Basics of Amorphous and Amorphous Solid Dispersions

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PPXRD Website – www.icdd.com/ppxrd  ICDD Website - www.icdd.com
Amorphous Products

Amorphous active pharmaceutical ingredients (APIs) marketed as drug products:

- Accolate® (zafirlukast)
- Ceftin® (cefuroxime axetil)
- Accupril® (quinapril hydrochloride)
- Viracept® (nelfinavir mesylate)
Amorphous can be produced in a variety of situations:

- **Vapor condensation**
- **Precipitation from solution**
- **Supercooling of liquid**
- **Disruption of crystalline lattice**

**Intentional**
- solvent evaporation
- freeze drying
- spray drying

**Unintentional**
- wet granulation
- drying
- polymer film coating

**Intentional**
- grinding

**Unintentional**
- grinding
- desolvation
- compaction

Amorphous

- No long range order
- Exhibit a halo in XRPD patterns (vs crystalline peaks)
- Do possess short range order
- Less physically and chemically stable than crystalline materials
- Higher apparent solubility and faster dissolution than crystalline materials

Solubility

The term "solubility" (unless otherwise specified) refers to the "equilibrium solubility" of the most stable crystal form in equilibrium with the solvent.

The solubility of anything other than the most stable form is reported as the "apparent solubility".

Yalkowsky, personal communication.
Solubility

• Theoretical estimates of solubility ratios calculated from heat capacity measurements of crystalline and amorphous
• Theoretical estimates of solubility ratios higher than experimental values
• Solubility profiles show conversion of amorphous to crystalline form

Dissolution

- Amorphous materials will usually result in an increase in dissolution rate
- Remained amorphous over time frame of experiment

Ritanovir
0.1 N HCl at 37°C

Law et al. *J. Pharm. Sci.* 2004, 93, 563-570
Glass Transition Temperature

- Amorphous solids can exist in two states
  - Super-cooled liquid (or rubbery state): a viscous equilibrium liquid form of the material
  - Glass: a solid non-equilibrium form of the same material
- The temperature at which one form converts to the other is the glass transition temperature, $T_g$
- Structural factors affecting $T_g$ include
  - Molecular size and shape
  - Extent, strength, and direction of any hydrogen bonding
- These effect the strength of intermolecular interactions and packing (free volume)
Glass Transition Temperature

- Energy temperature (ET) diagram for amorphous and crystalline material
  - $T_{f\text{II}}$: melting of crystal II
  - $T_{f\text{I}}$: melting of crystal I
  - $T_g$: glass transition temperature where supercooled liquid changes to glass
- Upon cooling
  - Melt $\rightarrow$ supercooled liquid $\rightarrow$ glass

Glass Transition Temperature

- ET diagram for volume (V) or enthalpy (H)
- Depending on thermal history, glass can form with slightly different energies, resulting in variable $T_g$
- This is not polyamorphism, just different energy levels of the glass

Bhurg and Pikal. *J. Pharm. Sci.* **2008**, *97*, 1329-1349
Glass Transition Temperature

Commonly measured with differential scanning calorimetry (DSC) or modulated DSC

\[ \frac{dH}{dT} = f(\Delta C_p) \]

\[ T_f = \text{onset } T_g \]

\[ T_m = \text{midpoint or inflection } T_g \]
# Glass Transition Temperature

## Common sugars

<table>
<thead>
<tr>
<th>Sugar</th>
<th>Molecular Weight (g/mol)</th>
<th>$T_g$ (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>180</td>
<td>30</td>
</tr>
<tr>
<td>Fructose</td>
<td>180</td>
<td>13</td>
</tr>
<tr>
<td>Sucrose</td>
<td>342</td>
<td>74</td>
</tr>
<tr>
<td>Trehalose</td>
<td>342</td>
<td>115</td>
</tr>
<tr>
<td>Maltose</td>
<td>342</td>
<td>100</td>
</tr>
<tr>
<td>Lactose</td>
<td>348</td>
<td>102</td>
</tr>
<tr>
<td>Raffinose</td>
<td>504</td>
<td>108</td>
</tr>
<tr>
<td>Maltodextrin</td>
<td>860</td>
<td>169</td>
</tr>
<tr>
<td>Dextran</td>
<td>10K</td>
<td>197</td>
</tr>
</tbody>
</table>
Glass Transition Temperature

