Using Thermal Techniques for Amorphous Materials

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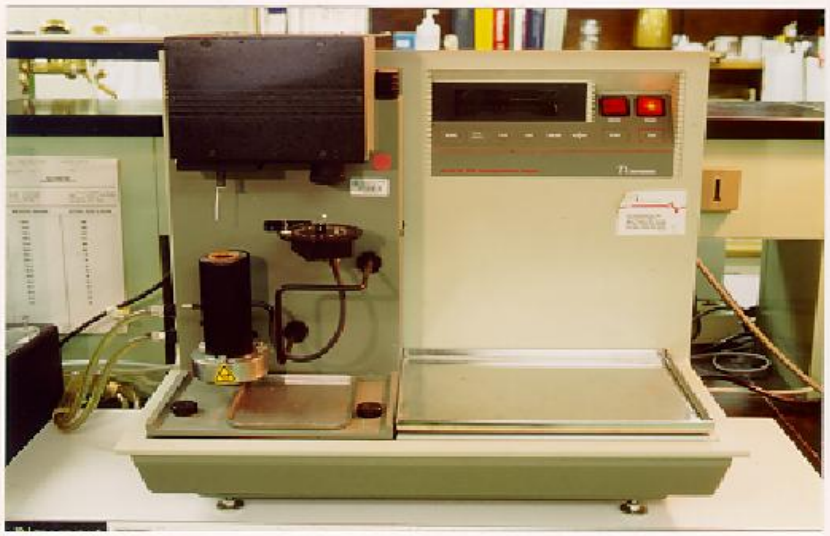
Thermal Analysis

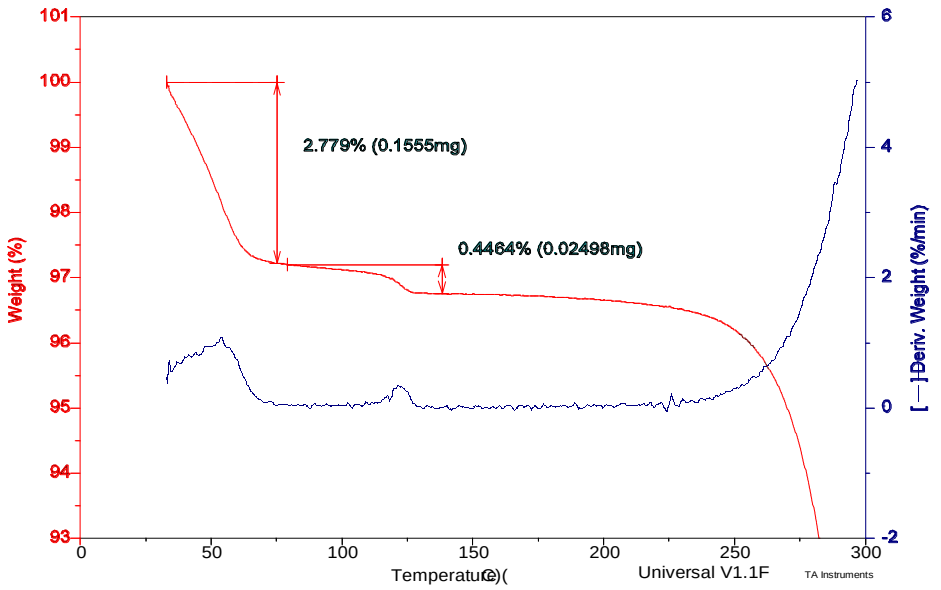
- TG
  - Routine
  - TG-IR
- DSC
  - Routine
    - Glass transition temperature (Tg)
    - Enthalpy relaxation
    - Fragility
    - Molecular mobility
    - Miscibility
  - Modulated
  - Hyper DSC

- 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

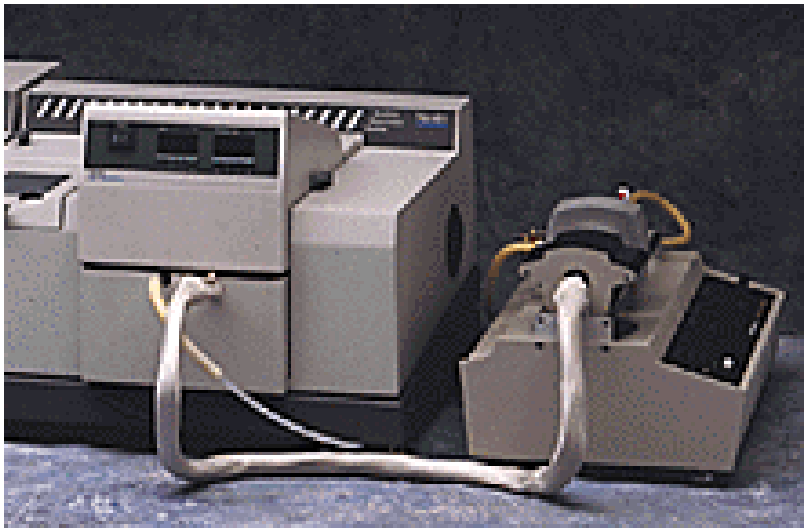


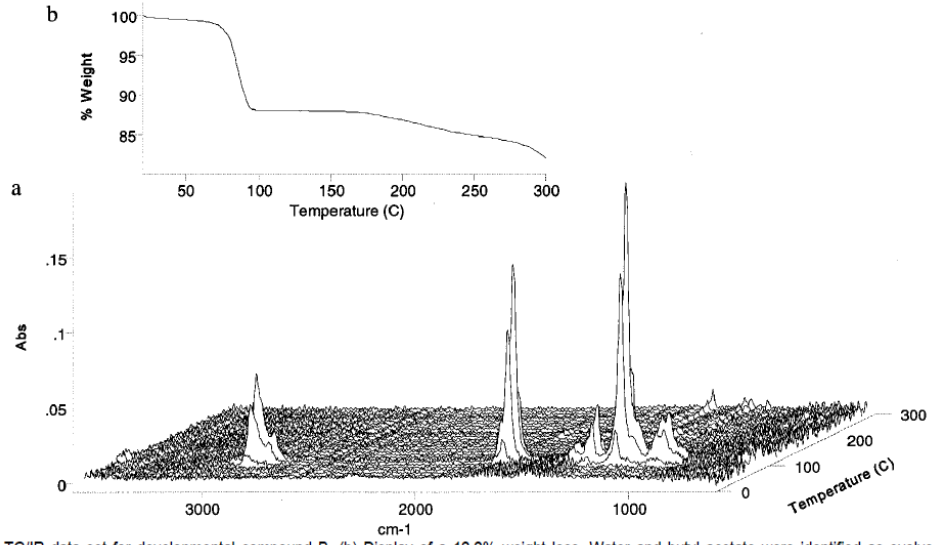
- Measures the amount of weight change in a material as a function of temperature
- Temperature calibration performed using Curie point based on magnetism of metal standard
- High resolution option available
- Approximately 10 mg needed for analysis
- Amorphous materials may show weigh loss during equilibration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



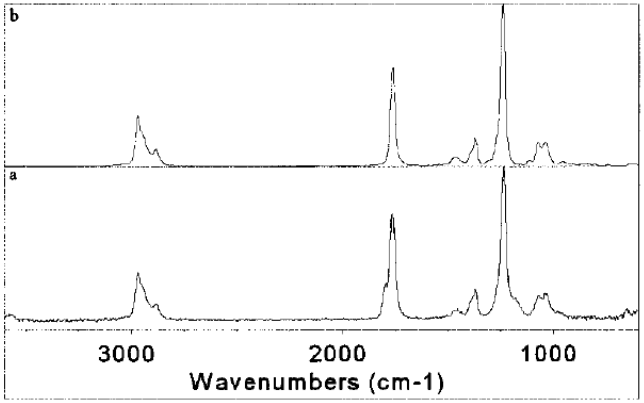
TG-IR

- 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





TG/IR data set for developmental compound B. (b) Display of a 12.2% weight loss. Water and butyl acetate were identified as evolved components.

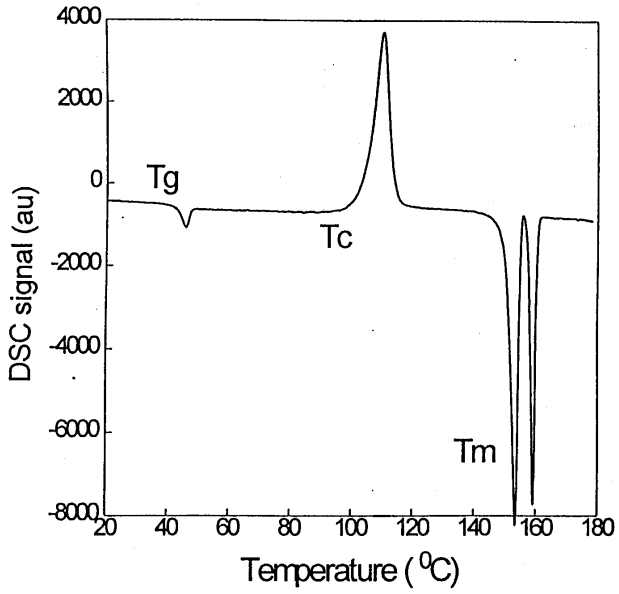


–Spectrum a represents the averaged IR spectra acquired from 60 to 100 °C for developmental compound B. Comparison with the reference IR spectrum of butyl acetate is shown in spectrum b.

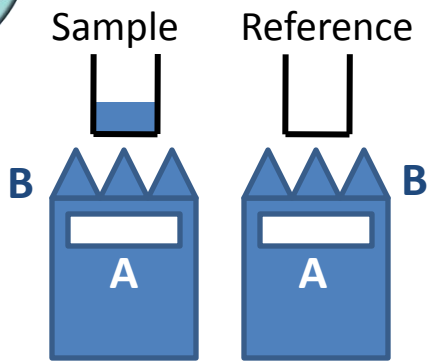
Rodriguez and Bugay. *J Pharm Sci* **1997**, *86*, 263-266

Differential Scanning Calorimetry (DSC)

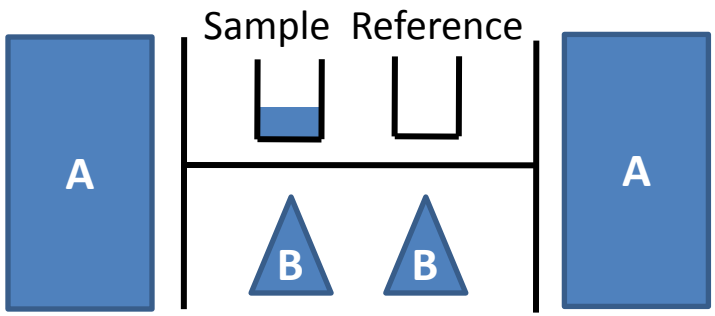
- Detects thermal transitions relative to reference pan
- Endotherm: heat absorbing transitions such as a melt or volatization
- Exotherm: heat releasing transition such as decomposition or recrystallization
- Heats of fusion and heats of vaporization can be calculated
- Can be used for qualitative or 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



