An Overview of Solid Form Screening During Drug Development

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Definitions

• Polymorph
  – FDA: crystalline and amorphous forms as well as solvated and hydrated forms
  – Purists: crystalline forms with the same molecular composition (for example two anhydrous forms can be polymorphs, or two monohydrates can be polymorphs, but an anhydrate and a monohydrate can not be polymorphs)
  – How polymorph is used in journal articles and regulatory documents is important in understanding what is being said

• Solid form
  – Alternative to include all solid materials
    • Polymorphs, solvates, hydrates, amorphous, salts, cocrystals, amorphous dispersions

FDA definition: http://www.fda.gov/CDER/GUIDANCE/7590fnl.htm#_Toc167002781
Solid Forms

Classes of multicomponent molecular crystals

= API  = water/solvent  = neutral guest  = counterion


Polymorphs
Amorphous

- Amorphous
  - No long range order
  - Do possess short range order
  - Less physically and chemically stable than crystalline materials
  - Higher dissolution than crystalline materials

- Amorphous solid dispersions
  - Amorphous drug with polymer
  - Polymer stabilizes amorphous drug
  - Results in better stability and higher dissolution

Schematic hypothetical energy cartoon showing the amorphous drug, crystalline drug, and several single phase amorphous solid dispersions ($\mu$ represents the chemical potential of the drug and $E_a$ represents the activation energy barrier for crystallization).

Harmon et al. AAPS Newsmagazine, 2009, Sept, 14-20
Form Characterization

• XRPD is front line technique to determine
  – Crystalline vs amorphous
  – Crystalline form
  – Changes in amorphous materials
• Once new patterns are found other techniques can be used to determine
  – Solvation state
  – Stoichiometry
  – Possible mixtures
  – Etc.

Why We Screen

89% of compounds screened exhibited multiple forms (based on 245 screens)
- includes 10 steroids, 7 peptide-based structures, 5 cephalosporins, 4 organometallics, 2 macroline antibiotics

Form Screening vs Selection

• Screening
  – Find possible forms under various conditions
  – Search for seeds/forms, not a search for a process

• Selection
  – Determine which form has the best properties for development

• Screen and selection are sometimes considered the same function
  – Not all forms found in a screen will be relevant when choosing a lead candidate (example- solvates)
  – However, knowing the possible forms will help in developing robust processes (API and drug product)
Screening and Selection

**Screening**
- Characterize starting material
  - XRPD, DSC, TG, etc
- Generate samples
- Analyze samples
- Data analysis
- Preliminary characterization
- Scale-up
  - Scale-up of select materials may be needed

**Selection**
- Characterize materials
  - XRPD, DSC, TG, moisture uptake, solubility, etc
- Select form
  - Material with best properties

Solvent and nonsolvent conditions

Usually one technique used (XRPD, Raman)

Group data to determine possible forms

Collect specific data (solvent content, stoichiometry)
When to Screen

- Different screens can be performed at various stages of development
- Should have a good idea of form by end of Phase II meeting

![Diagram showing stages of development process]

- Synthesis
- Process Development
- API Manufacture
- Preformulation
- Formulation
- Drug Product Manufacture
- Clinical Trials

Years

Discovery ➔ Preformulation ➔ Formulation ➔ Process Development ➔ API Manufacture ➔ Drug Product Manufacture ➔ Clinical Trials ➔ Launch

preliminary stable  focused/solid form  comprehensive
Screening Strategy

Early Development

1. Characterize material as received
2. Carry out a polymorph screen
3. Carry out a salt screen (if applicable)
4. Carry out a cocrystal screen
5. Carry out an amorphous dispersion screen

Late Development

6. Evaluate alternative formulation strategies using new forms
7. Patent new formulations
8. Evaluate the need for additional screening
9. Carry out additional studies if necessary
10. Patent new forms
Manual Screens

- Salts, cocrystals, polymorphs, dispersions, amorphous
- Samples produced individually
- Solvent or solid methods used
  - Solvent methods
    - Vials
      - Glass, silanized glass, acid or base washed, or polymer vials can be used
      - Check stability of plastic vials with various solvents
    - Capillaries, templates (polymers, gold, etc)
  - Solid methods
    - Temperature or RH equilibration
    - Grinding, compression, sublimation
    - Cool from melt
XRPD Sample Holders

- Large variety of sample holders available
- Can be specific to instrument or autosampler
- Need to maintain sample in random orientation
- Select a holder to accommodate the amount of sample produced

- Top fill
- Back fill
- Wire loop
- Transmission
- Air tight
- Variable temperature
- Rotation
- Zero background
- Capillary
High Throughput Screens

Screening

- Usually done in an array with wells, tubes, or vials
- Limited to solvent based methods
- Limited crystallization conditions
- Can generate large numbers of samples

• Analysis
  - XRPD instrument needs to be configured for plate
  - Issues with plate screens
    - Small sample size
    - Solid not always on bottom of vessel

