Solid-Form Screening and Selection: Challenges and Strategies of Difficult Molecules

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Objectives

• Pharmaceutical impact
• HT solid-state form screening and selection processes
• Can Raman spectroscopy differentiate ALL solid-forms of an API?
• Salt screening strategies to crystallize highly soluble and difficult to crystallize compound
• Polymorph screening and selection of highly polymorphic compounds/salts
Pharmaceutical Impact of Solid-State Forms

- Manufacturing Processes
  - API purification and isolation
  - Drug product (dosage form)
- Material Properties
  - Solubility (bioavailability)
  - Stability (chemical and physical)
  - Physical properties
- Product Performance
  - Efficacy
  - Safety
  - Shelf life
- Regulatory & IP
  - CMC
  - Patents

Fit-for-Purpose

- Risks related to target and mechanism viability, toxicology (tolerance, safety), efficacy, etc.
- Portfolio considerations
- Financial considerations
- Timeline considerations

Development Timeline

Salt & Polymorph Screening: Timing and Scope

**Solid-Form Screening**
- 50-1000 crystallization experiments
- Yields uncertain (a few crystals to ~mg)
- Diverse range of solvent properties (e.g., viscosity, boiling point)
- Salts and crystal-form differentiation
- Material limitations (1~5 g)
- Fast-to-decision (~1 month)

**Development Timeline**

- Lead Optimization
- Preclinical Efficacy
- Lead Nomination
- Preclinical Toxicology
- Clinical Studies
- NDA
- Commercial

Salt selection
Polymorph selection
Optiform™ Technologies

- High-throughput platform for salt, crystal-form, and cocrystal screening
- Developed and refined over the past ten years
- Applied to more than 500 compounds, spanning from early stage lead compounds through launched products

Filtration and Analysis Plate
Tiered Analytical Strategy

Crystal → Raman → Scale-up

- XRPD, DSC, TGA-IR
- PLM, PXRD
- DSC/TGA-IR
- NMR, IC, HPLC
- GVS
PXRD vs. Raman

- **PXRD**
  - Gold standard
  - Sensitivity & sample size
  - Sample presentation
  - Data quality and interpretation (resolution, preferred orientation)

- **Raman**
  - Sample presentation
  - High sensitivity with small samples (single crystal)
  - Chemical information
  - Can Raman differentiate different crystals forms reliably?
Dispersive vs. FT-Raman

• **Dispersive Raman Microscope**
  – Better sensitivity (single crystal)
  – Microscope (µm laser spot) → Orientation effect
  – System stability and calibration introduce larger spectral variation
  – Local heating and fluorescence

• **FT-Raman**
  – Lower sensitivity with small samples (<50 µg)
  – Great spectral reproducibility (HeNe laser reference, < 0.1 cm⁻¹)
  – Larger laser spot (50 µm ~ 1 mm)
  – Less fluorescent interference (1064 nm)

FT-Raman Spectroscopy

Camera

XYZ stage
FT-Raman Spectra of Compound A

Particle sizes: <20 ~ >600 µm
Peak positions
SD: < 0.16 cm⁻¹
Range: < 0.51 cm⁻¹

Compound B: Samples from Screening

![Graph showing Raman shift (cm⁻¹) vs. Int]
Compound C: Two Different Polymorphs
Succinylsulfathiazole (SST)

Six anhydrous polymorphs
Three polymorphic monohydrates
Solvates (acetone, 1-butanol)

Inter-conversion Chart of SST


S.R. Burns; R.R.Pfeiffer; J.G. Stowell, *Solid-State Chemistry of Drugs*, 2nd Ed. p.171
Overlaid Spectra of All SST Samples

163 samples

Temp. Cycling - 88
Fast Evaporation - 30
Slow Evaporation - 39
Cooling - 6
SST - Raman Spectra of Unique Groups

Raman shift (cm⁻¹)

Int

SST HI monohydrate
SST HII
SST-2 Form I
SST-2m Form IV
SST 1-butanol solvate
SST acetone solvate
SST dioxane solvate
SST-2 THF solvate
SST 1-pentanol solvate
SST-2 (formamide) solvate
SST (ethanol) solvate
SST-2 (ACN) solvate
SST-2 (methylacetate) solvate