A- furnace; B-platinum resistance thermometers; C-crucibles



A- furnace; B-thermocouple

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

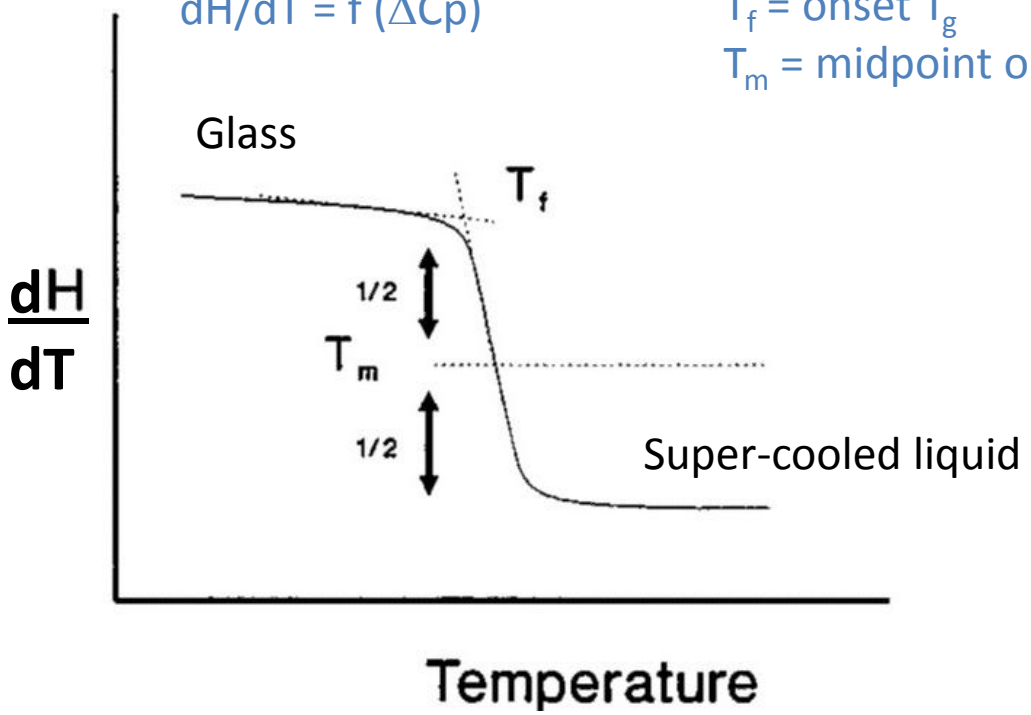
Glass Transition Temperature

- 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

$dH/dT = f(\Delta Cp)$

T_f = onset T_g

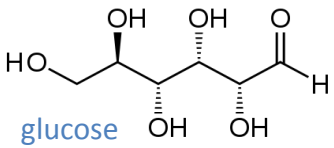
T_m = midpoint or inflection T_g



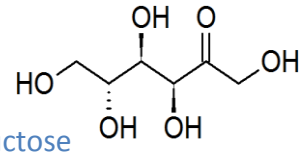
Glass Transition Temperature

- Common sugars

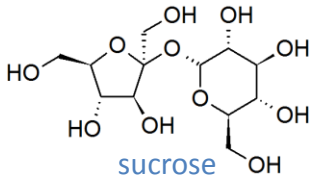
Sugar	Molecular Weight (g/mol)	T_g (° C)
Glucose	180	30
Fructose	180	13
Sucrose	342	74
Trehalose	342	115
Maltose	342	100
Lactose	348	102
Raffinose	504	108
Maltodextrin	860	169
Dextran	10K	197



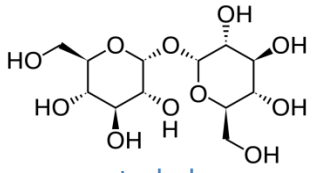
glucose



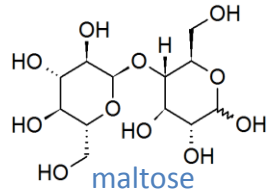
fructose



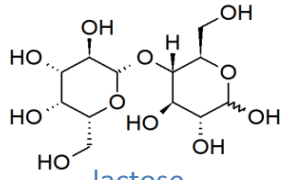
sucrose



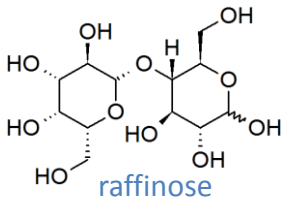
trehalose



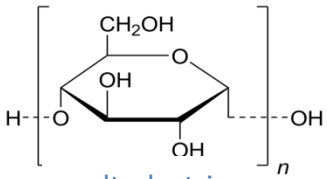
maltose



lactose

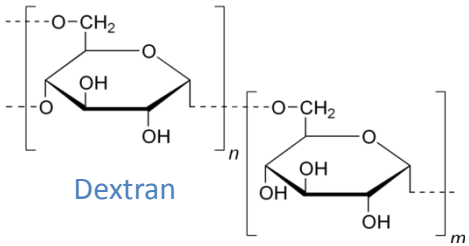


raffinose



maltodextrin

$2 < n < 20$

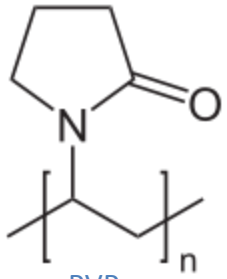


Dextran

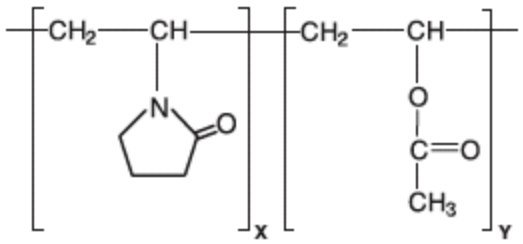
Glass Transition Temperature

- Different grades of poly(vinylpyrrolidone) (PVP)

Sample	Molecular Weight (g/mol)	T_g (° C)
PVP K90	1500 K	177
PVP K30	50K	156
PVP K17	10K	136
PVP K12	2K	101
PVP/VA (60:40)	50K	102



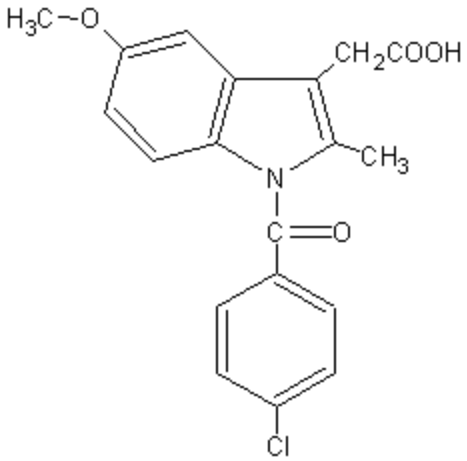
PVP

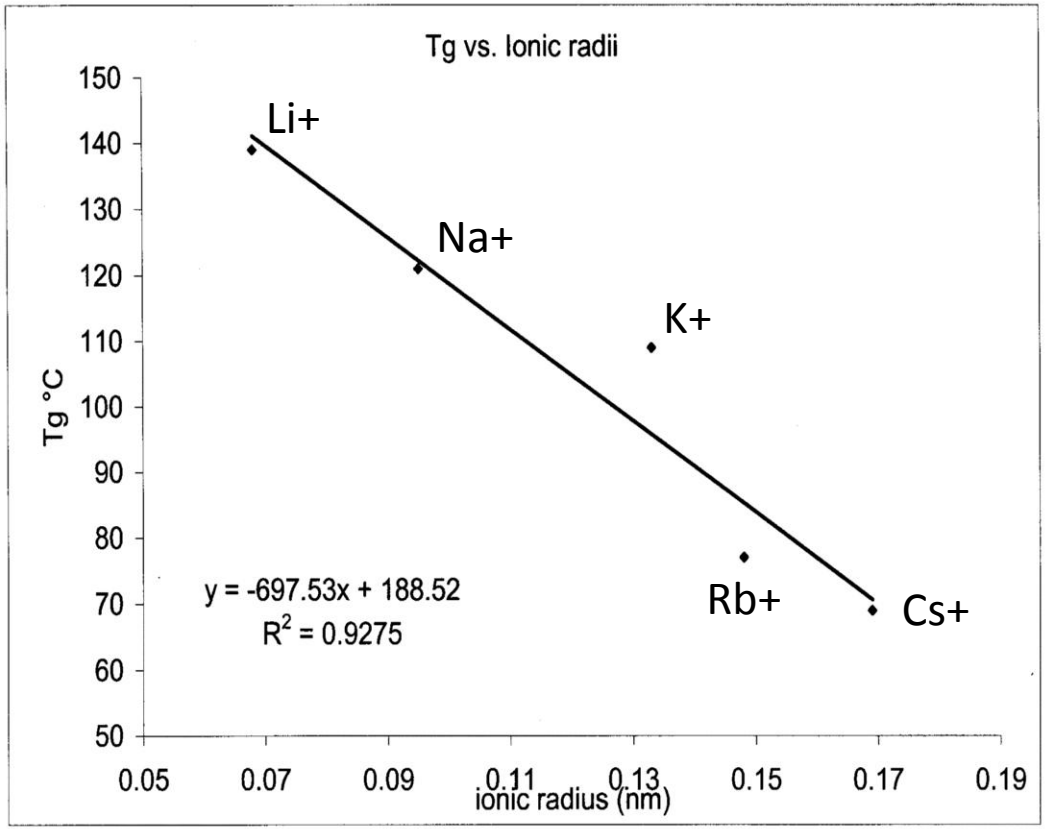


PVP/VA

Glass Transition Temperature

- Effect of different counterions on the Tg of indomethacin salts





Tong et al, *Pharm.Res*. **2002**, *19*, 649-654.

