



Characterisation of processing induced changes in morphology by Solution Calorimetry

Introduction

Solution calorimetry measures the heat of solution of a solid dissolving into a solvent. Hogan & Buckton (2000) have shown there is a measurable difference in the enthalpies of solution between the amorphous and crystalline form of a material. Typically, the dissolution of a crystalline material is an endothermic process and exothermic for an amorphous material. Such an ability to differentiate between the amorphous and crystalline form of a material is important to formulators of solid dosage forms for drug delivery.

In all of these forms the assessment of the order or possible disorder associated with the solid material is vital for stability and compatibility testing. Generally the presence of amorphous material influences the physical integrity and usually the kinetics of degradation. Often, only a small amount of amorphous material can produce severe effects on the stability of a particular formulation.

Many crystalline materials require a reduction in particle size to improve process parameters, for

example micronisation to increase the respirable fraction for a formulation designed for inhalation delivery. In addition milling is often used to improve the compression properties of a crystalline powder required for tablet manufacture. However, the various methods used for reducing particle size all include a mechanical force or particle – particle attrition in order to fracture the crystals. The common techniques, e.g. micronisation by air-jet milling, hammer milling and grinding, have a high energy input that can often lead to disruption within the crystal lattice on the surface of the powder. These disordered regions are domains of amorphous material that can lead to a higher rate of water sorption, chemical degradation, and the possibility of agglomeration of the powder increasing the particle size. Thus, it is imperative to have methodologies available for the characterisation of disorder.

This application note outlines the use of solution calorimetry to investigate the effect of micronisation on two common excipients, lactose and sucrose. Hogan & Buckton (2000) describe the development of a calibration curve for the

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Fields of application

Material Sciences
Pharmaceuticals
Amphiphicity
Solution Calorimetry

Instrument configuration

2277 TAM
2225 100ml Precision Solution Calorimeter
2225-150 1ml Crushing Ampoules with Stoppers

References

1. Hogan, S. E., Buckton G., *Int. J. Pharm.* (2000) 207, 57-64
2. Sunner, S., "Basic Principles of Combustion Calorimetry" *Experimental Chemical Thermodynamics, Volume 1 Combustion Calorimetry*, Pergamon Oxford, (1971), Chapt. 2
3. *Instruction Manual 1.2, Precision Solution Calorimeter*, (1996) Thermometric AB Sweden
4. Gao, D., Rytting, J. H., *Int. J. Pharm.* (1997) 151, 183-192
5. Craig, D. Q. M., Barsnes, M., Royall, P. G., Kett, V. L., *Pharm. Res.* (2000) 17, 696-700
6. Royall, P. G., Craig, D. Q. M., Doherty, C., *Int. J. Pharm.* (1999) 192, 39-46

quantification of amorphous content. This study supports their work by illustrating the ability of solution calorimetry to characterise materials that have been processed by a selection of techniques commonly used in the pharmaceutical industry.

Experimental

A Thermometric 2225 Precision Solution Calorimeter, (Thermometric AB Sweden), was used to measure the enthalpies of solution. The solution calorimeter was thermostated in a Heto precision water bath. Between 50 and 200 mg of sample were placed in glass crushing ampoules. The ampoules were double sealed with beeswax using the method previously described¹ and each sample was run in triplicate. All the experiments were performed using 100 ml of de-ionised water. The stirrer within the calorimeter was set at 500 rpm.

Both samples of lactose and sucrose were micronised in a Fryma air jet mill. After passage through the air jet mill the samples were stored in a desiccator over silica gel at room temperature. The sample of lactose was divided immediately after micronisation and a portion was passed through the air-jet mill again. This was repeated for a further pass, producing a sample that had undergone three passes through the mill. A portion of the third pass lactose was dried at 50°C in a vacuum oven for 24 hours. Spray dried lactose was produced using a Niro Mobile Minor 2000 and a 20% aqueous feed solution. After spray drying, the sample was stored over silica gel at room temperature.

