Characterising the Amorphous State in a Pharmaceutical Powder Using Moisture and Organic Vapour Sorption

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Overview

I. Introduction into the Technique

II. Applications
   a) Glass Transition Determination
   b) Video Microscope Observations
   c) Amorphous Content Quantification

III. Summary
Amorphous Materials

- No long-range or well-defined molecular structure - only short range molecular order
- Often introduced via spray-drying, freeze-drying, milling, or processing

Desired qualities
- Higher solubility, higher dissolution, or better compression characteristics

Undesired qualities
- Decreased chemical and physical stability
- Thermodynamically metastable compared to crystalline state
Amorphous Materials and Water

- Water vapour present during processing and storage

- Hydrophilic amorphous solids often absorb higher amounts of water vapour compared to crystalline phase

- Sorbed water can act as plasticizing agent, lowering effective $T_g$
  - Lowering glass transition temperature
  - Spontaneous phase transition and/or lyophilic collapse

- *Critical threshold RH at processing, storage, or delivery conditions to prevent spontaneous glass transition*
Dynamic Vapour Sorption

- Experiment time reduced to hours instead of days
- Small sample size reduces time needed to establish equilibrium
- Continuous monitoring of mass as a function of relative humidity (0 to 98% RH)
- Full control and monitoring of sample environment
- Fast sorption/desorption kinetics may be studied
- Gravimetric automated flowing gas system
- Range of temperatures
- Full use of water and organic vapours
Material Morphology and Vapour Sorption

- **Amorphous-Glassy Solid**
  - $T < T_g$
  - Mainly surface adsorption
  - Fast kinetics and low uptake levels

- **Amorphous-Rubbery Solid**
  - $T > T_g$
  - Deep bulk sorption
  - Slow kinetics and large uptake levels

- **Crystalline**
  - No $T_g$
  - Surface adsorption
  - Fast kinetics and very low uptake
Glass Transition RH (T_g RH)

➤ Linearly ramp from 0 to 90% RH for a spray-dried lactose powder

➤ Shift in vapour sorption mechanism at glass transition

➤ Surface adsorption versus bulk absorption as molecules begin to move into bulk

➤ Higher free volume in amorphous phase

➤ Higher surface area and/or energy for amorphous state

➤ Perform experiments over a range of ramping rates

➤ Extrapolate to an infinitely long ramping rate or 0% RH/hour

➤ Determine threshold RH at a specific T to prevent glass transition at particular temperature \( T_g \text{ RH} \)
0 to 90% RH for Different Ramping Rates

Amorphous Lactose

Temp: 25.0 °C

Net Change In Mass

Time/mins

Glass Transition Humidity ($T_g$ RH) versus Humidity Ramping Rate

$y = 1.155x + 29.822$

$R^2 = 0.979$

- Critical $T_g$ RH = 30% +/- 1% RH at 25 °C
Critical Collapse RH = 58% RH at 25 °C
Video Results (25 °C, 6% RH/hour)
Comparisons with DSC Data

\[ T_g = \sim 35 \, ^\circ\text{C} \text{ at } 0.30 \text{ water activity (30\% RH)} \]

- Similar to \( T_g \) RH measured with DVS
- Active RH control in DVS experiments

Source: Y. H. Roos, Department of Food Science, Food Technology, and Nutrition; University College Cork, Ireland
Comparisons with Microcalorimetry Data

- Moisture-induced thermal activity trace with 3% RH/hour ramp
- Similar structure to DVS results
- ~30% RH-internal structure change, critical storage RH
- ~58% RH-re-crystallization

Similar results for any second order phase transition
Comparisons with IGC data

Glass Transition Temperature of Amorphous Lactose versus Relative Humidity

Values between 25% RH (27.1°C) and 30% RH (22.2 °C) compare well with DVS data at 25 °C (30 %RH)
Quantification of residual amorphous content of pharmaceutical materials is a crucial and commonly difficult analysis.

A number of issues need to be considered for choice of an appropriate methodology.
Choosing a Technique for Amorphous Content Determination

Factors to consider:

- Online or off-line analysis
- Quality or resolution of analysis required
- Amount of sample to be characterized
- Time available for analysis
- Knowledge base within lab or group
- Destructive or Non-destructive
- Sample preparation requirements
My Ideal Choice?

- Could be used online or off-line
- Resolution of 0.01%
- Sample size - 1mg
- Analysis time - 5 minutes
- Equipment- Easy to use
- Approach- Non-destructive
- Minimal sample preparation or method development
Amorphous Content Analysis

Techniques in usage including detection limit and analysis time:

- Differential Scanning Calorimetry (DSC) 10% (<1 hour)
- Powder X-ray Diffraction (PXRD) 5% (<1 hour)
- Thermal Stimulated Current Spectroscopy 2% (<1 hour)
- Density 10% (<1 hour)
- Solution Calorimetry 1% (<10 minutes)
- FT-Raman 1% (<1 hour)
- Near IR 1% (<1 hour)
- Modulated DSC 1% (<2 hours)
Amorphous Content Analysis

The most sensitive techniques in usage include:

- **Solid State NMR 0.5% (<1/2 day)**
  Difference in NMR spectra of crystalline and amorphous phases

- **Microflow Calorimetry 0.4% (<1/2 day)**
  Heat of crystallization of amorphous phase

- **Parallel Beam XRPD 0.4% (<1 hour)**
  Difference in diffraction behaviour of crystalline and amorphous phases

- **Gravimetric Vapour Sorption 0.2% (<1 day)**
  Mass uptake due to preferential solute uptake by amorphous phase including inducing amorphous to crystalline transformation.
DVS change in mass profiles for a sample of X with a 4.8% amorphous content
Octane adsorption of mixtures of amorphous lactose and α-lactose monohydrate

DVS Isotherm Plot

Temp: 25.0 °C

- 100% Crystalline
- 2.170% Amorphous
- 6.017% Amorphous
- 24.801% Amorphous
- 100% Amorphous
Octane Uptake versus Amorphous Content

Calibration curve for lactose at 0.95 p/po

\[ y = 1.797E-03x + 1.773E-02 \]

\[ R^2 = 0.9994 \]

Commercially available \( \alpha\)-lactose monohydrate from Acros

Amorphous content:

0.9 % (+/- 0.3%)
Future Studies

- Perform additional experiments over range of temperatures
- Study other amorphous systems (i.e. excipients, API’s, complete formulations)
- Closer look at DSC, microcalorimetry, and modelling results to elucidate nature of discrepancies and confirm assignment of features in DVS data
Conclusions

- New technique for simply measuring the critical RH for a glass transition event
- Study kinetics of water-induced morphologic changes
- Determine the threshold storage conditions to prevent glass transition and recrystallization
- Determination of amorphous content without the need to recrystallize amorphous phase
Thanks!

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