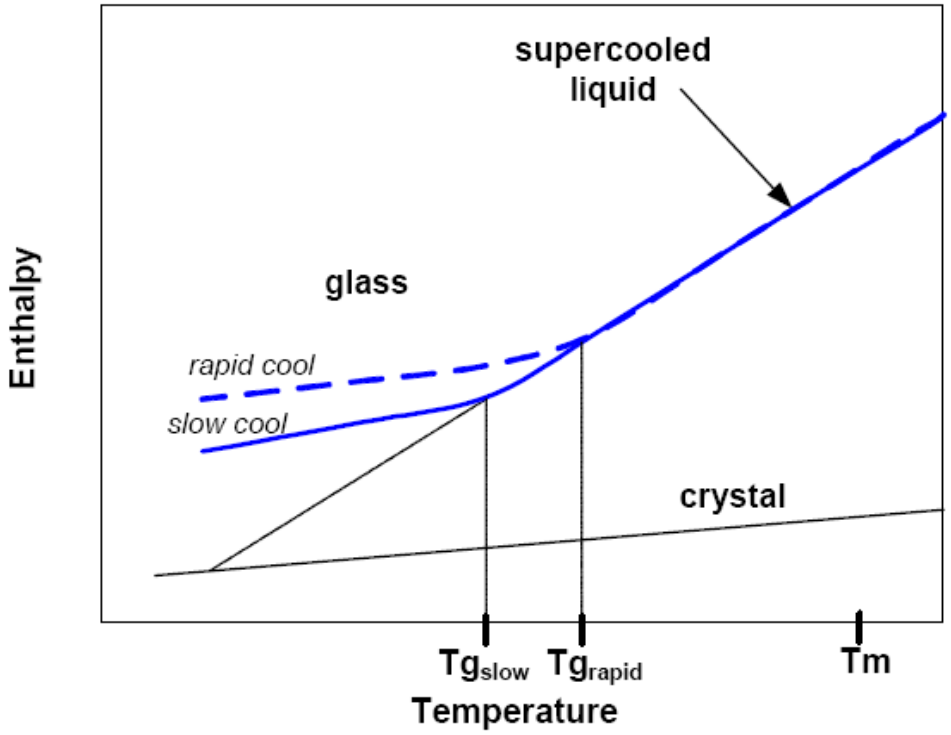
Glass Transition Temperature

- Estimation of T_g
  - T_g is roughly (0.67)T_m (the melting temperature of the crystalline material in K)
  - "2/3 rule"

Sample	Tg (K)	Tm (K)	Tg/Tm
Poly(ethylene terephthalate)	343	538	0.64
Nylon 66	333	538	0.61
Polyacrylonitrile	378	590	0.64
Isotactic polypropylene	268	435	0.62
Aspririn	243	408	0.60
Indomethacin	315	434	0.73
Sodium indomethacin	393	543	0.72
Nifedipine	323	447	0.72
Cholocalciferol	293	352	0.84

Glass Transition Temperatures

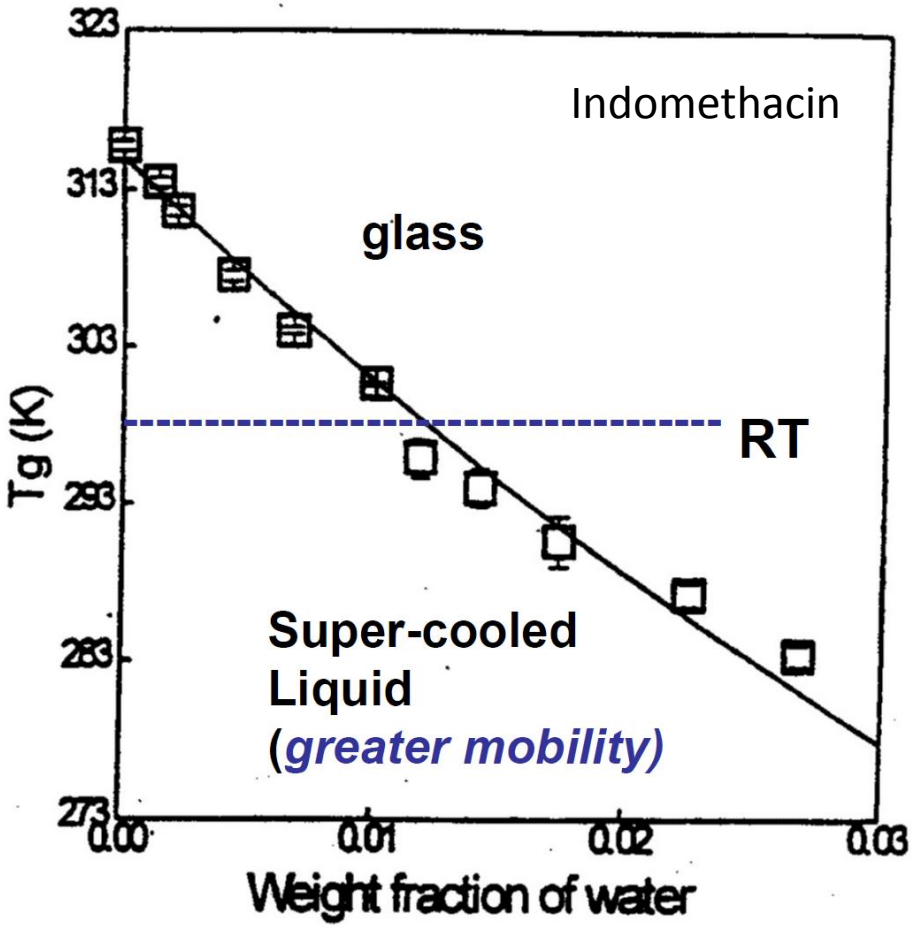
- Tg is dependent on the rate of heating and cooling



Taylor and Shamblin. Amorphous Materials in Polymorphism of Pharmaceutical Solids, 2nd edition, Informa Healthcare 2009.

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

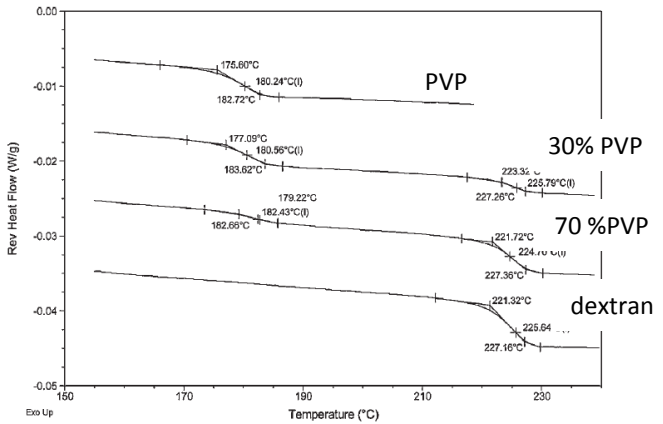
Amorphous Solid Dispersions or Polymer Mixtures

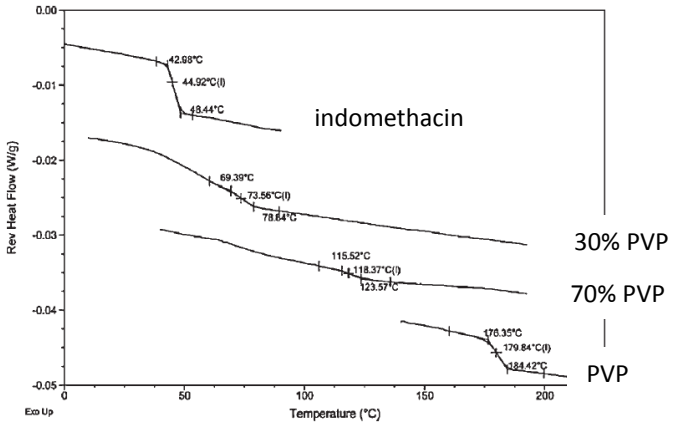
- Two glass transition temperatures (Tg) indicate a physical mixture
- One Tg indicates miscible system
  - Can estimate Tg based on the Gordon Taylor (different densities) or Fox equation (assuming densities are similar)

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

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

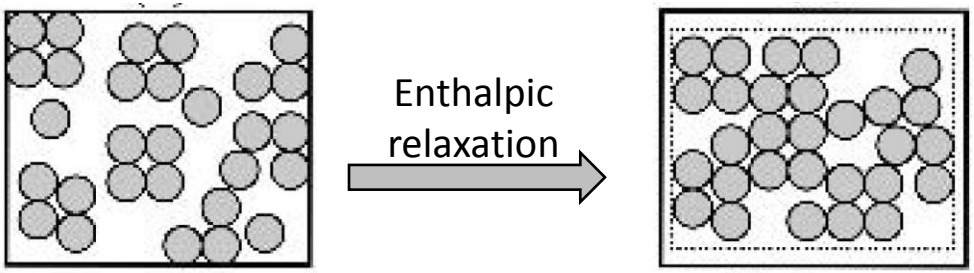




Newman et al. *J Pharm. Sci*. **2008**, *97*, 4840-4856

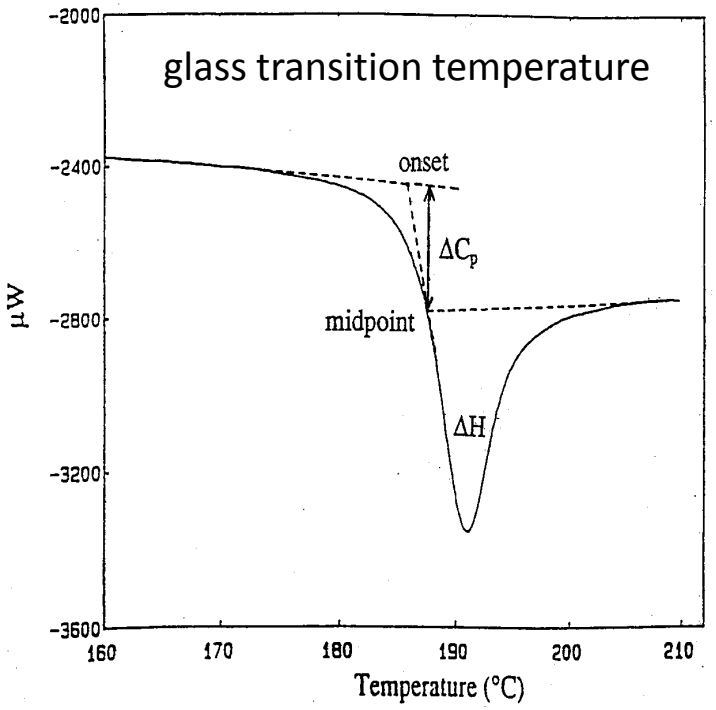
Relaxation

- 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

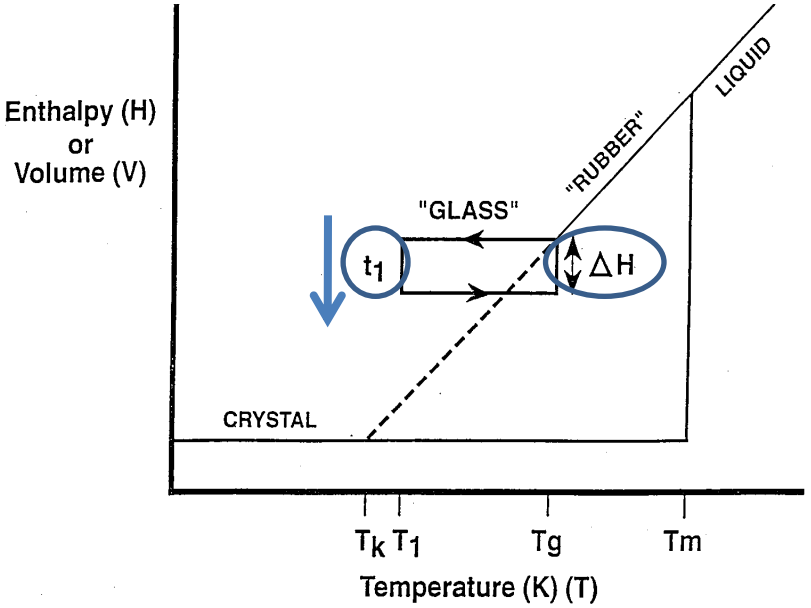


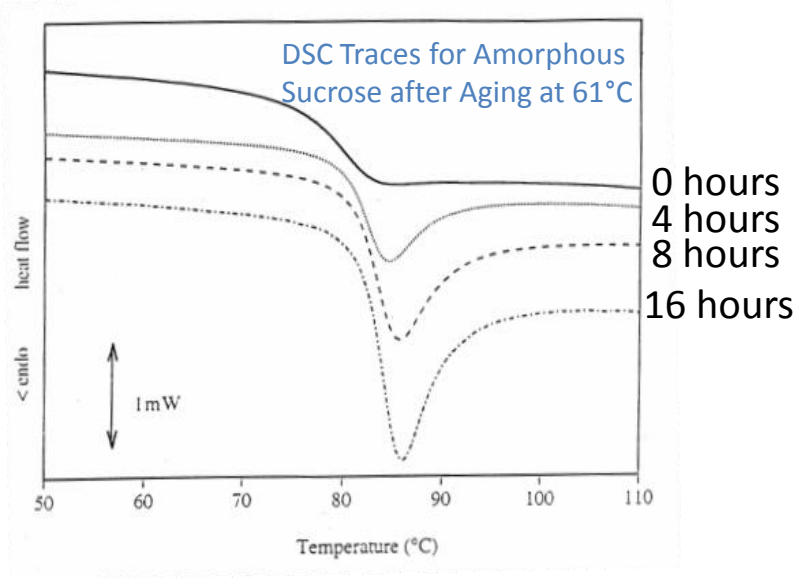
Hancock and Zografi. *J. Pharm. Sci*. **1997**, *86*, 1-12

Surana et al. *Pharm. Res*. **2004**, *21*, 867-874.