- Different grades of poly(vinylpyrrolidone) (PVP)

<table>
<thead>
<tr>
<th>Sample</th>
<th>Molecular Weight (g/mol)</th>
<th>$T_g$ (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVP K90</td>
<td>1500 K</td>
<td>177</td>
</tr>
<tr>
<td>PVP K30</td>
<td>50K</td>
<td>156</td>
</tr>
<tr>
<td>PVP K17</td>
<td>10K</td>
<td>136</td>
</tr>
<tr>
<td>PVP K12</td>
<td>2K</td>
<td>101</td>
</tr>
<tr>
<td>PVP/VA (60:40)</td>
<td>50K</td>
<td>102</td>
</tr>
</tbody>
</table>
Glass Transition Temperature

- Effect of different counterions on the Tg of indomethacin salts

## Glass Transition Temperature

- **Estimation of $T_g$**
  - $T_g$ is roughly $(0.67)T_m$ (the melting temperature of the crystalline material)
  - “2/3 rule”

<table>
<thead>
<tr>
<th>Sample</th>
<th>$T_g$ (K)</th>
<th>$T_m$ (K)</th>
<th>$T_g/T_m$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly(ethylene terephthalate)</td>
<td>343</td>
<td>538</td>
<td>0.64</td>
</tr>
<tr>
<td>Nylon 66</td>
<td>333</td>
<td>538</td>
<td>0.61</td>
</tr>
<tr>
<td>Polyacrylonitrile</td>
<td>378</td>
<td>590</td>
<td>0.64</td>
</tr>
<tr>
<td>Isotactic polypropylene</td>
<td>268</td>
<td>435</td>
<td>0.62</td>
</tr>
<tr>
<td>Aspirin</td>
<td>243</td>
<td>408</td>
<td>0.60</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>315</td>
<td>434</td>
<td>0.73</td>
</tr>
<tr>
<td>Sodium indomethacin</td>
<td>393</td>
<td>543</td>
<td>0.72</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>323</td>
<td>447</td>
<td>0.72</td>
</tr>
<tr>
<td>Cholocalciferol</td>
<td>293</td>
<td>352</td>
<td>0.84</td>
</tr>
</tbody>
</table>
DSC can also give information on changes with temperature

- **Exotherm**: crystallization of amorphous \( (T_c) \)
- **Endotherm**: melt of crystalline indomethacin \( (T_m) \)

Hancock and Zografi. *J. Pharm. Sci.* **1997**, *86*, 1-12
Relaxation

- Amorphous materials can age or relax over time
- DSC shows an enthalpy relaxation endotherm
- Upon relaxation
  - Density increases
  - Free volume decreases

Hancock and Zografi. *J. Pharm. Sci.* 1997, 86, 1-12

Relaxation

- Once the glass is formed, it can be aged or annealed at a specific temperature ($t_1$) for a period of time.
- The relaxation results in a decrease in $H$ or $V$.
- Upon reanalyzing the material, enthalpy of relaxation is seen as an endotherm ($\Delta H$).
- Longer aging times will result in larger enthalpy relaxation.

Hancock et al. *Pharm. Res.* 1995, 12, 799-806
Aged materials show decreased physical and chemical reactivity compared to unaged materials.

Exposure to water can reverse the aging of an amorphous material and make it more reactive.

Stability

• Chemical stability
  – Amorphous materials can be less chemically stable than crystalline materials

• Physical stability
  – Amorphous materials are less physically stable and will tend to crystallize over time and under stress (temp, RH, etc)
Stability

Amorphous Na indomethacin

- $T_g$ of 121 °C dry, 53 °C at 21% RH
- 15 days at elevated temperature (below $T_g$) and RH
  - Amorphous material remained amorphous at 21% RH and 40 °C
  - Amorphous material had highest chemical decomposition highest temperature, closer to $T_g$
- Crystallization increased with higher T and RH conditions

Physical Stability

Temperature

• Sucrose stored at 47, 32, and 16 °C below $T_g$
• Enthalpy relaxation measured over time
• Samples stored at $T_g - 47$ showed no change
• Rule of thumb: store amorphous samples 50 °C below $T_g$ to minimize changes

Hancock et al. Pharm. Res. 1995, 12, 799-806
Physical Stability

• Water can absorb (dissolve) into amorphous solids via hydrogen bonding due to the disordered structure