Results & Discussion

A typical response from the SolCal is shown in Figure 1. The calorimeter operates under semi-adiabatic conditions, so the initial temperature was offset, typically by 150 mK, from the air bath temperature of 25°C, (298.15K). The baseline sections in figure 1 were used to check that the observed temperature increase was conforming to an exponential decay. Before and after the ampoule was broken, the calorimeter was calibrated electrically. From these calibrations and the baseline sections, SolCal software determines an accurate value for the enthalpy of solution when the sample ampoule is broken into the 100mls of water contained in the calorimeter vessel, (marked Break in figure 1). The SolCal software uses well-known heat balance equations² to determine the change in enthalpy of the process being observed from the change in offset temperature as a function of time. A more in depth description of the operation of SolCal and the heat balance equations used by SolCal software can be found in the manufacturers manual³.

The response from a sample of α -lactose monohydrate is shown in figure 1. After the break, where the glass ampoule was broken and the lactose dispersed within the 100mls of water, the offset temperature falls rapidly. This response is typical of the endothermic dissolution of crystalline materials. The observed value for the enthalpy of solution was 55.8 ± 0.5 J/g. This is within the experimental error of the literature value for 100% crystalline α -lactose monohydrate¹. This shows that the sample of lactose used had no detectable level of amorphous content, and can be considered to be over 99% crystalline.

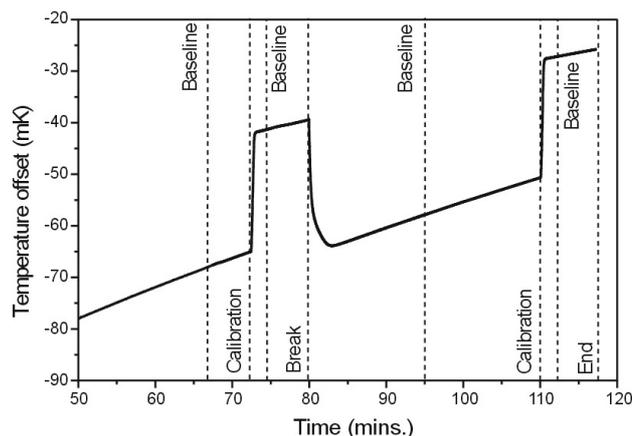


Figure 1. A typical example of the response from the SolCal, in this example, as received α -lactose monohydrate.

The enthalpies of solution for all the samples of lactose and sucrose are summarised in figure 2. β -Lactose, the other crystalline modification of lactose, had a much lower enthalpy of solution, but it was still endothermic. The significant difference between the α and β forms indicates that SolCal is potentially useful for the characterisation and identification of different polymorphs. Indeed, it should be possible to detect the relative amounts of each modification in mixtures of polymorphs by solution calorimetry.

Two samples of spray dried lactose are shown in figure 2. The first marked with a single asterisk is a previously published value for 100% amorphous spray dried lactose¹. The sample prepared in this study was stored over silica gel whereas the literature value was dried in a vacuum oven at 50°C. A previous study with spray dried lactose indicates that the amorphous material readily absorbs water which increases the enthalpy of solution¹. Therefore, as the sample in this study was not dried it is reasonable to assume a similar explanation. The significance of this

result is that the enthalpy of solution for amorphous materials is sensitive to water content of the sample.

The three samples of micronised α -lactose monohydrate all show a reduction in their enthalpy of solution. This can be attributed to the generation of small amounts of amorphous material within the micronised sample. DSC experiments, data not shown, indicate that no β -lactose was formed and only traces of amorphous material could be detected. DSC is useful for the qualitative detection of amorphous material but lacks the sensitivity for the quantification of small amounts of amorphous content. Vacuum drying reduced the enthalpy of solution for the partially amorphous lactose that underwent three passes through the air-jet mill. This is similar to the response from the totally amorphous lactose, whereby drying in a vacuum oven reduces the enthalpy of solution. The water absorbed by the amorphous domains present in the micronised powder could have originated from two sources. Either the hydrated water, released when the structure of the crystalline material was destroyed by the attrition and fracture of particles in the formation of the amorphous fraction, or from the background humidity present in the lab

when the sample was collected at the bottom of the mill.

The enthalpy of solution for the dried micronised material was assumed to reflect the true contribution from the main crystalline fraction and the contaminating amorphous fraction. Using this value on an extrapolation of Hogan & Buckton's calibration curve¹ indicated that three passes through the air-mill produced a $14.5 \pm 0.5\%$ w/w amorphous contamination of the crystalline powder.

