Working with Amorphous API’s

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Avantium Technologies BV

Drug Development of Tomorrow
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Agenda

- Solid form selection
- Marketed examples
- Amorphous state
- Properties and generation of amorphous material
- Amorphous Solid Dispersion Screen
- Case study 1 (solution process)
- Case study 2 (melt process)
Candidate Molecules
Pfizer candidate molecules

- Increasing lipophilicity
- Increasing number of neutral compounds

Source: Chris Lipinski, J. Pharm. Tox. Meth, 44, 2000
Formulation strategies that can influence the drug properties (solubility……..)

- Micronization
- Solubility enhancers (complexing agents)
- Pro drugs
- Solid forms
  - Polymorphs
  - Salts
  - Co-crystals
  - Amorphous forms
Polymorphs (55 compounds, 81 solubility ratios): improvement trend 1-5 x

Hydrates (17 compounds, 24 ratios): improvement only in exceptional cases
Benefits of Salts

Solubility of saccharin salts

- Haloperidol: 600 x
- Mirtazapine: 40 x
- Quininie: 3 x

Drug products:
- Marketed
- Saccharin

Sources:
Pudipeddi & Serajuddin, J. Pharm. Sc 94(5), 2005
Bhatt et al., Chem. Commun., 2005
Benefits of Co-crystals

Dissolution rate of carbamazepine co-crystals increased.

Avantium Study
Working with Amorphous Forms
Amorphous in pharmaceutical development

1) Processing induced disorder
   - milling,
   - granulation

2) Stabilising macromolecules

3) Naturally Amorphous excipients
   - polymers: PVP, HPMC

4) Rendered amorphous excipients
   - spray dried lactose for direct compression

5) Amorphous API
# Amorphous API
*(products for oral use)*

<table>
<thead>
<tr>
<th>Compound (Discoverer/Manufacturer)</th>
<th>Year licensed</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir (Abbot)</td>
<td>USA 2000</td>
<td>Co-formulated with ritonavir as Kaletra to treat HIV/AIDS. Lopinavir exists as an amorphous form and 4 crystalline forms. The commercial material is a mixture of the amorphous form and Form I crystals.</td>
</tr>
<tr>
<td></td>
<td>Europe 2001</td>
<td></td>
</tr>
<tr>
<td>Cefuroxime axetil (GSK)</td>
<td>USA 1977</td>
<td>Second generation cephalosporin antibiotic, trade names Ceftin, Zinacef, Zinnat. Crystalline form is a mixture of two diastereomers. Amorphous form recently dispersed with HPMC 2910 / PVP K-30 to increase dissolution rate.</td>
</tr>
<tr>
<td>Zafirlukast (Astra-Zeneca)</td>
<td>1999</td>
<td>Oral leukotriene receptor agonist for maintenance treatment of asthma, trade names Accolate, Accoleit, Vanticon. Forms A (amorphous), B (unstable crystal), X (stable crystal) discovered, also ethanol &amp; methanol solvates. X has poor bioavailability, B is difficult to prepare reliably. A is used in formulations.</td>
</tr>
</tbody>
</table>
# Amorphous API
(products for oral use)

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<th>Compound (Discoverer/Manufacturer)</th>
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<tbody>
<tr>
<td>Rosuvastatin calcium (Astra-Zeneca)</td>
<td>USA 2003</td>
<td>High potency statin for reducing high blood cholesterol levels, trade name Crestor. Amorphous solid, slightly soluble in water (7.8 mg.mL$^{-1}$ @ 37°C).</td>
</tr>
<tr>
<td></td>
<td>154 other countries 2004</td>
<td></td>
</tr>
<tr>
<td>Itraconazole (Janssen Pharmaceutica)</td>
<td>Europe 1987, USA 1992</td>
<td>Triazole antifungal agent, trade name Sporanox. Absorption in the body is difficult and unreliable, and dosing with a solution containing cyclodextrin is employed.</td>
</tr>
<tr>
<td>Quinapril hydrochloride (Pfizer)</td>
<td>1989</td>
<td>ACE (angiotensin converting enzyme) inhibitor for treating hypertension and congestive heart failure, trade name Accupril. Amorphous powder, freely soluble in water and organic solvents.</td>
</tr>
</tbody>
</table>
Useful properties of the Amorphous state

