Use of thermal analysis as primary tool for generation and assessment of complex co-amorphous mixtures.

Dr Milan D. Antonijević
Overview of presentation

• Rational/Aims
• Introduction to amorphous and co-amorphous materials
• Methodology
• Results and Discussion
• Conclusions
• Future work
1 in 5000 drugs makes it from the lab to FDA approval
Solutions

• Improve existing drugs and engineer new drug candidates
• Active component
  • Physical modification
    • Amorphous
    • Crystalline
  • Chemical modification
    • Hydrates
    • Salts
    • Co-Crystals
• Dosage form
  • Many innovative ways
    • HME, Lyophilisation, Buccal drug delivery, 3D printed medicines etc.
Amorphous vs Crystalline

- Non-periodic molecular arrangement.
- Better apparent solubility and dissolution rate than their crystalline counterpart.
- Thermodynamically unstable, stability issues.
- Glass transition (Tg) vs Melting point (Tm)
Co-Amorphous

• Co-amorphous mixtures are homogeneous single-phase dispersions of amorphous materials.
• A co-amorphous system is primarily identified by one glass transition (Tg) indicating that the components are interacting.
• Higher glass transition temperatures indicate increased stability.
• Improved dissolution rates over single component amorphous systems.
• Not all materials can be converted into amorphous phase
Aims

• Identify whether a three component co-amorphous system can be generated by Newtonian cooling from melt
• Determine how the properties of an amorphous material are altered by the addition of a compound with the propensity to form an amorphous or crystalline material.
• Learn how to manipulate Tg (stability) by altering composition
  • Pharmaceutical formulations are often multicomponent systems
  • Small amounts of impurities may have impact on quality of product
Method

1:1:1 Molar Ratio

1. Mettler Toledo FP90 Central processor with FP82HT Hot Stage.

2. Q2000 DSC (TA Instruments, UK)

3. Q5000 IR TGA (TA Instruments, UK)
DSC method

• EQUILIBRATION -80°C
• HEATING TO 180°C AT 10°C/MIN
  • Erase previous thermal history of sample and improve interactions between mixed components
• COOLING TO -80°C AT 20°C/MIN
  • Cooling at 5°C/min was also tested
• HEATING TO 180°C AT 10°C/MIN
  • To analyse the solid state of the product, generated by melt quench method
Generation of co-amorphous outside the DSC

1. XRD patterns were recorded using a D8 Advance X-ray Diffractometer (Bruker, Germany) with CuKα radiation over the interval of 2° to 40° (2θ).

2. FTIR spectra were recorded on Perkin Elmer Spectrum Two with ATR attachment within 4000–650 cm⁻¹.
Selection of chemicals

- Piroxicam (PXC)
- Indomethacin (IND)
- PXC-IND co-amorphous

Graph showing:
- Heat Flow (W/g) vs. Temperature (°C)
- Exo Up
- Peaks at:
  - 45.17°C
  - 57.15°C
  - 64.73°C
  - 132.25°C
  - 138.08°C
  - 176.17°C
  - 181.36°C
Selection of a third component

![Graph showing heat flow (W/g) against temperature (°C) with peaks at 22.08°C, 80.96°C, 156.72°C, and 158.64°C.](image)

- **Clotrimazole (CTMZ)**
- **Acetaminophen (AC)**

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**EXO UO**

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1:1:1 systems

- PXC IND CTMZ physical mixture
- PXC-IND-AC physical mixture

Temperature (°C):
- 110.33°C
- 124.54°C
- 123.81°C
- 130.65°C

Heat Flow (W/g)

Exo Up

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1:1:1 systems quench cooling after melting
1:1:1 systems second heating

- PXD IND CTMZ co-amorphous
- PXD-IND-AC co-amorphous

Heat Flow (mW/g)

Temperature (°C)

54.07°C
43.67°C
## Overview of the results

<table>
<thead>
<tr>
<th>Chemicals</th>
<th>Melting point on initial heating (°C)</th>
<th>Crystallization on cooling (°C)</th>
<th>Thermal events on 2nd heating (°C)</th>
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</thead>
<tbody>
<tr>
<td>PXC</td>
<td>203.1</td>
<td>-</td>
<td>Tg 64.6  Tc 138.1  Tm 181.4</td>
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<tr>
<td>IND</td>
<td>161.1</td>
<td>-</td>
<td>Tg 45.7</td>
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<tr>
<td>CTMZ</td>
<td>145.5</td>
<td>-</td>
<td>Tg 28.0</td>
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<tr>
<td>AC</td>
<td>169.8</td>
<td>-</td>
<td>Tg 22.6  Tc 87.9  Tm 158.6</td>
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<tr>
<td>PXC-IND</td>
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<td>-</td>
<td>Tg 57.6</td>
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<td>PXC-IND-CTMZ</td>
<td>129.3</td>
<td>-</td>
<td>Tg 53.3</td>
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<tr>
<td>PXC-IND-AC</td>
<td>130.7</td>
<td>-</td>
<td>Tg 44.1</td>
</tr>
</tbody>
</table>

\(^a\) Tg – Glass transition, Tc – Crystallisation, Tm – Melting.