Storey et al. *Crystallography Rev.* 2004, 10, 45-56
XRPD Analysis

Issues with plate screens

• Small sample size
• Possible poor signal to noise ratio
• Broad peaks with variable shapes
• Strong background
• Preferred orientation

Carbamazepine screen

Wyttenback et al. Pharm Res. 2007, 24, 888-898
Analysis

Sample Analysis
XRPD, IR, Raman

Data

Storey et al. Crystallography Rev. 2004, 10, 45-56
## Planning a screen

### Variables to consider during crystallization/screening

### Crystallization composition and processing variables

<table>
<thead>
<tr>
<th>Composition type</th>
<th>Process variables&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polymorph/solvates</strong></td>
<td><strong>Thermal</strong></td>
</tr>
<tr>
<td>Solvent/solvent combinations</td>
<td>Heating rate</td>
</tr>
<tr>
<td>Degree of supersaturation</td>
<td>Cooling rate</td>
</tr>
<tr>
<td>Additive type</td>
<td>Maximum temperature</td>
</tr>
<tr>
<td>Additive concentration</td>
<td>Incubation temperature(s)</td>
</tr>
<tr>
<td>Polynomial and co-crystals</td>
<td>Incubation time</td>
</tr>
<tr>
<td>pH</td>
<td></td>
</tr>
<tr>
<td>Ionic strength</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Applicable to all types of screens.

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# Planning a Screen

## Time Scales

<table>
<thead>
<tr>
<th>Months</th>
<th>Days</th>
<th>Hours</th>
<th>Minutes</th>
<th>Seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaporation</td>
<td>Ripening/Slurrying</td>
<td>Cooling Crystallization</td>
<td>Antisolvent Diffusion</td>
<td>Antisolvent Addition</td>
</tr>
<tr>
<td>Reverse Antisolvent Addition</td>
<td>Crystallization with Additives or Templates</td>
<td>Capillary Crystallization</td>
<td>Spray-drying</td>
<td>Salting out/pH Change</td>
</tr>
<tr>
<td>Lyophilization</td>
<td>Supercritical Fluid</td>
<td>Expose to Solvent Vapor</td>
<td>Grinding</td>
<td>Sublimation</td>
</tr>
<tr>
<td>Expose to High or Low Humidity</td>
<td>Heating/Temperature Cycle</td>
<td>Compression</td>
<td>Cool from Melt</td>
<td></td>
</tr>
</tbody>
</table>

**Adapted from Anderton. Amer. Pharm. Rev. 2007, 10, 34-40**
Salt Screening Strategy

Early salt screens

- Can be based on BCS
- Not as crucial for BCS class 1 materials
- More important for classes 2 and 4

Soluble salt defined as enabling human dose soluble in 250 mL water

*Ku. Amer Pharm Rev. 2010, 13, 22-30*
Salt Development

• Requirements and selection process for each compound will be unique

• Variables that need to be considered when developing salts
  – solubility targeted
  – acceptable final form
  – dissolution
  – solubility of free compound
  – stability of free compound
  – melting point
  – dosage form to be developed
  – route of administration
  – loading in dosage form
  – amount of material available
  – previous experience with counterions
  – toxicology of counterions
  – etc
## Counterion Selection

Consider size and shape of counterion and API

### Anions

<table>
<thead>
<tr>
<th>Counterion</th>
<th>Chemical Form</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>chloride</td>
<td>Cl⁻</td>
<td><img src="image" alt="Cl⁻" /></td>
</tr>
<tr>
<td>bromide</td>
<td>Br⁻</td>
<td><img src="image" alt="Br⁻" /></td>
</tr>
<tr>
<td>sulfate</td>
<td>SO₄⁻ (HSO₄⁻)</td>
<td><img src="image" alt="SO₄⁻" /></td>
</tr>
<tr>
<td>nitrate</td>
<td>NO₃⁻</td>
<td><img src="image" alt="NO₃⁻" /></td>
</tr>
<tr>
<td>phosphate</td>
<td>H₂PO₄⁻ (HPO₄⁻)</td>
<td><img src="image" alt="H₂PO₄⁻" /></td>
</tr>
<tr>
<td>bicarbonate</td>
<td>HCO₃⁻</td>
<td><img src="image" alt="HCO₃⁻" /></td>
</tr>
<tr>
<td>mesylate</td>
<td>CH₃SO₃⁻</td>
<td><img src="image" alt="CH₃SO₃⁻" /></td>
</tr>
<tr>
<td>esylate</td>
<td>CH₃CO₂⁻</td>
<td><img src="image" alt="CH₃CO₂⁻" /></td>
</tr>
<tr>
<td>isethionate</td>
<td>HOOC(SO₃⁻)</td>
<td><img src="image" alt="HOOC(SO₃⁻)" /></td>
</tr>
<tr>
<td>tosylate</td>
<td>CH₃C(SO₃⁻)</td>
<td><img src="image" alt="CH₃C(SO₃⁻)" /></td>
</tr>
<tr>
<td>napsylate</td>
<td><img src="image" alt="napsylate" /></td>
<td></td>
</tr>
<tr>
<td>besylate</td>
<td><img src="image" alt="besylate" /></td>
<td></td>
</tr>
</tbody>
</table>