- Higher dissolution rate (can give better bioavailability)
- Better compression characteristics
- Optimum stability of macromolecules (freeze dried systems are generally more stable than a liquid formulation)

Problems with Amorphous state

- Lower physical and chemical stability than crystalline state
- Higher Hygroscopicity (water absorption vs water adsorption of a crystalline form)
- Variability (batch to batch, change with time)
Glass versus supercooled liquid

Properties
Glass:
- $\eta > 10^{13}$ P
- High temperature dependence of $\eta$ and molecular motions

Properties
Supercooled liquid:
- $\eta \approx 10^{-2}$ P
- Molecular motion pico- nanoseconds
- Lower temperature dependence of $\eta$ and molecular motions

50 K below $T_g$ molecular mobility (Kauzmann temperature) can be considered low enough to ensure stability
Manipulating $T_g$ of the API by mixing with a higher $T_g$ excipient

Gordon-Taylor equation, and others to predict $T_g$ of a mixed system

Gordon-Taylor equation assumes volume additivity and no interactions

$T_g$ of the system different than predicted: interactions excipient-API and/or phase separation

Solid line: predicted
Data points: experimental $T_g$ value
HPMC-Itraconazole
Amorphous Solid Dispersions


One phase system
One glass transition

Two phase system
Glass transitions of each phase

Multiple phase system
Molecular Interactions: API - excipient/polymer

Fig. 1. Chemical structures of (a) griseofulvin, (b) indoprofen, and (c) repeat unit of PVP.

Carbonyl stretching region

Table II. Kinetics of Drug Phase Separation at 40°C/69% RH

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration (% w/w)</th>
<th>Moisture (% w/w)</th>
<th>Rate constant of phase separation ( k ) (day(^{-1})) ( \times 10^2 )</th>
<th>KJMA linear fit ( R^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griseofulvin</td>
<td>30</td>
<td>6.6 ± 1.5</td>
<td>12.50</td>
<td>0.868</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>7.8 ± 0.6</td>
<td>5.19</td>
<td>0.958</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>9.8 ± 0.7</td>
<td>4.66</td>
<td>0.970</td>
</tr>
<tr>
<td>Indoprofen</td>
<td>30</td>
<td>6.0 ± 0.5</td>
<td>1.25</td>
<td>0.988</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>9.3 ± 0.5</td>
<td>0.62</td>
<td>0.968</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>7.9 ± 3.0</td>
<td>NPS</td>
<td>NA</td>
</tr>
</tbody>
</table>

NPS, no phase separation; NA, not applicable.
\( N = 3 \).
Raman Mapping

10% API

30% API

50% API

Ratio $I_{1643}/I_{934}$

Karavas et al. (2007) IJP 340:76-83
Raman Mapping

Felodipine

PVP

Karavas et al. (2007) IJP 340:76-83
Ways to generate amorphous material

- Milling
- Supercooling of the melt
- Vapor condensation
- Precipitation from solution

Methods to prepare solid dispersions (API dispersed into a polymer/excipient)

Solvent removal method

- Lab scale: vacuum drying
- Larger scale: Spray drying

Cooling from the melt

- Melted Polymer and API
- Cooling
- Larger scale: hot stage extrusion

Diagram:
- Polymer
- API
- In solution
- Lab scale: vacuum drying
- Larger scale: Spray drying
- Melted Polymer and API
- Cooling
- Larger scale: hot stage extrusion
Examples of API’s prepared as amorphous forms

