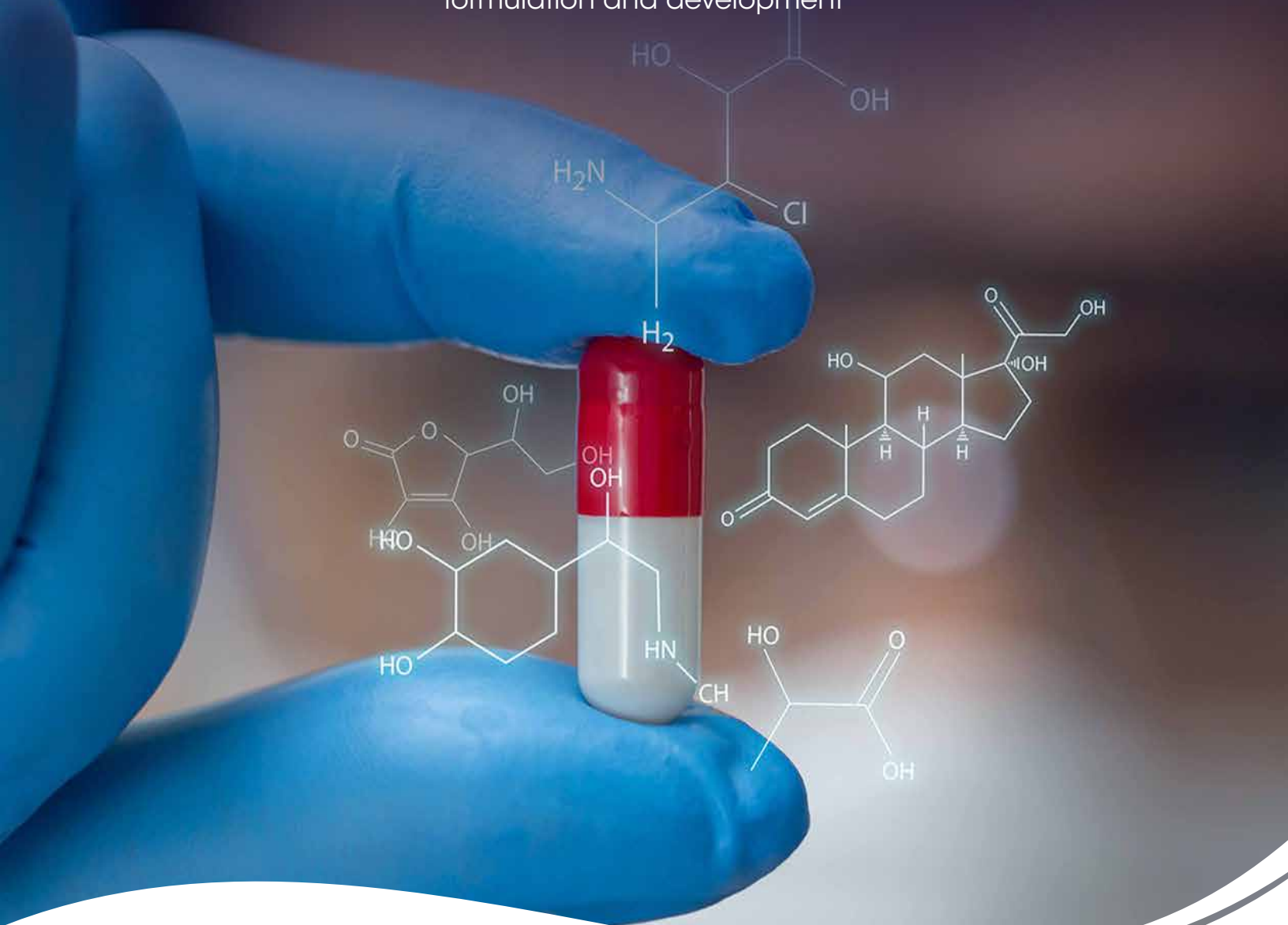
Key Analytical Techniques for Pharmaceutical Discovery and Formulation

A guide to enhance and refine your drug formulation and development



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Contents

INTRODUCTION

Pharmaceutical breakthroughs and successful development are facilitated by accurate material data. Material analysis helps pharmaceutical researchers ensure product stability, compatibility, and end use application. As a result, this information helps you eliminate undesirable formulations early and accelerate your product's time to market.

Without accurate material analysis, many pharmaceutical researchers struggle to:

- Optimize and shorten the lyophilization/freeze drying process
- Identify polymorphs which can alter API properties
- Determine crystalline versus amorphous structure – key for product stability, compatibility, processing, and storage
- Prevent undesirable chemical reactions during manufacturing, transportation, and storage
- Predict the effect of hygroscopicity on storage stability and end use application

The studies in this eBook focus on four material analysis techniques that can help researchers solve these common challenges and enhance pharmaceutical development.

Thermal analysis techniques including differential scanning calorimetry (DSC) and isothermal microcalorimetry (IMC) detect minute transitions caused by a drug's composition and conditions. Differential scanning calorimetry can detect glass transitions, melting, and crystallization, while isothermal microcalorimetry measures stability, small amounts of amorphic content, and helps characterize polymorphs.

Rheology is used to measure a drug's viscosity, which is crucial for delivery of injectables or application of topicals. Powder rheology is especially important for optimizing excipients' flowability, cohesion, stability, and compressibility. Sorption analysis (SA) measures a drug's moisture uptake and related transitions.

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Powder Rheology of Lactose: Impacts of powder morphology on performance of pharmaceutical excipients

Abstract

Powder flow measurements are increasingly important in pre-formulation and formulation stages as pharmaceutical developers continue to push towards quality-by-design approaches. TA Instruments **Powder Rheology Accessory** includes two cells for powder measurements: the Flow Cell and the Shear Cell. In this note, the processing behavior of two lactose excipients is studied by measuring shear and flowability of milled and spray-dried lactose. Milled lactose was found to have higher cohesion, yield strength, confined and unconfined flow energies when compared to spray-dried lactose. Additionally, milled lactose flow energy exhibited a dependence on impeller tip speed and more variability than spray-dried lactose. The multiple powder rheology measurements presented indicate better processability with spray-dried lactose than with milled lactose.

Introduction

Drug formulators must choose excipients that meet processing and performance needs such as flowability, cohesion, stability, and compressibility. Lactose is a commonly used excipient that typically undergoes a two-stage manufacturing process. It is first milled to a powder, creating particles with irregular size and morphology. To achieve characteristics desirable for different products and formulations, a secondary process is applied. Spray-drying is a secondary process that yields spherical particles of more uniform size, allowing the lactose to flow more easily [1]. This size control and flowability makes it desirable for dry granulation and has also shown advantages in wet granulation tableting.

With the increased push towards quality-by-design (QbD) approaches for developing pharmaceutical products, especially by regulatory authorities around the world, powder flow measurements are a critical part of the analytical workflow in the pre-formulation and formulation stages [2]. Powder rheology enables the quantification of properties in the lab to optimize formulations before scale-up. The flowability of free-flowing powder combined with the shear and compressibility of consolidated powder provide important key insights to not only formulators, but also suppliers as these measurements can guide hopper design. This study uses powder rheology measurements to characterize milled and spray-dried lactose.

Experimental

Milled lactose (Loudwolf Industrial and Scientific) and spray-dried lactose (SpecializedRx) were used in this study. All measurements were performed using a TA Instruments rheometer and the Powder Rheology Accessory, with interchangeable shear and flow cells, shown in Figure 1. For these tests, the Discovery HR-30 rheometer was used at ambient room conditions of 21 °C and 50% relative humidity.

Application Benefits

- The processability of a powder pharmaceutical formulation is impacted by the choice of ingredients.
- Powder rheology is a valuable technique to evaluate ingredients or formulations for unexpected behavior during processing.
- The HR Powder Rheology Accessory includes both Flowability and Shear measurements, providing a complete picture of powder flow behavior and particle interactions.
- Insights into powder rheology enable users to optimize formulations to ensure production success, accelerating new product development.

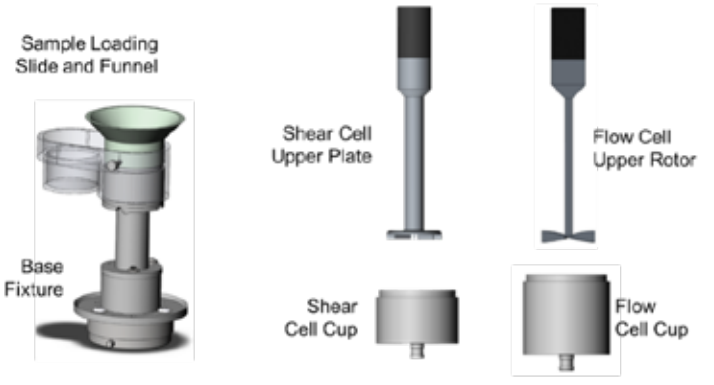

Figure 1. TA Instruments Powder Rheology Accessory kit with interchangeable Shear and Flow Cell fixtures

Powder Flowability

The Powder Flow Cell was used to measure flowability by moving an impeller rotor through a powder bed in a helical path. Unconfined flow is measured as the impeller moves up through the powder and confined flow is measured as the impeller moves down through the powder. Prior to testing, the powders were loaded into the cup and conditioned by moving the impeller upwards and downwards through the powder at a tip speed of 100 mm/s, then trimmed, as shown in Figure 2. This procedure ensures uniformity between test samples and improves reproducibility of results. After conditioning, the impeller followed a helical path with a tip speed of 100 mm/sec, with one testing cycle used to measure confined and unconfined flow. This was repeated seven times for a total of seven measurement cycles to evaluate stability. Upon completion of these seven cycles, one cycle each was performed at 100, 70, 40, and 10 mm/sec to evaluate rate dependence. Normal force and torque were measured to determine flow energy and testing was repeated three times using fresh samples.

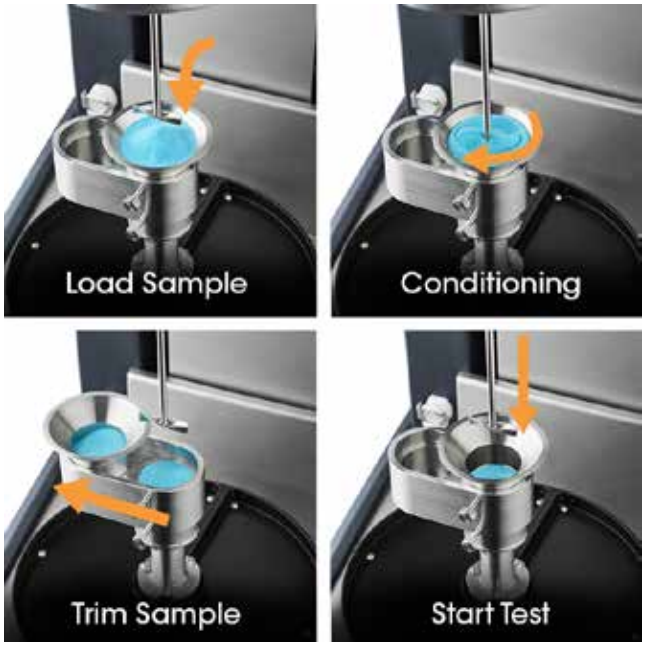

Figure 2. Process to load and test samples using the Powder Rheology Accessory

Powder Shear

Shear measurements were made using the Shear Cell accessory, shown in Figure 3, which has a serrated upper plate and cup to prevent slip when shearing the compacted powder. The lactose powders were loaded using the provided loading slide and funnel, then consolidated by applying a stress of 15 kPa. The sample was then trimmed to remove excess and level the surface for testing.

Testing was performed per ASTM D7891 [3], using a consolidation normal stress of 15 kPa. A pre-shear step was performed, maintaining the 15 kPa consolidation stress on the powder sample, and slowly rotating (angular velocity of 1*10-3 rad/sec) until the measured shear stress reached steady state. Next, the normal stress was reduced, and rotation applied until the powder showed an incipient yield, in form of a peak in shear stress. The pre-shear step was repeated with the same initial normal stress (15 kPa) to achieve consistent powder consolidation conditions, then followed with a shear measurement under a lower normal stress. A total of ten test cycles were completed under normal stresses from 12 kPa to 3 kPa.

Figure 3. Shear cell serrated upper plate and cup

Table 1. Multi-step powder shear test procedure

Cycle	Pre-Shear Stress (kPa)	Test Stress (kPa)
1	15	12
2	15	11
3	15	10
4	15	9
5	15	8
6	15	7
7	15	6
8	15	5
9	15	4
10	15	3

Results and Discussions

Powder Flowability

The flowability energy results for milled and spray-dried lactose are shown in Figure 4. The higher flow energy of the milled lactose has important implications in manufacturing and scale up processes. To flow the excipient into the industrial tableting mold, the milled lactose will require higher energy and other considerations to the critical process parameters (CPP).