Counterions: chloride, bromide, sulfate, nitrate, phosphate, bicarbonate, mesylate, esylate, isethionate, tosylate, napsylate, besylate. Counteranions: acetate, propionate, maleate, benzoate, salicylate, fumarate, citrate, lactate, malate, tartrate, pamoate, succinate, glycolate, hexanoate, octanoate, decanoate, stearate, oleate, aspartate, glutamate.
Counterion Selection

Not limited to inorganic counterions

cations

- sodium: Na⁺
- potassium: K⁺
- calcium: Ca⁡⁺⁺
- magnesium: Mg⁡⁺⁺
- lithium: Li⁺
- zinc: Zn⁡⁺⁺
- aluminum: Al⁡+++.
- arginine: \( \text{H}_2\text{N}\text{-}\text{H}-\text{H}-\text{CO}_2\text{H}^+ \)
- lysine: \( \text{H}_3\text{N}\text{-}\text{H}_2\text{-}\text{CO}_2\text{H}^+ \)
- histidine: \( \text{H}_2\text{N}\text{-}\text{H}_2\text{-}\text{CO}_2\text{H}^+ \)

Counterions:

- triethylamine: \((\text{CH}_3\text{CH}_2)_3\text{NH}^+\)
- ethanolamine: \(\text{HOCH}_2\text{CH}_2\text{NH}^+\)
- triethanolamine: \((\text{HOCH}_2\text{CH}_2)_3\text{NH}^+\)
- ethylenediamine: \(\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}^+\)
- choline: \(\text{HOCH}_2\text{CH}_2\text{N(CH}_3)_3^+\)
- meglumine: \(\text{HOCH}_2\text{CH}_2\text{N(CH}_3)_3\text{H}^+\)
- procaine: \(\text{HO}_3\text{C}\text{-O}\text{-CH}_2\text{-N}\text{-CH}_3\text{H}^+\)
- benzathine: \(\text{H}_2\text{N}\text{-CH}_3\text{N}\text{-CH}_2\text{N}\text{-CH}_3\text{H}^+\)
Counterion Selection

Frequency of counterion in marketed products can be considered

Anions

Cations

## Counterion Selection

Frequency in dosage form can also be evaluated – Will change over time

<table>
<thead>
<tr>
<th></th>
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<td>acetate</td>
<td>0.9</td>
<td>0.6</td>
<td>7.7</td>
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<tr>
<td>benzoate</td>
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<td>2.5</td>
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<tr>
<td>besylate</td>
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<td>0.6</td>
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<td></td>
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<td>4.1</td>
<td>5.2</td>
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<td></td>
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<tr>
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<td>55.8</td>
<td>65.4</td>
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<td>0.6</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>citrate</td>
<td>3.4</td>
<td>4.1</td>
<td>2.9</td>
<td>7.5</td>
<td></td>
<td></td>
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<td>ethandisulfonate</td>
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<td>0.6</td>
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<td></td>
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<tr>
<td>fumarate</td>
<td>1.6</td>
<td>0.6</td>
<td>4.2</td>
<td>2.9</td>
<td>5.0</td>
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<tr>
<td>gluconate</td>
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<td>0.6</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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</table>

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<tbody>
<tr>
<td>acetate</td>
<td>5.8</td>
<td>2.3</td>
<td>5.0</td>
<td>26.3</td>
<td>5.0</td>
<td>14.3</td>
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<td>5.0</td>
<td>5.0</td>
<td>7.1</td>
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<tr>
<td>bromide</td>
<td>4.3</td>
<td>3.9</td>
<td>5.0</td>
<td>5.3</td>
<td>5.0</td>
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<tr>
<td>chloride</td>
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<td>54.3</td>
<td>60.0</td>
<td>42.1</td>
<td>55.0</td>
<td>50.0</td>
<td>50.0</td>
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<td>chlorothéophyllinate</td>
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<td>0.8</td>
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</tr>
<tr>
<td>citrate</td>
<td>2.4</td>
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<td>5.0</td>
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<td>16.7</td>
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<tr>
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<td>0.8</td>
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<tr>
<td>fumarate</td>
<td>0.5</td>
<td>0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.0</td>
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<tr>
<td>gluceptate</td>
<td>0.5</td>
<td>0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>gluconate</td>
<td>0.5</td>
<td>0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Counterion Selection

pK\(a\) difference of 2 between API and counterion

- Generally accepted for salt formation
  - Cocrystals possible if ignored
- pK\(a\) values can change significantly in different solvents
- Based on solution chemistry
  - Need to think about solubilities of solids