<table>
<thead>
<tr>
<th>API</th>
<th>Preparation method</th>
<th>API</th>
<th>Preparation method</th>
</tr>
</thead>
<tbody>
<tr>
<td>(<strong>1</strong>) Separation / precipitation of solid from liquid</td>
<td><strong>(1a) Solidification from the melt</strong></td>
<td><strong>(1b) Spray drying</strong></td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Quench cooling with liquid N(_2); slow cooling from the melt over 30 min.</td>
<td>4”'-O-(4-methoxyphenyl) acetyltlosin</td>
<td>Spray drying a dichloromethane solution.</td>
</tr>
<tr>
<td>Felodipine</td>
<td>Cooling in liquid N(_2) or at ambient temperature.</td>
<td>Salbutamol sulfate</td>
<td>Spray-drying aqueous solution in a Buchi 90 spray dryer.</td>
</tr>
<tr>
<td>Lovostatin</td>
<td>Melting under N(_2), rapid cooling to 20°C below glass transition.</td>
<td>Digoxin</td>
<td>Spray-drying an aqueous solution with hydroxypropyl methylcellulose</td>
</tr>
<tr>
<td>(<strong>1c</strong>) Freeze drying (lyophilization)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dirithromycin</td>
<td>Freeze drying from methylene chloride solution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>Freeze drying an aqueous solution with 1% hydroxypropyl-β-cyclodextrin.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium ethacrynate</td>
<td>Rapid freezing of an aqueous solution to -50°C, freeze-drying.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalothin sodium; Cefamandol sodium</td>
<td>Freeze-drying from a 25% aqueous solution.</td>
<td></td>
<td></td>
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<th>Preparation method</th>
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<tr>
<td>(2) Mechanical disruption of an ordered structure</td>
<td>(2a) Milling</td>
<td>(2b) Desolvation</td>
<td></td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Ball milling.</td>
<td>Tranilast anhydrate</td>
<td>Dehydration of the monohydrate over $P_2O_5$.</td>
</tr>
<tr>
<td>Calcium gluceptate</td>
<td>Milling in a Pulverisette 2 grinder (Fritsch) for 4 hours.</td>
<td>Erythromycin</td>
<td>Heating the dihydrate for 2 hours at 135°C, and then cooling to room temperature</td>
</tr>
<tr>
<td>Chloramphenicol palmitate</td>
<td>Milling in a Pulverisette 0 grinder (Fritsch) for 85 hours.</td>
<td>Calcium DL-pantothenate</td>
<td>Drying the methanol:water 4:1 solvate <em>in vacuo</em> at 50-80°C.</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Milling in a Glen Creston Model M270 ball mill for 8 hours.</td>
<td></td>
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</tr>
</tbody>
</table>
Solid dispersion screening by solvent removal method

Factors that can be varied during the preparation of solid dispersion from solution by solvent removal method:

- Type of polymer
- Drug to polymer ratio
- Solvent system
- 3\textsuperscript{rd} component (surfactant, 2\textsuperscript{nd} polymer, etc)
- Evaporation rate
- etc

<table>
<thead>
<tr>
<th>Polymers</th>
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<tbody>
<tr>
<td>Screen</td>
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</table>

<table>
<thead>
<tr>
<th>Drug Loading</th>
<th>Solvent system A</th>
<th>Solvent system B</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
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<tr>
<td>B</td>
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<td>C</td>
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<tr>
<td>L</td>
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</tbody>
</table>
Solid dispersion screening by melt method

Factors that can be varied during the preparation of solid dispersion by melt method:

- Type of polymer
- Drug to polymer ratio
- Melting temperature
- 3\textsuperscript{rd} component (surfactant, 2\textsuperscript{nd} polymer, etc)
- Holding time
- etc
Solid dispersion screening by solvent removal and melt methods

Prerequisites and timelines

- number of experiments: 80-160 at ml scale
- Amount of API: minimum 0.5 g (depending on the number of experiments)
- Stress conditions stability study (usually several weeks)
- Drug loading (10-30%)
- Timelines: 5 weeks (assuming a 1 week stability study)
Amorphous Solid Dispersion Screen

• XRPD for first selection of amorphous systems

• Storage at stress conditions (high temperature and humidity)

• XRPD for selection of what remained amorphous

• Further characterization of the stable amorphous systems (thermal analysis, spectroscopy, solubility & dissolution)
Conclusion

- The selection of the appropriate API solid form to optimize the properties of the drug as needed for further development
- Solubility enhancement by selecting appropriate solid forms such as polymorphs, salts, co-crystals or amorphous
- Stabilization of amorphous solids in dispersion
- Developing/scalability practical solid dispersion
Working with Amorphous API’s

Avantium Technologies
Amsterdam, The Netherlands
http://www.avantium.com

Accelerating R&D