Unconfined flow is sensitive to the particles' tendency to interlock [4]. Milled lactose shows higher unconfined flow energy than spray-dried lactose due to different particle shapes. Milling breaks lactose into shards with rough surfaces and high aspect ratio, while the spray-drying process forms spherical particles that more easily slide past each other during flow, as seen in Figure 5. Both samples show reproducible results on the first cycle, with flow energy values within 1.5% for the 3 replicates. Spray-dried lactose shows very little change during repeated testing.

Milled lactose also exhibits a rate dependency not seen with the spray-dried particles. In Figure 6, the confined flow energy of the milled lactose decreases with increasing tip speed whereas the spray-dried lactose does not show a rate dependency. This is key information for a formulator during early stage drug development as a change in the excipient source can lead to significant differences in processability during scale up. If a formulator changes the excipient source from spray-dried to milled, they may see performance differences during low-speed processes such as flowing into a mold before pressing into a tablet. Furthermore, the dependency of the confined flow energy on the transfer speed can cause inconsistencies in the final dosing of the excipient resulting in a wider-than-acceptable spread of the critical quality attributes (CQA) of the final product.

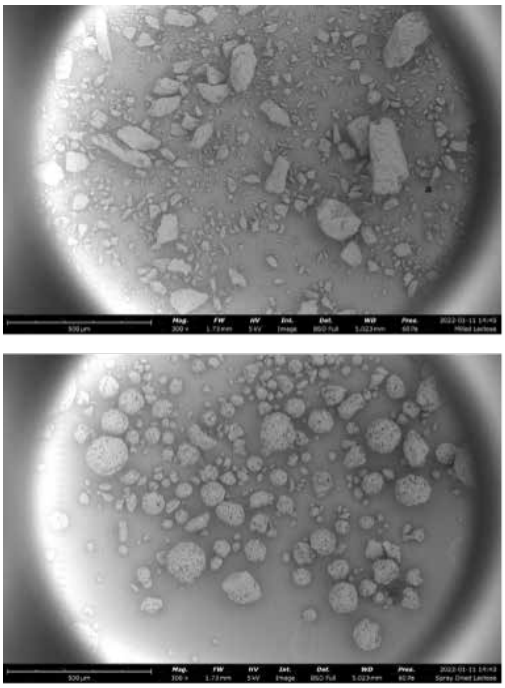

Figure 5. SEM images of milled lactose (top) and spray-dried lactose (bottom)

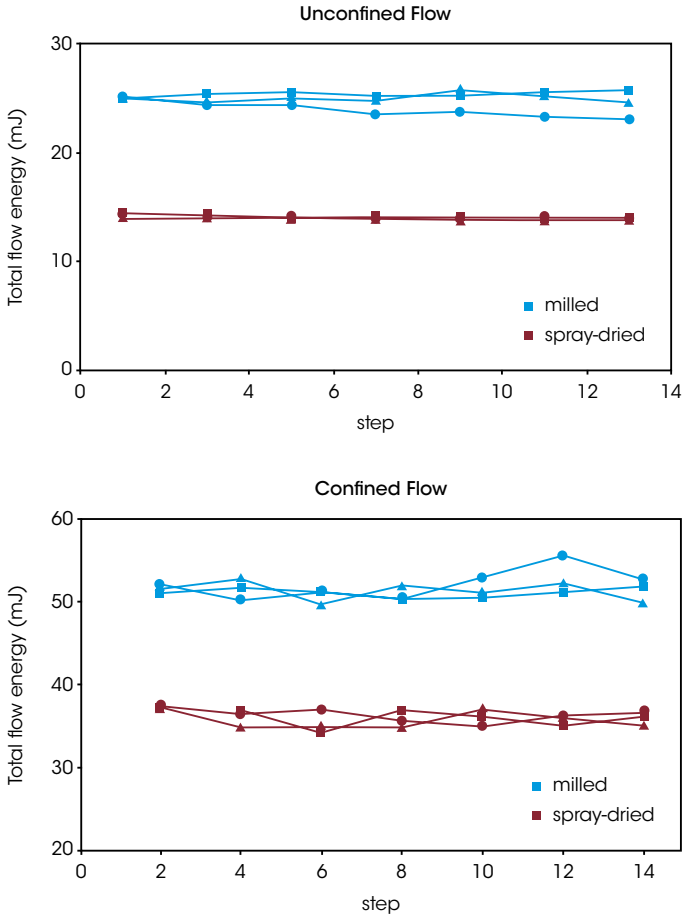

Figure 4. Unconfined (top) and confined (bottom) flow energies for milled (blue) and spray-dried (red) lactose. Results shown are three separate test samples for each type of lactose.

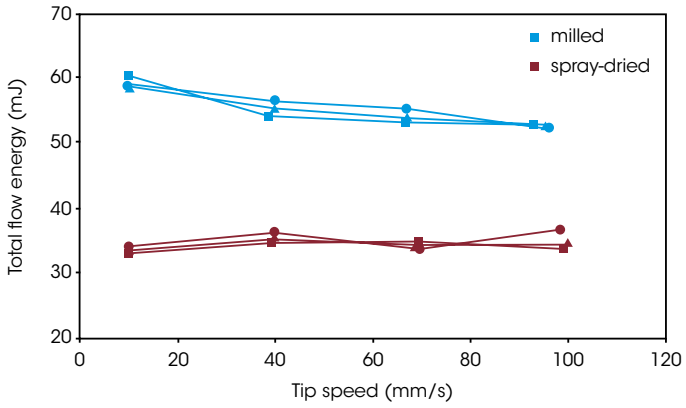

Figure 6. Flow energy with respect to testing speed for three samples each of milled (blue) and spray-dried (red) lactose. The milled lactose exhibits a rate dependency, requiring more energy at lower speeds.

Powder Shear

Figure 7 and Table 2 show the shear results of spray-dried and milled lactose samples. TRIOS software was used to perform Yield Locus Analysis and calculate results as defined by ASTM D7891. Steady-state stress of all pre-shear steps is determined and averaged (circle symbol). For each shear step, the incipient yield points are identified and plotted (square symbols).

The yield locus line is a line of best fit drawn through the shear data points. The y-intercept indicates the cohesion between particles. A Mohr circle is drawn such that it passes through the graph origin and lies tangent to the yield locus line; the x-intercept of this circle indicates unconfined yield strength. A second Mohr circle is drawn such that it passes through the pre-shear average coordinates and lies tangent to the yield locus line. The greater x-intercept indicates major principal stress (maximum internal stress under consolidation).

Table 1. Multi-step powder shear test procedure

Shear Results (kPa)	Milled Lactose	Spray-Dried Lactose
Cohesion	1.01	0.10
Unconfined Yield Strength	4.24	0.37
Major Principal Stress	33.33	27.72

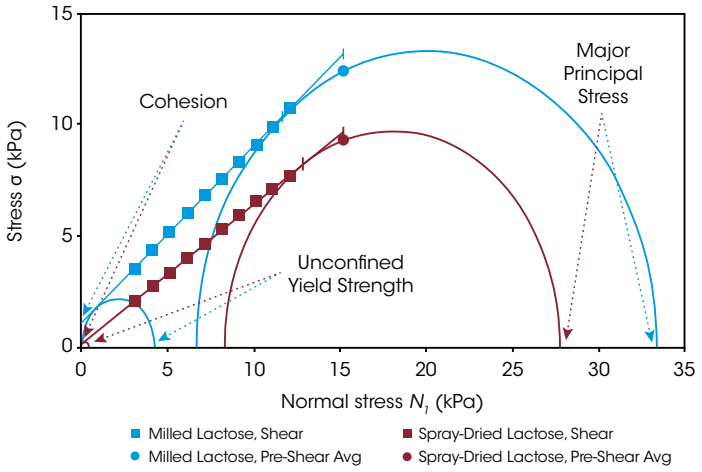

Figure 7. Shear cell results for milled and spray-dried lactose under 15 kPa consolidation stress

As shown in Figure 7 and Table 2, spray-dried lactose has negligible cohesion and shear strength, which is desirable for processing. Due to particle morphology, interactions occur between milled particles, resulting in higher cohesion and yield strength. This higher yield strength will impact the dispensing of the lactose powder as flow will not occur until the yield strength is overcome. To achieve uniform dispersion, the milled particles may also require longer mixing to break up interactions due to the higher cohesion, ultimately impacting the dispersion of the active pharmaceutical ingredient (API) into the excipient.

Conclusions

Flow properties of milled and spray-dried lactose were measured using the TA Instruments Powder Rheology Accessory. The Flow Cell was used to measure confined and unconfined flow, while the Shear Cell measured shear and cohesion of the powders. This information is critical as manufacturers increasingly use QBD approaches for drug development. The irregular morphology of the milled lactose results in higher flow energies, and a rate dependence not seen in spray-dried lactose. Spray-dried lactose, with lower flow energy, better flow stability, and negligible cohesion, has better processability than milled lactose. This information is important in understanding process development during the scale up stage and recognizing that changes to excipients impact transfer speed and CQA of the final product.

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2. K. Pramod, M. A. Tahir, N. A. Charoo, S. H. Ansari and J. Ali, "Pharmaceutical product development:: A quality by design approach," International Journal of Pharmaceutical Investigation, vol. 6, no. 3, pp. 129-138, 2016.

3. "ASTM D7891-15 Standard Test Method for Shear Testing of Powders Using the Freeman Technology FT4 Powder Rheometer Shear Cell," ASTM International, 2016.

4. K. Johanson, "Effect of particle shape on unconfined yield strength," Powder Technology, vol. 194, no. 3, pp. 246-251, 2009.

Acknowledgement

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TA Instruments has been long recognized as an innovator and leader in modulated thermal analysis.

Characterization of Polymorphic Transitions in a Pharmaceutical by DSC

Introduction

Because crystalline drugs generally have better storage stability, pharmaceutical companies prefer to use crystalline compounds for development of new drug formulations. However, a frequently encountered problem is the ability of the drug to exist in multiple crystal forms called polymorphs. Since polymorphs can have significantly different physical properties, such as dissolution rate and therefore bioavailability, it is important to control both concentration and crystal form.

Details

Differential scanning calorimetry (DSC) and modulated DSC® (MDSC®) are often used to detect polymorphic forms because they typically have different melting points and heats of fusion. For example, the three crystalline forms of sulfanilimide are shown in Figure 1 at heating rates of 1 and 10 °C/min. Heating rate has no significant effect on the melting peaks except for the width of the largest peak near 165 °C. This shows that the sample is quite stable and there is little tendency for one polymorph to transform into another.

Use of multiple heating rates is an excellent way to detect kinetic events such as decomposition or transformation of one crystalline form into another. This is illustrated in Figures 2 and 3 showing the effect of heating rate on two different drugs, phenacetin and ciprofloxacin hydrochloride (Cipro). At high heating rates (20 °C/min) the melting peak of phenacetin broadens but is essentially unchanged from the melt observed at 1 °C/min. This small difference indicates that the sample is truly melting and there are no observed kinetic events.

Cipro behaves quite differently when the heating rate is increased from 1 to 20 °C/min. According to its Material Safety Data Sheet, Cipro is reported to decompose upon melting. If a single heating rate is used, such as seen in the 5 °C/min data, it could easily be interpreted as melting at 319 °C followed by decomposition. However, this would be wrong. The difference of 29 °C between the observed "melting" endotherms for the 1 and 20 °C/min data shows that the endotherm is really part of the decomposition process and not due to melting.

