CRYSTAL ENGINEERING APPROACHES FOR THE DESIGN OF FOOD AND PHARMACEUTICAL FORMULATIONS

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Formative formulation
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Overview of the presentation

Crystal engineering: motivation and some experimental strategies

Engineering crystals for the complex soft food structures
• Multiphase formulations for food and pharma applications
• Particle stabilization (Pickering)
• Crystal properties and implications for Pickering particles

Modelling Methodology
• Model compound: quercetin and its hydrates
• Attachment energy model for the prediction of intermolecular interactions and crystal anisotropy

Results and Discussion
• Bulk intermolecular interactions and surface chemistry for the three quercetin polymorphs
• Experimental techniques for model validation

Conclusions and future developments
Main crystal properties

- Size
- Shape
- Structure (polymorphs etc.)
- Purity

- Same compound but different structures
- Different properties (thermodynamic, kinetics, mechanical, surface)
- Problem with stability when metastable forms are produced

CONTROL IS THE KEY!
How to engineer crystals

The Crystal Engineering Approach utilises the understanding of the intermolecular interactions within crystalline materials to design specifically tailored solid materials in terms of shape, size and polymorphism.

Choice of solvent
Temperature profile
Use of additives
Three known forms of OABA

- Form I and II are normally nucleated from solution
- Form III is very difficult to nucleate
Equilibrium of OABA in water

- OABA can exist in solution as a neutral molecule, with positive or negative charge or as a zwitterion.
- Different forms of OABA presents different UV/Vis spectra.


Zapala et al., *Biophysical Chemistry*, 2013
Changes in the UV/Vis spectrum of OABA solutions can be associated with different amount of zwitterions in solution.

- **Blue shift** (water)
  - IPA, methanol, ACN, dioxane, ethanol...
- **Red shift (IPA)**
  - Water

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Zapala et al., *Biophysical Chemistry*, 2009
Murugan et al., *PCCP Communication*, 2011
Experimental results

- In water and IPA mixtures a limiting peak position for UV/Vis and Raman (benzene ring vibration) was found over which only form II nucleates.

Simone & Nagy, *CrystEngComm*, 2015, **17**, 6538-6547
Shape manipulation of succinic acid (SA) via temperature cycling

- SA in water (20 °C saturation temperature)
- Initial cooling from 30 °C to 10 °C at -0.5 °C/min
- Temperature cycling varying heating/cooling rate and cycles’ amplitude
- Sampling and off-line analysis (Optical and Raman spectroscopy, single crystal XRD) during the experiments

<table>
<thead>
<tr>
<th>Experiment n°</th>
<th>Cycles amplitude (°C)</th>
<th>Heating/ Cooling rates (°C/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.5</td>
<td>+0.3</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>+0.3</td>
</tr>
<tr>
<td>3</td>
<td>7.5</td>
<td>+0.3</td>
</tr>
<tr>
<td>4</td>
<td>4.5</td>
<td>+0.1</td>
</tr>
<tr>
<td>5</td>
<td>4.5</td>
<td>+0.5</td>
</tr>
</tbody>
</table>
The (100) face intercepts chains of succinic acid molecules linked by hydrogen bonded carboxylic acid dimers (polar face).

Water molecules interact with the (100) face, inhibiting growth along the direction perpendicular to this face.

Temperature cycling generates a diamond shape.

Face (110) and (01-1) outgrow face (100).

Effect of Pluronic P123 on succinic acid crystal shape

- Pluronic P123 inhibit growth of the side faces of the crystal leading to a **needle-like shape** along the (100) direction.

Klapwijk et al., *Crystal Growth and Design*, 2016
Multiphase formulations: emulsions and foams

- Multiphase formulations are widely used for several applications within the **food**, **cosmetic** and **pharmaceutical** industries;
- Used for oral or topical **controlled delivery** of poorly water soluble drugs and nutraceuticals;
- Extremely common food structures;
- Common formulations for cosmetic products, fast adsorption and low greasiness;
- They can be **thermodynamically unstable** and undergo phase separation over time (limited shelf-life);
- Reducing the **interfacial tension** using surfactants or solid particles (Pickering) can improve long term stability.
Particle stabilization of multiphase systems (Pickering)

- Pickering formulations are more stable than surfactant based ones because particles adsorb more strongly at the interface;
- Less adverse effects, possibility to use biocompatible, naturally sourced particles (consumer acceptability);
- The free energy \( E \) required to desorb a spherical particle from an interface can be expressed as:

\[
E = \gamma \pi r^2 (1 - \mid \cos \theta \mid)^2
\]

Where \( \gamma \) is the interfacial tension between the two phases, \( r \) is the particle radius and \( \theta \) is the contact angle.

