Using Thermal Techniques for Amorphous Materials

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Thermal Analysis

- TG
  - Routine
  - TG-IR

- DSC
  - Routine
    - Glass transition temperature (Tg)
    - Enthalpy relaxation
    - Fragility
    - Molecular mobility
    - Miscibility
  - Modulated
  - Hyper DSC

- Dielectric Analysis
  - A and β relaxations
  - Stability prediction

- Thermally stimulated current (TSC)

- Dynamic Mechanical Analysis (DMA)

- Thermomechanical Analysis (TMA)
  - Viscosity

- Local TMA and Heated Tip Atomic Force Microscopy (AFM)
Thermogravimetry

- Measures the amount of weight change in a material as a function of temperature
- Temperature calibration performed using Curie point based on magnetism of metal standard
- High resolution option available
- Approximately 10 mg needed for analysis
- Amorphous materials may show weight loss during equilibration
- Amorphous materials may not show nicely defined weight loss steps
TG-IR

- Sample heated in TG
- Evolved gas is analyzed by IR to identify volatiles
- Developmental compound showed 12.2% weight loss
  - Volatiles identified as water and butyl acetate

Differential Scanning Calorimetry (DSC)

- Detects thermal transitions relative to reference pan
- Endotherm: heat absorbing transitions such as a melt or volatization
- Exotherm: heat releasing transition such as decomposition or recrystallization
- Heats of fusion and heats of vaporization can be calculated
- Can be used for qualitative or quantitative analysis
- Dynamic technique
- Other techniques (TG, hot stage) needed to understand the transitions
- Sample pan and ramp rate can effect thermal transitions
Differential Scanning Calorimetry

Power Compensated DSC
- Sample and reference pans have separate heaters
- Different amounts of heat are added to maintain temperature during scan
- Difference in energy output is monitored to give heat flow

Heat Flux DSC
- Sample and reference pans have one heater
- Heat is transferred to the pans and the sample temperatures are monitored
- Difference between reference and sample pan converted into heat capacity

Figures adapted from Thermal Analysis of Pharmaceutics, D. Craig and M. Reading, ed., CRC Press, 2006
Glass Transition Temperature

• The temperature at which glass and supercooled liquid interconvert is the glass transition temperature, $T_g$
• 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>

![Sugar Structures](image1.png)

- glucose
- fructose
- sucrose
- trehalose
- maltose
- lactose
- raffinose
- maltodextrin
- Dextran
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 in K)
  - “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>
Glass Transition Temperatures

• $T_g$ is dependent on the rate of heating and cooling.

Glass Transition Temperature

- Water and solvents can act as plasticizers
  - Water Tg: -137 °C
  - lower the Tg of amorphous materials

- Rule of thumb: 1% water will decrease Tg about 10 deg

Andronis et al., J.Pharm.Sci. 1997, 86, 346-351
Glass Transition Temperature

Wet vs dry Tg

• Wet Tg
  – Want to know the effect of water/solvent on Tg
  – Use hermetically sealed pan to prevent volatilization

• Dry Tg
  – Want to remove all solvent and thermal history
  – Use DSC cycling experiment
    • Heat above Tg, cool, heat again through Tg
    • Use second cycle for Tg value
Glass Transition Temperatures

Amorphous Solid Dispersions or Polymer Mixtures

• Two glass transition temperatures (Tg) indicate a physical mixture
  – Can estimate Tg based on the Gordon Taylor (different densities) or Fox equation (assuming densities are similar)

\[ \frac{1}{T_g} = \frac{w_a}{T_{g,a}} + \frac{w_b}{T_{g,b}} \]

Fox Equation

• \( T_{g,a} \): glass transition of component a
• \( T_{g,b} \): glass transition of component b
• \( w_a \): weight fraction of component a
• \( w_b \): weight fraction of component b
• Assumes no interaction between components

Relaxation

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

Unaged amorphous matrix

Aged matrix
↑ density
↓ free volume

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 below $T_g$
• 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
Relaxation

• 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.