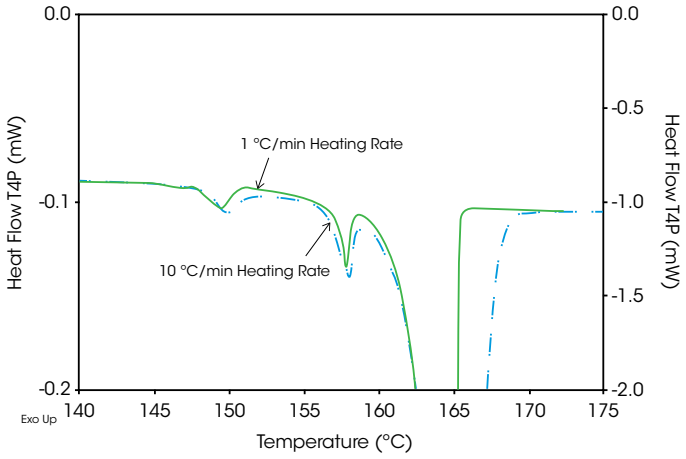

Figure 1. Comparison of 1 and 10 °C/min Heating Rates on Melting of Three Polymorphs for Sulfanilimide

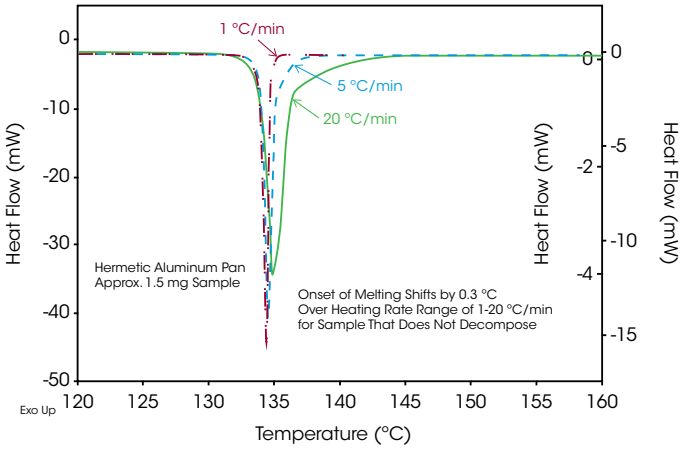

Figure 2. Effect of Heating Rate on the Melting Point of Phenacetin (No Decomposition)

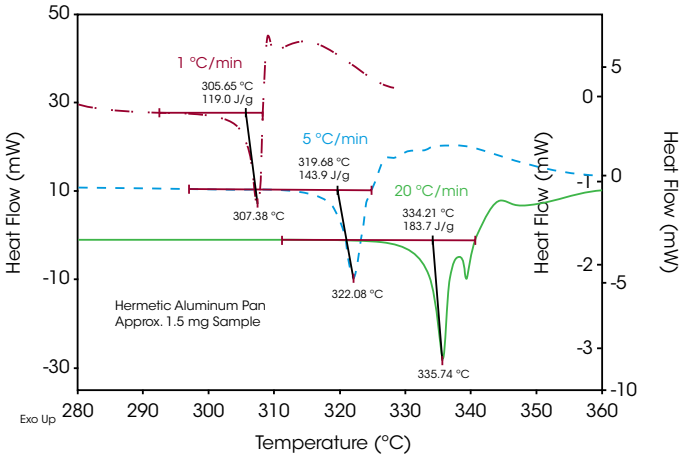

Figure 3. Effect of Heating Rate on the Claimed Melting Point of Ciprofloxacin Hydrochloride (Supposedly Decomposes During Melting)

The value of using multiple heating rates for characterizing crystalline drugs that have the ability to exist in several polymorphic forms is seen in Figures 4 – 6. At 10 °C/min heating rate (Figure 4), there appear to be two melting peaks at 155 and 161 °C. It might be interpreted that both forms exist in the original sample. At 1 °C/min (Figure 5), the peaks at 155 and 161 °C still exist but they have a very different size ratio.

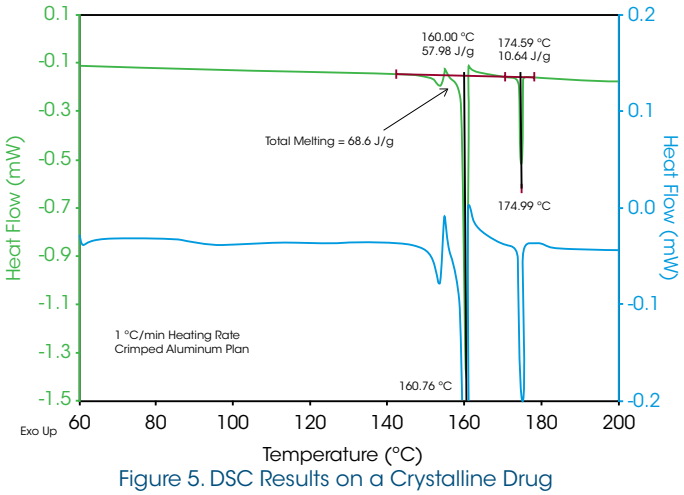

Figure 5. DSC Results on a Crystalline Drug (1°C/min heating rate)

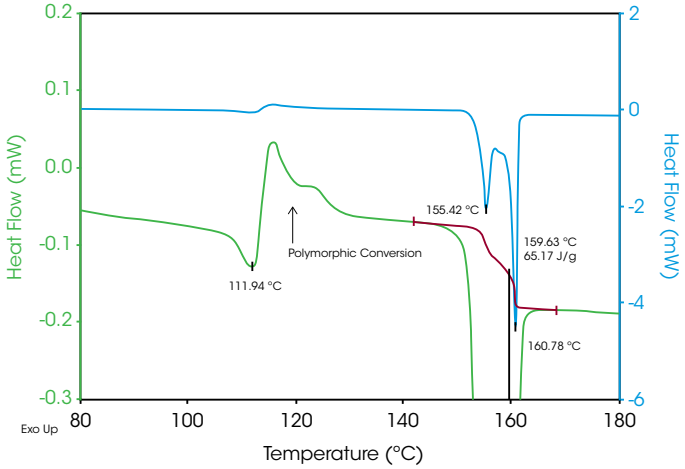

Figure 4. DSC Results on a Crystalline Drug (10°C/min heating rate)

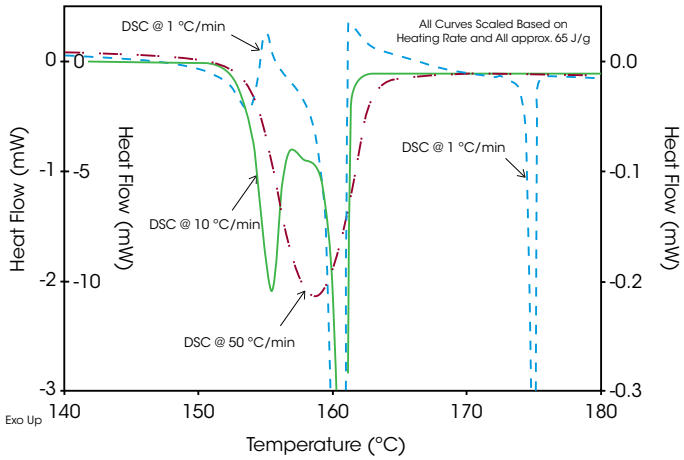

Figure 6. Effect of Heating Rate on Transitions in a Phamaceutical Drug

Summary

DSC is an excellent tool for characterizing crystalline drugs. However, just as with any other analytical technique, it should not be used without some thought being given to experimental conditions. Use of multiple heating rates is a good approach for detecting transitions in materials as well as their tendency to undergo kinetic processes as the sample is heated.

"Apparent Melting": A New Approach to Characterizing Crystalline Structure in Pharmaceutical Materials

Abstract

Differential Scanning Calorimetry (DSC) is an analytical technique frequently used to detect and quantify crystalline content of pharmaceuticals, foods, polymers and many other materials. The presence of crystalline structure is seen as an endothermic peak during heating in a DSC experiment. The temperature and area of the peak can be used to help identify, qualify, and quantify crystalline structure. Most DSC users and materials researchers typically know or suspect if their material contains crystalline content. Most commonly, a DSC thermogram containing an endothermic peak is often interpreted as "thermodynamic melting" of crystalline structure. However, this interpretation of the data may not always be correct. For example, numerous papers1,2,3 have been published in the last few years to illustrate how the start of chemical reactions (hydrolysis) and thermal decomposition in many common sugars, such as sucrose, cause loss of crystalline structure as much as 70 °C below typically reported melting temperatures. However, some researchers remain skeptical of the interpretation of these findings.

The purpose of this paper is to provide a universally acceptable definition of "Melting" and then illustrate that loss of crystalline structure in many materials can be caused by numerous chemical processes other than thermodynamic or "True Melting". Loss of crystalline structure caused by a chemical process will be called "Apparent Melting" in this paper.

Some may think that since crystalline structure is lost by both True and Apparent melting, it makes no difference in the usefulness and application of the DSC data. That is an incorrect assumption as will be discussed and illustrated. The most important point of this paper is to show how the accuracy (melting temperature and heat of fusion) and utility of the data is greatly diminished for materials that undergo Apparent Melting.

Introduction

Melting of substances is a commonly observed phase change from a crystalline solid to an amorphous liquid. There is a typical assumption that loss of crystalline structure while heating in a DSC at typical rates of 1 to 25 °C/min is True (thermodynamic) Melting. As will be shown, loss of crystalline structure can be caused by numerous processes (kinetic) other than thermodynamic melting. The only common characteristic between True and Apparent melting is conversion from crystalline to amorphous structure.

Although others may have suggested parts of a definition prior to Wunderlich4, his seems to be the most complete. His definition states that thermodynamic melting occurs:

1. At a single, time-independent (and therefore heating rate independent) temperature where the corresponding crystalline solid and liquid amorphous phase are in thermal equilibrium (ΔG = 0) at constant pressure

2. Without chemical change

An example of Apparent Melting is seen in Figure 1. Most DSC users would assume that the peak is due to True Melting. As will be shown, it takes only two DSC experiments to distinguish between True and Apparent Melting.

If a researcher is unfamiliar with Acetylsalicylic Acid, they will likely do a literature search to find information on the melting point as shown in Figure 2.

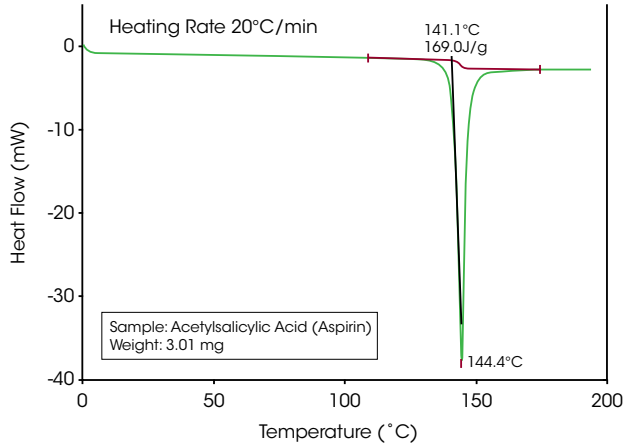

Figure 1: Endothermic peak for Acetylsalicylic Acid indicates loss of crystalline structure during heating at 20°C/min. Is this due to True Melting?

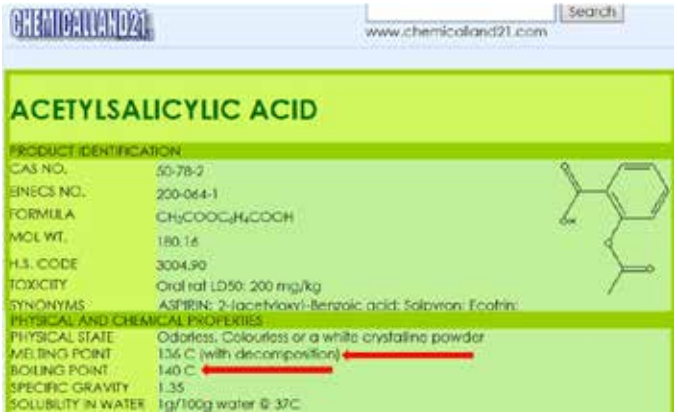

Figure 2: A search of the literature for Acetylsalicylic Acid shows that decomposition occurs at the melting point. Therefore, loss of crystalline structure does not meet criteria #2 (without chemical change) of the definition for True Melting. www.chemicalland21.com/lifescience/phar/ACETYLSALICYLIC%20ACID.htm

A common term used in the literature for materials that decompose prior to or during melting is "melts with decomposition". If the term "melts" is an accurate description for loss of crystalline structure then the onset temperature of the endothermic peak would remain constant with heating rate because, as stated in the definition, thermodynamic melting occurs at a single, time independent temperature. Conversely, decomposition is a kinetic process that is time dependent (heating rate dependent). If loss of crystalline structure is due to the onset of thermal decomposition then the onset temperature will shift to higher temperatures at higher heating rates. The series of heating rates illustrated in Figure 3 shows that loss of crystalline structure for acetylsalicylic acid meets none of the requirements for thermodynamic (True) melting and is therefore an apparent melting material. A more accurate term than "melts with decomposition" would be "loss of crystalline structure due to a kinetic process" or Apparent Melting. For new users of DSC, the assumption may be that the shift in peak onset temperature with heating rate for Acetylsalicylic Acid is an instrumental effect caused by thermal lag. This is easy to disprove with a known melting point standard such as indium or phenacetin, a purity standard obtained from NIST (Figure 4). The effect of the change in heating rate from 1 to 20 °C/min is about 0.3 °C as compared to 10 °C with Acetylsalicylic Acid.

Before we consider other chemical processes that cause loss of crystalline structure, it is necessary to answer the question "If the endothermic peak is not True Melting then why does it look like a typical DSC melting peak?". The answer to that question is not complicated and is based on the First Law of Thermodynamics, which states that energy cannot be created nor destroyed. As illustrated in the enthalpy plot of Figure 5, there is an absolute difference in enthalpy between crystalline and amorphous structure. If any process (thermodynamic, mechanical, or chemical) causes conversion of crystalline to amorphous structure then the material must absorb the absolute difference in enthalpy between the two phases at that temperature. The absorption of that energy difference would appear as an endothermic peak in the DSC curve, regardless of the cause.

Enthalpy plots are created by taking the absolute integral of heat flow rate (W/g) relative to time, or heat capacity (J/g°C) relative to temperature, over the temperature range of interest.