• Water has low $T_g$
  • 135 K (-138 °C)
  • Plasticizing effect
  • Lowers $T_g$ of most pharmaceutical systems

• Estimation of $T_g$
  • Fox Equation:
    $$\frac{1}{T_{g_{mix}}} = \left(\frac{w_1}{T_{g_1}}\right) + \left(\frac{w_2}{T_{g_2}}\right)$$
    where $w = \text{weight fraction}$

  Water content: 5.0% w/w
  $T_g$: 50 °C (323K)
  $T_{g_{mix}} = \frac{(0.05/135) + (0.95/323)}{1}$
  $T_{g_{mix}} = 302K$ or 29 °C
Physical Stability

- Indomethacin-water
- Absorbed water lowers the $T_g$ of an amorphous solid
- Rule of thumb: 1% water will decrease $T_g$ by about 10 deg

Andronis et al., *J. Pharm. Sci.* 1997, 86, 346-351
Physical Stability

Loss of water at 85% RH indicative of amorphous material crystallizing into Form A
Molecular Mobility

- For any physical or chemical transformation to take place in the solid state
  - must be a thermodynamic driving force
    - a net loss in free energy
    - sufficient diffusional motion (translational and rotational) over the desired time scale
- Generally, molecular mobility follows the order: liquid > super cooled liquid > glass > crystal

- Molecular motions
  - Primary Relaxations
    - $\alpha$ relaxations
    - “slow” cooperative diffusion (translational and rotational motion of whole molecules or polymer segments)
    - corresponds to $T_g$
  - Secondary Relaxations
    - $\beta$ relaxations
    - “faster” non-cooperative local motions associated with individual molecules or polymer main-chain segments, as well as with polymer side-chains
    - Important secondary relaxations are often called “Johari-Goldstein” relaxations. They are precursors to the primary $\alpha$ relaxations

Molecular Mobility

• Molecular mobility is best expressed in terms of a relaxation time, $t_s$
  – $t_s$ represents the time scale over which a unit dynamic event occurs

• Rate of relaxation expressed as “the fraction unrelaxed” or the relaxation parameter, $\phi(t)$
  – $t = 0$, $\phi(t) = 1$
  – $t = t$, $\phi(t) = \text{between 1 and 0}$

• In a disturbed system, observe rate of return to equilibrium
  \[ \phi(t) = \exp(-t/\tau_s) \]

• Methods to Measure Relaxation Time
  – Dynamic Mechanical Analysis
  – Dielectric Relaxation
  – Enthalpy and Volumetric Relaxation
  – NMR
  – Dynamic Light scattering
  – Dynamic Neutron Scattering
  – Optical Probes

• In combination these cover $t = 10^6$ to $10^{-12}$ s
Molecular Mobility

• Kohlrausch, Watts, Watkins (KWW) stretch exponential relationship:

\[
\phi(t) = \exp\left(-\frac{t}{\tau_{\text{KWW}}}\right)^\beta
\]

\(\beta = 1\) for single relaxation mode

\(0 \leq \beta < 1\) for multiple modes

\(\beta \approx 0.3-0.5\) near \(T_g\); approaches 1.0 at high temperatures

relaxation parameter, \(\phi(t)\)

relaxation time, \(\tau_{\text{KWW}}\)

• Critical considerations in estimating relaxation times for predicting molecular mobility:

• The values of \(\tau_s\) obtained experimentally are average values

• There are multiple modes of relaxation reflected in the value of \(\beta\) from the KWW equation
Fragility

• Fragile:
  – greater the change in molecular mobility with temperature, and the more non-Arrhenius it is, the more “fragile” the system is considered

• Strong:
  – Less change with temperature and the more Arrhenius-like this change the more the system is considered to be a “strong liquid”

