Solvent Selection in Pharmaceutical Crystallisation

Oct/2020

Accelerating the development of quality, life-changing medicines to patients
Material to Medicine Process Research

- Chemistry
- Engineering
- Bioprocessing
- Continuous
- Scale-up
- Containment
- Analytical
- Formulation
Solvent Selection in Pharmaceutical Crystallisation Process Development

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Technobis webinar

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• Introduction

• *In-silico* predictive modelling

• APC Crystallisation Early Phase Workflow

• Early Development Case study 1: Antisolvent crystallisation

• Early Development Case study 2: Cooling crystallisation

• Summary
• **Solvent choice** - cornerstone of good crystallisation development
  
  – Solubility (Yield and Productivity)
  
  – Growth and nucleation kinetics (Seedability)
  
  – Impurity rejection
  
  – Polymorph control
  
  – Solvation/Oiling propensity
  
  – Crystal morphology
  
• Solvent selection Platform: *In-silico predictive modelling* and *smart experimentation*

• Reduce early development timeframes and risk
**In-Silico predictive modelling**

**Molecular simulations**
- First-principles

**UNIFAC (group-contribution)**
- Semi-empirical
  - Molecular structure, Tm, dfH,
  - Existing solubility data

**Regression**
- Empirical
  - Solubility $f(T, X)$

**Input:**
- **Molecular structure only**

**✓ Relative solubility**
**✓ Solvate/cocrystal propensity**
**✓ Impurity purge**
**✓ Oiling propensity**
**✓ Crystal shape**
**✓ Polymorphism**

**Early stage**
- Solvent screen

**Solubility prediction**

**Late stage**
- Crystallisation Design

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COSMOtherm
Quantum Mechanics + Statistical Thermodynamics

- Relative Solubility
  \[ \mu_S^x = \sum_\sigma p^x(\sigma)\mu_S(\sigma) + \mu_C^x \]

- Solvate/Cocrystal prediction

\[ H_{\text{mix}} = H_{AB} - (H_A + H_B) \]

Materials Studio
Molecular Mechanics/Molecular Dynamics

- Conformational search
- Lattice energy calculations
- Crystal shape prediction
Solvent Selection – Workflow

Computational Solvent Screen
- Solubility
- Solvate/Oiling Propensity
- Impurity Purge

Experimental validation
2-point solubility
- Yield, Productivity
- Purity, Form

Small scale crystallisation experiments
- MSZW
- Form, Purity
- Crystal shape
- Yield
- Productivity

70 solvents
8 solvents
2-3 solvents

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Solvent Selection – Workflow

Computational Screen
- 70 solvents
- ✓ Solubility (Yield, Throughput)
- ✓ Solvate Propensity
- ✓ ICH class, b.p.

Experimental 2-point solubility
- 8 solvents
- ✓ Yield, Throughput
- ✓ Form, purity

Screening crystallisations (unseeded)
- 3 solvents
- ✓ MSZW
- ✓ Form, purity
- ✓ Morphology
- ✓ Yield

Process definition

Computational binary mix screen
- 6 antisolvents
- ✓ Miscibility
- ✓ ICH class

Experimental 6-point isothermal solubility
- 3 antisolvents
- ✓ Antisolvent efficiency
- ✓ Cosolvency
- ✓ Synergistic effects

Yield < 75%

Yield > 75%

poor

2 solvent systems

3 antisolvents x 2 solvents:
@ 15w% synergistic max
@ 50w% antisolvent/solvent

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Crystallisation Early Development – Case Study 1

\[ T_m(\text{API})=215 ^\circ \text{C} \]
**Case Study 1 – Background**

- **Polymorphism:**
  - Form 1 (stable below 50 °C) and Form 2
  - Enantiotropically related
  - Two forms clearly distinguishable by DSC/Raman
  - High Solvate formation propensity

- **Purity:**
  - Crude input material variability
  - Identified and unidentified impurities

- **Desired particle attributes:**
  - Good filterability, no specific output PSD
  - Spray drying technology (formulation)

  ![DSC Chart](image.png)

  ![Raman Chart](image.png)

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Case study 1 – Relative Solubility and Solvates

1) Relative Solubility Ranking

<table>
<thead>
<tr>
<th>Solvent</th>
<th>rel. S</th>
<th>μ kcal/mol</th>
<th>UPLC mg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMP</td>
<td>1</td>
<td>-5.90</td>
<td>-</td>
</tr>
<tr>
<td>DMPU</td>
<td>0.62</td>
<td>-5.71</td>
<td>714</td>
</tr>
<tr>
<td>DMI</td>
<td>0.61</td>
<td>-5.63</td>
<td>-</td>
</tr>
<tr>
<td>NBP</td>
<td>0.34</td>
<td>-5.36</td>
<td>417</td>
</tr>
<tr>
<td>THF</td>
<td>0.33</td>
<td>-5.01</td>
<td>242</td>
</tr>
<tr>
<td>MeOAc</td>
<td>0.09</td>
<td>-4.73</td>
<td>56</td>
</tr>
<tr>
<td>MeTHF</td>
<td>0.05</td>
<td>-3.94</td>
<td>47</td>
</tr>
</tbody>
</table>

