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Isothermal microcalorimetry water sorption experiments: calibration issues

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Abstract

Isothermal microcalorimetry gas flow vapour sorption experiments can be used to assess the surface energetics of crystals, the formation and/or loss of hydrates as a function of humidity and the onset of deliquescence, and to identify the presence of amorphous content in powders. These applications require different aspects of calibration. For gas flow instruments, it is simple to calibrate the humidity in the measuring cell by use of a saturated salt solution. To allow the power output to be compared between laboratories, there is a need for a standard test reaction for adsorption behaviour. The use of sealed ampoules containing reservoirs of saturated salt solutions has provided a means by which physical transformations (such as crystallisation) in powders can be followed. The study of crystallisation of amorphous samples involves a complex mixture of exotherms and endotherms which make it difficult to standardise the exact conditions which are used. Comparison of data between different laboratories can therefore become difficult. It is difficult to think of a calibration standard for these type of experiments, as the sample is usually thermodynamically unstable (a physical change is induced during the experiment). The use of water sorption in isothermal microcalorimeters is growing in popularity as a means of characterising both adsorption to and absorption into powders, but there are complex calibration issues that still need to be addressed. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Isothermal microcalorimetry; Water sorption; Calibration; Amorphous; Hydrates; Surface energetics

1. Introduction

The aim of this paper is to highlight calibration issues that need to be considered when using isothermal microcalorimetry to study the interaction of water vapour with powders. The examples used will be for organic samples or low molecular weight (100's). However, the concepts described have application in many disciplines and for many sample types, including inorganic zeolites, metal oxides etc.

Water can interact with materials in a number of ways and whilst it is not the purpose of this paper to consider these interactions, it may be useful to at least describe the types of interaction which can exist in a simple, generalised manner. Firstly water can adsorb from the atmosphere onto the surface of solids. For adsorption only a few layers of water molecules would form on the surface, even at high relative humidity (RH), so the total mass change throughout an adsorption isotherm is small (generally much less than 1% W/W). The total water uptake will be directly related to the available surface area of the sample, thus a ceramic with high surface area can adsorb much more

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water than a large particle size non-porous crystal. The shapes of adsorption isotherms can be used to interpret the nature of the powder surface (whether water interaction with the surface is favoured or not). Potentially the water sorption isotherms can be used to calculate surface areas, however due to the nature of the water molecule the surface area will be very different to that seen for more inert gasses such as nitrogen, krypton and argon. In general adsorbed water is not a major threat to chemical stability as the molecules do not have the form of bulk water. However, should condensation occur, where drops of bulk water exist as point contacts, then instability can result.

Water can also be taken into the bulk of crystals as part of the crystal structure, which is known as a hydrate. The presence of these water molecules can either be in stoichiometric proportions (hemihydrate, monohydrate, dihydrate etc.) or in a non-stoichiometric amount. Stoichiometric hydrates can result in greater stability for the crystal lattice or can give rise to some strain on the lattice. Non-stoichiometric hydrates are those crystalline materials in which water can gain access through channels in the crystal lattice. For these materials the water will tend to have less impact on the physico-chemical properties of the crystal than is seen for stoichiometric hydrates. Any form of hydrate gives rise to the risk of chemical instability if the water should be released during storage.

Certain materials, for example, freely soluble inorganic salts, will dissolve in water vapour above a critical RH. This is known as deliquescence. These salts are then used as a means of controlling the humidity in a sealed container, as the RH above a saturated solution of the salt will be the same as the critical RH as which that salt will deliquesce at that temperature. For many materials deliquescence is a problem which needs to be avoided and consequently there is a need to calculate the critical RH for deliquescence.

Finally water can absorb into many amorphous materials (very common with hydrophilic materials and also possible with some hydrophobic amorphous samples), where it often acts as a plasticiser. The action of a plasticiser is to lower the glass transition temperature (T_g) of the amorphous form. The lowering of the T_g can result in changes in the material, including the transition from the brittle to the rubbery form, followed by tendency for amorphous particles (but not films) to collapse and then finally for the material to crystallise. The tendency to crystallise will only happen for lower molecular weight samples as polymers can remain amorphous.

