



The Application of Solution Calorimetry to Quantify Amorphous Lactose Occurring at 10% w/w or less

Introduction

The processing of crystalline pharmaceuticals is often responsible for introducing small amounts of amorphous material. This disorder often occupies only a small percentage of the total mass, and is thus apparently insignificant. However it is capable of affecting that material's behaviour since it resides primarily on the particle surface, making that surface predominantly amorphous and consequently altering interfacial interactions.

For the purposes of this work, the solution enthalpies of samples of less than 10% w/w amorphous content were measured in order to establish the resolution offered by solution calorimetry in studying materials of small degrees of disorder. The impact of sorbed water on the measured enthalpy of solution was also investigated.

Experimental

Quantities of dried amorphous (spray-dried) and crystalline lactose were accurately weighed and combined to produce powder mixes of 0-10% w/w amorphous lactose. Sample storage was at 0% relative humidity (RH) in a

desiccator over phosphorous pentoxide at room temperature (20 °C) or in a vacuum oven at 50 °C (Sanyo-Gallenkamp). All experiments were carried out at 25 °C, with between three and five replicates.

Samples of approximately 200 mg (accurately weighed) were used and ampoules were double-sealed with 'bees' wax in order to prevent water vapour penetration into the sample.

Results

Enthalpy of solution was found to increase in a linear fashion with decreasing amorphous content. 100% amorphous lactose exhibited an exothermic response, giving rise to an enthalpy of solution of -56.50 J/g, whilst the heat of solution of 100% crystalline lactose was endothermic (56.2 J/g). Figure 1 shows the typical experimental profile for a predominantly crystalline (endothermic) sample.

Enthalpy of solution measurements comprise several processes. These include an initial wetting of the powder surface, dissolution (involving the disruption of the bonding between the solid

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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

"The quantification of small degrees of disorder in lactose using solution calorimetry"
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molecules and the formation of bonds between the solute and solvent molecules) and rearrangement of bonds within the solvent to accommodate solute molecules. The sorption of water by a powder is the first stage of wetting, and this sorption of the first few layers of water molecules on the surface is thought to be responsible for the majority of the overall wetting response. Amorphous lactose is able to sorb substantial amounts of water and this would be expected to alter the initial wetting (immersion) response and thus change the net enthalpy of solution value.

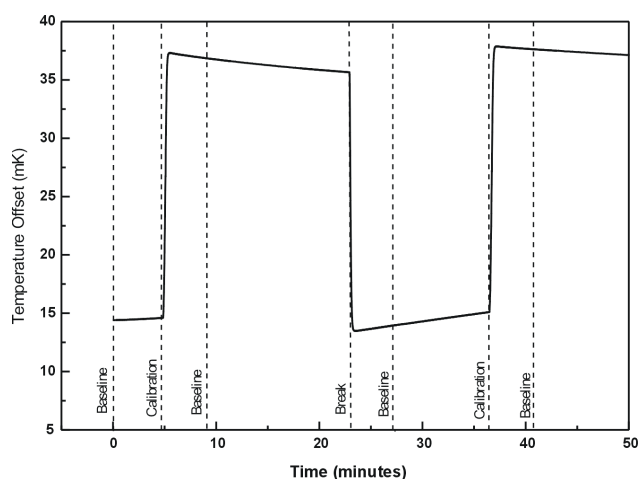


Figure 1. Plot of temperature offset against time for a 5% w/w amorphous lactose sample, with a stirring rate of 600 rpm. This trace shows the calibration sections of the experiment, which occur before and after the ampoule is broken, as well as the baseline periods, which aid calculations to adjust for any heat lost to or gained from the water bath, as well as the heat generated by the stirrer. Following the breaking of the ampoule, a drop in temperature is seen, implying that the response in this case is endothermic

The enthalpies of solution were calculated for both the vacuum-dried and desiccated partially amorphous samples (figure 2).

A line of best fit was drawn based upon those enthalpies calculated for the vacuum-dried samples. To assess the limit for quantification, the range of amorphous content that could be described by the spread of the error bars on figure 2 was assessed. Based upon these results the amorphous content of samples stored desiccated was found to be accurate to within 1.0 % w/w as opposed to 0.5 % w/w for those stored under vacuum. The increased variability in those results of the desiccated samples can be

attributed to the higher levels of residual moisture contained within them. It should be remembered, however, that a proportion of the error in this low amorphous content region could relate to weighing and preparing a uniform mix containing such small amounts of the amorphous material.

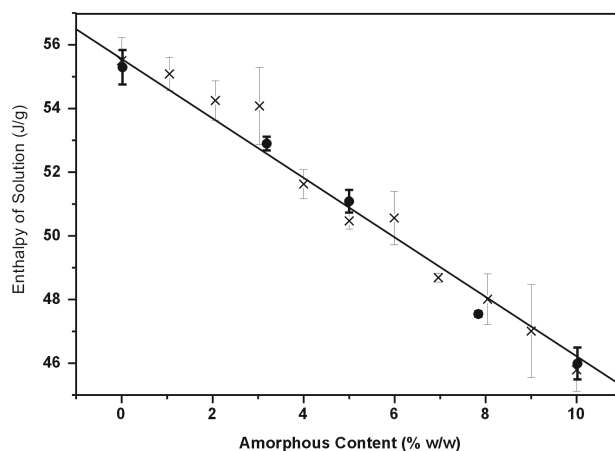


Figure 2 Average enthalpies of solution and their standard deviations for samples stored under two conditions: filled circle = under vacuum at 50°C; x = desiccated over phosphorous pentoxide at 20°C. The line represents the best fit for the vacuum-stored data, with a correlation of $R = 0.991$.

The quantification limits calculated here for lactose will not be the same for all materials, as the sensitivity will depend upon the difference in enthalpy of solution between the amorphous and the crystalline forms. Obviously the larger the difference the greater the sensitivity for quantification will be and vice versa.

Conclusions

Solution calorimetry provides a good method by which to detect and quantify the amorphous composition of materials of small degrees of disorder. In addition, it has been shown capable of differentiating between samples of different moisture content and providing an indication of how moisture sorption contributes to the thermodynamics of the solution process.