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 (ΔH)
- Longer aging times will result in larger enthalpy relaxation

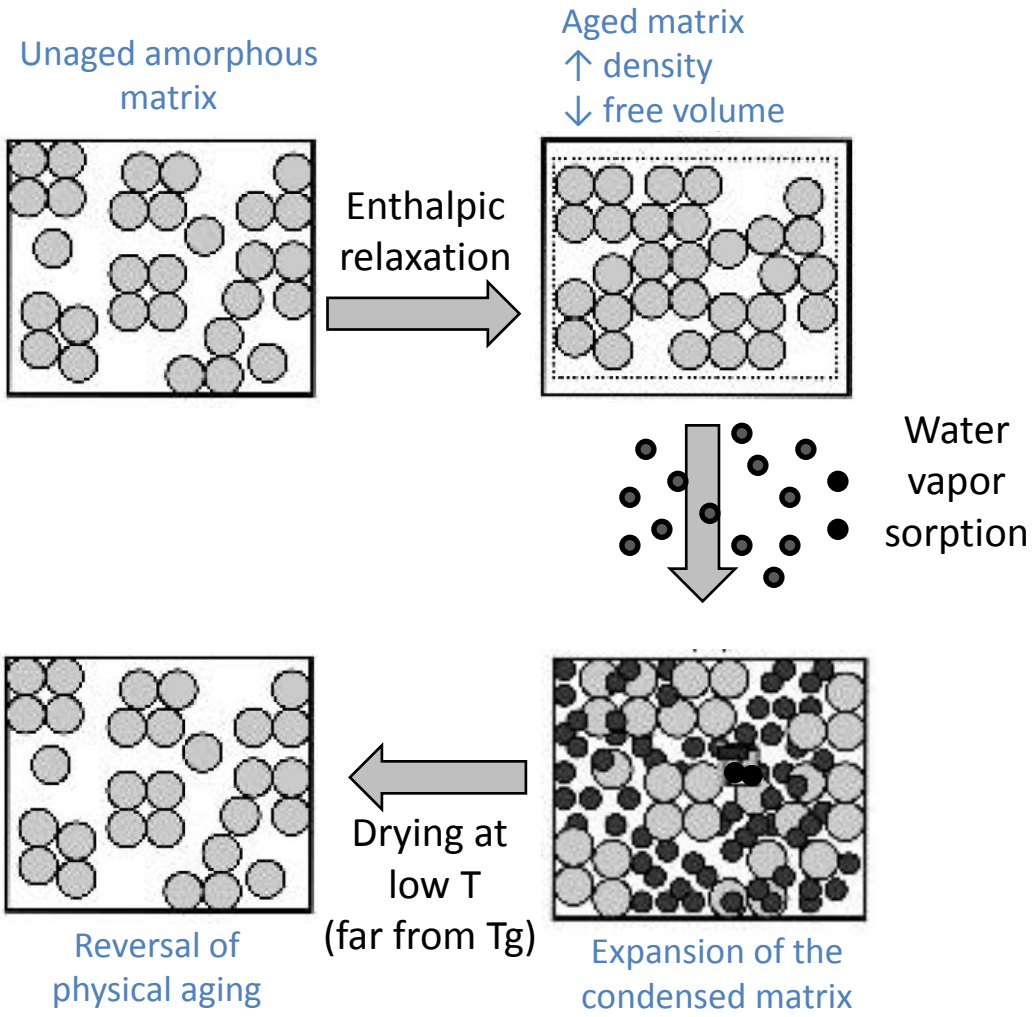




Hancock et al. *Pharm. Res*. **1995**, *12*, 799-806
Shamblin and Zografi. *Pharm . Res*. **1998**, *15*, 1828-1834

Relaxation

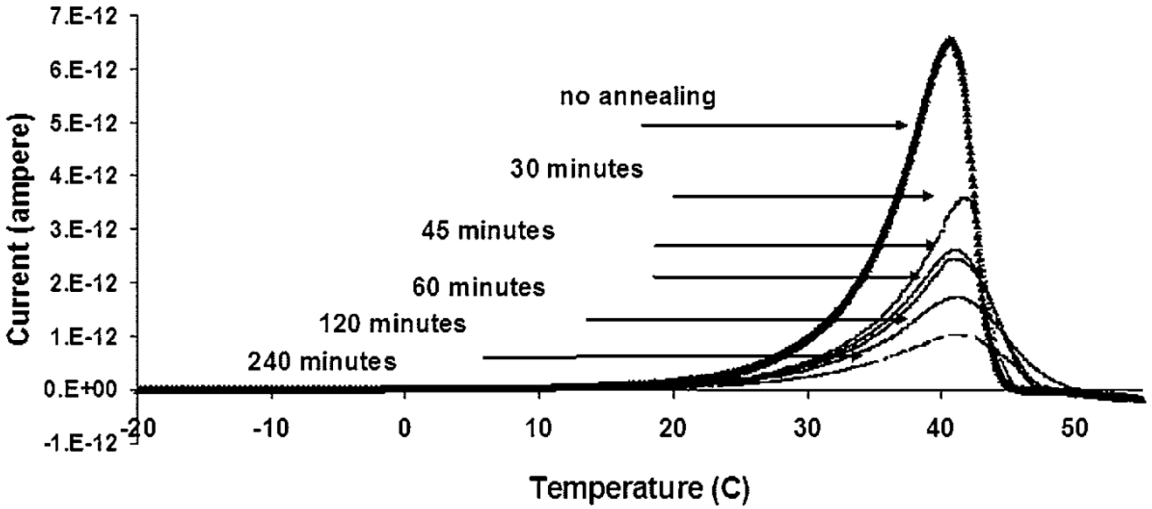
- Aged materials show decreased physical and chemical reactivity compared to unaged materials
- Exposure to water can reverse the aging of an amorphous material and make it more reactive



Surana et al. *Pharm. Res*. **2004**, *21*, 867-874.

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

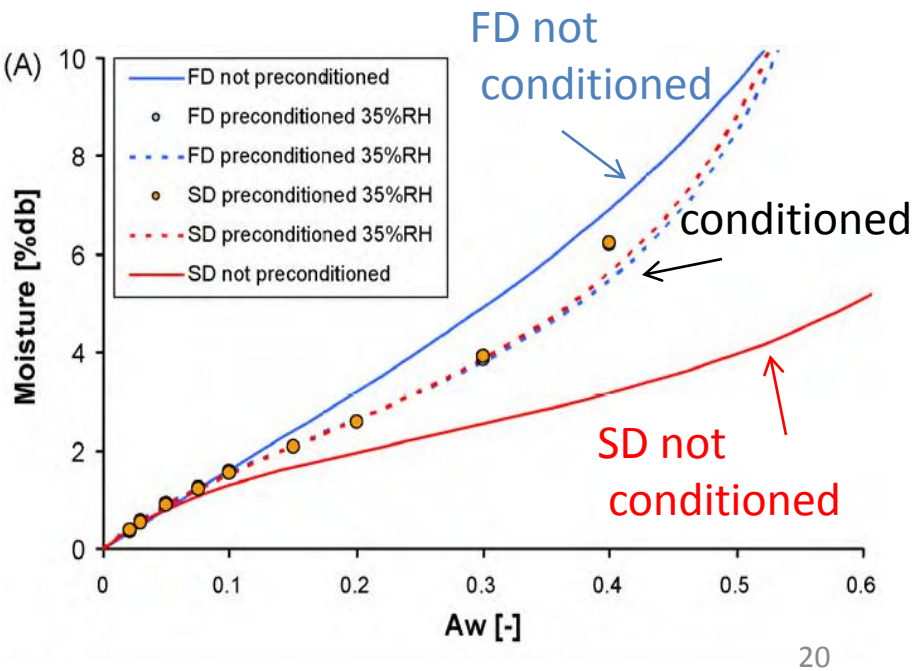


Bhugra et al. J Pharm Sci. 2008, 97, 4498-4515

Conditioning or Aging Step

- Found that lactose samples prepared by freeze drying (FD) and spray dring (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