Vogel, Tamman, Fulcher (VTF) Equation

$$\log \tau_s = \log \tau_o + \left[ \frac{(D \tau_o)}{(T-T_o)} \right]$$

$$\tau_s = \text{structural relaxation time at } T = T$$

$$\tau_o = \text{structural relaxation time at } T = \infty$$

$$D = \text{strength parameter}$$

$$T_o = \text{temperature at infinite relaxation time}$$

$$D = 2-30 \text{ “Fragile Liquid”}$$

$$D = > 30 \text{ indicates a “Strong Liquid}$$

Angel. Polymer. 1997, 38, 6261
Fragility

Relaxation time vs temperature scaled to Tg described by VTF D values

2-30 Fragile, >30 Strong

<table>
<thead>
<tr>
<th>Material</th>
<th>T_g (K)</th>
<th>T_o (K)</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>B_2O_3</td>
<td>557</td>
<td>320</td>
<td>27</td>
</tr>
<tr>
<td>sorbitol</td>
<td>270</td>
<td>214</td>
<td>9</td>
</tr>
<tr>
<td>o-terphenyl</td>
<td>249</td>
<td>195</td>
<td>10</td>
</tr>
<tr>
<td>indomethacin</td>
<td>317</td>
<td>237</td>
<td>13</td>
</tr>
<tr>
<td>Na indomethacin</td>
<td>389</td>
<td>276</td>
<td>15</td>
</tr>
<tr>
<td>nifedipine</td>
<td>322</td>
<td>228</td>
<td>15</td>
</tr>
<tr>
<td>diazepam</td>
<td>398</td>
<td>249</td>
<td>10</td>
</tr>
<tr>
<td>felodipine</td>
<td>416</td>
<td>247</td>
<td>10</td>
</tr>
</tbody>
</table>

Similar D values means similar T_m – T_g values, and therefore, similar T_g/T_m.

Amorphous Solid Dispersions

Amorphous solid dispersions

- Amorphous drug with polymer
- Polymer stabilizes amorphous drug
- Results in better stability, higher apparent solubility, faster dissolution
- Usually prepared on large scale by spray drying or melt extrusion
Amorphous active pharmaceutical ingredients (APIs) marketed as drug products:

- Accolate® (zafirlukast)
- Ceftin® (cefuroxime axetil)
- Accupril® (quinapril hydrochloride)
- Viracept® (nelfinavir mesylate)

Amorphous solid dispersions marketed as drug products:

- Cesamet® (nabilone)
- Gris-PEG® (griseofulvin)
- Isoptin® (verapamil)
- Kaletra® (lopinavir/ritonavir)
- Sporanox® (itraconazole)
- Rezulin® (troglitazone)
Terms

• Early literature referred to **solid dispersions** as mixtures of polymer and **crystalline** drug
  – Small particle size of crystalline drug would sometimes help improve dissolution

• **Amorphous solid dispersion** is used to describe solid mixtures of polymer and **amorphous** drug

• Other terms that have been used
  – Amorphous dispersion
  – Amorphous solid solution
  – Molecular dispersion

• Need to determine the type of system that is being described when reading literature reports
  – Review characterization data to determine if API is amorphous or crystalline
Polymers

Wide variety of polymers available

- Polymers used as excipients can be used for dispersions

- Handbook of Pharmaceutical Excipients

- Other polymers can be used; tox properties need to be evaluated

<table>
<thead>
<tr>
<th>Polymers</th>
<th>Abbreviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>carboxymethylcellulose</td>
<td>CMEC</td>
</tr>
<tr>
<td>cellulose acetate phthalate</td>
<td>CAP</td>
</tr>
<tr>
<td>D-alpha-tocopheryl polyethylene glycol 1000 succinate</td>
<td>TPGS</td>
</tr>
<tr>
<td>ethyl cellulose</td>
<td>EC</td>
</tr>
<tr>
<td>gelucire 44/14</td>
<td>HEC</td>
</tr>
<tr>
<td>hydroxyethyl cellulose</td>
<td>HEC</td>
</tr>
<tr>
<td>hydroxypropyl cellulose SL</td>
<td>HPC-SL</td>
</tr>
<tr>
<td>hydroxypropylmethyl cellulose</td>
<td>HPMC</td>
</tr>
<tr>
<td>hydroxypropylmethyl cellulose acetate succinate</td>
<td>HPMC-AS</td>
</tr>
<tr>
<td>hydroxypropylmethyl cellulose phthalate</td>
<td>HMPCP</td>
</tr>
<tr>
<td>methacrylic acid copolymer (Eudragit)</td>
<td></td>
</tr>
<tr>
<td>methylcellulose</td>
<td>MC</td>
</tr>
<tr>
<td>pluronic F-68</td>
<td>P188</td>
</tr>
<tr>
<td>poloxamer 188</td>
<td>PEG</td>
</tr>
<tr>
<td>polyethylene glycol</td>
<td>PEG MME</td>
</tr>
<tr>
<td>polyethylene glycol monomethyl ether</td>
<td></td>
</tr>
<tr>
<td>polyoxyethylene (40) stearate</td>
<td>S40</td>
</tr>
<tr>
<td>polyoxyethylene–polyoxypropylene copolymers (Poloxamer® 188)</td>
<td></td>
</tr>
<tr>
<td>polysorbate 80</td>
<td></td>
</tr>
<tr>
<td>polyvinyl acetate phthalate</td>
<td>PVAP</td>
</tr>
<tr>
<td>polyvinylacetal diethylaminoacetate (AEA®)</td>
<td></td>
</tr>
<tr>
<td>polyvinyl pyrrolidone</td>
<td>PVP</td>
</tr>
<tr>
<td>polyvinylpyrrolidone vinylacetate</td>
<td>PVP/VA</td>
</tr>
</tbody>
</table>

