Crystal Engineering Strategies: Design of new Synthons and Enhancement of API’s Solubility

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Solubility Enhancement of an API

- Physical modification: particle size reduction
- Drug dispersion in carriers: solid dispersions
- Additives/Complexation: cyclodextrins
- Surfactants: microemulsions
- Co-solvents (GRAS approved)
- Solid-state modification: salt formation, solid-state stabilisation of the amorphous state, etc...
Solid State Methods For Improving Solubility And Dissolution Rates

- Habit modification
- Crystal Polymorphism
- Solvates and hydrates
- Salts
- Cocrystals
Crystal Engineering Strategies For Improving Solubility And Dissolution Rates

- Habit modification
- Crystal Polymorphism
- Solvates and hydrates
- Salts
- Cocrystals
OVERVIEW

Crystal Engineering Strategies

- Enhancement of solubility and other properties
  - Salts
  - Hydrates
  - Cocrystals

- Study of Supramolecular Synthons
  - Squaramides
A Supramolecular Synthon is...

“... a structural unit within supermolecules which can be formed and/or assembled by known or conceivable synthetic operations involving intermolecular interactions”

G. Desiraju. Angew. Chem Int. Ed 1995, 34, 2311
A Supramolecular Synthon is...

Component A

Component B

Complementary Functional Groups
A Supramolecular Synthon is...
A Supramolecular Synthon is...
A Supramolecular Synthon is...
A Supramolecular Synthon is...
A Supramolecular Synthon is...
A Supramolecular Synthon is...
Using Graph Sets in Hydrogen-bond arrays

To define the morphology of hydrogen bonding patterns in crystal structures

\[ G_{d}^{a}(n) \]

- **H-bonding motif**
  - D: Dimer or finite
  - C: Chain
  - S: Intramolecular
  - R: Ring

- **Symbols**
  - \( n \): number of atoms
  - \( a \): number of acceptors
  - \( d \): number of donors

Three case-studies

Solvates/Hydrates

Solvent

API

Coformer

Cocrystals

Acid/base

Salts
Three case-studies

Portell, A; Barbas, R; Font-Bardia, M; Dalmases, P; Prohens, R; Puigjaner, C. CrystEngComm 2009, 11(5), 791
Three case-studies

Solvates/Hydrates

Norfloxacin

Puigjaner, C; Barbas, R; Portell, A; Font-Bardia, M; Alcobe, X; Prohens, R. *Crystal Growth & Design*, 2010, 10(7), 2948
Three case-studies

API
Coformer
Cocrystals

API Capsules
Design and study of new synthons

Coformer 1

Synthon 1

Coformer 2

Synthon 2
Ziprasidone

- Low Solubility in water \( \sim 0.3 \, \mu \text{g/mL} \)
- Two ionisable groups in the molecule with \( pK_a \) values 8.4 and 13.3
Salt or Cocrystal?

\[ \Delta pK_a = pK_a \text{ (base)} - pK_a \text{ (acid)} \]

Salt  \( \Delta pK_a > 3 \)

Cocrystal  \( \Delta pK_a < 3 \)
## Microscale salt screening

<table>
<thead>
<tr>
<th>Acid</th>
<th>$pK_a$</th>
<th>Salt</th>
<th>Acid</th>
<th>$pK_a$</th>
<th>Salt</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{H}_3\text{PO}_4$ (Phosphoric)</td>
<td>1.96</td>
<td>√</td>
<td>$\text{HO}\text{C}\text{OO}\text{H}$ (Fumaric)</td>
<td>3.03</td>
<td>√</td>
</tr>
<tr>
<td>$\text{HO}\text{C}\text{O}\text{OH}$ (Citric)</td>
<td>3.13</td>
<td>√</td>
<td>$\text{HO}\text{C}\text{OO}\text{H}$ (Oxalic)</td>
<td>1.27</td>
<td>√</td>
</tr>
<tr>
<td>$\text{HO}\text{C}\text{O}\text{OH}$ (Malic)</td>
<td>3.46</td>
<td>√</td>
<td>$\text{HO}\text{C}\text{SO}_2\text{H}$ (Isethionic)</td>
<td>1.66</td>
<td>√</td>
</tr>
<tr>
<td>$\text{HO}\text{C}\text{O}\text{OH}$ (Lactic)</td>
<td>3.85</td>
<td>X</td>
<td>$\text{HO}\text{C}\text{O}\text{NH}_2\text{OH}$ (Glutamic)</td>
<td>4.25</td>
<td>X</td>
</tr>
<tr>
<td>$\text{HO}\text{O}\text{H}$ (Gluconic)</td>
<td>3.86</td>
<td>X</td>
<td>$\text{HO}\text{SO}\text{SO}_2\text{H}$ (Armstrong’s)</td>
<td>-3.37</td>
<td>X</td>
</tr>
<tr>
<td>$\text{HO}\text{O}$ (Maleic)</td>
<td>1.97</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Aqueous solubilities of Ziprasidone salts