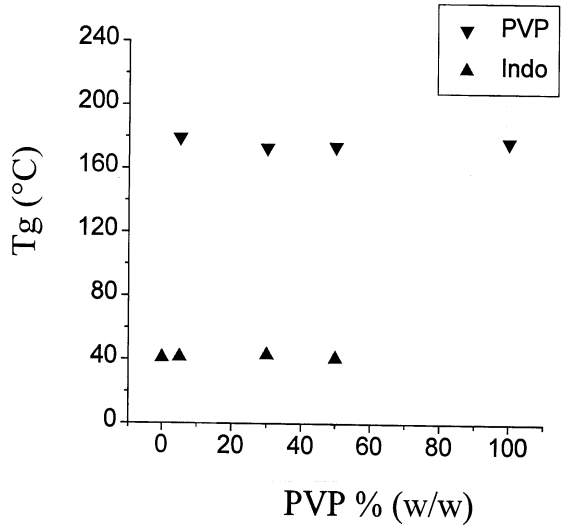


Vollenbroek et al. Int J. Pharm. 2010, 395, 62-70

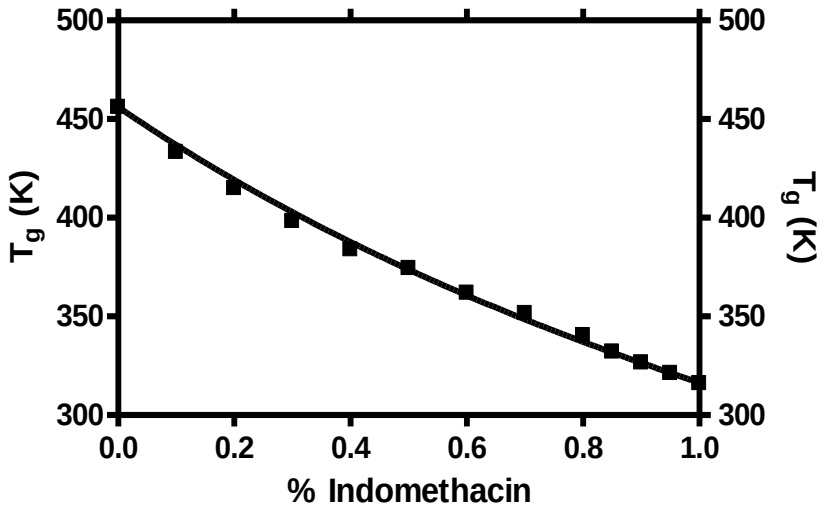
Miscibility

- 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



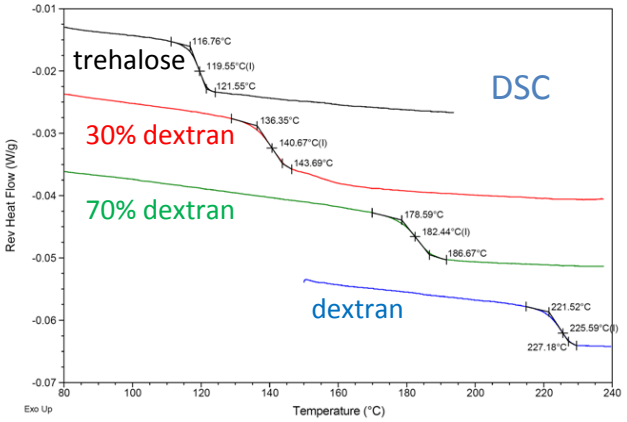
Matsumoto and Zografi. *Pharm. Res*. **1999**, *16*, 1722-1728

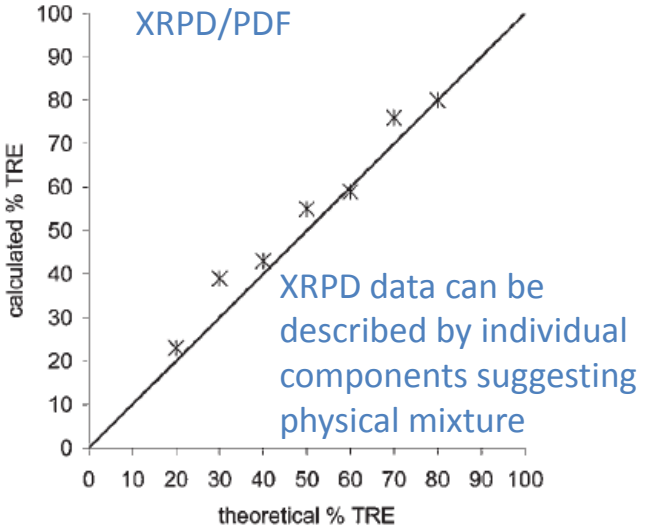
Miscibility

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

- Trehalose:dextran

One Tg in DSC suggests miscible system





System	Tg Values Observed (Aging)	PDF Computational Studies
Phase separated amorphous mixtures	2	Described by individual components
Miscible	1	Not described by individual components
Solid nanosuspension	1 (→2)	Described by individual components

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

Newman et al. *J Pharm Sci.* **2008**,*97*,4840-4856

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)

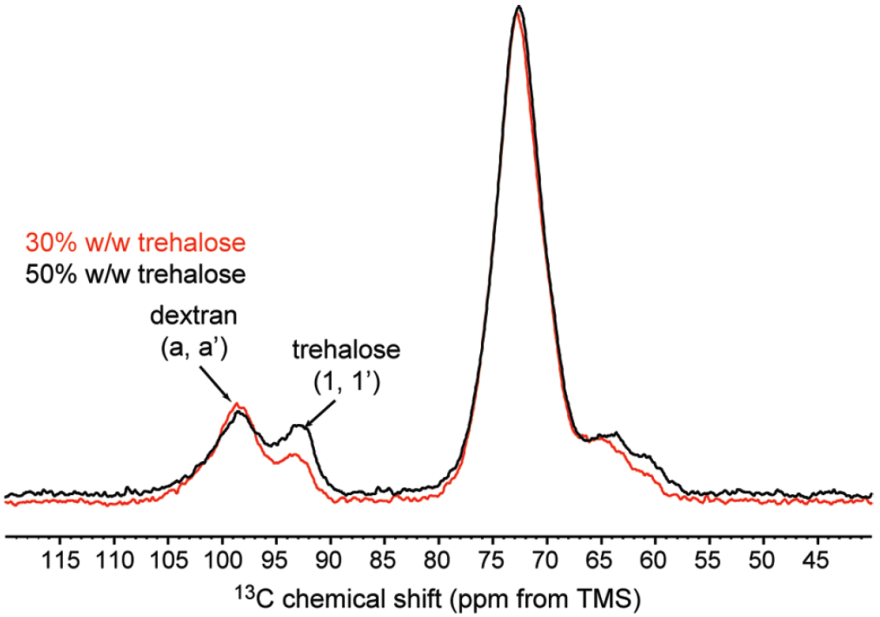
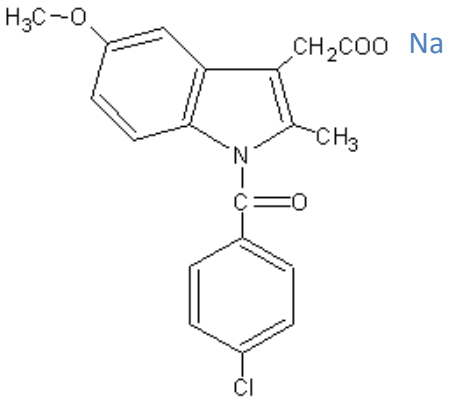


Figure 9. ^{13}C CP-TOSS spectra (υ_r = 8 kHz) of two dispersions of trehalose (**IV**) and dextran (**V**). The spectrum of the sample containing 50% w/w **IV** is shown in black, while the spectrum of the 30% w/w **IV** sample is shown in red. Characteristic peaks for dextran and trehalose are marked 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 Tg than indomethacin (I)

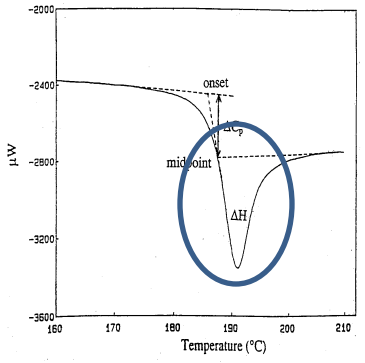


	Preparation method	Tg (°C)	ΔC_p (mJ/mg.K)
SI	grinding	121 ± 0.3	0.33 ± 0.03
	freeze-drying	121 ± 1.0	0.33 ± 0.03
	solvent evaporation	120 ± 0.7	0.32 ± 0.05
IN	quench melt	44.7	0.47

SI: sodium indomethacin, IN: indomethacin

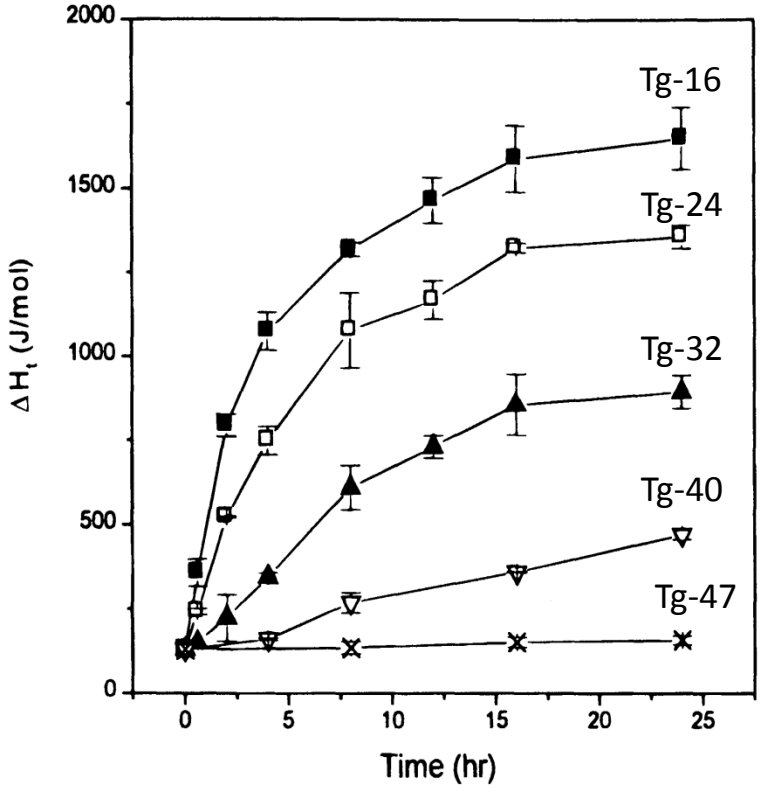
Tong and Zografi. Pharm Res. 1999, 16, 1186-1192

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

$$\log \tau_s = \log \tau_o + [(DT_o) / (T-T_o)]$$

τ_s = structural relaxation time at T = T
τ_o = structural relaxation time at T = ∞
D = strength parameter
T_o = temperature at infinite relaxation time

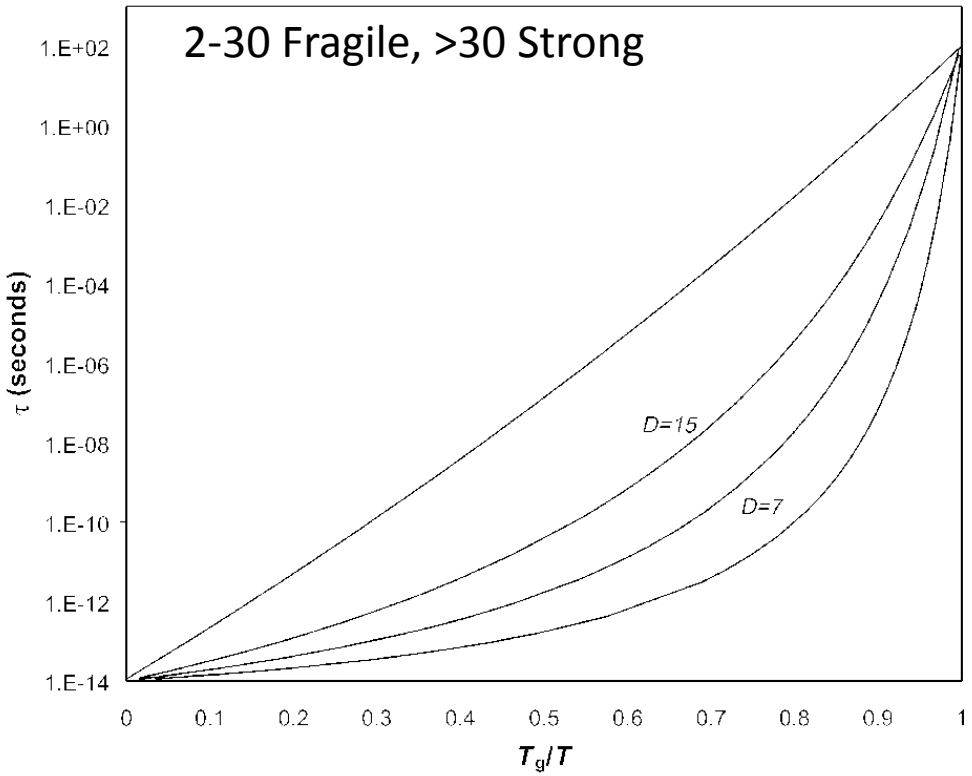
D = 2-30 "Fragile Liquid"