Particle stability, solubility and wettability are critical properties for Pickering particles!
Faceted crystals as Pickering particles: the issue of anisotropy

- Most solid particles are not spherical but they are faceted;
- Different composition and surface chemistry on each face;
- Anisotropy can affect Pickering stabilization!

Macroscopic crystals of (a) paracetamol, (b) aspirin, and (c) S-(+)-ibuprofen.

Which shape and polymorph work best?

Heng et al. (2006) AAPS PharmSciTech
Molecular modelling for crystal properties prediction

- The intermolecular interaction energies within the crystal structure can be calculated using an interatomic potential (Momany);
- The calculated interactions can be ranked based on their contribution to the total lattice energy;
- The Attachment Energy Model identifies which intermolecular interactions contribute to the growth of the specific crystal faces \((hkl)\);
- Assumes a slice of \(d_{hkl}\) thickness added to the surface and the energy of the interactions between the new slice and surface proportional to growth rate;
- The chemistry of the interactions dominating the growth of a particular surface (e.g. H-bonding, dispersive etc.) can give an indication of crystal properties.

\[ E_{\text{crystal}} = E_{\text{slice}} + E_{\text{attachment}} \]

\[ E_{\text{attachment}} \propto \text{Surface Growth Rate} \]

Momany et al. (1974) JACS
Rosbottom et al. (2015) CrystEngComm
Model compound: quercetin

- Quercetin is flavonoid molecule found in fruits and vegetables;
- It is known to be an antitumor agent and to exhibit antiallergic, anti-inflammatory and antioxidant activity;
- Due to the wide range of health benefits, quercetin finds use in nutraceuticals and food supplements;
- Three different structures: anhydrous (QA), monohydrate (QMH) and dihydrate (QDH);
- Poorly soluble in both water and oil → good candidate particle for Pickering water in oil emulsions.
Molecular modelling methodology

- The crystal structures of the three quercetin polymorphs were retrieved from the Cambridge Crystallographic Data Centre (CCDC);
- The Mercury software was used to image each calculated intermolecular interaction;
- The Habit 98 software (developed in Leeds), was used to predict strength, directivity and dispersive nature of the intermolecular interactions in the crystal structure (Momany force-field);

<table>
<thead>
<tr>
<th></th>
<th>Quercetin anhydrous</th>
<th>Quercetin monohydrate</th>
<th>Quercetin dihydrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td>C₁₅H₁₀O₇</td>
<td>C₁₅H₁₀O₇·H₂O</td>
<td>C₁₅H₁₀O₇·2H₂O</td>
</tr>
<tr>
<td>Space Group</td>
<td>P ₂/n 2, a Orthorhombic</td>
<td>P 2₁/c Monoclinic</td>
<td>P 1 Triclinic</td>
</tr>
<tr>
<td>Cell Volume (Å³)</td>
<td>1721.6</td>
<td>1272.61</td>
<td>701.931</td>
</tr>
<tr>
<td>Cell Density (g/Å³)</td>
<td>0.702</td>
<td>1.007</td>
<td>0.964</td>
</tr>
</tbody>
</table>
QA structure and main intermolecular interactions in the crystal structure

1. First strongest interaction (38.4% of lattice energy): Hydrogen bonds between OH groups and permanent dipole-dipole interactions

2. Second strongest interaction (25.8% of lattice energy): Zig-zag chain structure formed by hydrogen bonds between OH groups and permanent dipole-dipole interactions

3. Third strongest interaction (14.1% of lattice energy): Permanent dipole-dipole interactions from COOH groups, dimers arrangement
QMH structure and main intermolecular interactions

1. First strongest interaction (24.5% of lattice energy): π-π stacking interactions between quercetin-quercetin molecules

2. Second strongest interaction (10.2% of lattice energy): double hydrogen bonding interaction between two quercetin molecules

3. Third strongest interaction (9.8% of lattice energy): hydrogen bonding between quercetin-water molecules
QDH structure and main intermolecular interactions

1. First strongest interaction (37.8% of lattice energy): \( \pi-\pi \) stacking interactions between quercetin-quercetin molecules, uninterrupted stack

2. Second strongest interaction (7.9% of lattice energy): hydrogen bonding interaction between water and quercetin molecules

3. Third strongest interaction (3.5% of lattice energy): permanent dipole-dipole interaction quercetin-quercetin (dimer)
QA calculated morphology and face specific surface chemistry