Annealing

- Annealing
  - Sample moves towards lower energy and lower free volume
  - Relaxation time should increase with annealing
- TSC was used to analyze ketoconazole annealed at different times
- Increased annealing resulted in more molecules entering the relaxed state
  - Decrease in current observed
- Need to determine how this will affect physical stability

Bhugra et al. J Pharm Sci. 2008, 97, 4498-4515
Conditioning or Aging Step

- Found that lactose samples prepared by freeze drying (FD) and spray drying (SD) had different water uptakes.
- Added a precondition step at 35% RH to obtain the same uptake from the different preps without crystallization.
- Resulted in more consistent standard material regardless of prep.
- Need to consider for other techniques that will show variability such as DSC, etc.

Vollenbroek et al. Int J. Pharm. 2010, 395, 62-70
Miscibility

• A physical mixture will give two glass transition (Tg) temperatures
• A solid amorphous dispersion will give a single Tg

Tg for physical mixtures of indomethacin and PVP

Tg for lyophilized molecular dispersion of indomethacin and PVP

Miscibility

May be cases where one Tg indicates a miscible system but other data indicate a physical mixture

– Trehalose:dextran

<table>
<thead>
<tr>
<th>System</th>
<th>Tg Values Observed (Aging)</th>
<th>PDF Computational Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase separated amorphous mixtures</td>
<td>2</td>
<td>Described by individual components</td>
</tr>
<tr>
<td>Miscible</td>
<td>1</td>
<td>Not described by individual components</td>
</tr>
<tr>
<td>Solid nanosuspension</td>
<td>1 (→2)</td>
<td>Described by individual components</td>
</tr>
</tbody>
</table>

Thermal measurements have an estimated spatial resolution limit of ~ 30nm

Miscibility

- NMR also used to confirm that trehalose:dextran mixtures were a solid nanosuspension
- Domain size estimated using relaxation times
- Found to be less than
  - 82 nm (50% trehalose)
  - 55 nm (30% trehalose)

*Figure 9. $^{13}$C CP-TOSS spectra ($v_r = 8$ kHz) of two dispersions of trehalose (IV) and dextran (V). The spectrum of the sample containing 50% w/w IV is shown in black, while the spectrum of the 30% w/w IV sample is shown in red. Characteristic peaks for dextran and trehalose are marked with arrows. Spectra were obtained at 8.5 T and 273 K.*

Pham et al. *Mol Pharmaceutics, 2010*, early view
Sodium Indomethacin

- Three methods used to make amorphous material
  - Grinding, freeze drying, solvent evaporation
- All amorphous based on XRPD data
- DSC data collected showed the same thermal properties for all three preparations
- Sodium indomethacin (SI) exhibits higher $T_g$ than indomethacin (I)

<table>
<thead>
<tr>
<th>Preparation method</th>
<th>$T_g$ (°C)</th>
<th>$\Delta C_p$ (mJ/mg.K)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>grinding</td>
<td>121 ± 0.3</td>
<td>0.33 ± 0.03</td>
</tr>
<tr>
<td>freeze-drying</td>
<td>121 ± 1.0</td>
<td>0.33 ± 0.03</td>
</tr>
<tr>
<td>solvent evaporation</td>
<td>120 ± 0.7</td>
<td>0.32 ± 0.05</td>
</tr>
<tr>
<td>IN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>quench melt</td>
<td>44.7</td>
<td>0.47</td>
</tr>
</tbody>
</table>

SI: sodium indomethacin, IN: indomethacin

Tong and Zografi. Pharm Res. 1999, 16, 1186-1192
Sodium Indomethacin

Enthalpy relaxation

- Measured with freeze dried sodium indomethacin
  - Sample heated to 135 °C to remove any residual water
  - Quench cooled using a cooling rate of 40 °C/min to 100 °C below T_g
  - Temperature raised to aging temperature
    - T_g-47, T_g-40, T_g-32, T_g-16 °C
  - Aging process terminated by cooling the sample at 40 °C to 0 °C
  - DSC data collected through T_g
  - Enthalpy relaxation measured at different times
- Relaxation at T_g-47 °C too small to be detected at experimental time scale

Tong and Zografi. Pharm Res. 1999, 16, 1186-1192
Fragility

• Fragile:
  – greater the change in molecular mobility with temperature, and the more non-Arrhenius it is, the more “fragile” the system is considered
  – Larger heat capacity changes at $T_g$
  – $T_m/T_g < 1.5$

• Strong:
  – Less change with temperature and the more Arrhenius-like this change the more the system is considered to be a “strong liquid”
  – Smaller heat capacity changes at $T_g$
  – $T_m/T_g > 1.5$