2) Solvate Formation Propensity

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- Antisolvent screen

- Water synergistic solvation effect
- **Heptane** best option – 96% Yield & 12g/100g Throughput
Case Study 1 – Process Definition to Scale-up

**Process definition** at 100 ml scale
✓ Yield 96%, Throughput 12g/100g, desired Form I, rods/needles

**Optimised process** successfully scaled-up:
✓ Form I, Rods/good filterability, low residual THF content
➢ Strong fluorescence (baseline) observed in the supplied Crude 1, Crude 2 and Crude 3
➢ Fluorescence observed in Purified-1 exhibited some fluorescence
➢ Purified-2 and Purified-3 no fluorescence (flat baseline)
➢ Raman able to detect (fluorescence) impurities not detectable by UPLC (ppm)
Crystallisation Early Development – Case Study 2

$T_m(\text{API})=126\,^\circ\text{C}$
Case Study 2 – Background

- Polymorphism:
  - Supplied **Form 1 (stable)** and **Form 3 (metastable)**
  - Two forms clearly distinguishable by DSC/Raman

- Purity:
  - API unstable at elevated temperatures

- Particle Engineering:
  - PSD and crystal morphology
  - Select suitable solvent system for further **Kinetic assessment for continuous crystallisation (MSMPR)**
  - Pascual G. et al AIChE Orlando, 2019

- Raman useful tool in Early Development

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Case study 2 – Solubility Trends

- Method: COSMO-RS, SLE/LLE
- $T_m=126 \, ^\circ C \Delta_f H=37.3 \, \text{kJ/mol}$ as reference

**Selection criteria** - cooling crystallisation preferred, high yield and throughput:
- Low solubility at 20°C, steep solubility curve, high solubility 50°C
### Case study 2 – Experimental solubility

- **Experimental 2-point solubility:**
  - Isothermal slurry method
  - Isolated solid (form) and mother liquor (solubility, purity)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility 20°C (mg/g)</th>
<th>Solubility 48°C (mg/g)</th>
<th>Form</th>
<th>Impurity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEK</td>
<td>173</td>
<td>548</td>
<td>I</td>
<td>RT 15.0</td>
</tr>
<tr>
<td>Acetone</td>
<td>94</td>
<td>448</td>
<td>I</td>
<td>N/A</td>
</tr>
<tr>
<td>1-butanol</td>
<td>83</td>
<td>329</td>
<td>I</td>
<td>RT 15.0</td>
</tr>
<tr>
<td>2-butanol</td>
<td>75</td>
<td>244</td>
<td>I</td>
<td>RT 15.0</td>
</tr>
<tr>
<td>2-propanol</td>
<td>53</td>
<td>249</td>
<td>I</td>
<td>N/A</td>
</tr>
<tr>
<td>Anisole</td>
<td>53</td>
<td>170</td>
<td>I</td>
<td>N/A</td>
</tr>
<tr>
<td>IPrOAC</td>
<td>35</td>
<td>99</td>
<td>I</td>
<td>N/A</td>
</tr>
</tbody>
</table>

- Selection criteria: *high yield, throughput, purity, desired form*
Case study 2 – Small scale crystallisation

- **Crystalline 5 ml – Proof-of-concept crystallisation experiments**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility at 48 °C (mg/g)</th>
<th>$T_N$ (°C)</th>
<th>Morphology</th>
<th>Concentration at 0°C (mg/g)</th>
<th>Yield (%)</th>
<th>Form</th>
<th>Impurity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-propanol</td>
<td>249</td>
<td>35.6</td>
<td>rod</td>
<td>28.39</td>
<td>88</td>
<td>I</td>
<td>N/A</td>
</tr>
<tr>
<td>isopropyl acetate</td>
<td>99</td>
<td>24.3</td>
<td>rod</td>
<td>19.94</td>
<td>80</td>
<td>I</td>
<td>N/A</td>
</tr>
<tr>
<td>anisole</td>
<td>170</td>
<td>24.3</td>
<td>rod</td>
<td>32.06</td>
<td>81</td>
<td>I</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Antisolvent screen in IPA:

- Heptane the best antisolvent (some synergistic effect)
- Yield > 94%, 1 Vol (throughput ½ reduced)
Case Study 2 - Process Definition

- **Process Definition assessment**
  - Seeding point – MSZW and induction time (100 and 400 ml)
  - Yield > 94%, High throughput (12 g/100g), high purity, no solvation, particle morphology acceptable
Crystal morphology: Predicted vs Experimental

API 2: Rod-like morphology

Predicted

Experimental

API 3: Parallelogram morphology

Attachment Energy Method; COMPASS II Force-Field, Vacuum Morphology
Solvent influence on crystal morphology

No interaction with external environment

Crystal morphology of API 4 predicted in different solvents calculated with Dmol3 and implicit solvation model (COSMO)
Early Phase Crystallisation Development Workflow demonstrated:
- Case study 1 – Isothermal Antisolvent Crystallisation
- Case Study 2 – Cooling Crystallisation

**In-silico** predictive modelling with smart experimentation
- Minimise dev time, material consumption, maximising the value of the choice
- Avoid incorrect thermodynamic choices for **yield**, **form**, **solvation** etc being made in Early stage Development

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Thank you!

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