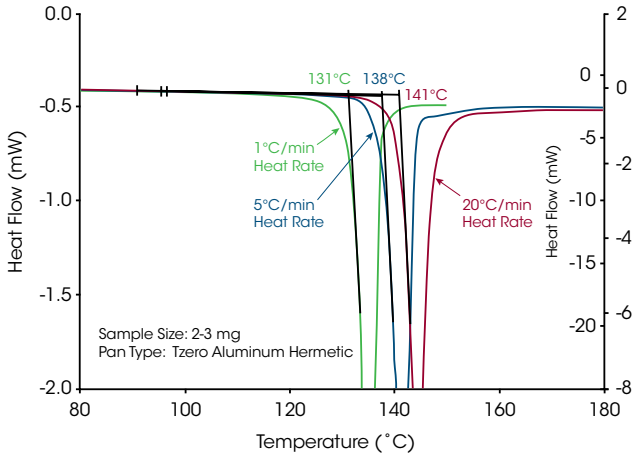

Figure 3: The temperature for loss of crystalline structure in Acetylsalicylic Acid does not occur at a single temperature, a requirement for True Melting. The shift in temperature with heating rate indicates a kinetic process, such as thermal decomposition, which was identified in the literature search. This is an example of Apparent Melting.

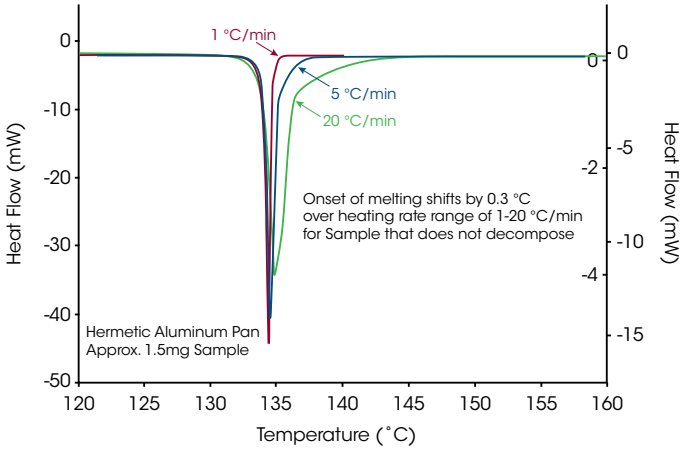

Figure 4: Phenacetin is a purity standard that is known to melt without chemical change, a requirement for true/thermodynamic melting. The effect of changing the heating rate from 1 to 20 °C/min is only 0.3 °C as compared to 10 °C with Acetylsalicylic Acid, a material that undergoes apparent melting. The melting of phenacetin is an example of True melting.

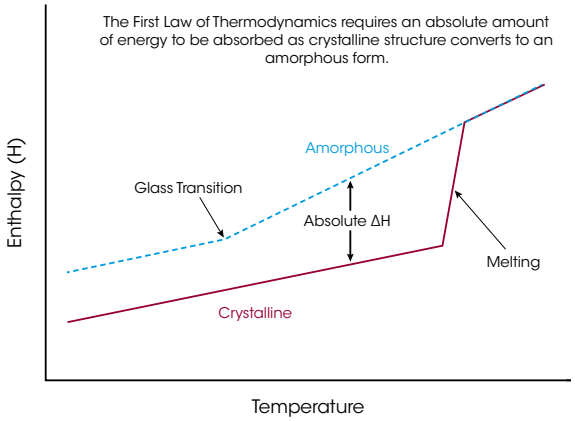

Figure 5: There is an absolute difference in enthalpy between crystalline and amorphous structure. Loss of crystalline structure for any reason requires the sample to absorb the difference in enthalpy at that temperature. This energy difference appears as an endothermic peak in the DSC plot.

Other Causes of Apparent Melting

There are numerous chemical processes, other than decomposition, which can cause loss of crystalline structure and create an Apparent Melting peak in DSC data. They include:

Chemical Interaction

Pharmaceutical companies must always deal with the issue of drug-excipient incompatibility where the active pharmaceutical ingredient (API) reacts with a component of the formulation and results in a change in potency with time. The API is typically crystalline in order to improve stability and reduce chemical interaction. One of the most studied and reported interactions (Figure 6) is between magnesium stearate and acetylsalicylic acid (aspirin).

As these materials are easy to obtain and safe to use in the laboratory, anyone interested in Apparent Melting or drug-excipient interaction is encouraged to obtain these materials and do experiments similar to that seen in Figure 7. The DSC experiments include analysis of the individual components and then a 50/50 mixture. It is important to note that when the materials were mixed, no visible reaction was detected at room temperature. After mixing, a few milligrams were loaded into a hermetic DSC pan and then heated at 1°C/min, which was the same rate used for the individual components. The slow heating rate of 1°C/min was used to provide adequate time for the interaction to occur as temperature was increased. The small peak near 90°C in magnesium stearate was due to a small amount of hydrated form which was identified on the label of the container.

Figure 6: Text from Pharma Treasures, an informatory site that shares pharma related articles, identifies the incompatibility issue between magnesium stearate and aspirin. It refers to this interaction as "induced decomposition". pharmatreasures. blogspot.com/2011/10/in-aspirin-tablets-magnesium- stearate.html

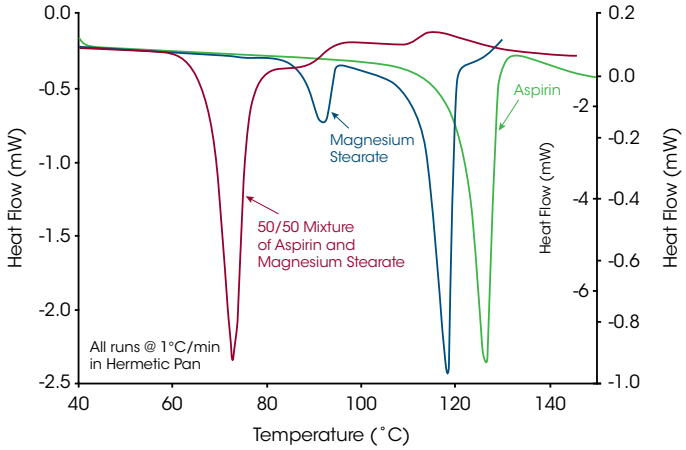

Figure 7: DSC data at 1 °C/min for Acetylsalicylic Acid (aspirin), Magnesium Stearate, and a 50/50 (wt./wt.) mixture of those two materials. The chemical interaction between these materials causes a loss in crystalline structure at a much lower temperature; an indication of Apparent Melting.

Desolvation

Dehydration, the most common form of desolvation, is the removal of a water molecule from a crystalline hydrate with the breaking of a covalent bond. The breaking of the bond disrupts the crystalline lattice and typically results in an amorphous anhydrous form and evolved water. Figure 8 compares the effect of pan type (hermetic vs. non-hermetic) on the dehydration of a crystalline hydrate with 5% bound water. The data from the non-hermetic pan (hermetic pan with pinhole) shows a broad endothermic peak due to evaporation of the water lost during the dehydration process. This is followed by a sharp exothermic crystallization peak near 120 °C which is crystallization of the amorphous material to form one of several possible polymorphic forms that then melts near 170 °C. Loss of water cannot occur in the hermetic pan and this prevents dehydration long enough to reach 100 °C, where crystalline structure is lost.

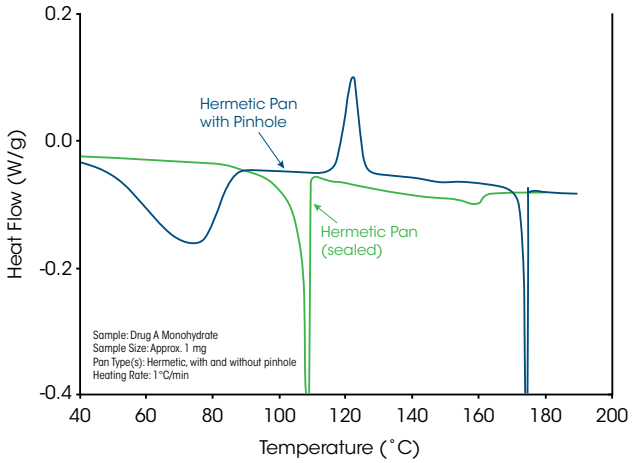

Figure 8: DSC data of a crystalline monohydrate drug with 5% water. The blue curve was done in a pan with a pinhole and shows a broad endothermic peak due to evaporation of the water of dehydration. Loss of water converted the crystalline structure to anhydrous amorphous that then recrystallized near 120 °C. Dehydration is a kinetic process (not thermodynamic) that can cause loss of crystalline structure (Apparent Melting).

Dissociation

Dissociation is a general process seen in ionic compounds, such as salts, where the crystalline molecule is broken into smaller particles. As expected, this disrupts the crystalline lattice and causes a loss of crystallinity. An example of dissociation is seen in Figure 9 for Ciprofloxacin Hydrochloride. Even though the dissociation process is very exothermic, it is very important to notice that the first observed event is an endothermic peak. As required by the first law of thermodynamics, a material must absorb the enthalpy difference between the crystalline and amorphous states as it begins to lose crystalline structure.

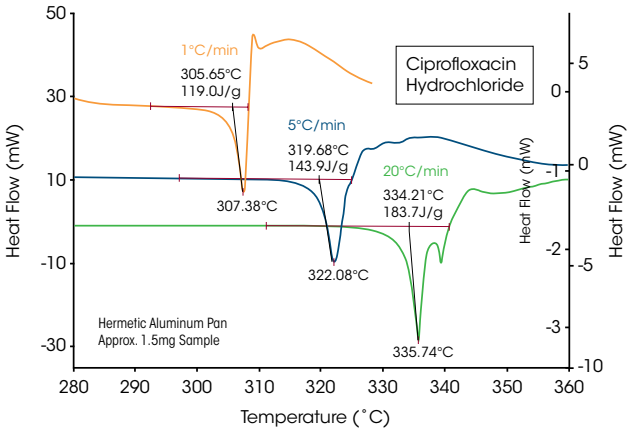

Figure 9: Salts, such as Ciprofloxacin Hydrochloride, typically dissociate rather than undergo thermodynamic melting. The shift in the endothermic peak with heating rate indicates loss of crystalline structure due to a kinetic process (Apparent Melting).

Thermal Decomposition

Thermal decomposition was discussed and illustrated in the Introduction section for acetylsalicylic acid, but a significant amount of research has been done and published4 on the loss of crystalline structure in sugars, especially sucrose. The shift in peak onset temperatures in Figure 10 is due to hydrolysis (kinetic process) that starts within mother liquor occlusions in the cane sucrose crystal.

Figure 11 illustrates a very interesting approach to understanding chemical changes that occur during loss of crystalline structure in the sucrose. As stated in the Wunderlich definition, thermodynamic melting occurs "without chemical change". This approach uses Modulated DSC (MDSC®) to follow loss of crystalline structure as a function of time at 120 °C and HPLC to analyze for thermal decomposition products of samples.

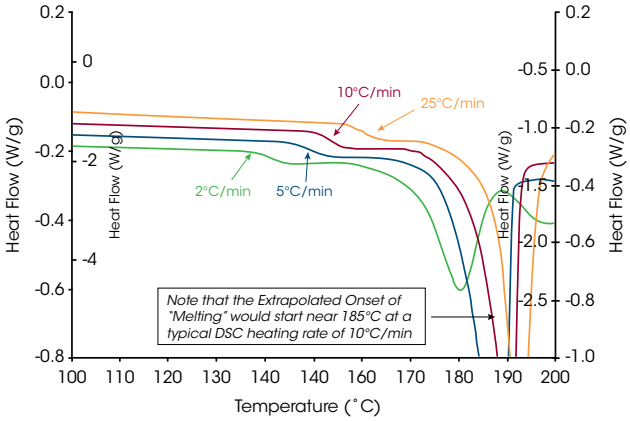

Figure 10: DSC data for Sigma cane sucrose (≥ 99.5% pure) at typical DSC heating rates of 2, 5, 10 and 25 °C/min shows how peak onset temperature increases with heating rate. There is no "specific melting point" and therefore the endothermic peaks are due to Apparent Melting.

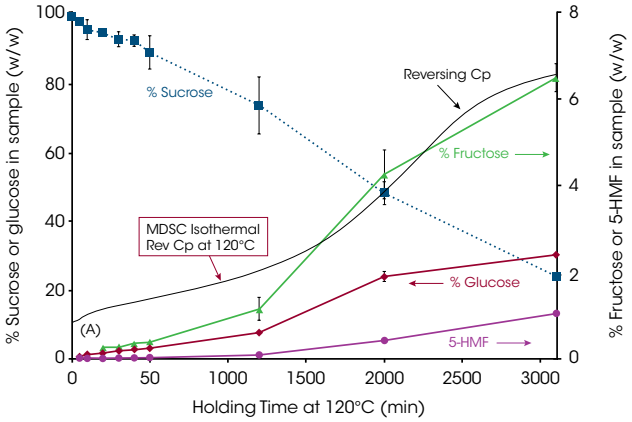

Figure 11: An overlay of HPLC analyses performed at specific times during an isothermal temperature of 120 °C and heat capacity from an MDSC experiment also at 120 °C confirms that crystalline structure is lost and decomposition products are created as much as 70 °C below the literature reported melting point of sucrose.