Faces 011 / 011 / 0-11 / 0-11, \( \varepsilon_{hkl} = 52.5\% \), Dominant surface
Quercetin-quercetin H-bonding & Van der Waals interactions from phenyl & pyrone rings

Faces 101 / 10-1 / -101 / -10-1, \( \varepsilon_{hkl} = 71.2\% \), Dominant surface
Quercetin-quercetin H-bonding, - OH and C=O contributions, Polar interactions

Faces 111 / 11-1 / -111 / 1-11 / 1-11 / -11-1 / -1-11, \( \varepsilon_{hkl} = 40.9\% \)
Faces 210 / -210 / 2-10 / -2-10, \( \varepsilon_{hkl} = 29.4\% \)
Faces 020 / 0-20, \( \varepsilon_{hkl} = 24.9\% \)
Non-Dominant surfaces
Quercetin-quercetin H-bonding & Van der Waals interactions

Faces 200 / -200, \( \varepsilon_{hkl} = 59.8\% \), Dominant surface
Quercetin-quercetin H-bonding, zig-zag stacking of quercetin molecules, Polar interactions
QMH calculated morphology and face specific surface chemistry

**Faces 002 / 00-2**, $\varepsilon_{hkl} = 85.6\%$
- Dominant surface
- Quercetin-quercetin double H-bonding between –OH and C=O groups, no interaction with water molecule, Polar interactions

**Faces 100 / 10-0**, $\varepsilon_{hkl} = 69.6\%$
- Dominant surface
- Quercetin-quercetin H-bonding between –OH groups, no interaction with water molecule, mostly polar interactions

**Faces -102 / 10-2**, $\varepsilon_{hkl} = 58.2\%$
- Dominant surface
- Hydrogen bonding between quercetin-quercetin and quercetin-water, polar interactions

**Faces 11-1 / 1-1-1 / -111 / -1-11**, $\varepsilon_{hkl} = 32.7\%$
- Faces 110 / 1-10 / -110 / -1-10, $\varepsilon_{hkl} = 31.2\%$
- Faces 011 / 0-11 / 01-1 / 0-1-1, $\varepsilon_{hkl} = 27.5\%$
- Non-Dominant surfaces
- Apolar $\pi-\pi$ stacking interactions, hydrogen bonds between quercetin-quercetin and quercetin-water

**Faces 110 / 10-1**, $\varepsilon_{hkl} = 32.7\%$
- Faces 011 / 0-11 / 01-1 / 0-1-1, $\varepsilon_{hkl} = 27.5\%$
- Non-Dominant surfaces
- Apolar $\pi-\pi$ stacking interactions, hydrogen bonds between quercetin-quercetin and quercetin-water
QDH calculated morphology and face specific surface chemistry

**Faces 10-1 / -101, $\varepsilon_{hkl}=34.9\%$, Both quercetin-quercetin and quercetin-water apolar interactions**

**Faces 01-1 / 0-11, $\varepsilon_{hkl}=21.6\%$, Combination of polar and non polar interactions (both quercetin-quercetin and quercetin-water)**

**Faces 0-10 / 010, $\varepsilon_{hkl}=91.0\%$, Dominant Surface Mostly growing via quercetin-quercetin apolar interactions ($\pi - \pi$ stacking)**

**Faces -110 / 1-10, $\varepsilon_{hkl}=73.2\%$, Dominant Surface Polar quercetin-quercetin interactions contributes to growth**

**Faces 100 / -100, $\varepsilon_{hkl}=69.6\%$, Dominant Surface Polar water-quercetin interactions (including hydrogen bonds) contributes to growth**

**Faces 00-1 / 001, $\varepsilon_{hkl}=19.6\%$ and Faces -111 / 1-11, $\varepsilon_{hkl}=33.1\%$, Combination of polar and non polar interactions (both quercetin-quercetin and quercetin-water)**
Experimental validation

- Face specific wettability can be measured via contact angle and single crystal XRD face indexing;
- This information is NOT enough to understand the effect of crystal anisotropy;
- **Advance imaging** for better understanding of interface orientation and interaction.
Conclusions and future work

- Molecular modelling using the Attachment Energy Model is a promising tool to estimate face specific chemical properties of biocompatible crystals;
- These information can help in the design of tailor made crystals for Pickering stabilization;
- Experimental validation is still needed (advance microscopy, contact angle, single crystal XRD face indexing);
- Better understanding of the relation between crystal anisotropy and orientation at the interface is necessary for efficient particle design.
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