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



Material	T_g (K)	T_o (k)	D
B_2O_3	557	320	27
sorbitol	270	214	9
o-terphenyl	249	195	10
indomethacin	317	237	13
Na indomethacin	389	276	15
nifedipine	322	228	15
diazepam	398	249	10
felodipine	416	247	10

Similar D values means similar $T_m - T_g$ values, and therefore, similar T_g/T_m

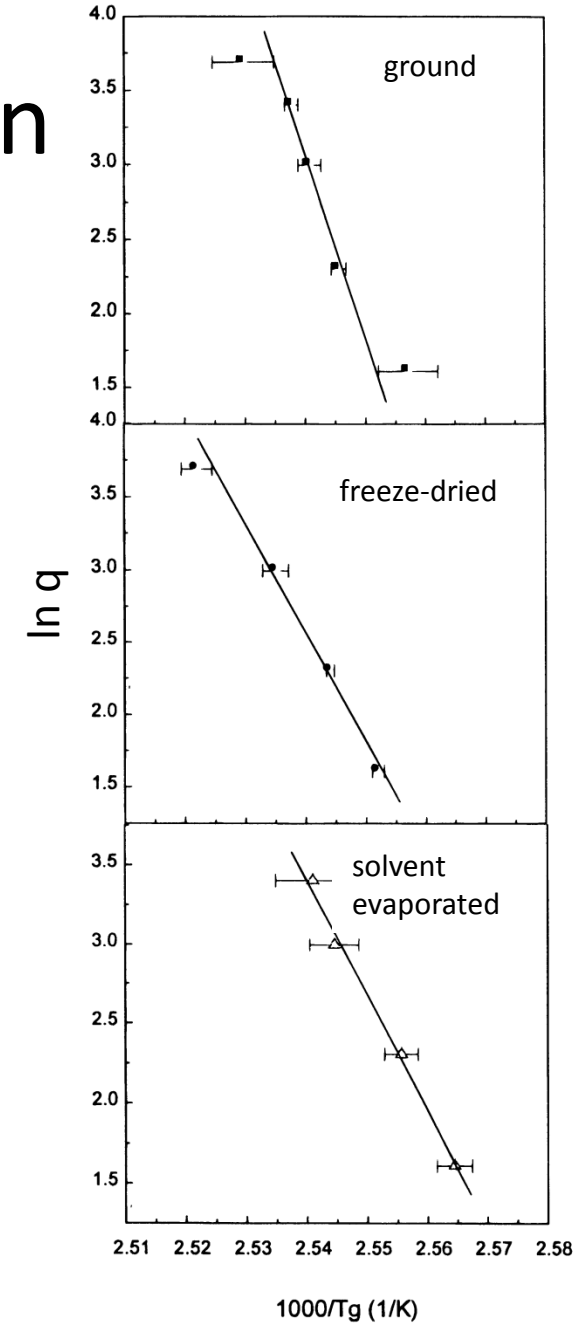
Crowley and Zografi. *Thermochimica Acta* **2001**, *380*, 79-83

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 Tm/Tg is not significantly different
- Differences in ΔH* (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 Tg essentially unchanged
  - No significant network structure, characteristic of a strong glass, is introduced in the sodium salt

	SI			
	Freeze-dried	Ground	Solvent evaporated	IN[a] quench cooled
T_m/Tg	1.32	1.32	1.32	1.37
T_0 (K)	311	319	310	246
ΔH* (kJ/mol)	609	677	609	464
m	81	90	81	77
D	10	9	10	11

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 τ_{KWW}
  - Need $\phi(t)$

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

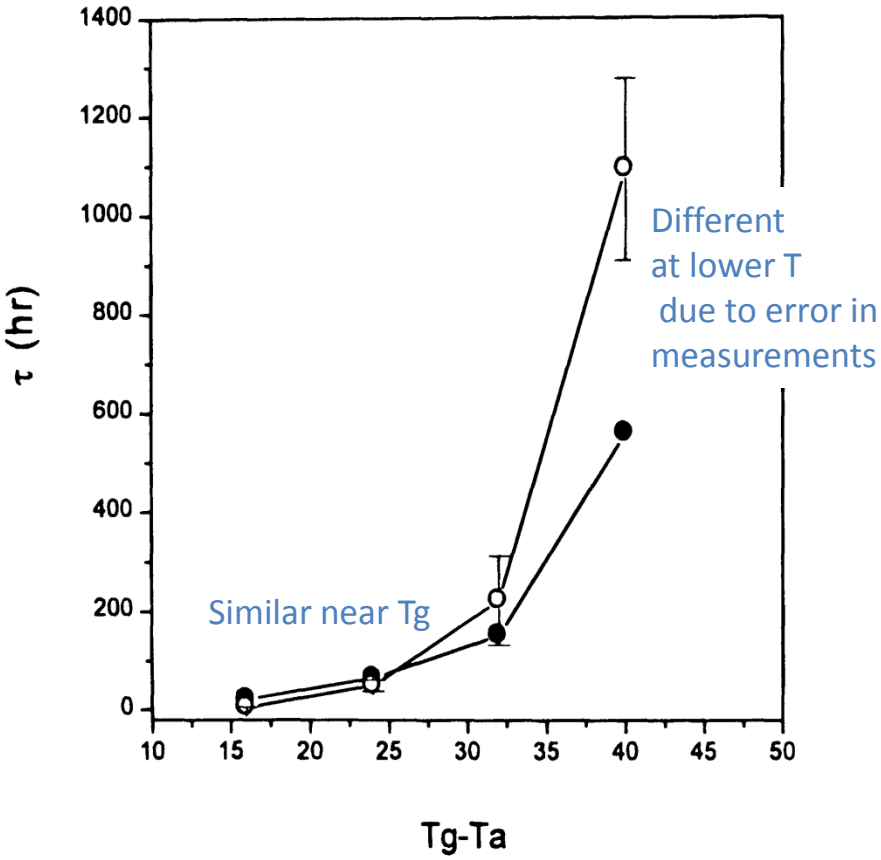
- For $\phi(t)$, need ΔH_t and ΔH_∞

$$\phi(t) = 1 - \left(\frac{\Delta H_t}{\Delta H_\infty}\right)$$

- ΔH_∞ calculated from DSC data

$$\Delta H_\infty = \Delta C_p\,(Tg - T)$$

- ΔH_t obtained from enthalpy relaxation experiments at time t



Relaxation time τ for indomethacin (●) and sodium indomethacin (○) at storage temperatures up to 40°C below their *Tg* values.

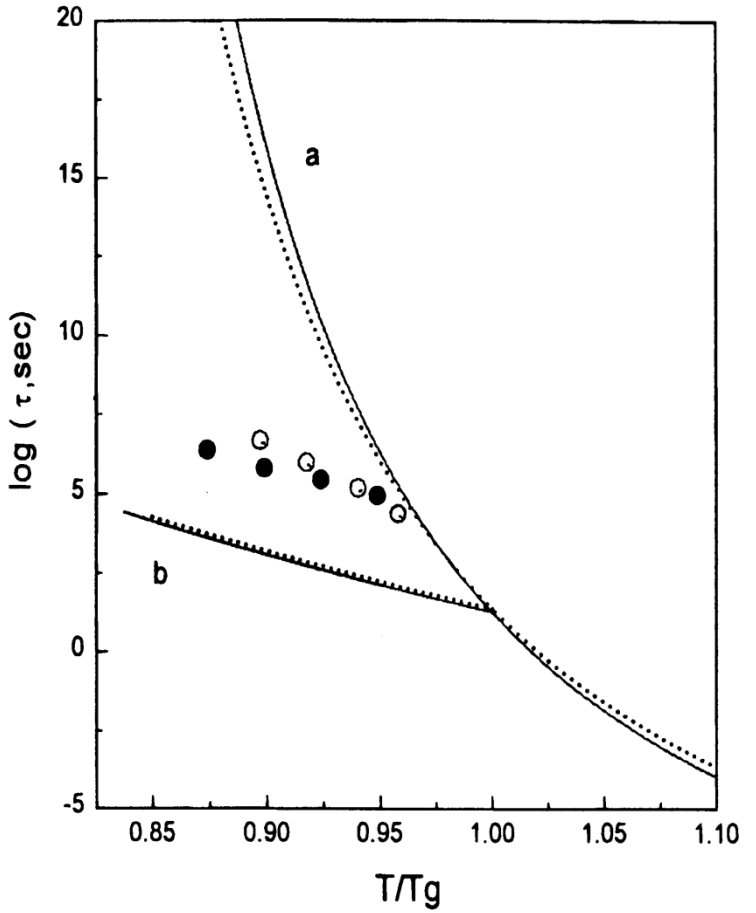
Tong and Zografi. Pharm Res. 1999, 16, 1186-1192

Sodium Indomethacin

- Shown for indomethacin that real relaxation times below Tg are usually smaller than estimated
- Can construct plot of log τ vs T/Tg
  - Use D, T_0 and VTF equation

$$\tau = \tau_0 \exp\left(\frac{DT_0}{T - T_0}\right)$$

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



Relaxation time for indomethacin (●) and sodium indomethacin (○) obtained from the scanning rate-dependence method. Lines are fits for (a) VTF and (b) AGV equations as indicated in the text. Solid lines are for sodium indomethacin and dotted lines for indomethacin.