Importance of Distinguishing Between True and Apparent Melting

Some may think that it is not important to distinguish between True and Apparent Melting since crystalline structure is converted to amorphous structure in both cases. This is not a good assumption for the reasons below. These are the limitations imposed on the data from loss of crystallinity due to Apparent Melting, which is always the result of an underlying kinetic process.

1. Cannot Measure Accurate (Thermodynamic) Melting Point

Endothermic peaks due to Apparent Melting change with heating rate due to a kinetic process. The amount of change varies from material to material and is a function of the activation energy of the process. This can be seen in Figure 12 from a paper of Magon et al.5 where melting temperature is plotted against heating rate for both the small and large peaks seen in sucrose. The conclusion reached by Magon et al. in the paper is that the equilibrium melting point is 424.4°K (approx. 151°C) as compared to reported values as high as 190°C. This clearly demonstrates the problem of measuring the melting point of materials that undergo Apparent Melting.

2. Cannot Measure Accurate Heat of Fusion

Just as the melting point cannot be accurately measured with materials that undergo Apparent Melting, it is not possible to measure an accurate heat of fusion. In the event of Apparent Melting the heat contribution from the underlying kinetic process renders the measured enthalpy a temperature dependent variable which is not the case for a true melt transition. This is illustrated in Figure 13 from Magon et al.

3. DSC Purity Cannot Be Measured

DSC purity analysis requires thermodynamic melting in order to detect and quantify impurities. In addition, the purity measurement is typically done at a low heating rate, such as 1°C/min, to ensure thermal equilibrium throughout the sample. Apparent melting creates impurities because of the thermal decomposition process that is causing the loss in crystalline structure.

4. Accurate Glass Transition Temperatures Cannot be Obtained from Melt-quenched Materials that Undergo Apparent Melting

If loss of crystalline structure is caused by a chemical process, as happens with Apparent Melting, the chemistry of the cooled sample is different than the original crystalline material. The change in chemistry creates smaller molecules and typically results in a lower glass transition temperature than expected for an amorphous material that has not been partially decomposed.

5. Identification of Polymorphic Forms Can Not Be Based on Melting Point

Polymorphs have the same chemical structure, but different crystalline structure and different melting points, which may differ by only a few degrees. Materials that undergo Apparent Melting do not lose crystallinity at specific temperatures and therefore the data cannot be used to identify polymorphic forms.

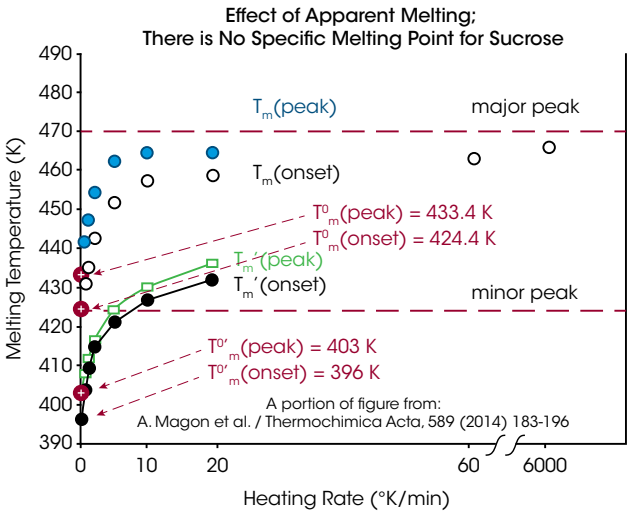

Figure 12: An accurate melting point cannot be obtained with materials that undergo Apparent Melting because the temperature of crystallinity loss changes with heating rate. Image rendered from reference 5.

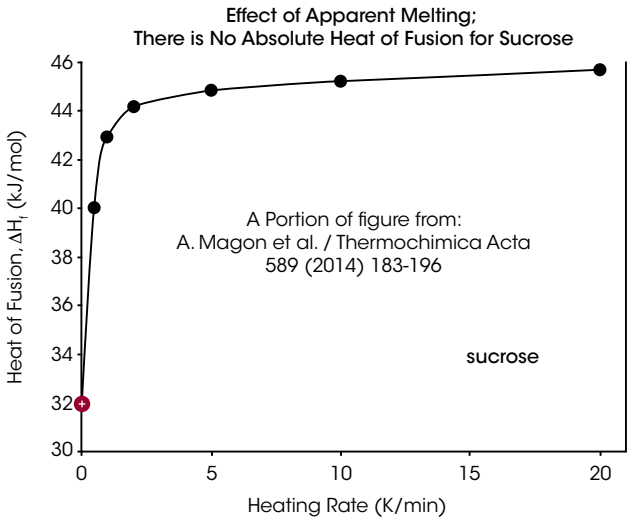

Figure 13: An accurate heat of fusion cannot be obtained with materials that lose crystalline structure due to Apparent Melting because the DSC peak area changes with heating rate. Image rendered from reference 5.

Conclusions

As illustrated with a range of materials, it is important to distinguish between True (thermodynamic) and Apparent (kinetic) Melting in order to obtain accurate and reliable results that can be correctly interpreted. It is very easy to make the determination by simply doing experiments at two heating rates (2 and 10 °C/min are recommended) on crystalline samples that have not been previously fully characterized. If the difference in onset temperature between the two rates is less than 1 to 2 °C then the material is showing thermodynamic melting behavior. If the difference is larger, then rates of 1 and 25 °C/min should be done to prove the presence of a kinetic process that is causing Apparent Melting.

The Wunderlich definition is very helpful because it contains a set of criteria that can be used for interpretation of DSC data. It is suggested that the terms True and Apparent Melting be used when reporting results either internally or in publications.

References

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2. Lee, J.W. et al; Investigation of Thermal Decomposition as the Kinetic Process That Causes the Loss of Crystalline Structure in Sucrose Using a Chemical Analysis Approach (Part II). J. Agric. Food. Chem. 2010. DOI: 10.1021/jf1042344

3. Lu, Y. et al. Impact of Sucrose Crystal Composition and Chemistry on its Thermal Behavior, Journal of Food Engineering 214: 193-208 (2017)

4. Wunderlich, B. Thermometry. In Thermal Analysis, 1st ed.; Academic Press: San Diego, CA, 1990; Chapter 3, pp 79-121.

5. A Magon et al.; Heat Capacity and transition behavior of sucrose by standard, fast scanning and temperature-modulated calorimetry, J. Agric. Food Chem. 2011, 59, 702–712 DOI:10.1021/jf104235d

Acknowledgement

This note was written by Leonard C. Thomas, DSC Solutions and Shelly J. Schmidt, Ph.D., Professor of Food Chemistry, University of Illinois at Urbana-Champaign

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- Yingshuang Lu, PhD.

Isothermal Microcalorimetry: Pharmaceutical Applications of Microcalorimetry

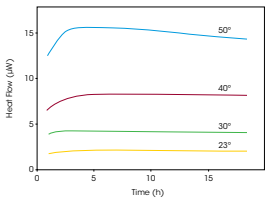
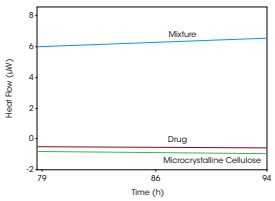
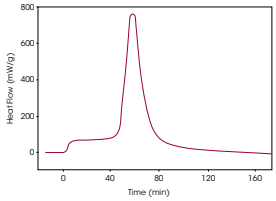
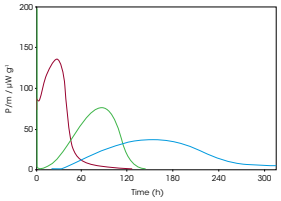
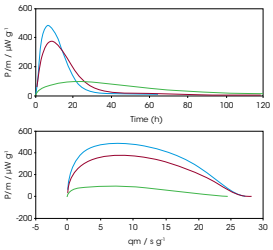
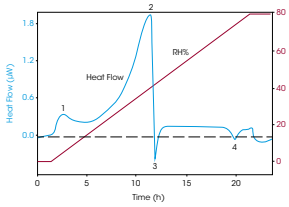
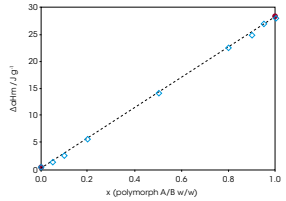
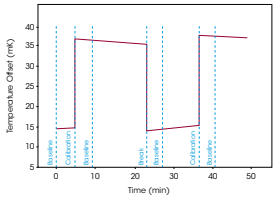
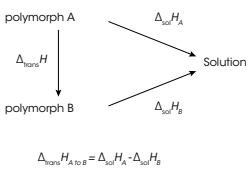
Introduction

This application note will review the microcalorimetric techniques that are most commonly used within pharmaceutical science: including stability and compatibility tests, determination of small amounts of amorphic content and characterizing polymorphism.

A microcalorimeter can quantify the amount and rate of heat release from chemical or physical processes associated with stability and shelf life of a drug or a formulation. Examples include processes caused by the interaction of one component with another or physical processes as crystallization or polymorphic transformations. The data can be both qualitative and quantitative and can be used to determine relevant characteristics of a sample.

Microcalorimetry has the advantage of being general, non-destructive and very sensitive. The high sensitivity of the technique makes it possible to obtain reliable stability data within hours or days and close to ambient storage conditions. It is general in the way it can detect both chemical and physical changes within the sample, both being critical for the performance of the pharmaceutical. The non-destructive nature of the technique gives the possibility to further analysis of the sample after completion of the calorimetric measurement.

TAM is a flexible, and sensitive microcalorimetry system with an exceptional long-term measuring stability. TAM is a modular system consisting of a precisely controlled thermostat that can be equipped with a wide range of calorimeters, sample handling system and accessories to be able to conduct the required tests described in this application note.

	Stability	Compatibility	Amorphicity	Polymorphism
Ampoule Calorimetry				
Perfusion Calorimetry		Effect of atmosphere Air/N_2 and/or RH		
Solution Calorimetry		Interactions in solution		

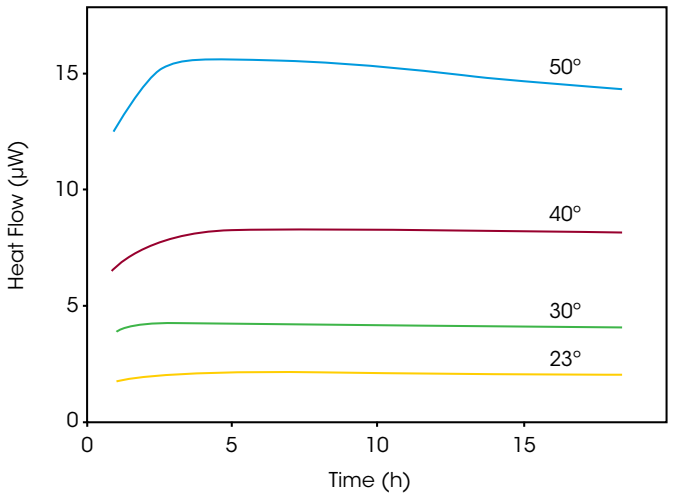
Stability

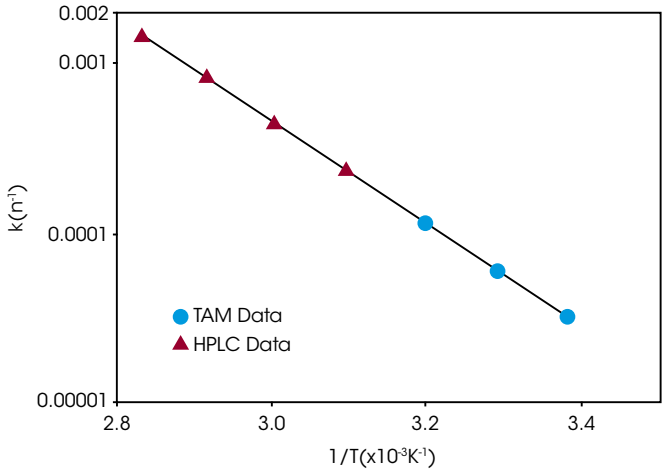
Isothermal microcalorimetry can detect both chemical and physical changes within a sample, it is being used to obtain reliable stability data within hours or days and under near ambient storage conditions.

Chemical degradation is conventionally studied by HPLC, which has the drawback of being relatively insensitive to small changes in concentration. To accelerate any degradation reactions taking place in the sample and shorten the analysis time, elevated temperatures are often used. The data generated when using such accelerated timelines typically require extrapolation to predict the stability at the temperature selected for storage.

