Perspectives on the use of amorphous dispersions

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APS Biopharmaceutics Focus Group 9 June 2011
Biopharmaceutics & early drug development - current best practice and emerging science
Perspectives on the use of amorphous dispersions

Introduction

Considerations for amorphous formulation development

Dissolution and BA performance

♦ *In vivo* performance model
♦ Drug X: Use in enabling drug delivery
♦ Drug Y: Use in mitigating gastric pH effect

Summary
The amorphous state

Zhou et al.
J. Pharm. Sci. 91:8 2002

BENEFIT
Dissolution and BA

RISK
Physical stability (recrystallisation)
Applicability maps for amorphous technology

Solubilization Applicability Maps have been developed to identify regions where solubilization technologies are applicable.

Key Properties:

- **Melting Point (Tm)** – Measure of crystal forces
- **Glass Transition Temperature (Tg)** – Measure of amorphous state mobility
- **Log P or ClogP (Calculated)** – Lipophilicity
- **Ratio of Tm/Tg (°K/°K)** – Propensity for compound to crystallize from the amorphous state

Additional Maps of Interest:

- **Dose vs Tg** - deliverability in dosage form
- **Tm vs Tg** – rules of thumb for physical stability
- **Dose/solubility ratio vs Log P** - degree of difficulty of solubilization challenge

Considerations for amorphous form development

Formulation
Process
Additional factors
Key for stability and dissolution performance:

- **Choice of polymer and drug loading**

  - HPMC-AS
  
  \[ R_1 = -H \]
  \[ R_2 = -\text{COCH}_3 \]
  \[ -\text{CH}_3 \]
  \[ -\text{CH}_2\text{CH} (\text{CH}_3) \text{OH} \]

  - PVP-VA
  
  \[ n = 1.2 \]
  \[ m \]
  \[ n \]
  \[ m \]

- Polymer ideally has high Tg, low moisture uptake, opportunities for interactions

- Lower drug loading increases physical stability.

Effect on dissolution?
Formulation Considerations

Additional components in dispersion

- Surfactant, disintegrant etc.

Dosage form excipients

- Moisture uptake properties
- Plasticiser effects e.g. migration from film coat
Process Considerations

Spray-drying

- Drug & polymer in solvent
- Spray Solution
- Spray Drying
- Secondary Drying

Initial Solution Droplet
- 10^{-6} sec
- Hot Drying Gas Contacts Droplet
- 10^{-2} sec
- Skinned Droplet
- ~1 sec
- Dried SDD Particle

Feeding cooling
- Barrel & Screw

Pressure Nozzle
- M_{\text{soln}}, T_{\text{soln}}, P_{\text{nozzle}}

Feed Soln
- M_{\text{gas}}, T_{\text{in}}, T_{\text{cond}}

Drying Chamber
- Residence Time ~10^{-30} sec

SDD Nitrogen Solvent Vap
- T_{\text{out}}

Also Freeze-drying

Hot-melt extrusion

- Feed Hopper
- collars for heating and cooling
Process Considerations

For physical stability:
- No residual solvent
- Dispersion needs to be homogenous

Example: Drug/PVP-VA extruded using screw speed 50 rpm or 225 rpm

50 rpm material showed poorer physical stability
Raman microscopy indicated initial poor homogeneity/phase separation:

Is a distinctive single Tg a reliable indicator for the homogeneity of amorphous solid dispersion?
Process Considerations

Also consider powder properties

- May be important for dissolution performance
- Effect of scale-up

<table>
<thead>
<tr>
<th>SD-Micro</th>
<th>PSD-1 Spray Dryer</th>
<th>PSD-2 Spray Dryer</th>
<th>PSD-5 Spray Dryer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk density</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Particle Size (Dv(4,3))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD-Micro</td>
<td>PSD-1</td>
<td>PSD-2</td>
<td>PSD-5</td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Compactibility (high pressure Hg Intrusion)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD-Micro</td>
<td>PSD-1</td>
<td>PSD-2</td>
<td>PSD-5</td>
</tr>
</tbody>
</table>
Process Considerations

...and dosage form manufacturing operations

- potential of unit operations to cause amorphous → crystalline

Diagram: Blend → Roller compact → Size-reduce → Compression → Shear → Heat → Film-coat → Tablet → Blend
**Additional Considerations**

**Product control and analysis**
- CQA’s of raw materials and dispersion
- Dissolution methodology challenges

**Manufacturing Operations**
- Internal vs external manufacture of dispersion
- Dispersion packaging, storage, hold time

**Commercial**
- Dose vs dosage form size
- Cost of goods

**Regulatory**
Dissolution and BA of amorphous dispersions

In vivo performance model

Drug X: Use in enabling drug delivery

Drug Y: Use in mitigating gastric pH effect
Assuring rapid disintegration of tablet is key but bioperformance is function of dispersion itself - both are optimized to “tune” product performance.
**In vivo performance model - speciation**