Vogel, Tamman, Fulcher (VTF) Equation

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

$\tau_s$ = structural relaxation time at $T = T$
$\tau_o$ = structural relaxation time at $T = \infty$
$D$ = strength parameter
$T_o$ = temperature at infinite relaxation time

$D = 2$-$30$ “Fragile Liquid”
$D = > 30$ indicates a “Strong Liquid”

Angel. Polymer. 1997, 38, 6261
Fragility

Relaxation time vs temperature scaled to $T_g$ 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 $T_g/T_m$

Sodium Indomethacin

Fragility (m)
• Used heating rate dependence of Tg
  – Different preps measured at multiple heating rates (q)
    • 5, 10, 30, 30, and 40 °C/min
    – Plot ln q vs 1/Tg
    – Apparent activation energy (ΔH*) and m can be obtained from the slope
• Can use m to calculate D
  \[ D = \frac{2.303 \times 17^2}{m - 17} \]

Tong and Zografi. Pharm Res. 1999, 16, 1186-1192
Sodium Indomethacin

Fragility

- $T_g$ is different, but $T_{m}/T_g$ is not significantly different
- Differences in $\Delta H^*$ (activation energy for enthalpy relaxation) observed between salt and free base
- The $m$ and $D$ values are not significantly different for sodium indomethacin and indomethacin
  - Temperature dependence of molecular mobility in vicinity of $T_g$ essentially unchanged
  - No significant network structure, characteristic of a strong glass, is introduced in the sodium salt

<table>
<thead>
<tr>
<th></th>
<th>Freeze-dried</th>
<th>Ground</th>
<th>Solvent evaporated</th>
<th>quench cooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_m/T_g$</td>
<td>1.32</td>
<td>1.32</td>
<td>1.32</td>
<td>1.37</td>
</tr>
<tr>
<td>$T_0$ (K)</td>
<td>311</td>
<td>319</td>
<td>310</td>
<td>246</td>
</tr>
<tr>
<td>$\Delta H^*$ (kJ/mol)</td>
<td>609</td>
<td>677</td>
<td>609</td>
<td>464</td>
</tr>
<tr>
<td>$m$</td>
<td>81</td>
<td>90</td>
<td>81</td>
<td>77</td>
</tr>
<tr>
<td>$D$</td>
<td>10</td>
<td>9</td>
<td>10</td>
<td>11</td>
</tr>
</tbody>
</table>

D= 2-30 fragile

Tong and Zografi. Pharm Res. 1999, 16, 1186-1192
Sodium Indomethacin

Relaxation

- KWW equation and enthalpy relaxation experiments used to calculate $\tau_{KWW}$
  - Need $\phi(t)$
    \[
    \phi(t) = \exp\left[-\frac{t}{\tau_{KWW}}\right]^{\beta}
    \]

- For $\phi(t)$, need $\Delta H_t$ and $\Delta H_\infty$
  \[
  \phi(t) = 1 - \left(\frac{\Delta H_t}{\Delta H_\infty}\right)
  \]

- $\Delta H_\infty$ calculated from DSC data
  \[
  \Delta H_\infty = \Delta C_p (T_g - T)
  \]

- $\Delta H_t$ obtained from enthalpy relaxation experiments at time t

Different at lower T due to error in measurements

Similar near Tg

Relaxation time $\tau$ for indomethacin (●) and sodium indomethacin (○) at storage temperatures up to 40°C below their $T_g$ values.

Tong and Zografi. Pharm Res. 1999, 16, 1186-1192
Sodium Indomethacin

- Shown for indomethacin that real relaxation times below T_g are usually smaller than estimated.