Note: representative list only
Polymers

Polymer selection

- Empirical approach: choose common polymers
- Manufacturing: need low melting polymers for melt extrusion, need solubility in solvent for spray drying
- Interactions: look at common H-bonding motifs or ion dipole interactions between drug and polymer
  - try to disrupt bonding in crystalline material (example PVP disrupts indomethacin dimers)
- Miscibility and solubility using Flory-Huggins theory: miscible systems show melting point depression, non-miscible systems do not show significant melting point depression
- Melting point ($T_m$) and glass transition ($T_g$) ratio ($T_m/T_g$)- high ratios may crystallize more easily
Polymers stabilize amorphous drug in solid-state.

Upon exposure to aqueous media, dissolution is believed to generate a supersaturated state due to the amorphous state of the drug.

Matrix polymer is believed to have a role in preventing precipitation or crystallization from the supersaturated state.

- Drug-polymer interactions
- Preventing or retarding nucleation and crystal growth
Dispersions

Tg of an Ideal Molecular Dispersion

• Assume Ideal Mixing :

\[ T_{g_{mix}} = V_1 T_{g_1} + V_2 T_{g_2} \]

where \( V \) = volume fraction

• On the basis of weight fraction (w)

\[ T_{g_{mix}} = \left\{ \left( w_1 T_{g_1} \right) + \left( K w_2 T_{g_2} \right) \right\} \left/ \left( w_1 + K w_2 \right) \right\}

where : \( K \sim \frac{\rho_1 T_{g_1}}{\rho_2 T_{g_2}} \) (Gordon-Taylor where \( \rho \) is density)

or : \( K \sim \frac{\Delta C_p_1}{\Delta C_p_2} \) (Couchman-Karasz where \( C_p \) is heat capacity)

• Fox Equation

when \( \rho_1 = \rho_2 \) in the Gordon Taylor Equation

Useful for approximate estimates

\[ \frac{1}{T_{g_{mix}}} = \frac{w_1}{T_{g_1}} + \frac{w_2}{T_{g_2}} \]
Dispersions

Why does non-ideal mixing lead to a greater or smaller Tg than expected?

- Depends on the net free volume change

\[ (T_g \text{ mix} < T_g \text{ ideal}) \]
\[ (T_g \text{ mix} = T_g \text{ ideal}) \]
\[ (T_g \text{ mix} > T_g \text{ ideal}) \]

Manufacture

• Small scale
  – Solvent methods
    • Fast evaporation, rotary evaporation, spray drying
  – Thermal
    • Melt
  – Other
    • Supercritical fluid, lyophilization, ultra-rapid freezing

• Large scale
  – Spray drying
  – Melt extrusion
Characterization

- **Diffraction**
  - Powder diffraction, low angle scattering, computational methods
- **Thermal**
  - DSC, Dynamic mechanical analysis (DMA), dielectric analysis (DEA)
- **Spectroscopic**
  - IR, Raman, NMR spectroscopy
- **Solution calorimetry**
- **Microscopy**
  - Optical, scanning electron microscopy (SEM), atomic force microscopy (AFM)
- etc
Miscibility

• Miscible system more stable than physical mixtures

• Ways to investigate miscibility
  • DSC
    – One Tg indicates miscible system
  • XRPD Computational
    – Pair distribution function (PDF)
    – XRPD data cannot be described by individual components indicates a miscible system
  • Spectroscopy
    – Shows association of molecules in a miscible system
Miscibility