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

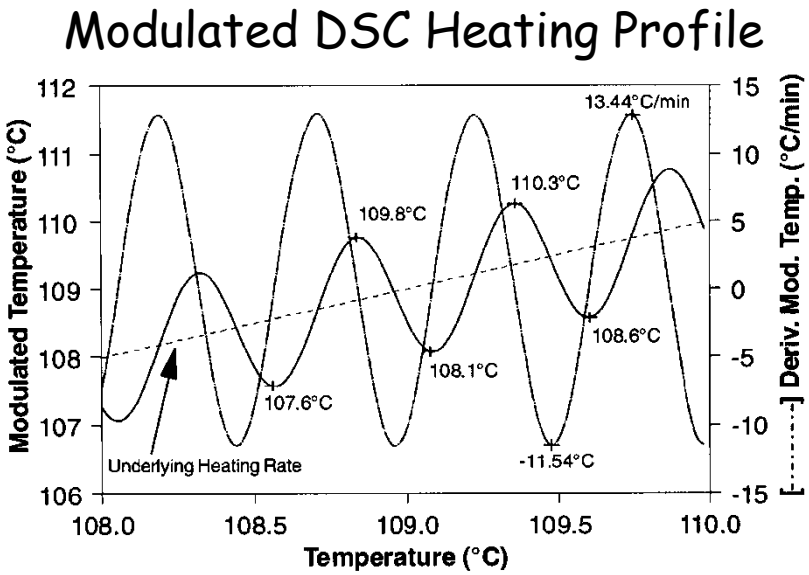
Sodium Indomethacin

Summary

- Amorphous form of salt made by three methods are similar
- Salt and free base show different T_gs (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 Tg 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)

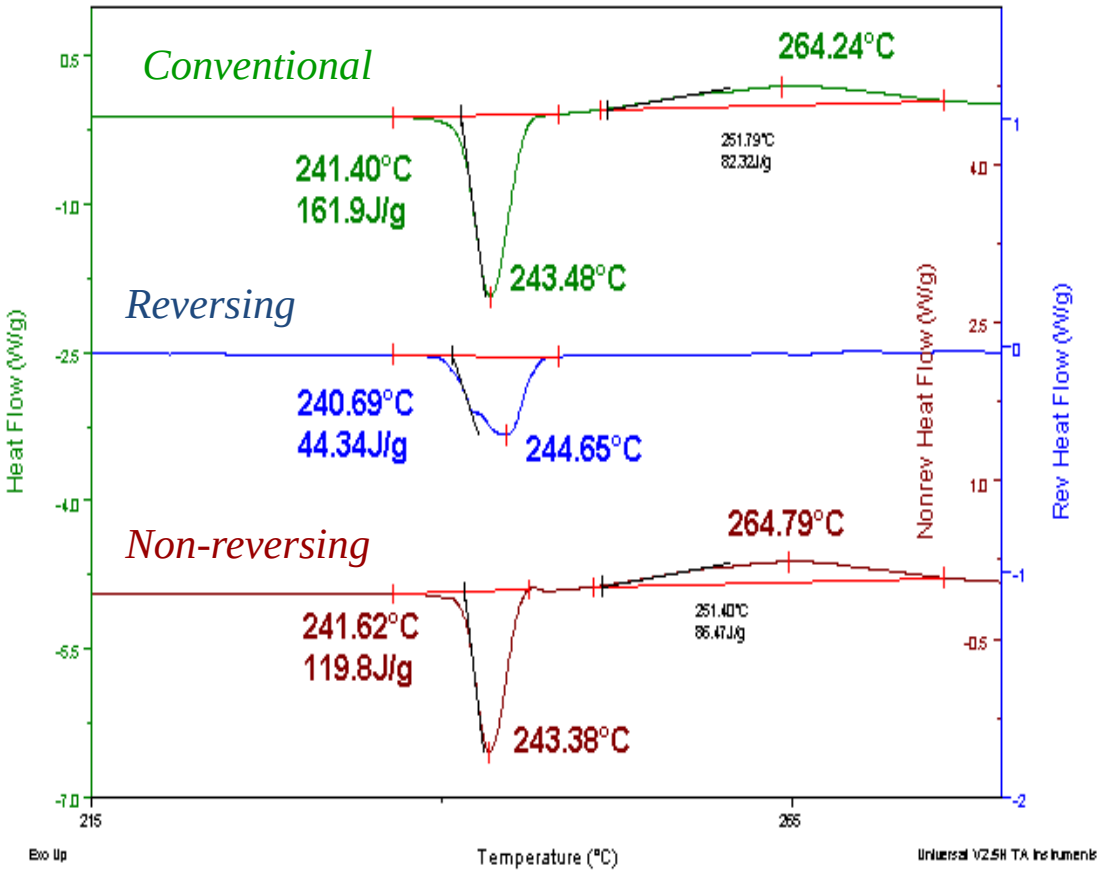
- Uses same heat flux DSC cell arrangement utilized in conventional DSC
- Different heating profile applied to sample
  - Sinusoidal modulation is overlaid on the conventional linear temperature ramp
  - Yields a heating profile which is continuously increasing with time, but in an alternating heating/cooling 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)

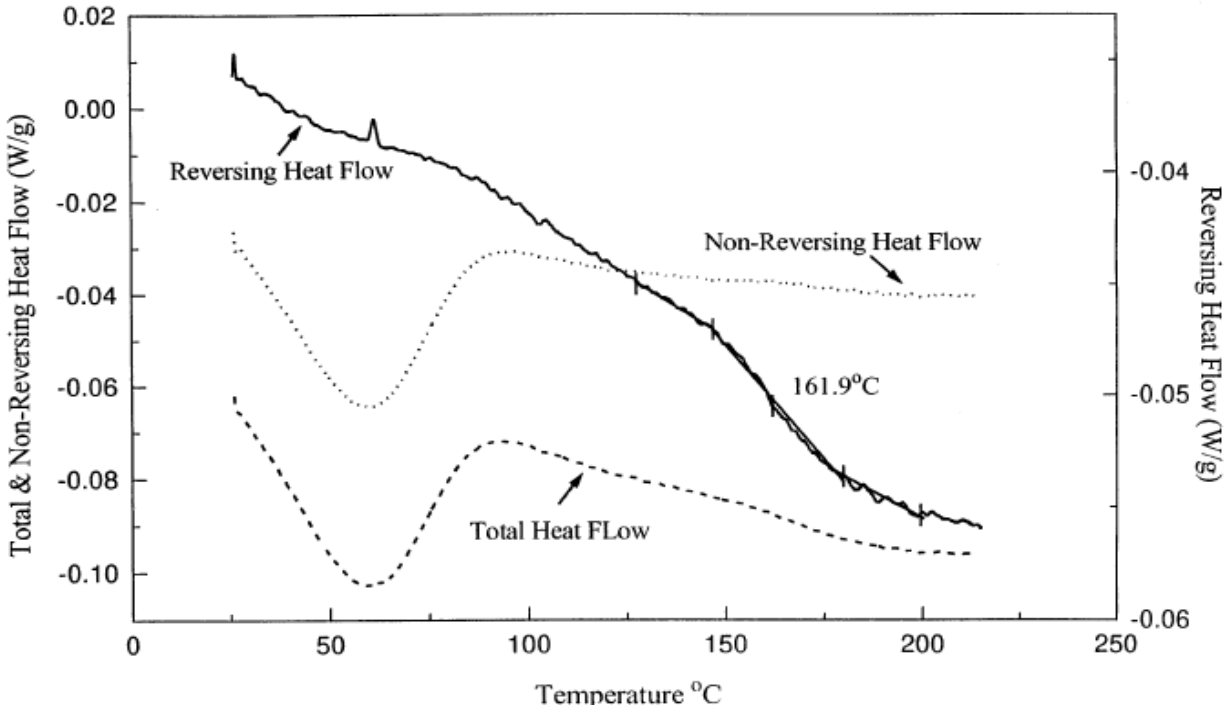
Data are composite of three curves

- 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



McPhillips et al. *Int. J. Pharm*. **1999**, *180*, 83-90.

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 (ΔH*)
  1. scanning rate (q) dependence
  2. width of Tg (ΔTg)
  3. relaxation enthalpy (ΔH) over time
  4. complex heat capacity (Cp*) and modulation frequency

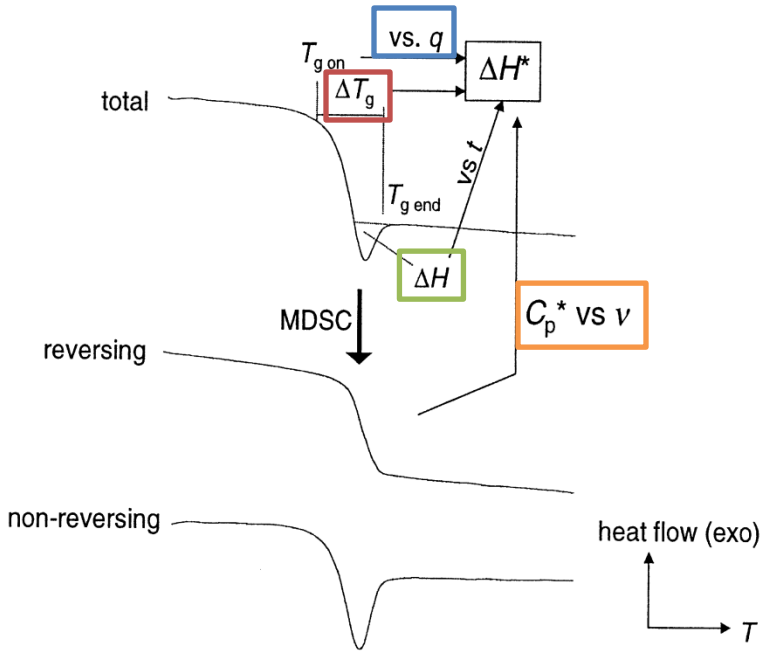


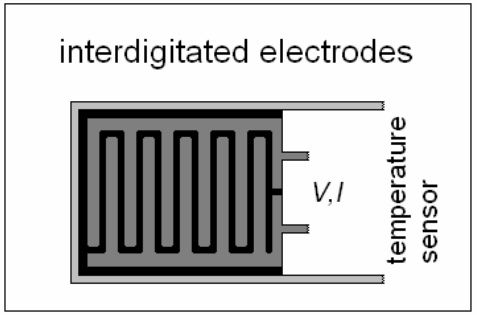
Fig. 3. Illustration of the uses of DSC data for measuring T_g and ΔH^* (the activation energy for enthalpy relaxation). $T_{g\,on}$, $T_{g\,end}$, and ΔT_g indicate the onset, end, and width of the glass transition. Modulated DSC (MDSC) allows the separation of the total heat flow into reversing and non-reversing components. ΔH^* can be evaluated from (*i*) the dependence of $T_{g\,on}$ on scanning rate q, (*ii*) ΔT_g, (*iii*) the dependence of the "relaxation enthalpy" ΔH (area of the "overshoot") on annealing time, and (*iv*) the dependence of the complex heat capacity C_p^* (obtainable by MDSC) on modulation frequency ν. See text for details.

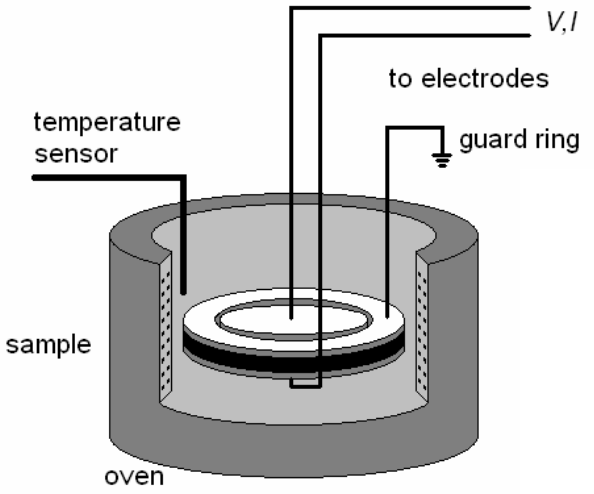
Yu. Drug Delivery Rev. 2001, 48, 27-42.