The figure below shows the oxidation of dl-α-tocopherol at different temperatures (50 °C, 40 °C, 30 °C and 23 °C). As the temperature increases, the heat flow curves get larger in magnitude, i.e., the rate of reaction increases. The heat flow data was fitted for first order kinetics and the rate constant was plotted in an Arrhenius relationship together with HPLC data on the oxidation product. The TAM data (circles) and HPLC data (triangles) fall into the same linear Arrhenius relationship, indicating it is the same reaction being detected, although TAM is capable of detecting the reaction at much lower temperatures.

Thus, microcalorimetry is particularly useful for quantifying very slow reaction rates.

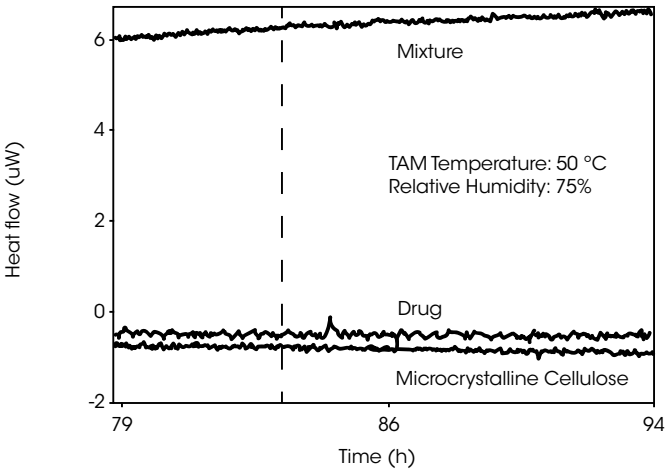




Compatability

Compatibility testing is a form of stability testing that evaluates the possible interaction between the constituents of a multi-component sample, e.g., an API with an excipient. Microcalorimetry has proven to be particularly useful for compatibility testing; in some cases, data is obtained after only a few hours. The difference between the measured response and the expected or non-interactive response from combining the responses of the individual components indicates incompatibility.

Screening for stability and compatibility can be performed as stress tests with increased temperature (e.g., 40°C) and/or relative humidity (e.g., 50 or 75 %). The tests can be performed both qualitatively (Yes/No) and quantitatively (understanding the kinetics of the process) as it is possible to kinetically model the heat flow data. These tests can be performed on the API alone, in combinations with excipients – compatibility. It can also be performed on the formulated product as well as with packaging materials.



Amorphicity

The degree of crystallinity is a measure of crystal perfection. The crystallinity of all real crystals lies somewhere between that of a perfect crystal and a totally amorphous material corresponding to zero crystallinity. Crystals with a relatively small amount of imperfections are said to possess high crystallinity while crystals with high amounts of imperfections are said to have low crystallinity.

A pharmaceutical can be produced intentionally in an amorphous form for increased bioavailability. Stability needs to be demonstrated and controlled as discussed in the previous section. Small amounts of amorphous content in a supposedly crystalline material can be formed by processing e.g., by milling or compression and it is critical to detect and to be able to quantify.

Processed induced amorphous regions can have a great impact even if the percentage is small because these regions are typically located on the particle surface. The presence of imperfections (amorphicity) in a crystal affect properties as solubility, dissolution rate and surface energy and even small amounts need to be detected and sometimes quantified.

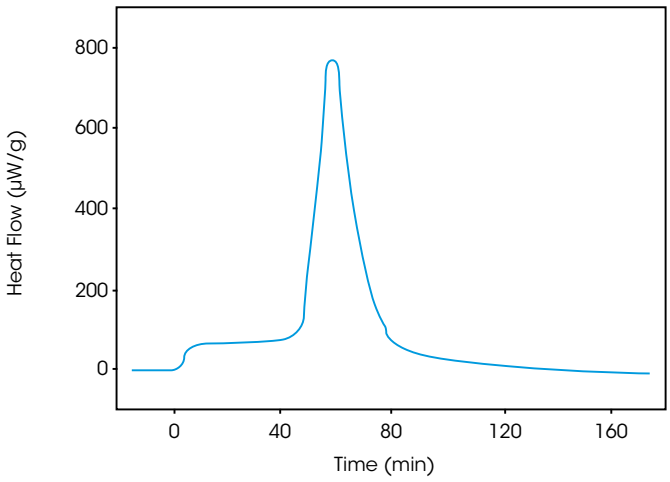
Imperfections in a crystal increase the energy (enthalpy) of the crystal. This enthalpy increase compared to a reference crystal of high crystallinity can be measured by calorimetry by two methodologies that are described in the USP 696 Characterization of crystalline solids by microcalorimetry and solution calorimetry:

- Heat of crystallization – induced by humidity (or solvent vapor pressure) by lowering the glass transition.
- Heat of solution by measuring the dissolution enthalpy.

Heat of crystallization with the micro-hygrostat method

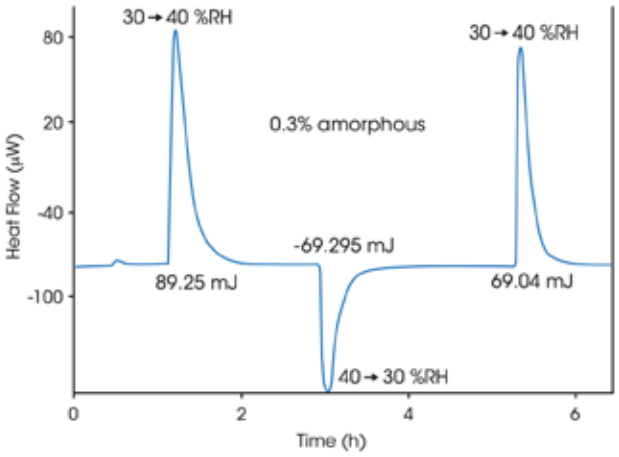
A dry sample is inserted into a closed disposable glass ampoule together with a small tube partly filled with pure solvent or a saturated salt solution to give a certain relative humidity (i.e., vapor activity). The sample preparation takes place on the bench where after the ampoule assembly is thermally equilibrated and introduced into the measuring position of the calorimeter. Vapor from the liquid in the tube will evaporate and sorbs preferentially on the accessible amorphous regions of the particles. This will lower the glass transition temperature or increase the plasticity of the amorphous regions and a recrystallisation of the vapor accessible amorphous regions can be initiated provided that the vapor activity and the calorimetric temperature is high enough.

A typical recrystallisation result consists of an initial sorption period where after a sharp peak due to the crystallization process is obtained. The integrated value is directly related to the amount of amorphous material that has crystallized. For quantification the specific heat of crystallization must be known from a separate experiment with a known amount of amorphous material, e.g., a sample representing 100% amorphous material.



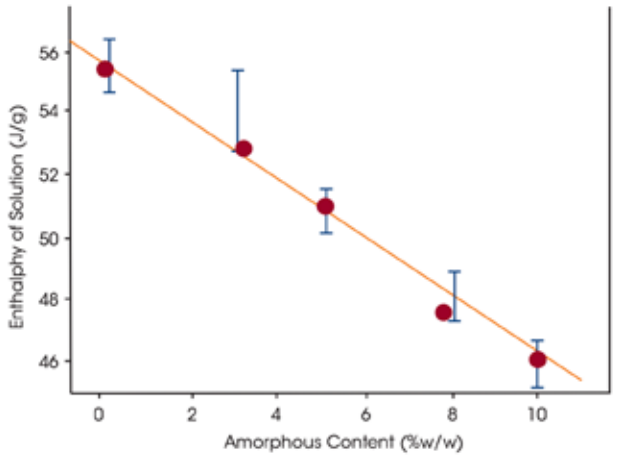
Heat of crystallization with the controlled relative humidity perfusion (cRHp) method

This technique can be very sensitive and fractions of a percentage of amorphous phases in crystalline samples can be detected. The sample is contained in a flow through ampoule where the vapor activity (e.g., RH) can be controlled and changed. Sample is equilibrated at a temperature and RH that do not induce crystallization. The RH is subsequently changed up and down in three equal and well-defined steps: The first step will involve absorption and crystallization, the second desorption and the third only adsorption. The difference between the integrated heat of the first and third peak is attributed to crystallization.



Heat of dissolution

By dissolving the crystals in a suitable solvent in a Solution Calorimeter the crystal structure breaks up and the heat of dissolution is measured. The heat of dissolution is strongly related to the enthalpic content of the crystals. A higher enthalpic content relative to that of a perfect crystal correspond to a lower degree of crystallinity. To attain a quantitative measure of crystallinity the heat of solution of a reference material corresponding to a highly crystalline reference material and a material corresponding to 100% amorphicity must be determined in separate measurements.



Technique	Sensitivity % amorphous content	Time for analysis	Sample amount needed	Throughput	Method setup and evaluation	Other
TAM – Microhygrost	Around 1%	1-5 hours	10-500 mg	1-48 simultaneous measurements/maximum samples per day: 96	• Easy to adapt method to substance and not limited to water soluble substances • Calibration is important	• Determines surface amorphicity • Suitable in production control • USP method
TAM – cRHp method	Down to 0.1%	5-20 hours	10-50 mg	1-4 simultaneous measurements/maximum samples per day: 2 (8)	• Easy to adapt method to substance and not limited to water soluble substances • Calibration is important	• Determines surface amorphicity • More for R&D
TAM – SolCal method	Down to 1% depending on substance	2 hours	50-500 mg	1-4 simultaneous measurements/maximum samples per day: 3 (12)	• Easy to adapt method to substance and not limited to water soluble substances • Calibration is important	• Determines total amoutn of amorphicity • More for R&D • USP method

Isothermal microcalorimetry has several benefits compared to other methods to assess amorphicity and these include sensitivity, versatility and sample throughput. A summary of the IMC methods can be seen in the table above:

Polymorphism

Polymorphism refers to the ability of a substance to crystallize into different crystal forms. Since the physical and chemical properties of a substance are closely related to its crystal structure, polymorphism is of great importance to activities related to solid-state materials.

The study of polymorphism and pseudo-polymorphism is a critical part of the drug development process because pharmaceutical properties can be impacted depending on which forms exist in the final product. For example, since polymorphs are in different energy states (including metastable forms), solubility can be affected, which in turn can impact bioavailability. Interconversion from a more soluble to a less soluble form may occur during manufacture of the pure drug, during formulation processes, and after long-term storage, thereby changing the pharmaceutically active properties of the final product.

With TAM it is possible to:

- Determine relative stability of polymorphic pairs
- Get transition temperatures (if solubility data exists)
- Answer the question is my powder in a meta-stable state?
- Process monitor: which factors can kinetically stabilize / destabilize the system

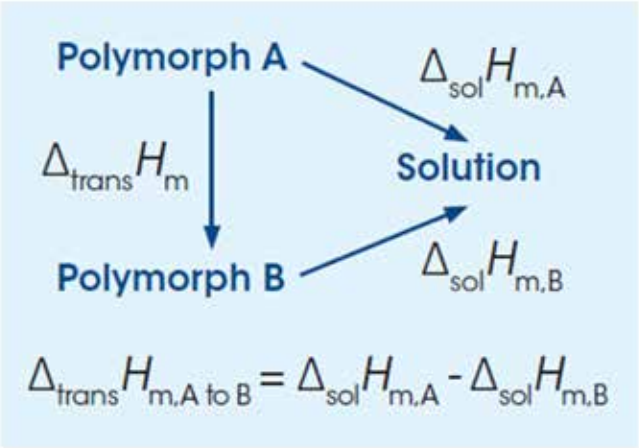
The thermodynamics and kinetics of transfer of one polymorphic form to another of lower energy is very important to quantify. For instance, the relative stability of two forms can be assessed by solution calorimetry. A "yes or no" answer as to whether a given form of a substance that might be meta-stable can be transformed into another form of lower energy.

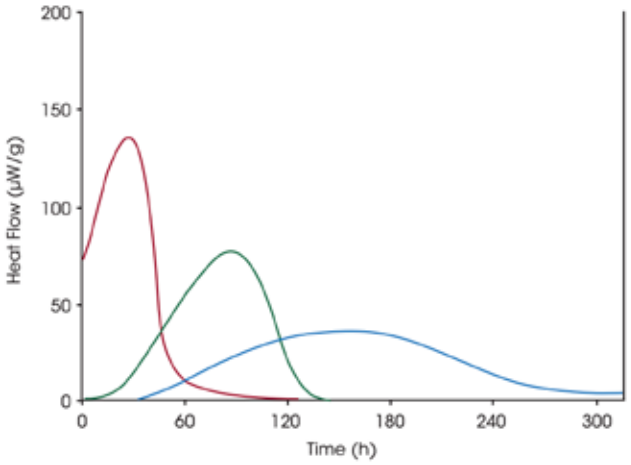
Calculations of the enthalpy of transition between two polymorphs from the heats of solution. By measuring the heat of solution of two different polymorphic forms, it is possible to calculate the transformation enthalpy (ΔtransH) for the transition of form A to form B by taking the difference in the heat of solution between the two forms (ΔsolHA and ΔsolHB). The direction of the transformation (A to B or B to A) is an indication of the relative stability of the pair and is more likely to occur if the transformation enthalpy is negative (exothermic). In addition, if the solubility of the two forms is known the thermodynamic transition temperature between the two forms can be obtained for enantiotropic (reversible) polymorphic pairs.