The pK\(a\)s of Selected Acids in Water and Methanol

<table>
<thead>
<tr>
<th>Compound</th>
<th>pK(a) Water</th>
<th>pK(a) Methanol</th>
<th>ΔpK(a) Water</th>
<th>ΔpK(a) Methanol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ephedrine</td>
<td>9.74</td>
<td>8.69</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>4.76</td>
<td>9.63</td>
<td>4.98</td>
<td>—</td>
</tr>
<tr>
<td>Benzoic acid</td>
<td>4.19</td>
<td>9.30</td>
<td>5.55</td>
<td>—</td>
</tr>
<tr>
<td>Malonic acid</td>
<td>2.83, 5.70</td>
<td>7.66, 10.64</td>
<td>6.91, 4.04</td>
<td>1.03, −1.95</td>
</tr>
<tr>
<td>Fumaric acid</td>
<td>4.38</td>
<td>9.78</td>
<td>5.36</td>
<td>−1.09</td>
</tr>
<tr>
<td>Succinic acid</td>
<td>4.19, 5.61</td>
<td>9.14, 11.30</td>
<td>5.55, 4.13</td>
<td>−0.45, −2.61</td>
</tr>
<tr>
<td>L-tartaric acid</td>
<td>3.02</td>
<td>8.12</td>
<td>6.72</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Counterion Selection

Effect of Solvent on pKa

– 25 counterions used to make ephedrine slats

<table>
<thead>
<tr>
<th>Carboxylic Acids</th>
<th>Dicarboxylic Acids</th>
<th>Hydroxy Acids</th>
<th>Inorganic Acids</th>
<th>Sulfonic Acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic</td>
<td>Adipic</td>
<td>Citric</td>
<td>Hydrochloric</td>
<td>Benzene sulfonic</td>
</tr>
<tr>
<td>Benzoic</td>
<td>Fumaric</td>
<td>d-(-)-gluconic</td>
<td>Nitric</td>
<td>1,2-Ethane disulfonic</td>
</tr>
<tr>
<td>Formic</td>
<td>Maleic</td>
<td>Glycolic</td>
<td>Phosphoric</td>
<td>Ethane sulfonic</td>
</tr>
<tr>
<td>Salicylic</td>
<td>Malonic</td>
<td>L-(-)-malic</td>
<td>Sulfuric</td>
<td>Methane sulfonic</td>
</tr>
<tr>
<td>Trichloroacetic</td>
<td>Succinic</td>
<td>L- (+)-tartaric</td>
<td>—</td>
<td>2-Naphthalene sulfonic</td>
</tr>
<tr>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>p-Toluene sulfonic</td>
</tr>
</tbody>
</table>

A Summary of all Crystallization Results

<table>
<thead>
<tr>
<th>Acids</th>
<th>Water Results</th>
<th>Methanol Results</th>
<th>ΔpK&lt;sub&gt;a&lt;/sub&gt; Water</th>
<th>ΔpK&lt;sub&gt;a&lt;/sub&gt; Methanol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong Inorganic Sulfonic</td>
<td>9/10 crystalline</td>
<td>6/6 crystalline</td>
<td>8 to 12 units</td>
<td>2 to 6 units</td>
</tr>
<tr>
<td>Weak Carboxylic</td>
<td>8/15 crystalline including: 3 hydrates</td>
<td>0/9 crystalline</td>
<td>4 to 6 units</td>
<td>–2 to 1 units</td>
</tr>
<tr>
<td></td>
<td>4 conversions from an initial amorphous phase</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Counterion Selection

• Toxicity
  – Depends on molecule and daily dose
  – Will be different for short term vs chronic dosing
  – Toxic reaction products need to be considered
    • Methyl and ethyl formate esters associated with formic acid under certain conditions
    • Methyl methanesulfonate, a known mutagen, associated with methanesulfonic acid
      – Usually an issue when methanol is used as solvent
Salt Formation

• Solvent methods
  – Evaporation
  – Cooling
  – Antisolvent addition
  – Sonic slurry
  – Capillaries

• Number of parameters to investigate
  – Solvent, concentration/stoichiometry, cooling rates, evaporation rates
  – Manual or automated crystallization

• Solubilities
  – API and counterion/guest need to be soluble in same solvent or miscible solvents

• Try to get precipitation
  – reduce volume
  – cool solution
  – add anti-solvent (if known)
  – different ways of combining compounds
  – different temperatures

• Evaporations can result in physical mixture of materials rather than salt, or other unknown forms of free compound
Salt Formation

• A variety of less traditional methods are also available
  – binary melt (cocrystal formation as well)
  – grinding (cocrystal formation)/trituration
  – salt exchange
  – bubble gas (HCl, HBr) through solution
  – vapor diffusion
  – ion exchange resins
  – phase solubility (solubility as a function of pH)
  – precipitation of unwanted counterion first (ex. Silver salts used as counterion source and silver precipitated as silver iodide leaving desired anion)

• Try to get salts for evaluation or use process that is scaleable?