Raman shift (cm⁻¹)
SST - XRD Patterns of Unique Groups

![Powder X-ray Diffraction Patterns](image)

- possible new non-solvated form or solvate from formamide
- ethanol solvate
- tetrahydrofuran solvate
- dioxane solvate
- 1-butanol solvate
- form IV
- form I
- hydrate II
- hydrate I

2.0 5.0 8.0 11.0 14.0 17.0 20.0 23.0 26.0 29.0 32.0 35.0 38.0 41.0 44.0 47.0

Deg.
SST - IR Spectra of Unique Groups

Absorbance

Wavenumbers (cm⁻¹)
SST - DSC of Unique Groups

- hydrate I
- hydrate II
- form I
- form IV
- 1-butanol solvate
- dioxane solvate
- tetrahydrofuran solvate
- ethanol solvate
- new polymorph or solvate from formamide

Heat Flow (W/g) vs. Temperature (°C)
Case Study #1: Improve Solubility and Polymorphism

**Project Background**
- MW: ~ 600
- high dose (100-400 mg IR tablet/capsule)
- pKa = 5.2 (acyl sulfonamide)

**Free-acid (FA)**
- Two polymorphs
- Practically insoluble
- Poor exposure (<1%F in dog)

**Na Salt**
- Good aqueous solubility and exposure (30%F in dog)
- 19 crystal forms (anhydrate, hydrate, many solvates)
- Preparation of the “anhydrous” form in large scale was not feasible due to channel solvate formation (Form 9).
- Residual solvent in the channel solvate was extremely difficult to remove.
Case Study #1: Single Crystal Structure of Na Salt

Channel solvate
• residual solvents
• hygroscopic

First campaign batch was dried at 65 °C for 3 days!
Case Study #1: Salt & Polymorph Screening

Salt Screening & Evaluation

- Crystalline $K^+$, $Mg^{++}$, $Ca^{++}$, choline, ethanolamine salts
- $K^+$, $Mg^{++}$, $Ca^{++}$, and ethanolamine salts have complicated polymorphism and/or poor aqueous solubilities/PK

Choline Salt is the Optimal Salt

- Aqueous solubility (60 mg/mL)
- Bioavailability (60% in dog)
- Polymorph – 1 (mp ~180C)
- Non-hygroscopic
- Good stability
Case Study#2 – Improve Crystallinity and Chemical Stability

Project background

- Aggressive timeline (FTIH start in <9 months)
- Highly soluble
- No crystalline form
- Improve chemical stability w/strong acid salts

MW=427
HT salt screen identified two crystalline salts:

- Acetate salt is unstable & eliminated quickly
  - mp ~ 136°C
  - Loss of acetic acid starts ~ 80°C on TGA-IR
  - Loss of acetic acid when dried at 50°C overnight.
- Fumarate salt (mp ~ 180°C) was supplied to support DRF studies
  - Good phys. prop. & solubility
  - Risks associated with the fumarate salt
    - Acyl migration
    - Poor solubility of fumaric acid (CD)
    - Potential API and DP stability (Michael addition)
Case Study #2 – Crystallinity and Chemical Stability

Carefully designed manual expts crystallized HCl salt

- Good phys. prop. (mp ~ 211°C)
- A single anhydrous form
- Good solubility in bio-relevant media (~80 mg/mL)
- No acyl migration and Micheal addition risks

![Graph showing the solution stability of GSK2110183 in MeOH](image)
Case Study #3: Co-crystal to Improve Crystallinity

- Sodium-dependent glucose cotransporter (SGLT) inhibitor
- Highly soluble
- Difficult to crystallize
- Cocrystals to confer crystallinity and improve mp.