Ampoule calorimetry can be used to study the kinetics of transition of one form into another in terms of the heat flow as a function of time. Transformation of a meta-stable form into the thermodynamically more stable form can occur either directly in the solid state or via a solvent phase in slurry (solvent mediated polymorphic transition).

Direct transformations in the solid state are in many cases very slow or too insignificant to observe in a calorimetric experiment. The slurry method can provide a "yes or no" answer as to whether the studied polymorphic form is in a meta-stable state.

The solvent mediated process increases the rate of the process and works by adding a small amount of solvent to the sample. The least stable polymorph will be dissolved into a saturated solution and will crystallize into the more stable form. This reaction will continue until the sample has been completely transformed. The plot shows the polymorphic transformation for different lots of a drug that have been generated with different processes, blue: lot A, green: lot B, red: micronized lot A. The calculated enthalpies are the same, but the reaction rates are different due to differences in the stability of the samples.





Summary

Isothermal microcalorimetry and TAM is an acknowledged tool for some specific applications in the pharmaceutical industry. These applications are particularly relevant to pre-formulation studies, formulation development and analytical development. In these environments, techniques based on TAM are used to assess chemical stability of drugs, stability of polymorphs, drug-excipient compatibility and degree of crystallinity.

TAM offers non-destructive real-time and continuous measurements of chemical and physical processes at high sensitivity and with possibility of high sample throughput.

Acknowledgement

This application note is a summary of several TA Instruments applications notes and was written by Malin Suurkuusk at TA Instruments.

TA Instruments has been long recognized as an innovator and leader in modulated thermal analysis.

Optimization of the Freeze Drying Process Using Modulated Differential Scanning Calorimetry®

Introduction

Freeze-drying, or lyophilization as it is often called, has become a standard process in the pharmaceutical industry for the manufacture of biologically active substances[1, 2, 3]. However, it is not without limitations due to its high cost in capital and energy, long processing time, and difficulty in selecting parameters of time, temperature, pressure (vacuum) and component concentration. All of these parameters must be optimized in order to achieve full recovery of activity and complete reconstitution of the often-labile drug, acceptable appearance of the freeze-dried cake and good storage stability[4].

The process of freeze-drying relies on the vapor pressure of ice. Even at temperatures as low as -50 °C, the ice sublimes and leaves a very porous, low-density cake containing the stabilized drug. Since the sublimation rate (drying rate) is very temperature-dependent, approximately doubling for a 5 °C increase[5], use of the highest possible temperature during primary drying provides maximum drying efficiency and lowest process cost. The limitations of the process arise in the selection of the optimum drying temperature that can vary with time in the process as well as with the other parameters listed above.

In order to select the optimum drying temperature, it is necessary to understand the physical characteristics of the components used in the formulation that is to be freeze-dried. In decreasing order of mass, these are typically water, bulking agents, buffers or stabilizers and finally the drug itself. The bulking agent, which can be either crystalline or amorphous, and its interaction with the unfrozen water and ice in the frozen solution, define the physical structure which is essential to successful freeze-drying. This structure manifests itself in the form of transitions that occur at specific temperatures. Physical properties of the bulking agent such as modulus or viscosity can change by orders of magnitude depending on whether the process temperature is a few degrees above or below the transition temperature. Therefore, knowledge of this structure and the temperature where it changes is required for successful drying.

For many materials, it is relatively easy to measure crystalline or amorphous structure and to determine transition temperatures with the technique of Differential Scanning Calorimetry (DSC). However, DSC has been used with only modest success on frozen solutions used for freeze-drying because multiple transitions can occur at the same temperature, and DSC can only measure the sum of them. In this paper, we will illustrate how the technique of Modulated DSC® can more accurately and precisely measure important structure and the temperature where changes occur.

Materials and Instrumentation

Samples of various concentrations were prepared from analytical-grade sucrose and HPLC-grade distilled water. They were contained in hermetically sealed pans to measure structure and in an inverted hermetic pan lid for measuring structural changes during the early stages of primary drying. All samples were run on a TA Instruments DSC capable of Modulated DSC® experiments (e.g., DSC 250) equipped with a Refrigerated Cooling System (RCS) and purged with dry helium gas.

Test Method: Modulated DSC® (MDSC®)

The traditional technique of DSC uses linear temperature change to measure the sum of all endothermic or exothermic heat flows within the sample and the environment in which it is contained. In contrast, MDSC® uses both an underlying linear temperature change, and a small sinusoidal temperature modulation (Figure 1).

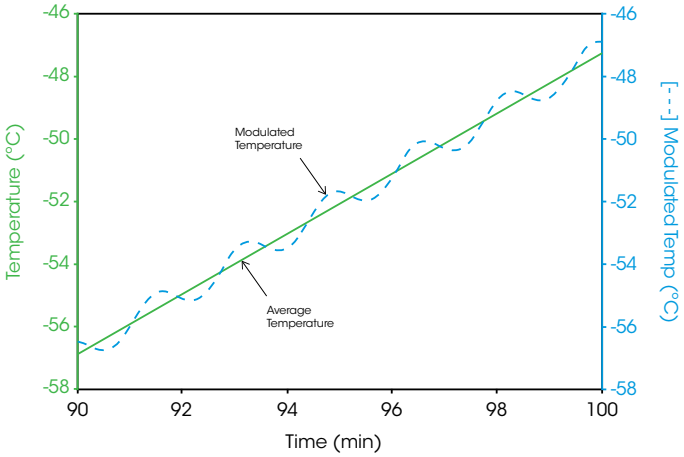


Figure 1. Overlay of MDSC temperature modulation and average linear ramp

The sinusoidal modulation gives MDSC® the ability to measure the sample's heat capacity at the same time that it is measuring the Total heat flow, which is equivalent to the measurement made by DSC. By subtracting the measured heat capacity component from the Total signal, the kinetic component can also be obtained.

Figure 2 illustrates the unique ability of MDSC® to analyze the complex transitions observed in frozen solutions. The sample is a 40% sucrose/water solution, which was quench-cooled to a starting temperature of -70 °C. The heat capacity signal shows a glass transition between -50 and -35 °C, while a crystallization peak is seen in the kinetic component between -45 and -30 °C. The Total signal shows only the sum of these two events and illustrates why DSC measurements on these types of materials are often difficult to interpret. Crystallization of unfrozen water at the glass transition temperature of these materials is common as seen in Figure 3, which shows the maximum rate of ice formation occurring between -48 and -35 °C.

Results and Discussion

As previously stated, "an understanding of the physical states of solutes after freezing is important since this determines not only the processing characteristics of the formulation but also the characteristics of the final product, such as reconstitution, appearance, and stability." [6] In these studies, the solute was amorphous sucrose at concentrations between 2.5 and 10 weight percent, which is a typical range for freeze-drying formulations.

The physical state or structure of an amorphous solute can be characterized by an analysis of its glass transition. The temperature at which the glass transition occurs in the sample, often abbreviated as Tg, is critical because the physical properties of the solute can differ by several orders of magnitude over a temperature range of just 5 - 10 °C.

Figure 4 shows the structure (heat capacity) of a 10% sucrose solution as it is cooled and heated at 1 °C/min over the temperature range of the glass transition. By taking the time-based derivative of the heat capacity signal, step changes in heat capacity can be seen as peaks which makes it easier to determine the temperature mid-point of the transition. In this data, there are actually two step changes in heat capacity due to the glass transition of the sucrose. They are centered at approximately -44 and -34 °C for both the cooling and heating data. The reasons for the two steps go beyond the purpose of this paper and will not be discussed.

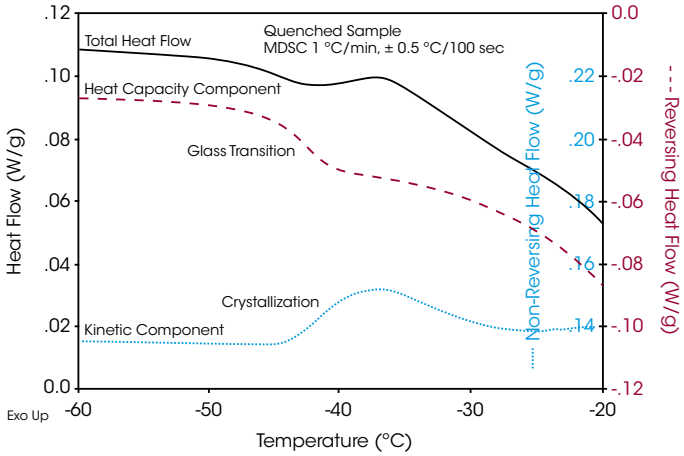


Figure 2. MDSC data for 40% sucrose/water solution

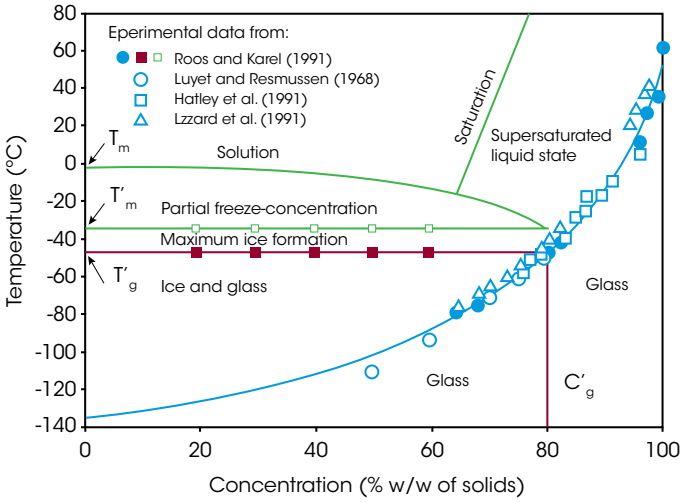


Figure 3. Phase diagram of sucrose solutions

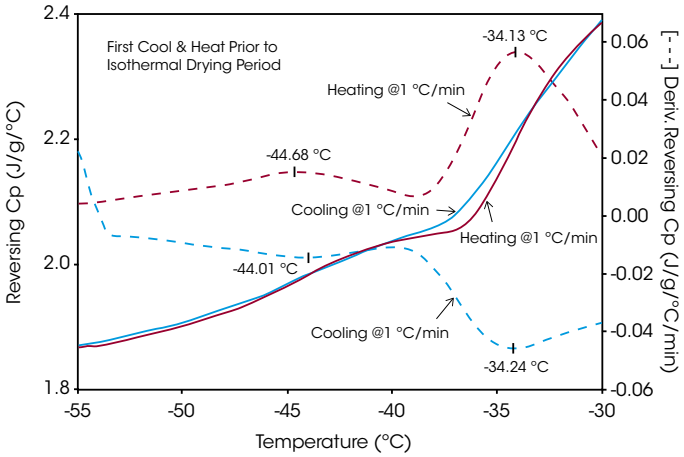


Figure 4. MDSC heat capacity data for a 10% sucrose solution.

The results in Figure 4 show the structure of the sucrose immediately after the solution is frozen. Figure 5 shows this same structure, as measured during just the heating experiment and compares it to the structure obtained after approximately 18 hours at -40 °C, which would be typical freeze-drying temperature for this formulation. Notice that the structure has changed and that the low-temperature step has increased by 4 °C from -44.6 to -40.3 °C, which is the temperature at which the sample was held. As will be discussed, the fact that the low-temperature transition increased to the isothermal temperature of -40 °C is no coincidence.

The results for the four concentrations between 2.5 and 10 weight percent are summarized in Table 1. They show that the low-temperature transition increased to -40 °C for all concentrations while the high-temperature step near -34 °C was unaffected. No results for the low-temperature transition in the 2.5% concentration sample are shown because the signal was too weak to be reliably measured.

The cause of this change in structure is believed to be due to the crystallization of the unfrozen water that is trapped within the sucrose phase. Figures 2 and 3 show that crystallization does occur at the temperature of -40 °C. Since unfrozen water acts as a plasticizer, which tends to broaden a glass transition and lower its temperature, the conversion of unfrozen water to ice crystals would be expected to cause an increase in the glass transition temperature.

Another piece of data that supports the water crystallization theory is contained in the heat capacity change which occurs during the 18-hour isothermal period at -40 °C. This data is shown in Figure 6, which shows the decrease in heat capacity with time at -40 °C. Notice that the heat capacity drops rapidly during the first five to six hours and then goes through a small but reproducible step at seven hours into the experiment. The cause of this step is believed to be due to the fact that the low-temperature transition, which starts at -44 °C, advances in temperature until it reaches the isothermal temperature. At that point in time, the mobility of the molecule decreases, which causes the decrease in heat capacity. After that point in time, changes in structure occur very slowly, and any further change in heat capacity is due to decreasing mass as sublimation of the ice crystals continues.