Salt Formation

• Different stoichiometries can be tried
  – more than one site on free compound
  – diacid counterion used (fumarate, malate, maleate, tartrate, etc)

• Control of stoichiometry may be an issue if pKα values are close
Characterization

- API with two basic sites
  - similar pKₐ values
- HBr salt prepared with different molar ratios
  - Same XRPD pattern
  - Same elemental analysis
  - Different yields
- Favors formation of disalt

<table>
<thead>
<tr>
<th>Element</th>
<th>1:1 HBr:API</th>
<th>2:1 HBr:API</th>
<th>Expected Values for Disalt</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>49.77</td>
<td>49.92</td>
<td>49.48</td>
</tr>
<tr>
<td>H</td>
<td>4.05</td>
<td>3.97</td>
<td>3.97</td>
</tr>
<tr>
<td>N</td>
<td>14.83</td>
<td>14.91</td>
<td>15.05</td>
</tr>
<tr>
<td>Br</td>
<td>28.86</td>
<td>29.20</td>
<td>28.63</td>
</tr>
</tbody>
</table>

Characterization

X-ray Powder Diffraction (XRPD)

Crystallinity
Crystalline form

Crystalline pattern

Spectroscopy

• Infrared (IR)
• Raman
• NMR

Interactions
Crystalline form
Mapping/imaging

Interactions between
drug and counterion
Stoichiometry

Thermal Methods

• DSC (mDSC, HyperDSC)
• Thermogravimetry (TG)
• Hot Stage Microscopy

Melting point/Tg
Form changes
Volatile content

One melt
Identify additional transitions

Moisture Sorption

Water uptake
Form changes

Low water uptake

Solubility, stability, formulation
Evaluation

• Solubility in water
  ✷ 0.1-10 mg/mL for solid oral dosage forms
  ✷ ≥10 mg/mL for parenterals
• pH of aqueous solution
  ✷ 3-10 for parenterals
• Melting point
  ✷ >100 °C
• Hygroscopicity
  ✷ Non-deliquescent at 60-75% RH
• Chemically and physically stable (excipient compatibility)
• Dissolution rate
• Crystal size, shape
Evaluation

<table>
<thead>
<tr>
<th>Tier 1</th>
<th>Hygroscopicity</th>
<th>(7 salts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tier 2</td>
<td>Solubility/Crystal Changes</td>
<td>(4 salts)</td>
</tr>
<tr>
<td>Tier 3</td>
<td>Stability and Compatibility</td>
<td>(1 salt and alternate)</td>
</tr>
</tbody>
</table>

Sodium 180431-03
Calcium 180431-04
Zinc 180431-05
Magnesium 180431-06
Potassium 180431-07
Lysine 180431-08
Arginine 180431-09

BMS 180431

Morris et al. *Int. J. Pharmaceutics* 1994, 105, 209
Salt Selection

Decision tree

- General properties
- Needs to be tailored to each system
Crystallization

- Scale-up needs to be considered
- Ternary phase diagrams can be useful to determine concentrations

Salt Screening

- A variety of salts are available
  - Salts, salt hydrates/solvates, salt cocrystals, salt cocrystal hydrates/solvates
- Salt screening can be used to find new salts
  - Solvent methods most common
  - Manual vs automated
- Characterization of salts needed
  - Form, protonation
- Scale-up can be an issue
- Salts can significantly alter properties of API
  - Melting point, solubility, stability, dissolution, bioavailability
- Salts can exhibit polymorphism - polymorph screen should be performed
Polymorph Screening

• **Search for seeds, not a search for a process**
  – Do not limit to Class III solvents
  – Do not limit to solvent experiments
  – Can gain information on crystallization process  
    (example- solvate formation, slurry expts)
  – Can always use the initial crystals as seeds for a 
    crystallization process

• Need to determine which forms are relevant to development
  – Anhydrates vs hydrates vs solvates
  – Initial goal is to find the most thermodynamically stable form

• **No screen can guarantee to find all forms**
Sample Generation

- Solvent based methods can be employed based on solubility in various solvents
  - High solubility systems
    - High concentrations can result in gels/oils
    - Antisolvent additions, cooling experiments below supersaturation
  - Low solubility systems
    - Want to increase solubility or allow time for conversion
    - Slurry experiments, cooling crystallization from elevated temperature
    - Start with amorphous material to increase solubility
- Can tailor crystallization experiments to increase success
Sample Generation

- Nonsolvent methods can be tailored based on other properties/data
  - Heating/desoluvation temperature based on TG loss
  - Heating/melting temperature based on DSC, hot stage data
  - Exposure to RH conditions based on water uptake data

Polla et al., *Int. J. Pharm.* 2005, 301, 33-40
Reutzel-Edens et al. *J. Pharm. Sci.* 2003, 92, 1196-1205
Planning a Screen

Understand goal of screen and what information is needed
• For early screens want to know most stable form
• For later screens, may want additional information for processing or IP