μg/mL

0 200 400 600 800 1000 1200

Free base  HCl  Mesylate  H_3PO_4  Citrate  Fumarate  Oxalate  Isethionate  Malate

0.3 80 28 1121 236 475
Polymorphic Salt Screening

AcOEt / 60ºC

Malic acid

Form A

AcN / 60ºC

Malic acid

Form B

AcN / r.t.

Malic acid

Form C
Polymorphism of Ziprasidone Malate

Form A

Form B

Form C

Form A

Form B

Form C
Polymorphism of Ziprasidone Malate

A - B Enantiotropy
B - C Monotropy

Form A
Form B
Form C
Aqueous solubilities of Ziprasidone malates

Free base: 0.3
HCl: 80
Mesylate: 1000
Malate A: 475
Malate B: 989
Malate C: 1084
Ziprasidone Malate Form C

Possible Synthons

Carboxylic homo synthon

R$_2^2$ (8)

Ionic interaction

Observed Synthons

R$_2^2$ (9)

34%

66%
Hierarchy of Synthons: 32 malate structures in the CCDC
Norfloxacin

3 polymorphic anhydrous forms
Methanolate
Several Hydrates
Salts
Cocrystals
Norfloxacin Bioavailability

“It is a rule that a solvate is always the most stable and therefore the least soluble form in its own solvent”


Neutral Anhydrous forms

Zwitterionic hydrates

Piperazinyl protonated ring in hydrates explains greater solubility
A new polymorphic sesquihydrate

Cooling

Heating

22 °C

-69 °C

-35 °C
A new polymorphic sesquihydrate

Form I

Form II
A new polymorphic sesquihydrate
A new polymorphic sesquihydrate

Form I
One conformation

Form II
Two conformations

Different Ethyl Conformation
Hydrates vs Anhydrous

$R^2_2(8)$

$R^2_2(10)$
API: non-disclosure agreement

The most stable polymorph (Form A) is protected by patent.

Polymorph Screening

3 new metastable polymorphs obtained always with traces of Form A.
Polymorphism Screening

Concomitant Polymorphs

Form A

C and D

B

Metastable forms

Form A

Form C

Concomitant Polymorphs

Significantly different synthons
Polymorphism Screening

Metastable forms

Form A

B

C and D

Enantiotropy

Temperature (°C)

Form C

50°C

100°C

120°C

140°C

Form D

2θ (°)

10 15 20 25
Polymorphism Screening

Metastable forms

Form A

G

B

C and D

Enantiotropy

100 120 140 160
Temperature (°C)

C → D

Form A

Form C

Form A

Form C → D

Form A

Form C → D

Form A

Form D

23 °C

113 °C

116 °C

119 °C
Polymorphism Screening

C and D forms cannot be obtained totally free of the patented form A

C and D forms cannot be obtained totally free of the patented form A

Cocrystal Screening
Ammonia Cocrystal

API-NH$_3$ - Cocrystal

Form D

2.9 %

Intensity (a.u.) vs Temperature (°C)