The types of interaction described above can happen in many types of material in many different industrial and academic disciplines. In the discussion which follows most of the examples will relate to the interaction of water with non-polymeric organic solids. However, the calibration issues that are highlighted are usually equally important for other sample types.

As mentioned water sorption experiments with powdered materials can have the following functions and each of these will be considered in turn:

1. to gain information on the surface energetics of crystalline powders
2. to assess hydrate formation and/or loss
3. to investigate the critical relative humidity (RH) for deliquescence
4. to probe amorphous and partially amorphous materials

2. Water adsorption to crystalline solids

2.1. *Surface energetics using a flow of air with controlled relative humidity*

It is possible to obtain information of powder surface energetics by studies of water adsorption to the surface. Water vapour will adsorb to the surface of crystalline powders. One approach to studies of water sorption is to gradually increase RH to which the powder is exposed, and to measure the calorimetric response as the humidity is increased. Experience has shown that the commercial gas flow cell supplied by Thermometric (after suitable adaptations to ensure even flow of dry nitrogen into the cell) mounted in a Thermal Activity Monitor (TAM, Thermometric) is able to detect water adsorption to samples which appear to have no water uptake when studied using the best gravimetric systems (e.g. Dynamic Vapour Sorption apparatus, Surface Measurement Systems). As the DVS instrument can measure water uptake to a resolution of a fraction of a microgram, it follows that the gas flow cell in the TAM is able to detect water adsorption to the powder at levels in the region of nanogram uptake. The measured calorimetric response for water sorption, at any selected humidity, will be related to the amount of water which has adsorbed and the energetics of the interaction between the water molecules and the powder surface. By equilibrating the powder to 0% RH and then making sequential increments in RH, it is possible to understand the energetics of interaction at various levels of surface coverage. This style of experiment provides an understanding of the populations of sites on the surface which have different energetics.

2.2. Calibration issues for water adsorption to crystals

For water adsorption experiments, the two key issues are the power measurement from the calorimeter and the quality of the humidity generation.

It is possible to check the humidity by use of chemicals that are known to have a critical RH at which deliquescence occurs. Examples are selected inorganic salts, saturated solutions of which are regularly used to control RH in a sealed container (at a selected temperature) [1]. For example, over a reasonable temperature range a saturated solution of sodium chloride produces an atmosphere which is 75% RH. Thus, if a saturated solution of sodium chloride is added to the calorimeter gas flow cell then at RH values below 75% water will evaporate (to increase the RH in the measuring cell), whereas at RH values above 75%, water will condense into the saturated salt solution (to lower the RH). This can be observed as a change between an endotherm and an exotherm. In Fig. 1 a typical experiment is shown for small steps in RH around the known critical RH of sodium chloride at 25°C. The point where the response crosses the baseline shows when the input gas was at the critical RH of the salt, thus the target RH can be compared to the true RH for the flow cell. In this respect it is simple to obtain a good calibration of the humidity being used in the experiment. Workers do obviously need to be aware that RH is a ratio of partial pressures and thus if the temperature is changed air of the same absolute water content will have a different RH. As the Thermometric Gas Flow Cell works by dispensing different percentages of dry and totally water saturated gas it is necessary to correct the mixtures of the two to give a required RH when working away from near ambient temperatures.

The second issue is the calibration of the response of the calorimeter (i.e. the power or heat flow output). Most often this is achieved by use of an electrical heater, which usually is housed in the calorimeter, rather than in the reaction cell. This minor difference in position for the electrical heater may well cause