- Can construct plot of log \( \tau \) vs \( T/T_g \)
  - Use D, \( T_0 \) and VTF equation
    \[ \tau = \tau_0 \exp\left( \frac{D T_0}{T - T_0} \right) \]

- Relaxation times for salt and free base are not different
  - Even with large difference in T_g

Tong and Zografi. Pharm Res. 1999, 16, 1186-1192
Sodium Indomethacin

Summary

• Amorphous form of salt made by three methods are similar
• Salt and free base show different $T_g$'s (120 vs 44 °C)
  – Due to strong ionic interaction to give a reduced free volume relative to less dense free base
• Temperature dependence of molecular mobility shows both forms are fragile
  – From scanning rate dependence of $T_g$ experiments
• Molecular mobility below $T_g$ showed similar relaxation patterns
  – From enthalpy relaxation recovery experiments
• Salt formation will enhance physical and chemical stability due to increase in $T_g$
Modulated DSC (MDSC)

- Uses same heat flux DSC cell arrangement utilized in conventional DSC
- Different heating profile applied to sample
  - Sinusoidal modulation is overlaid on the conventional linear temperature ramp
  - Yields a heating profile which is continuously increasing with time, but in an alternating heating/cooling program
- Advantages:
  - Separation of complex transitions into components
  - Increased sensitivity for weak transitions
  - Increased resolution without loss of sensitivity
  - Direct measurement of heat capacity
Modulated DSC (MDSC)

Data are composite of three curves

- Conventional or "deconvoluted" curve
- Heating rate dependent "reversing" curve (heat capacity-related)
  - Melting
  - Glass transition
- Non-heating rate dependent "non-reversing" curve (kinetic)
  - Desolvation
  - Crystallization
  - Decomposition
Modulated DSC

- Hydroxypropyl methylcellulose (HPMC)
  - Glass transition temperature observed in reversing heat flow curves
  - Separate from dehydration in total and non-reversing heat flow curve
  - MDSC has better sensitivity for Tg

Modulated DSC

- Can also be used to separate the Tg (reversing) from enthalpy relaxation (non-reversing)
- Number of ways to measure activation energy for enthalpy relaxation ($\Delta H^*$)
  1. scanning rate ($q$) dependence
  2. width of Tg ($\Delta T_g$)
  3. relaxation enthalpy ($\Delta H$) over time
  4. complex heat capacity ($C_p^*$) and modulation frequency

Dielectric Analysis

Instrumentation

• Sample is presented as thin film between two parallel plates to make a capacitor
• Guard ring- grounded electrode
• Thermocouple placed in contact with plate(s) to measure specimen temperature
• Calibration
  – Measure dielectric properties of empty dielectric cell to account for stray capacitances
  – Temperature calibration performed with melting transition of a crystalline crystal, such as benzoic acid placed between the plates
• Sample subjected to a sinusoidal oscillating electric field
  – Dipoles in the material attempt to orient with electric field
  – Resulting current flow is measured
  – Can vary temperature as well

Dielectric Analysis

• Four major properties reported during DEA
  – $e'$ = permittivity
    • Proportional to capacitance and measures alignment of the dipoles
  – $e''$ = loss factor
    • Proportional to conductance and represents the energy required to align dipoles and move ions
  – $\tan \Delta = $ dissipation factor or $e''/e'$
  – $K = $ conductivity (PS/cm)
Dielectric Analysis

Telmisartan

- Used for high blood pressure and myocardial ischemia
- Practically insoluble in water (0.09ug/mL), highly soluble at high pH (521.55 ug/mL), weakly soluble at pH 6.8 (0.28 ug/mL)
- Absolute bioavailability is 42-58%
- Amorphous form and amorphous dispersions have been investigated to improve bioavailability
- Dielectric spectroscopy used to look at relaxation processes and predicted stability of amorphous material
  - Temp range: 264 to -140 °C
  - Frequency range: $10^9$ to $10^{-2}$ Hz
    - Primary $\alpha$ relaxations
      - Correspond to $T_g$
    - Two secondary relaxations $\beta$ and $\gamma$

Molecular Motions

• Primary Relaxations
  • $\alpha$ relaxations
  • “slow” cooperative diffusion (translational and rotational motion of whole molecules or polymer segments)
  • corresponds to Tg

• 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

Dielectric

- Glass transition defined at temperature at which dielectric relaxation time $\tau_\alpha$ is equal to 100 s
  - $T_g = 400 \text{ K} = 127^\circ \text{ C}$
- Dielectric loss ($\varepsilon''$) above $T_g$
  - Temp range 403-537 K
  - $\alpha$-process evident
  - Conductivity (dc) contribution due to presence of free ionic species present in most liquids
  - Corrected for dc-conductivity
- Peak for $\alpha$-relaxation increases with decreasing temperature