<table>
<thead>
<tr>
<th>Goal</th>
<th>Screen Type</th>
<th>Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determine propensity for polymorphism</td>
<td>preliminary</td>
<td>&lt;0.5 g</td>
</tr>
<tr>
<td>Find thermodynamically stable form</td>
<td>stable form</td>
<td>1-2 g</td>
</tr>
<tr>
<td>Confirm the selected form can be produced with GMP material</td>
<td>focused</td>
<td>1-2 g</td>
</tr>
<tr>
<td>Find the best form for development</td>
<td>solid form selection</td>
<td>2-5 g</td>
</tr>
<tr>
<td>Widest experimental scope to find all possible forms</td>
<td>comprehensive</td>
<td>variable</td>
</tr>
</tbody>
</table>
How Many Samples

Depends on

– Goal of screen and information needed
– Amount of material available
– Information already available (stability, solubility, etc)

<table>
<thead>
<tr>
<th>Goal</th>
<th>Screen Type</th>
<th>Material</th>
<th>Number of Experiments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determine propensity for polymorphism</td>
<td>preliminary</td>
<td>&lt;0.5 g</td>
<td>tens</td>
</tr>
<tr>
<td>Find thermodynamically stable form</td>
<td>stable form</td>
<td>1-2 g</td>
<td>tens</td>
</tr>
<tr>
<td>Confirm the selected form can be produced with GMP material</td>
<td>focused</td>
<td>1-2 g</td>
<td>tens</td>
</tr>
<tr>
<td>Find the best form for development</td>
<td>solid form selection</td>
<td>2-5 g</td>
<td>hundreds</td>
</tr>
<tr>
<td>Widest experimental scope to find all possible forms</td>
<td>comprehensive</td>
<td>variable</td>
<td>thousands</td>
</tr>
</tbody>
</table>
Stable Form Screen

- Targeted for early development to find the most stable form
- Small amount of compound needed (100-250 mg)
- Slurry experiments used (solvent mediated polymorphic transformation)
- Material suspended in diverse group of solvents for two weeks
- Solubility estimated using gravimetric method

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Dielectric constant (a measure of polarity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>80.1</td>
</tr>
<tr>
<td>Nitromethane</td>
<td>39.4</td>
</tr>
<tr>
<td>N,N-Dimethylformamide (DMF)</td>
<td>36.7</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>36.6</td>
</tr>
<tr>
<td>Methanol</td>
<td>33.0</td>
</tr>
<tr>
<td>Ethanol</td>
<td>25.3</td>
</tr>
<tr>
<td>Acetone</td>
<td>20.7</td>
</tr>
<tr>
<td>2-Propanol (isopropyl alcohol, IPA)</td>
<td>20.3</td>
</tr>
<tr>
<td>2-Butanone (methyl ethyl ketone, MEK)</td>
<td>18.6</td>
</tr>
<tr>
<td>Tetrahydrofuran</td>
<td>7.5</td>
</tr>
<tr>
<td>1,2-Dimethoxyethane</td>
<td>7.3</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>6.1</td>
</tr>
<tr>
<td>Chloroform</td>
<td>4.8</td>
</tr>
<tr>
<td>Methyl t-butyl ether</td>
<td>4.3</td>
</tr>
<tr>
<td>1,2-Xylene</td>
<td>2.6</td>
</tr>
<tr>
<td>Toluene</td>
<td>2.4</td>
</tr>
<tr>
<td>1,4-Dioxane</td>
<td>2.2</td>
</tr>
<tr>
<td>Hexanes</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Stable Form Screen

Pfizer Compound A

• Form I was initial form
• Transformation to more stable Form II observed
  – 6 out of 18 solvents in 2 days and 8 out 18 solvents in 2 weeks produced Form II
  – Dioxane solvate also found