Table 2 summarizes the results on the rate of heat capacity decrease (drying rate) for the four concentrations as measured during the last ten hours of the isothermal segment at -40 °C. Notice that the sample containing only 2.5% solute dries 6.6 times faster than the sample with 10% solute. In addition, the rate of drying does not appear to be linear with concentration.

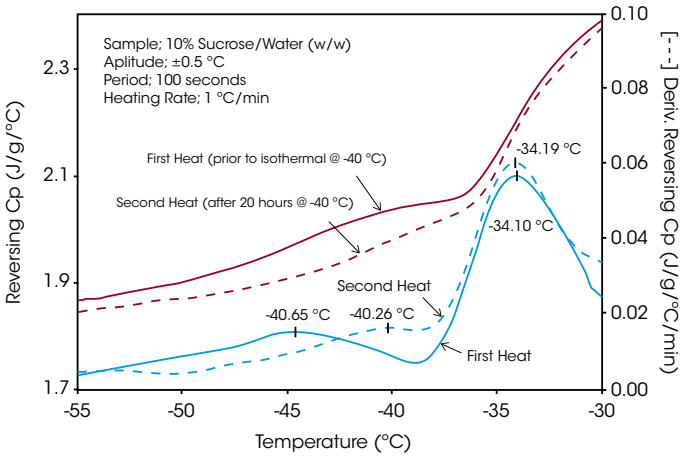


Figure 5. Effect of drying at -40°C on the glass transition.

Table 1

Structure of Glass Transition after approximately 18 hours at -40°C				
During the 18 hours at -40 °C, the structure of the amorphous sucrose changes. The first step in heat capacity increase to a temperature of approximately -40 °C.				
Concentrations	**Step 1-Midpoint (°C)**		**Step 1-Midpoint (°C)**	
	Pre Dry	**After Dry**	**Pre Dry**	**After Dry**
10%	-44.6	-40.3	-34.1	-34.2
7.5%	-43.2	-40.2	-34.3	-34.2
5.0%	-43.2	-40.4	-34.9	-35.2
2.5%	—	—	-34.9	-34.9

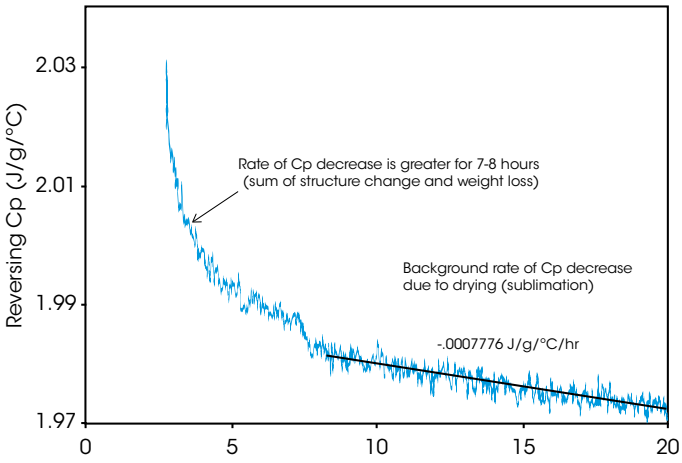


Figure 6. Isothermal tracking of the Cp of a 10% sucrose solution.

Table 2

Structure of the glass transition during drying and ability of MDSC to measure relative drying rates		
Once structural changes stop or reach an insignificant rate, the decrease in heat capacity with time is a relative measure of drying rate.		
Concentrations	**Rate of Cp Decrease J/g °C/hour**	**Drying Rate Relative to 10% Concentration**
10%	7.8×10^{-4}	1
7.5%	11.1	1.4
5.0%	41.6	5.4
2.5%	50.6	6.6

Conclusions

Modulated DSC® provides the ability to separate the complex transitions occurring in frozen solutions into their heat capacity and kinetic components. This results in many benefits for the researcher or process engineer trying to optimize formulations or process parameters. These include:

1. The accurate and precise analysis of the physical state or structure of the frozen solution. This permits a more reliable selection of process temperatures.

2. The ability to measure changes in structure with temperature and time, which should permit temperatures to be optimized as freeze-drying proceeds, thus reducing the time required.

3. The ability to measure the effect of additives and concentrations on drying rates. This should reduce the overall time required to develop reliable and cost-effective parameters for new or modified formulations

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Characterization of Water Adsorption and Absorption in Pharmaceuticals

Introduction

Dynamic vapor sorption (DVS) analysis can characterize material response to humidity changes. Typical responses are surface adsorption/desorption, bulk absorption, hydration / dehydration, and deliquescence. In surface adsorption, water can be weakly held to the surface by van der Waals forces (physisorption) or more strongly held (chemisorption). Physisorption is reversible by decreasing humidity or increasing temperature. Chemisorption is generally considered as irreversible. In bulk absorption, water is attracted deep into the internal structure of the material. Bulk absorption is reversible, but the kinetics are slower than for surface adsorption.

Experimental

Adsorption and absorption are evaluated by increasing humidity stepwise over a broad range, then decreasing it to the starting level and finally increasing it again to higher levels. The profiles are generated at constant temperature. The experiments were performed on a Sorption Analyzer from TA Instruments (e.g., Discovery SA).

Results and Discussion

Surface adsorption is characterized by increasing / decreasing humidity curves, which coincide (i.e., overlap), as well as by small total weight changes over a broad humidity range. Crystalline materials generally exhibit this type of profile.

Figure 1 (carbamazepine) illustrates a typical surface adsorption profile. Bulk absorption profiles are shown in Figures 2 and 3. Choline (Figure 2) exhibits overlapping adsorption/desorption curves similar to that observed for surface adsorption. However, since the total water uptake is too large (150 % from 0-90 % RH) to be a surface phenomenon, bulk absorption into the material is occurring. As there is no evidence that the structure of choline changes as water enters and exits the material's internal structure, that structure must be very open

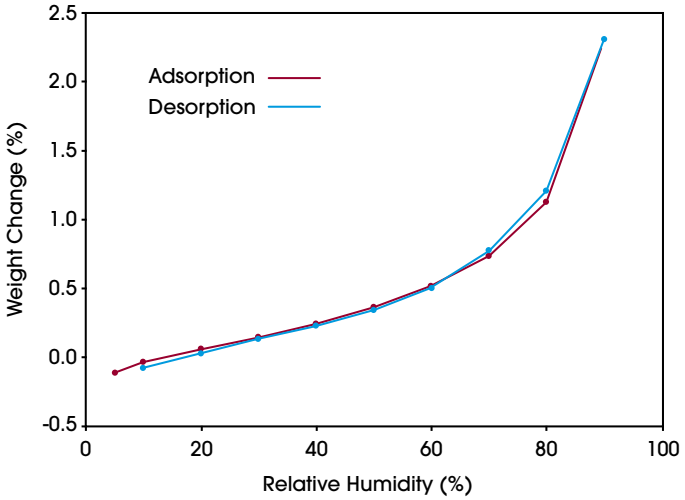

Figure 1 Carbamazepine Surface Adsorptio

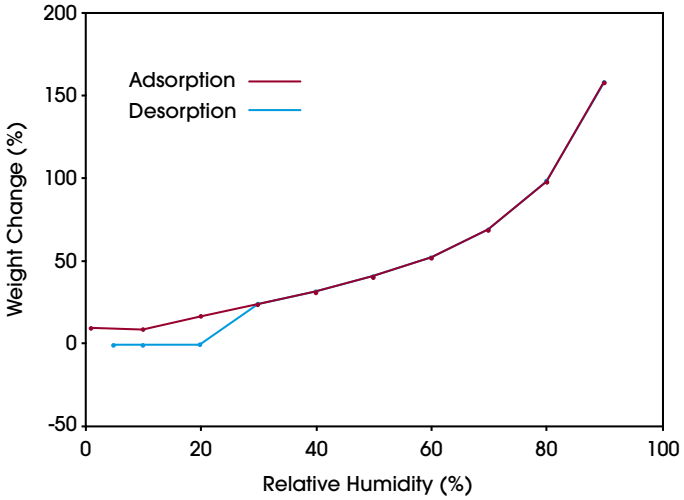

Figure 2. Choline Bulk Absorption

Partially amorphous, organic materials like starch (Figure 3) also show large water uptake indicative of bulk absorption. However, there is a slight but constant hysteresis (separation) between the water uptake and release curves, which probably reflects a slower diffusion of water back out of the starch's internal structure, which swells during water uptake.

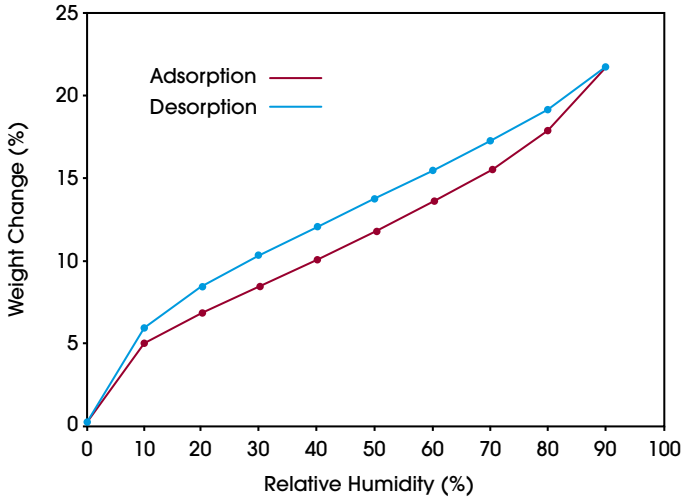

Figure 3. Starch Bulk Absorption

Materials, whose structures contain mesopores (internal cavities of 2-50 nanometers in diameter), show a rapid uptake of water (absorption) at higher humidities (Figure 4). The absorbed water results in capillary condensation, and the subsequent water release on decreasing humidity occurs more slowly resulting in hysteresis. The release occurs, however, over a narrow humidity range related to pore size.

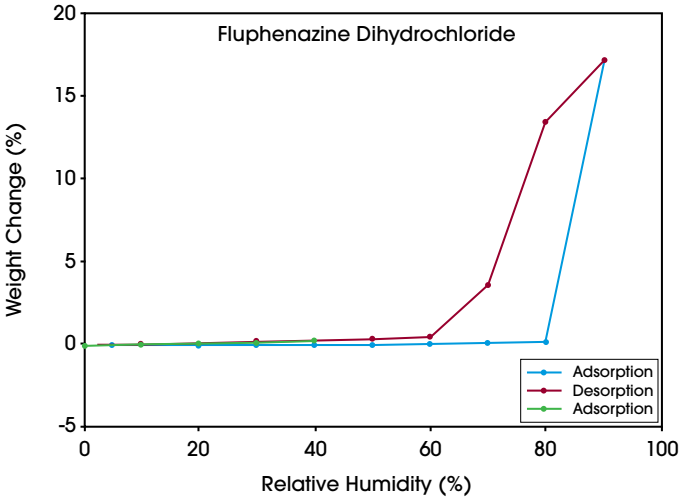

Figure 4. Absorption Into Mesopores

The previous examples all have reversible profiles indicating that the materials' structures are unchanged during water adsorption/desorption. Figure 5, on the other hand, shows a material whose morphology does change as bulk water absorption occurs. The slower release of absorbed water with decreasing humidity, and the associated significant hysteresis between the uptake and release curves over the entire humidity range, indicate the material has changed. Because there are no "step changes" in weight, the structural change is not the result of hydrate formation. The second increasing humidity curve follows the decreasing humidity profile as opposed to the original increasing humidity curve. Hence, the water-induced structural change is permanent. In addition, since the subsequent increasing and decreasing curves show no hysteresis, the new structure must be a fairly open one.

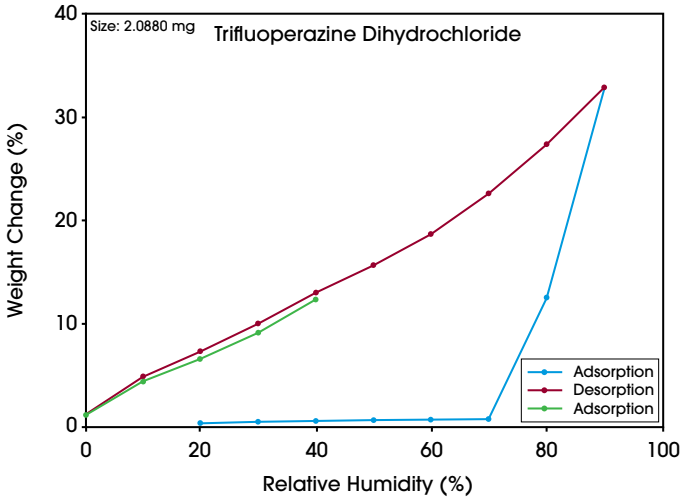

Figure 5. Bulk Absorption Induced Morphology Change

Summary

The shape and amount of water adsorbed during a DVS adsorption/desorption profile provides insight into a material's morphology. That information is valuable in projecting that material's suitability for specific end-use applications.

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