- A physical mixture will give two glass transition (Tg) temperatures
- A solid amorphous dispersion will give a single Tg that will change with composition
- Can have positive or negative deviations from theory
- May be a spacial resolution limit with DSC (30 nm)
- Thermal data and other characterization data may not agree
Dispersion Screening

- **Variables**
  - Different polymers
  - Drug:polymer ratio
  - Binary vs ternary mixtures
  - Solvent
  - Preparation conditions
    - Solvent (evaporation, freeze drying)
    - Melt
- **Manual and automated (plate) methods available**
Dispersion Screening

- Plates used initially
- Scaled up to melt press and then melt extruder
- Included in-vivo testing on five formulations


Schematic illustration of the different stages of experimentation. At each subsequent stage, fewer samples are examined; the samples are larger and more compound is used per sample; and the formulation preparation and characterization methods become more relevant to traditional scale formulation development work.
Dispersion Screening

- Oral bioavailability tested for five dispersions and compared to IV
  - HPMCP/TPGS was closest to oral solution for absolute bioavailability
- Did not look at crystallinity or physical stability as part of selection process

Properties

Physical Stability

- 1:4 Nifedipine:PVP amorphous dispersions compressed into tablets
- Stored at 60°C/75% RH
- Dissolution measured in 900 mL of water with 0.1% surfactant at 37°C
- Slow down in dissolution due to crystallization of nifedipine during storage

Properties

Dissolution

• Dispersions with polaxamer 188 (P188)
• Dissolution in SGF at 37 °C
• No crystallization observed
• Significant increase over API

Chokshi et al. *Drug Delivery* 2007, 14, 33-45
Properties

Dissolution

- Dispersions with HPMCAS made from hot melt extrusion (HME) and coprecipitation (CP)
- 40% drug loading
- Physical properties similar except for surface area
  - CP 6.19 m$^2$/g; HME 0.13 m$^2$/g
- Dissolution rate different for the preparations

Dong et al. *Int. J. Pharm.* **2008**, **355**, 141-149
Properties

Bioavailability

- 1:1 ER-34122:HPMC (TC-5RW™)
- Dispersion showed faster dissolution and higher bioavailability than crystalline material

Properties

Bioavailability
- Itraconazole (ITZ): CAP dispersions
- Sporonox faster dissolution and higher concentration
- 1:2 ITZ:CAP dispersion gave better bioavailability
- No IVIVC (in vitro-in vivo correlation)

Testing in 0.1N HCl for 2 hours followed by pH adjustment to 6.8 ± 0.5 with 250 mL of 0.2 M tribasic sodium phosphate solution. Dashed lines indicate time of pH change.

Dispersion Selection

Decision tree for dispersion screening

- Is material amorphous?
  - Yes: Continue dispersion attempts
  - No: Investigate other solubility enhancement approaches

- Does it have acceptable physical characteristics?
  - Yes: Investigate more protective packaging (bulk/finished product)
  - No: Continue dispersion attempts

- Does it have acceptable solubility?
  - Yes: Investigate more protective packaging (bulk/finished product)
  - No: Continue dispersion attempts

- Does it have acceptable stability?
  - Yes: Investigate more protective packaging (bulk/finished product)
  - No: Continue dispersion attempts

- Can the form be readily scaled-up?
  - Yes: Investigate more protective packaging (bulk/finished product)
  - No: Continue dispersion attempts

- Does it have acceptable performance?
  - Yes: FINAL CANDIDATE
  - No: Secondary candidate

Physical Properties

Stability and Processing

Performance
What Have We Learned

• Amorphous
  – Exhibits increased apparent solubility and dissolution rate compared to crystalline materials
  – Can result in poor physical and chemical stability
  – Characterization can include Tg, enthalpy relaxation, fragility

• Amorphous solid dispersions
  – Polymers added to stabilize amorphous material
  – Can perform screens to find possible dispersions
  – Manufacture: spray drying vs melt extrusion for larger scale
  – Performance
    • Dissolution, stability, bioavailability
    • May or may not have in vitro-in vivo correlation (IVIVC)
    • Can use simple prototype formulations (powder in capsule) for early studies; additional work may be needed for later studies
Resources

Amorphous
Hancock and Zografi, J. Pharm. Sci. 1997, 86-1-12

Amorphous Solid Dispersions
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