Case Study #4: Polymorphism of Opt0802

**Objective:** Examine form space of an API with moderate flexibility and MW

- API has several heteroatoms that can act as H-bond donors and acceptors thus propensity for polymorphism is expected to be high
- Screen was performed using 48 solvent systems and three crystallization modes (thermal treatments/temperature-cycling, evaporation, rapid cooling)
Case Study #4: Polymorphism of Opt0802

- Anhydrate 1 (Group A)
- Anhydrate 2 (Group D)
- Anhydrate 3 (Group G)
- THF Solvate (Group E)
- DMSO Solvate (Group F)
- Methanol Solvate (Group C)

Iso-structural Solvates (Group B):
- Acetonitrile
- Acetone
- 1-Butanol
- Chloroform
- Dichloromethane
- Diethyl Ether
- Ethanol
- Ethyl Acetate
- 2-Methoxyethanol
- 1-Methoxy-2-Propanol
- Methyl Acetate
- Nitromethane
- 2-Propanol
- Trifluoroethanol

Evaporation THF/H₂O:
- Anhydrate 1 and 2
- Slurry at 25°C

Evaporation from Acetone/H₂O:
- Anhydrate 1 and 2
- Slurry at 25°C

Evaporation from THF:
- Anhydrate 1
- Room Temperature
- Drying

Evaporation from DMSO:
- Anhydrate 1

Methanol Slurry:
- Anhydrate 3

Δ105°C
Case Study #4: FT-Raman Spectra of Opt0802
Case Study #4: Iso-structural Solvates of Opt0802

### Case Study #5: Complicated Polymorphism of GW786034B (Pazopanib)

**Votrient**, Pazopanib

#### 28 solid-state forms
- Polymorph control
- Data Analyses

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anhydrates</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anhydrate 1</td>
<td>MP = 290°C w/decomposition</td>
</tr>
<tr>
<td></td>
<td>Anhydrate 2</td>
<td>MP = 216°C, then recrys. to Anhydrate 1</td>
</tr>
<tr>
<td>Hydrates</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Monohydrate</td>
<td>3.8% water content (monohydrate)</td>
</tr>
<tr>
<td></td>
<td>Dihydrate</td>
<td>8.2% water content (dihydrate)</td>
</tr>
<tr>
<td>Solvates</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acetone, MeOH (1), EtOH, 2-butanone</td>
<td>1:1 stoichiometry; Desolvates to Anhydrate 2 (heat to ~150°C)</td>
</tr>
<tr>
<td></td>
<td>1-Propanol, cyclohexanone, DMSO, Chloroform, DMF, 1-Methyl 2-pyrrolindone</td>
<td>1:1 stoichiometry; Desolvates to Anhydrate 1 (heat to ~150°C)</td>
</tr>
<tr>
<td></td>
<td>ethylene glycol, chlorobenzene, MeOH (2), MIBK, THF</td>
<td>non-stoichiometric; Desolvates to Anhydrate 1 (heat to ~150°C)</td>
</tr>
<tr>
<td></td>
<td>1,4 dioxane</td>
<td>0.5:1 (solvent:API) stoichiometry; Desolvates to Anhydrate 1 (heat to ~150°C)</td>
</tr>
<tr>
<td></td>
<td>Acetonitrile Solvate</td>
<td>nonstoichiometric; forms desolvated solvate heated to 150°C, then conversion to Anhydrate 1 heated to 200°C</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Desolvated ACN solvate</td>
<td>structurally similar to ACN solvate</td>
</tr>
<tr>
<td></td>
<td>Dehydrated Dihydrate</td>
<td>structurally similar to dihydrate</td>
</tr>
</tbody>
</table>

Case Study #5: Unsupervised Clustering Analyses

Case Study #5: Final API Crystallization Process

**Situation:**
- Stable ACN solvate discovered
- Current process: 5%aq. ACN (water addition)

**Risk assessment:**
- Process-Relevant Forms:
  - Form 1
  - Monohydrate
  - ACN Solvate
  - ACN/water mixtures
  - T = 0-80°C

**Risk Mitigation:**
- Heated transformation of monohydrate in 10% aq. ACN
Concluding Remarks

• Solid-form selection is a critical development activity for small-molecule drug candidates.

• HT screening is valuable & effective in most cases, but some difficult molecules will require careful design and control of crystallization, and nucleation aid such as seeding with crystals of a structurally similar compound.

• Raman spectral differences between different solid-forms of an API are relatively small, and appears throughout the entire spectral range.

• All solid-state forms of an API can be differentiated with the appropriate Raman spectrometers and sampling parameters.
  — Spectral quality (S/N, resolution, minimal background)
  — Spectral reproducibility (better than 1 cm\(^{-1}\))

• FT-Raman is nearly ideal for solid-form screening & routine characterization.
discover more.

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