td>1:1</td>
<td>Amide–amide (I)</td>
<td>A</td>
</tr>
<tr>
<td>TMZ · DMSO</td>
<td>1:0.5</td>
<td>Amide–amide (I)</td>
<td>A</td>
</tr>
<tr>
<td><strong>TMZ coocrystals with COOH partners</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMZ · Formic acid · H$_2$O</td>
<td>2:1:1</td>
<td>Amide–acid (XI)</td>
<td>A + B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amide–amide (I)</td>
<td></td>
</tr>
<tr>
<td>TMZ · Acetic acid</td>
<td>1:1</td>
<td>Amide–acid (XI)</td>
<td>A</td>
</tr>
<tr>
<td>TMZ · Oxalic acid</td>
<td>1:0.5</td>
<td>Amide–acid (XI)</td>
<td>A</td>
</tr>
<tr>
<td>TMZ · Succinic acid</td>
<td>1:0.5</td>
<td>Amide–acid (XI)</td>
<td>A</td>
</tr>
<tr>
<td>TMZ · DL Malic acid</td>
<td>1:0.5</td>
<td>Amide–acid (XI)</td>
<td>A</td>
</tr>
<tr>
<td>TMZ · p-Aminobenzoic acid · H$_2$O</td>
<td>3:1:1</td>
<td>Amide–acid (XI)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amide–amide (I)</td>
<td></td>
</tr>
<tr>
<td>TMZ · Fumaric acid · H$_2$O</td>
<td>1:0.5:1</td>
<td>Amide–amide (I)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amide–tetrazinone (VI)</td>
<td></td>
</tr>
<tr>
<td>TMZ · Salicylic acid</td>
<td>1:1</td>
<td>Amide–acid (XI)</td>
<td>B</td>
</tr>
<tr>
<td>TMZ · Hydrolyzed TMZ · Cinnamic acid · H$_2$O</td>
<td>3:1:1:1</td>
<td>Amide–amide (XI)</td>
<td>A + B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acid–imidazole (XIII)</td>
<td></td>
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<tr>
<td><strong>TMZ coocrystals with CONH$_2$ partners</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>TMZ · Isonicotinamide</td>
<td>2:1</td>
<td>Amide–amide (I)</td>
<td>A + B</td>
</tr>
<tr>
<td>TMZ · Nicotinamide</td>
<td>2:1</td>
<td>Amide–amide (I)</td>
<td>A + B</td>
</tr>
<tr>
<td>TMZ · Pyrazinamide</td>
<td>1:1</td>
<td>Amide–pyrazine (III)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amide–imidazole (IV)</td>
<td></td>
</tr>
<tr>
<td>TMZ · 4-hydroxybenzamide</td>
<td>2:1</td>
<td>Amide–amide (I)</td>
<td>A</td>
</tr>
<tr>
<td>TMZ · Saccharin</td>
<td>1:0.5</td>
<td>Amide–amide (I)</td>
<td>B</td>
</tr>
</tbody>
</table>
Methods & Characterization

- Accelerate Co-Crystallization by
  - Solvent drop grinding, Ultra-sonication, Temp.
- Characterize Polymorphs and Cocrystals by
  - SC-XRD, XRPD
  - FT-IR, NIR, Raman, Confocal Raman, ss-NMR
  - DSC, TGA, HSM
Why make TMZ cocrystals?

- TMZ is non hygroscopic, rapidly and completely absorbed.
- **White color turns to light tan/pink powder, indicates degradation.**
- Store in Reduced humidity, desiccants, low O₂ atm, dim light.
- Solubility limited to polar solvents.
- Hydrolytic degradation in H₂O, MeOH and EtOH and rate of hydrolysis is higher in water compared to pure ROHs.
- Samples with 1.8% water content decompose faster than <0.1% water. Undergoes degradation at 45% RH.
- **Stable at pH < 5 but labile at pH > 7.**
A process for preparing temozolomide is described in US 2002/0095036. According to the teaching of Example 1 of US 2002/0095036, temozolomide is obtained as a white precipitate. However, the Temodar® drug leaflet and the Physician Desk Reference 60th Ed. (2006) state that the material is “a white to light tan/light pink powder.” The light tan/pink color is indicative of degradation.

In view of the apparent tendency of temozolomide to degrade, as evidenced by the change in color, there exists a need for products and methods, which improve the stability or shelf life of temozolomide. The present invention provides such products and methods.
Some slides removed

• Confidential material displayed at meeting but yet to be published is removed from this public view presentation
Pharma Cocrystals – Case Studies
Applicable to BCS Class II Drugs

- CBZ·COOH cocrystals – Mike Z, CGD, 2003
  - Cocrystals over less soluble hydrate
- CBZ·Sac cocrystal – Mike Z, Almarrson, 2007
  - Oral bioavailability of CC = marketed drug form
- Fluoxetine HCl·COOH – S Childs, JACS, 2004
  - Cocrystals of higher dissolution profile
- Itraconazole·COOH – Almarsson, JACS, 2003
  - Succinic acid cocrystal = amorphous drug
- AMG517·Sorbic acid – A Bak, JPS, 2008
  - 30 mg/kg of CC = 500 mg/kg of free base
Summary and future

• Rational crystal engineering approaches to tune PC-PK-PD of drugs
• Many drugs in pipeline thanks to HTS of combichem in 1990s
• Stability in control because crystalline forms of APIs
• Improved dissolution, controlled release, better tableting, superior medicines
• ICEs = improved chemical entities
Thank You