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## Effect of different cooling rates

<table>
<thead>
<tr>
<th>Chemicals</th>
<th>Thermal events on 2nd heating AFTER 20°C/MIN COOLING (°C)</th>
<th>Thermal events on 2nd heating AFTER 5°C/MIN COOLING (°C)</th>
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<tbody>
<tr>
<td>PXC-IND</td>
<td>Tg 57.6</td>
<td>Tg 53.3</td>
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<td>PXC-IND-CTMZ</td>
<td>Tg 53.3</td>
<td>Tg 48.4</td>
</tr>
<tr>
<td>PXC-IND-AC</td>
<td>Tg 44.1</td>
<td>Tg 41.6</td>
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<tr>
<td>SYSTEM</td>
<td>TIME (WEEKS)</td>
<td>Tg (°C)</td>
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<tr>
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<tr>
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<td>4</td>
<td>43.1</td>
</tr>
<tr>
<td>ΔTg</td>
<td></td>
<td>14.5</td>
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</table>
Selection of chemicals
Selection of chemicals
1:1:1 systems

PXC-IND-CAF – $T_g$ 40.3, $T_c$ 106.6, $T_m$ 131.3
PXC-IND-BZD – $T_g$ 25.6
## Temperature values of thermal events

<table>
<thead>
<tr>
<th>Chemicals</th>
<th>Melting point on initial heating (°C)</th>
<th>Crystallization on cooling (°C)</th>
<th>Onset of mass loss in TGA (°C)</th>
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</thead>
<tbody>
<tr>
<td>PXC</td>
<td>201.2</td>
<td>Tg 64.4, Tc 132.7, Tm 175.9</td>
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<td>IND</td>
<td>158.8</td>
<td>Tg 42.7</td>
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<tr>
<td>BZD</td>
<td>123.7</td>
<td>Tc 101.6 (cooling), Tm 123.7</td>
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<tr>
<td>CAF</td>
<td>149.6 (enantiotropic transition), 235.8</td>
<td>Tc 233.3 (cooling), Tm 235.6</td>
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<td>PXC-IND</td>
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<td>Tg 57.6</td>
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<td>PXC-IND-BZD</td>
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<td>Tg 25.6, Tc 90.0 (HSM), Tm 110.0 (HSM)</td>
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<tr>
<td>PXC-IND-CAF</td>
<td>129.3</td>
<td>Tg 40.3, Tc 106.6, Tm 131.3</td>
<td>184</td>
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</table>
A Comparison Of The XRD Diffractograms For The Prepared Mixtures And Co-Amorphous Samples

- Piroxicam
- Benzamide
- Co-amorphous PXC-IND-BZD
- Physical mix PXC-IND-CAF
- Indomethacin
- Physical mix PXC-IND-BZD
- Caffeine
- Co-amorphous PXC-IND-CAF
<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>TIME (WEEKS)</th>
<th>Tg (°C)</th>
<th>SYSTEM</th>
<th>TIME (WEEKS)</th>
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<th>SYSTEM</th>
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<td>2.1</td>
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<td>2.1</td>
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</tbody>
</table>
Hot-stage microscopy

PXC-IND-BZD

PXC-IND-CAF

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XRD OF COAMORPHOUS LEFT ISOTHERMAL AT THEIR CRYSTALLISATION TEMPERATURE
Conclusions

It is possible to create a 3 component co-amorphous material via a melt quench method using either a crystalline or amorphous third component.

The addition of a third component has lowered the $T_g$ in all cases.

Compounds that have propensity to crystallise generate more stable co-amorphous system ($\Delta T_g$ – low)

The co-amorphous materials created using a crystalline component show less relaxation and a smaller deviation in $T_g$ value upon storage (4 weeks).

$T_g$ of co-amorphous system can be altered using appropriate 3$^{rd}$ component.

Physical parameters (ie. $T_m$ and $T_g$) may not be sufficient, so knowledge of chemical interaction must be brought into equation when manipulating $T_g$. 
Future work

Determine the change in chemical environments that has occurred upon transformation to amorphous.

Explore influence of structural features on creation and stability of complex co-amorphous systems.

Analyse the influence of molar ration on properties of co-amorphous systems.

Define key parameters for design/management of co-amorphous systems.
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  • Alessandra D’Angelo
  • Benjamin Edgar
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  • Dr Andrew P. Hurt
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