Dielectric Analysis

- Aging experiments performed to estimate stability
  - 393.15, 373.15, 353.15, 331.15 K
  - $\alpha$ peak moves to lower frequencies, smaller contribution to $\beta$-process as temperature decreases
- Time scale of $\alpha$ relaxation at RT likely to exceed years
- Molecular mobility associated with structural relaxation would be negligible to cause crystallization during typical shelf-life storage
  - Confirmed with amorphous sample kept at RT for a few months with no crystallization

Dielectric Analysis

Summary

• Dielectric spectroscopy used to look at relaxation processes
  – Temp range: 264 to -140 °C
  – Frequency range: $10^9$ to $10^{-2}$ Hz
• Primary $\alpha$ relaxations found above $T_g$
• Two secondary relaxations $\beta$ and $\gamma$ dominate below $T_g$
• $T_g$ of 400 K, fragility index $(m) = 87$
• Determined $\alpha$ relaxation time at room temperature would exceed 3 years
  – Amorphous telmisartan should maintain physical and chemical stability over prolonged storage time

Thermally Stimulated Current

- Carvedilol used as model compound to compare techniques for low levels of amorphous material in crystalline
  - Thermally stimulated current (TSC)
  - MDSC
  - XRPD
  - Moisture uptake
- Amorphous made by melting above 135 °C and cooled to ambient in a desiccator. Stored at RT in desiccator.
- Mixtures made by blending 75:25 amorphous:crystalline sample in Turbula blender
  - Other blends (90:10 to 99:1) produced using blend and crystalline material by serial dilution

TSC

1 mm thick hand-pressed disk placed between electrodes

Thermally Stimulated Current 9000 Spectrometer

Polarization at 70 °C for 5 min by applying a DC electric field at 100 V/mm
  - Orient molecular dipoles

Rapidly cool the sample to 0 °C while maintaining the electric field to trap polarized dipoles

Short circuit electrodes for 1 min

Scan sample at 7 °C/min up to 110 °C while monitoring the current generated due to relaxation of polarized dipoles

Calculate normalized distribution of the glass transition relaxation using a fitted polynomial outside the 45-65 °C window
TSC

• LOD based on visual assessment of data based on standards
• TSC had lowest LOD at 2% amorphous
• Chemometric approaches not used

<table>
<thead>
<tr>
<th>Technique</th>
<th>Analysis</th>
<th>LOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSC</td>
<td>Polynomial fit</td>
<td>2%</td>
</tr>
<tr>
<td>MDSC</td>
<td>Complex heat capacity signals</td>
<td>5%</td>
</tr>
<tr>
<td>XRPD</td>
<td>Integrated peak intensities in four regions for crystalline drug and LiF standard</td>
<td>5%</td>
</tr>
<tr>
<td>Moisture uptake</td>
<td>Moisture uptake</td>
<td>5%</td>
</tr>
</tbody>
</table>
Comparison of Techniques

• Three techniques used to measure relaxation times
  – Modulated DSC (MDSC)
  – Isothermal microcalorimetry (TAM)
  – Thermally stimulated current (TSC)
• Different relaxation values below Tg found using different techniques
  – Preferentially measure different parts of the relaxation time distribution
  – TSC<TAM<MDSC
  – TSC captures some of the faster motions not captured by calorimetric techniques

<table>
<thead>
<tr>
<th>Compound</th>
<th>Temperature (°C)</th>
<th>MDSC (h)</th>
<th>TAM (MSE) (h)</th>
<th>TSC (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>35</td>
<td>17.8</td>
<td>0.65</td>
<td>0.06</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>35</td>
<td>19.8</td>
<td>0.065</td>
<td>0.061</td>
</tr>
</tbody>
</table>

Bhugra et al. J Pharm Sci. 2008, 97, 4498-4515
What Have We Learned

• A variety of thermal methods are available
  – DSC is most common
    • Many parameters can be calculated from DSC data
      • Tg, fragility, mobility, etc
  – DEA, DMA, TMA, etc

• Information obtained will depend on technique due to time scales

• Thermal analysis can give important information for development of the material
  – Tg, physical stability, viscosity, etc
References

- Marsac et al. Pharm Res 2009, 26, 139-151
- Hancock et al. Pharm Res. 1999, 16, 672-675
- Harding et al. Pharm Res. 2007, 11,