The amorphous and crystalline forms of sucrose showed a similar exothermic and endothermic difference with respect to their enthalpies of solution when compared to lactose. The enthalpy of solution for amorphous sucrose shown in figure 2 marked by two asterisks is a previously published value⁴, and the sample was prepared by a combination of quench cooling and freeze drying, and was subsequently vacuum dried. The crystalline sucrose used in this study gave an enthalpy of solution within in the experimental error of the literature value⁴. The micronised and as received material gave identical values for their enthalpies of solution within the experimental error. Both samples contained the same

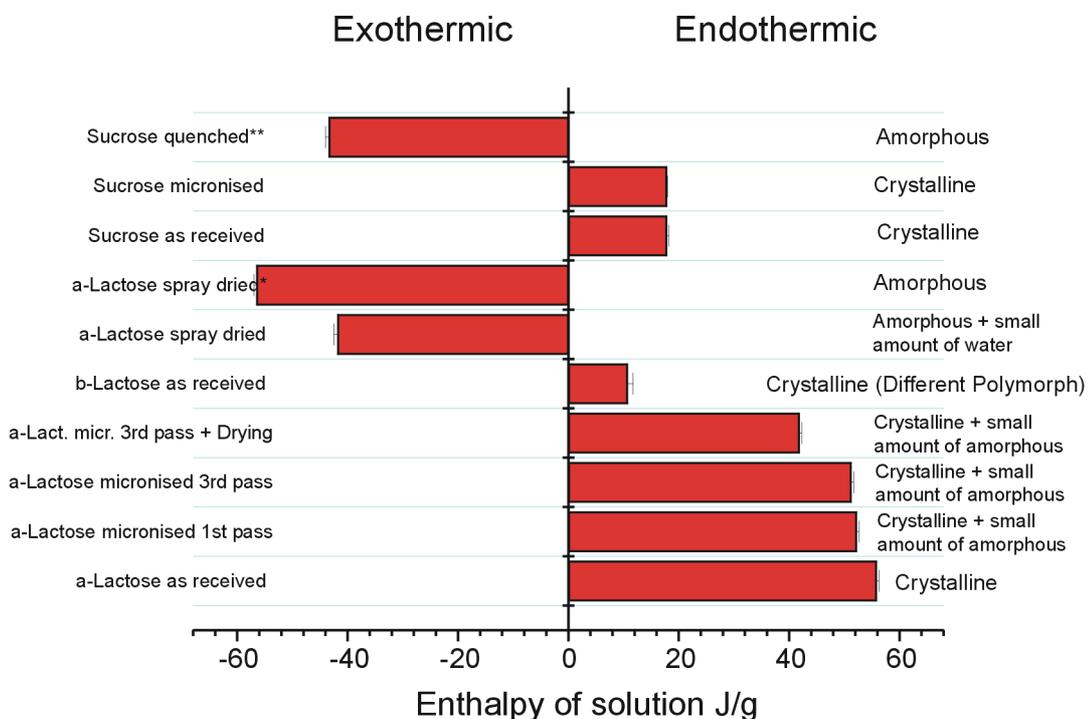


Figure 2. A summary of the enthalpies of solution at 25°C in water for lactose and sucrose processed and stored under different conditions. Each bar represents the average of three experiments (average standard error = 0.5 J/g).

amount of water, (determined by TGA). The observation of identical enthalpies suggests that the micronised sample was totally crystalline.

The different response between lactose and sucrose with respect to micronisation is explained by the difference in the glass transition temperature, T_g , of their respective amorphous forms. The T_g 's for amorphous lactose and sucrose are 116°C ⁵ and 57°C ⁴ respectively. Absorption of only very small amounts of water is known to considerably depress the T_g of an amorphous material and cause recrystallisation⁶. In the case of micronised sucrose, the residual amount of water present when stored over silica gel at room temperature was sufficient to lower the T_g of the amorphous fraction to allow recrystallisation to take place at the storage temperature. This recrystallisation took place before the enthalpy of solution was measured; within approximately 2 hours. Figure 3A confirms that the recrystallisation of the disordered amorphous regions has taken place.