API-NH$_3$ - Cocrystal

50 °C
70 °C
90 °C
100 °C
110 °C
120 °C

Form D
Squaramides in Supramolecular Synthons: a case study
Double Donor-Acceptor H-bonding Supramolecular Synthons

catemer

\[
\text{HN} \quad \text{D} \quad \text{R}
\]

\[
\text{HN} \quad \text{D} \quad \text{R}
\]

dimer

\[
\text{R} \quad \text{N} \quad \text{O} \quad \text{R'}
\]

\[
\text{R} \quad \text{N} \quad \text{O} \quad \text{R'}
\]

\[
\text{R} \quad \text{N} \quad \text{O} \quad \text{R'}
\]

\[
\text{R} \quad \text{N} \quad \text{O} \quad \text{R'}
\]

\[
\text{R} \quad \text{N} \quad \text{O} \quad \text{R'}
\]

anti / anti

R\text{\textsubscript{2}}\text{\textsubscript{2}}(n)

anti / syn
Head-to-tail H-bonding motif

Form A

Form B

C2/c

Only soluble in DMSO

Portell, A; Barbas, R; Braga, D; Polito, M; Puigjaner, C; Prohens, R. *CrystEngComm*, 2009, 11(1), 52-54
The anti/syn synthon is also geometrically favorable

Very insoluble
Conformational Equilibrium in Solution (CDCl₃)

The figure illustrates the conformational equilibrium in solution for a molecule. The left side of the figure shows the molecular structures in two different conformations, indicating the equilibrium between them. The right side shows the variation in the nuclear magnetic resonance (NMR) spectra of the molecule at different temperatures: 290 K, 260 K, and 240 K. The NMR spectra are labeled with the chemical shifts of the protons $H_a$, $H_b$, and $H_c$.
2D-NMR Dilution Experiment

[Diagram showing two structures connected by a double-headed arrow, with labels for protons Ha, Hb, and Hc.]
Thermodynamic Equilibrium in Solution

Approximate Values of the Equilibrium Constants

<table>
<thead>
<tr>
<th></th>
<th>$K_{CM}$</th>
<th>$K_{CD}$</th>
<th>$K_{Dab}$</th>
<th>$K_{Dc}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.5</td>
<td>0.56</td>
<td>8600</td>
<td>790</td>
</tr>
</tbody>
</table>

$K_{CM}$ fast

Increasing Concentration

$K_{CD}$ slow

or

$K_{Dab}$ fast

$K_{Dc}$ slow

1c

1b

1a
Molecular Electrostatic Potential Surface

Solution vs Solid State

\[ \beta_0 = 5.1 \quad \alpha = 2.1 \quad \beta_N = 4.2 \]

\[ \beta_0 = 5.1 \quad \alpha = 2.8 \quad \beta_N = 4.0 \]
Solution vs Solid State

1a

1b

1c

\( \beta_\text{O} 5.1 \)

\( \alpha 2.1 \)

\( \beta_\text{N} 4.2 \)

\( \beta_\text{O} 5.1 \)

\( \alpha 2.8 \)

\( \beta_\text{N} 4.0 \)
Two Polymorphs

^exo

Temperature (°C)
Melting and crystallization

Two Polymorphs

$^\text{exo}$
Two Polymorphs

120 ºC  130 ºC  150 ºC
Melting  Solid transition  Crystallization from the melt
Two Polymorphs

Form I

Form II

R_{2}^{2}(10)

Hirshfeld’s Surfaces
Two Polymorphs

Form I

Form II

Hirshfeld’s Surfaces

\[ R^2_2(10) \]
Breaking the head-to-tail motif

\[ \beta_N > \beta_O \]
Breaking the head-to-tail motif

2a

2b

2c

2

\( \beta_N > \beta_O \)
Breaking the head-to-tail synthon

\[ R^2_2(12) \]

\[ \beta_o 4.2 \]

\[ \alpha 2.9 \]

\[ \beta_N 4.8 \]

\[ \beta_N > \beta_O \]
Stronger competitors cannot inhibit the head-to-tail synthon

$\alpha = 3.4$

$\beta = 4.3$

$\beta = 4.9$
SQ head-to-tail as a scaffold for new cocrystal structures
SQ head-to-tail as a scaffold for new cocrystal structures
SQ head-to-tail as a scaffold for new cocrystal structures
Cocrystal Screening

Fumaric acid – squaramide cocrystal

Synthons not found
SQ head-to-tail as a scaffold for new cocrystal structures
Cocrystal Screening

Fumaric acid – squaramide cocrystal
SQ head-to-tail as a scaffold for new cocrystal structures
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