Solid SDD Particle (1-100 μm)

Drug-polymer Nanoparticle (10-100 nm)

Polymer Chains

Drug Nanostructures

Bile-Salt Micelles

Free Drug

Absorption

Hydration

Disintegration

Dissolution

Diffusion

Blood

Epithelium

Unstirred Mucus Layer

Drug Nanostructures

Bile-Salt Micelles

Free Drug

Absorption

Hydration

Disintegration

Dissolution

Diffusion

Blood

Epithelium

Unstirred Mucus Layer
Drug X:
Amorphous dispersion to enable drug delivery

BCS class II
- Log P = 4.6
- Aqueous solubility <1 µg/mL at RT
- Non-ionizable, pH-independent solubility

Dog studies showed no appreciable improvement in BA by API particle size reduction
- PEG 400 solution in capsule: 68 %F
- Aqueous suspension of micronized API: 5 %F
- Aqueous nano suspension: 10 %F

Amorphous dispersion approach selected to enable delivery
**In vitro dissolution assessment**

Studies to select polymer and drug loading

- Level of supersaturation
- Sustainment of supersaturation

**Tablet dissolution assessment**

- Gastric buffer → MFDS intestinal buffer (non-sink)
- QC method (sink)

**Dispersion particle size**

- Rate of dissolution
Level and sustainment of supersaturation

Non-sink conditions with MFDS intestinal buffer (Model Fasted Duodenal Solution)
0.5% NaTC/POPC in PBS pH 6.5 at 37°C
Tablet dissolution (non-sink)

Gastric buffer → MFDS intestinal buffer
(0.01N HCl)          (0.5% NaTC/POPC in PBS pH 6.5)
QC method:
phosphate buffer with 1% Brij 35, USP apparatus 2 (paddles at 75rpm)
In vivo performance: Dog study

**Graph:**
- **X-axis:** Time (h)
- **Y-axis:** Plasma (ng/ml)
- **Legend:**
  - SD Tab - HPMC-AS
  - SD Tab - PVP-VA
  - HME Tab - jet milled
  - Sol. Cap. (historic)

**Note:**
- n = 4 dogs
Dispersion particle size

Gastric buffer $\rightarrow$ MFDS intestinal buffer
(0.01N HCl) $(0.5\% \text{ NaTC/POPC in PBS pH 6.5})$
Sink conditions with intestinal buffer (2% NaTC/POPC in PBS pH 6.5 at 37°C)
Drug Y:
Amorphous dispersion to mitigate gastric pH effect

BCS class II
LogP = 2.6 (pH 6.4), pKa = 3.1

PK profile (monkey)

Range of technologies previously evaluated:
- Nano
- pH modified (buffered) tablet
- Solubilized (micro-emulsion)
- Amorphous dispersion (spray dried with PVP)
Amorphous dispersion with anionic polymer

- Provide for rapid high solubility
- Potential to sustain supersaturation
- HPMC-AS inherent pH solubility profile may assist pH mitigation
Level and sustainment of supersaturation

MFDS (0.5% NaTC/POPC in PBS pH=6.5)

Gastric pH 2 transfer to MFDS

HPMC-AS Amorphous
PVP Amorphous
Crystalline API
### In vivo performance

Amorphous dispersion has essentially removed pH effect

<table>
<thead>
<tr>
<th>Formulation Dosed</th>
<th>PK Parameter</th>
<th>% Change without / with famotidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet with crystalline API</td>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>-77</td>
</tr>
<tr>
<td></td>
<td>$AUC_{0-72h}$ (ng/mL*hr)</td>
<td>-32</td>
</tr>
<tr>
<td></td>
<td>$AUC_{0-\text{INF}}$ (ng/mL*hr)</td>
<td>-28</td>
</tr>
<tr>
<td>Tablet with dispersion 25:75 API: HPMC-AS (MG)</td>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>-5</td>
</tr>
<tr>
<td></td>
<td>$AUC_{0-72h}$ (ng/mL*hr)</td>
<td>+8</td>
</tr>
<tr>
<td></td>
<td>$AUC_{0-\text{INF}}$ (ng/mL*hr)</td>
<td>+3</td>
</tr>
</tbody>
</table>

N=6 monkeys

**PK profile (monkey)**

- Drug Y SDD alone
- Drug Y SDD + Famotidine
Use of amorphous dispersions - Summary

Key strategy to enable delivery of poorly soluble drugs
- Enhanced dissolution performance improves BA
- May also mitigate \textit{in vivo} pH effects

Mechanistic understanding of solution behaviour and \textit{in vivo} performance is evolving
- Role of nanostructures vs diffusion/erosion
- Influence of polymer
- Impact of dispersion properties e.g. particle size

Primary risk is physical stability

Strategy is challenging but rewarding!
Thank you for your attention