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solid form 2 days</th>
<th>Solid form 2 weeks</th>
<th>Solubility (mg/mL) 2 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexanes</td>
<td>I</td>
<td>I</td>
<td>0.12±0.02</td>
</tr>
<tr>
<td>Water</td>
<td>I</td>
<td>I</td>
<td>0.13±0.01</td>
</tr>
<tr>
<td>1,2-Xylene</td>
<td>I</td>
<td>I</td>
<td>0.22±0.02</td>
</tr>
<tr>
<td>Toluene</td>
<td>I</td>
<td>II</td>
<td>0.62±0.04</td>
</tr>
<tr>
<td>Nitromethane</td>
<td>I</td>
<td>I</td>
<td>0.66±0.07</td>
</tr>
<tr>
<td>2-Propanol</td>
<td>I</td>
<td>I</td>
<td>0.99±0.10</td>
</tr>
<tr>
<td>Methyl t-butyl ether</td>
<td>I</td>
<td>II</td>
<td>1.36±0.04</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>I</td>
<td>I</td>
<td>1.41±0.01</td>
</tr>
<tr>
<td>Ethanol</td>
<td>I</td>
<td>I</td>
<td>2.02±0.09</td>
</tr>
<tr>
<td>Methanol</td>
<td>I</td>
<td>I</td>
<td>2.72±0.05</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>II</td>
<td>II</td>
<td>3.42±0.07</td>
</tr>
<tr>
<td>Chloroform</td>
<td>II</td>
<td>II</td>
<td>6.04±0.12</td>
</tr>
<tr>
<td>Acetone</td>
<td>II</td>
<td>II</td>
<td>8.53±0.12</td>
</tr>
<tr>
<td>Hexamethylphosphine</td>
<td>II</td>
<td>II</td>
<td>13.3±0.7</td>
</tr>
<tr>
<td>2-Butanone</td>
<td>II</td>
<td>II</td>
<td>17.3±0.3</td>
</tr>
<tr>
<td>1,4-Dioxane</td>
<td>Solvate</td>
<td>Solvate</td>
<td>18.7±0.4</td>
</tr>
<tr>
<td>Dioxane</td>
<td></td>
<td></td>
<td>72.6±2.6</td>
</tr>
<tr>
<td>1,2-Dimethoxyethane</td>
<td>II</td>
<td>II</td>
<td>282±3</td>
</tr>
</tbody>
</table>

High throughput screening (HTS)

- Comparison of manual vs HTS
- Goal of screen was form diversity, not stable form
- 1500 experiments performed
  - 186 solids found after 7 days (13% hit rate)
  - After Raman clustering, 80 samples analyzed by XRPD

<table>
<thead>
<tr>
<th>Metric</th>
<th>Traditional</th>
<th>HT mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>number of experiments</td>
<td>ca. 100</td>
<td>1500</td>
</tr>
<tr>
<td>time frame (weeks)</td>
<td>ca. 32</td>
<td>4</td>
</tr>
<tr>
<td>people requirement</td>
<td>ca. 2</td>
<td>1–2</td>
</tr>
<tr>
<td>amount of material used</td>
<td>&gt; 10 g</td>
<td>&lt; 5 g</td>
</tr>
<tr>
<td>number of crystalline forms</td>
<td>9</td>
<td>18</td>
</tr>
</tbody>
</table>

MK-996

Almarsson et al. *Cryst Growth Des.* 2003, 3, 927-933
HTS

• HTS screen found 18 forms
  – 13 new patterns
  – 5 previously known forms

• Screen did not find 4 previously known forms
  – Forms B and C (unsolvated), F, H
  – Form D was found in HTS. Original paper could not reproduce Form D after Form I was found.

• Form I originally chosen for development

Almarsson et al. *Cryst Growth Des.* 2003, 3, 927-933
Polymorph Screens

• Need to understand the goal of the screen
  – most stable form, form diversity, change a specific property
• A variety of screens are possible
  – Manual, high throughput, etc
• Can tailor crystallization experiments to the properties of the molecules
  – Solubility for solvent based methods
  – Characterization data for solid experiments
• Multiple screens may be warranted throughout development
Case Study

AMG 837

- Treatment for type 2 diabetes
- Initially isolated as lysine salt
  - Poorly crystalline by XRPD
  - Hygroscopic above 65% RH
  - Difficult to scale up due to large volumes of solvent (>100 vol EtOH)
- Free acid investigated
  - Crystalline by XRPD
  - Poorly soluble (~0.5 mg/mL) and poor wettability
  - DSC showed low melting point of 80 C
  - Poor solution and solid-state stability
  - Benchtop polymorph screen conducted
    - Higher melting forms not identified
    - Samples usually thick oils and difficult to crystallize
- Salt screen performed to identify crystalline form with acceptable characteristics for development

Case Study

- Ten counterions used
- Crystallization included
  - Evaporation, slurries, antisolvent addition

Prioritized based on crystallization and information on counterions
- Choline and sodium listed as high priority
- Counterion use in marketed products also considered

<table>
<thead>
<tr>
<th>Counterion</th>
<th>XRPD Results</th>
<th>Priority</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Arginine</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>Amorphous</td>
<td>Low</td>
<td>Amorphous</td>
</tr>
<tr>
<td>Choline</td>
<td>Crystalline</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Ethanolamine</td>
<td>Crystalline</td>
<td>Low</td>
<td>No marketed oral drugs identified</td>
</tr>
<tr>
<td>L-Histidine</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>Amorphous</td>
<td>Low</td>
<td>Amorphous</td>
</tr>
<tr>
<td>Meglumine</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>Amorphous</td>
<td>Low</td>
<td>Amorphous</td>
</tr>
<tr>
<td>Sodium</td>
<td>Crystalline</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>TRIS</td>
<td>Crystalline</td>
<td>Medium</td>
<td>Marketed products identified, counterion not employed for oral chronic use</td>
</tr>
</tbody>
</table>

Case Study

• Salt Screen
  – Four crystalline hits identified
  – Ethanolamine and TRIS were considered second tier
  – Sodium had higher melting point than choline
  – Sodium salt chosen