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





http://www.sump4.com/publications/book004.pdf

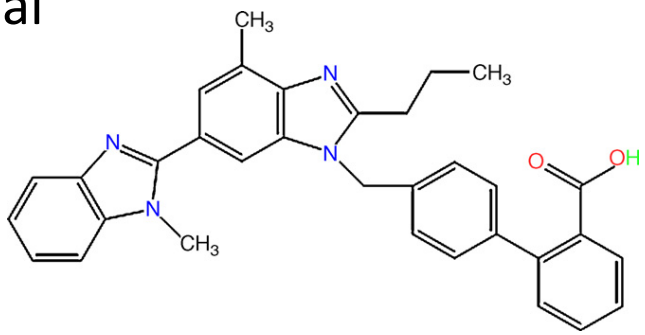
Dielectric Analysis

- 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 Δ = 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 α relaxations
      - Correspond to Tg
    - Two secondary relaxations β and γ



Adrjanowicz et al. Europ J Pharm Sci. 2009, 38, 395-404

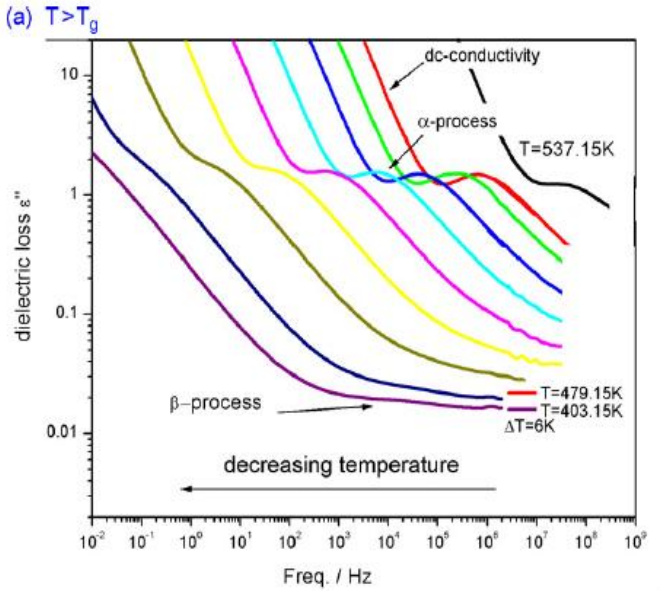
Molecular Motions

- Primary Relaxations
  - α relaxations
  - "slow" cooperative diffusion (translational and rotational motion of whole molecules or polymer segments)
  - corresponds to Tg
- Secondary Relaxations
  - β 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 α relaxations*

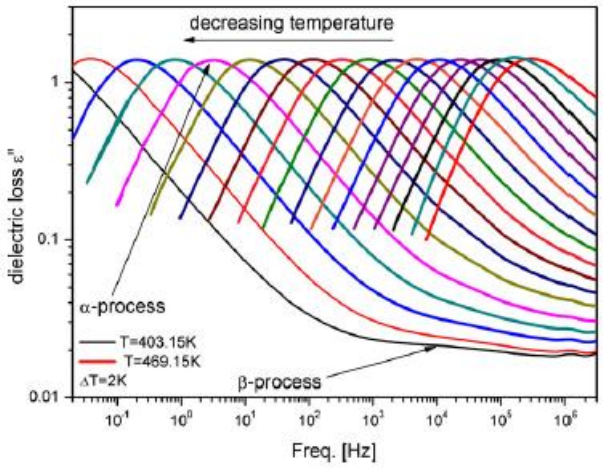
Johari and Goldstein. *J. Chem. Phys*. **1970,** *53,* 2372

Dielectric

- Glass transition defined at temperature at which dielectric relaxation time τ_α is equal to 100 s
  - Tg = 400 K = 127° C
- Dielectric loss (ε“) above Tg
  - Temp range 403-537 K
  - α- process evident
  - Conductivity (dc) contribution due to presence of free ionic species present in most liquids
  - Corrected for dc-conducitivity
- Peak for α-relaxation increases with decreasing temperature



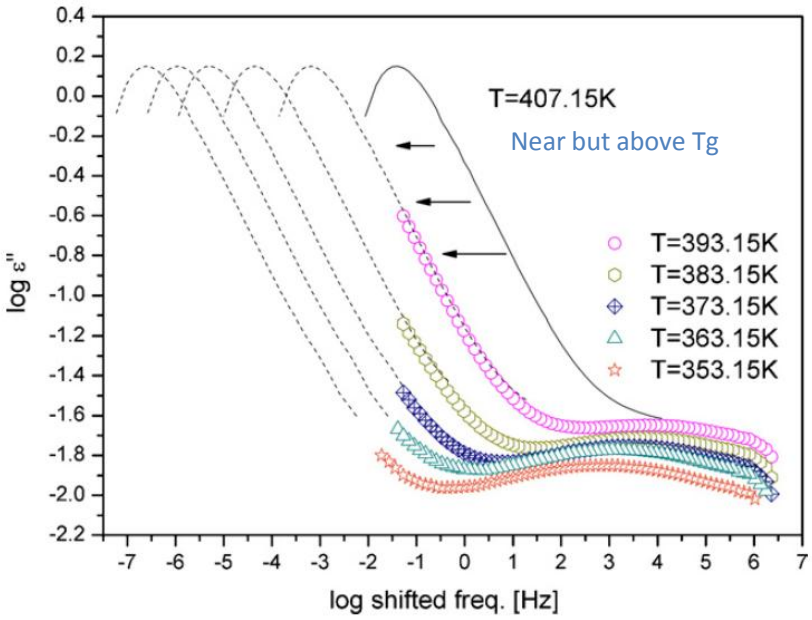
Minus dc conductivity



Adrjanowicz et al. Europ J Pharm Sci. 2009, 38, 395-404

Dielectric Analysis

- Aging experiments performed to estimate stability
  - 393.15, 373.15, 353.15, 331.15 K
  - α peak moves to lower frequencies, smaller contribution to β-process as temperature decreases
- Time scale of α 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

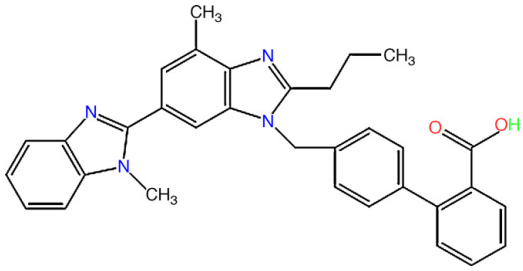


Adrjanowicz et al. Europ J Pharm Sci. 2009, 38, 395-404

Dielectric Analysis

Summary

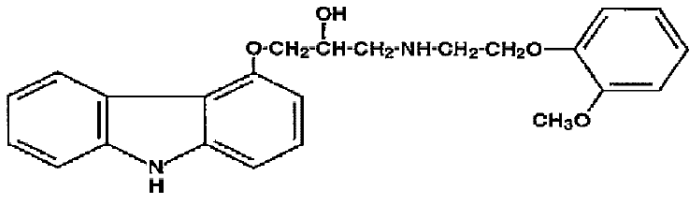
- Dielectric spectroscopy used to look at relaxation processes
  - –Temp range: 264 to -140 °C
  - –Frequency range: 10^{9} to 10^{-2} Hz
  - Primary α relaxations found above Tg
  - Two secondary relaxations β and γ dominate below Tg
- Tg of 400 K, fragility index (m) = 87
- Determined α relaxation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



Adrjanowicz et al. Europ J Pharm Sci. 2009, 38, 395-404

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



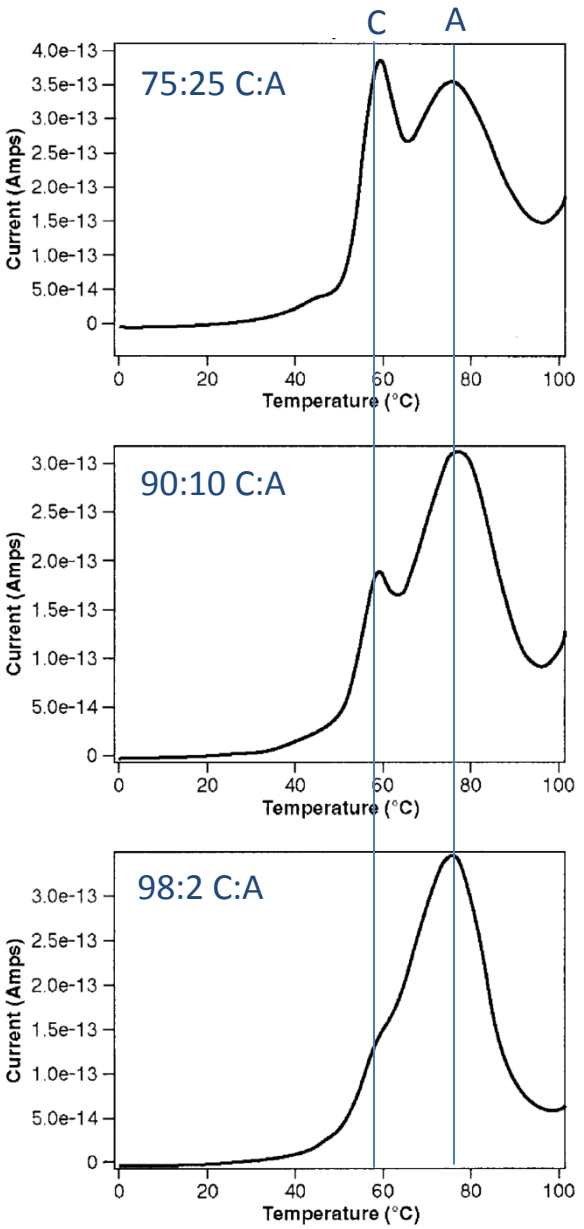
- Amorphous made by melting above 135 °C and cooled to ambient in a desiccator. Stored at RT in desiccator.
- Mixtures made by blending 75:25 amorphous:crystalline sample in Turbula blender
  - Other blends (90:10 to 99:1) produced using blend and crystalline material by serial dilution

Venkatesh et al, *Pharm Res* **2001**, *18*, 98-103

TSC

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

Technique	Analysis	LOD
TSC	Polynomial fit	2%
MDSC	Complex heat capacity signals	5%
XRPD	Integrated peak intensities in four regions for crystalline drug and LiF standard	5%
Moisture uptake	Moisture uptake	5%

Venkatesh et al, *Pharm Res* **2001**, *18*, 98-103

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

Most Probable Relaxation Time for Ketoconazole and Indomethacin as a Function of Technique

Compound	Temperature (°C)	MDSC (h)	TAM (MSE) (h)	TSC (h)
Ketoconazole	35	17.8	0.65	0.06
Indomethacin	35	19.8	0.065	0.061

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

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