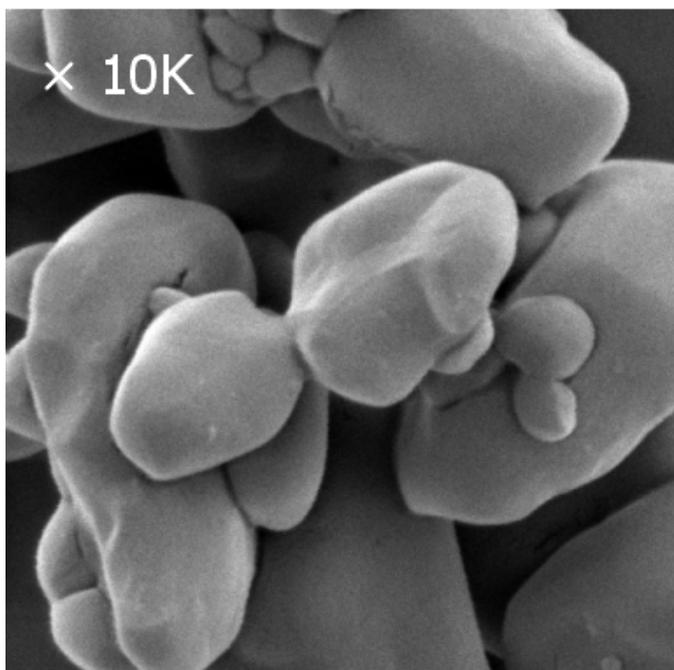


Figure 3A. An SEM of micronised sucrose stored at room temperature.

This is seen as smoothing of the surface and the formation of bridges between touching particles. Once re-crystallisation has taken place the water is expelled from the material thus giving the agglomerated crystalline powder the same water content as the starting crystalline material. If the micronised sucrose is immediately stored in a freezer recrystallisation is

prevented, as seen in figure 3B by the absence of smoothing and no observation of particle bridging. The storage temperature of the freezer sample is well below the lowered T_g of the amorphous fraction within the micronised powder. Thus the material does not divitrify i.e. pass through its T_g to a less viscous state, and re-crystallise. Lactose can not easily recrystallise because its T_g is much higher, so even after the depression of T_g by the presence of absorbed water, the lowered T_g is well above the storage temperature. Thus, re-crystallisation was so slow from the highly viscous amorphous fraction above its T_g , that the process was effectively stopped within the period of storage.

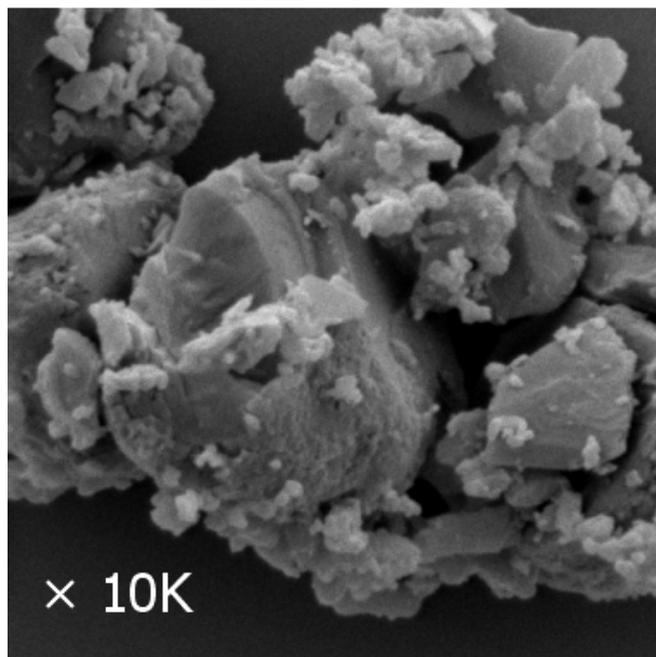


Figure 3B. An SEM of micronised sucrose stored in a freezer.

Conclusion

This study has explored the strengths and weaknesses of solution calorimetry, particularly for the characterisation of processed carbohydrate excipients. SolCal is clearly able to differentiate between different morphologies, i.e. between mixtures of crystalline and amorphous material and between mixtures of polymorphs. However, caution is required concerning the residual water content of the material under investigation, either with respect to the re-crystallisation of amorphous material with low T_g values or by the lowering of the enthalpy of solution by the absorbed water. SolCal is useful for the investigation of the physical stability of new drugs and novel dosage forms where morphological transitions are suspected.