Case Study

- Full polymorph screen of sodium salt performed
  - Eight patterns observed
  - Forms E and H showed highest crystallinity
Case Study

• Four forms examined in more detail

  Form E  acetonitrile solvate (8%)
  Form C  hemihydrate
  Form H  unsolvated
  Form G  unsolvated

  heating

• Form C chosen for further investigation
  • Found most often in screen
  • Solubility >100 mg/mL
  • Successfully scaled up for use as GLP and GMP material

Case Study

- Successfully scaled up for use as GLP and GMP material
  - Produced Form E solvate then desolvated to Form C
  - GMP more crystalline than GLP material

Case Study

- Form C exhibited multiple thermal transitions
  - Broad endo $\sim 61^\circ C$
  - Endos at $\sim 151$ and $182^\circ C$
  - Exo $\sim 186^\circ C$
  - Major endo at $187^\circ C$ (melt of Form G)
- VT-XRPD performed
  - 120 $^\circ C$
    - Slight changes to form isomorphous dehydrate
  - 165 $^\circ C$
    - New form (Form I) which melts at 182 $^\circ C$ and recrystallizes
  - 183 $^\circ C$
    - Form G which melts at 187 $^\circ C$

Case Study

• Form C showed mix of properties
  – Low crystallinity
  – Complicated DSC profile
  – Hygroscopic
  – Good short term physical stability at 68% RH, 60 C/26% RH, 60 C/50% RH

• Form C suitable for Phase I clinical trials
• Went back to original screen to find better candidate
• Sodium salt used to produce a crystalline hemicalcium salt
• Polymorph screen of calcium salt performed
Case Study

- Full polymorph screen conducted using both amorphous and crystalline calcium salt
- Five crystalline forms produced
Case Study

- All forms contained solvent
- Characterization showed that none of the forms exhibited a true melt
  - Desolvation upon heating produced amorphous materials
  - Crystalline forms needed solvent to stabilize the crystal lattice

<table>
<thead>
<tr>
<th>Form</th>
<th>Results</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>methanol solvate</td>
<td>solvate</td>
</tr>
<tr>
<td>B</td>
<td>dihydrate</td>
<td>candidate</td>
</tr>
<tr>
<td>C</td>
<td>dihydrate</td>
<td>candidate</td>
</tr>
<tr>
<td>D</td>
<td>isopropanol solvate</td>
<td>solvate</td>
</tr>
<tr>
<td>E</td>
<td>pentahydrate</td>
<td>Converted to Form C upon heating or exposure &lt;55% RH</td>
</tr>
</tbody>
</table>

- Solubility used to determine thermodynamic stability of Forms B and C
  - Form B had lower solubility at 5, 21, and 40 °C
  - Form B was more stable form
  - Form B stable to small scale wet milling conditions to simulate wet granulation

Case Study

- Both Form B calcium salt and Form C sodium salt were viable candidates
- A number of quality attributes were considered
- Calcium salt was recommended for product development

<table>
<thead>
<tr>
<th>Comparison of the sodium salt form C and calcium salt form B</th>
</tr>
</thead>
<tbody>
<tr>
<td>sodium salt</td>
</tr>
<tr>
<td>hygroscopicity</td>
</tr>
<tr>
<td>crystallinity</td>
</tr>
<tr>
<td>API stability</td>
</tr>
<tr>
<td>API manufacture</td>
</tr>
<tr>
<td>tablet manufacture</td>
</tr>
<tr>
<td>solubility</td>
</tr>
<tr>
<td>PK data</td>
</tr>
</tbody>
</table>
Case Study

• Summary
  – Initial salt screen performed due to unfavorable characteristics of free base
    • Low melt, poor stability, poor water solubility
    • Eleven counterions included in screen
      – Most yielded amorphous materials
      – Others not preferred due to lack of chronic oral use data and safety implications
      – Sodium salt moved forward
  – Second salt screen performed to improve properties
  – Calcium salts revisited based on crystallization of sodium salt
  – Polymorph screens performed on both sodium and calcium salts
    – 8 forms found for sodium, 5 forms found for calcium
    – Hemicalcium salt chosen for development based on properties
• More than one salt screen and more than one polymorph screen used to pick the best form during development
• Form matrix used for form selection

What Have We Learned

• X-ray powder diffraction is a key characterization technique for screening and selection studies
• Screening is different from selection
• Polymorph and salt screens
  – Are a search for seeds and should cover a wide crystallization space including solvent and nonsolvent methods
  – Can be tailored to the information needed for compound development
  – Should use information already known on the compound
  – Can be performed at various points during development
• One screen will likely not give you all the form information on a compound
• Finding and characterizing forms early will help
  – In choosing the best form for development
  – To avoid processing conditions that could produce another form
Resources

Polymorph Screening

• Cui et al. J Pharm Sci. 2007, 97, 2730-2743 (hydrates).

Salt Screenig