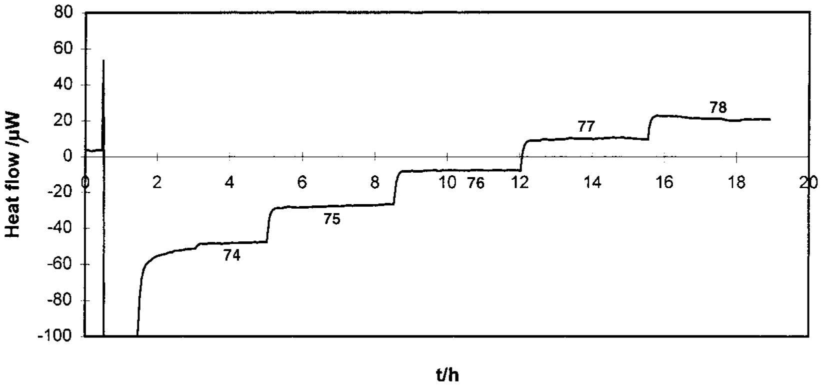

Fig. 1. Calibration of a gas flow cell that was in need of adaptation. The data are for a cell which contained saturated sodium chloride solution at 25°C. Six sequential steps in RH were used, starting with a set value of 73%, then 74, 75 and 76% RH, which all resulted in endothermic plateau responses because of the evaporation from the saturated solution in the cell. The final two increments (set at 77 and 78% RH) result in exothermic plateaus, due to condensation into the saturated salt solution from the atmosphere. If the cell were working efficiently the response should cross the baseline at 75% RH, however in this instance a set value of 76.5% is required to achieve an actual value of 75% RH.

inaccuracies in calibration. This can be improved if a heater is mounted in the actual cell that is used, however, it would still be desirable to have a standard water adsorption reaction to act as a 'chemical' calibration. If a standard surface could be agreed upon this could be used by all workers as a reference. Sadly, the identification of a suitable reference material is not easy. Any material selected for this purpose should have:

1. physical (i.e., no polymorphs, amorphous form, hydrates, solvates etc.) and chemical (i.e., no oxidation or hydrolysis etc.) stability
2. a water uptake which is similar to that used in practice (which for crystalline organic powders would be ca. 0.2% at 90% RH)
3. a uniform surface area per unit mass
4. no batch-to-batch variability

At present no suitable material has been identified. The best chance to find a solution may be to consider uniform size fractions of polymeric materials which do not allow water absorption, but which have a suitable level of water adsorption.

3. Hydrate formation and loss

The assessment of hydrate formation/loss is probably best achieved by use of a gas flow cell (although it is also possible to seal the powder in an ampoule with a salt solution to give a defined RH, as will be discussed for amorphous sample below). Many materials form or lose hydrates over the RH range 0–95% at ambient temperature, although often there are kinetic considerations (raising the difficult question: how long do you need to run an experiment to prove that a hydrate will not form or be lost at that condition?). The amount of water associated with the formation of a hydrate is very large compared to that associated with adsorption (for a typical pharmaceutical (molecular weight of ca. 350) a monohydrate would be ca. 5% W/W). This large change in water content would happen at a particular RH, but often over a long period of time. The interest would be to know at what RH (and T) the hydrate was formed and lost, hence there would be a need for calibration of the RH in the cell. The calibration of the RH in the cell is simple and has been described above. However, it would also be advantageous to have a standard reaction for hydrate formation which could be used a chemical calibration reaction. The author is not aware of any attempts to define such a chemical standard at this time.

4. The critical RH for the onset of deliquescence

To assess the critical RH for deliquescence it would be usual to employ a gas-flow cell in a ramp mode. Here the RH can be changed continuously with time at a predefine rate (this being different to the step changes described above for the adsorption experiments). The onset of deliquescence will result in a substantial deviation from the underlying water adsorption response [2]. Here the calibration need is to be aware of the true RH that is generated in the gas flow cell, which can be achieved as described in Section 2.2. Indeed the calibration of the true RH in the measuring cell uses the deliquescence of salts. Consequently, it can be suggested that the deliquescence of sodium chloride would be a good chemical calibration for this type of experiment (Fig. 1).

5. Amorphous and partially amorphous materials

In recent years there has been a growing realisation that 'crystalline' powders can have varying amounts of disorder in their structures. The presence of amorphous materials is known to be of great significance [3].

Amorphous regions in crystals of non-polymeric samples are generally thermodynamically unstable, i.e., they are in a higher energy state than the crystalline form. Within an amorphous material there will often be substantial absorption of water vapour (over 20% W/W), which can cause physical and chemical transitions to occur. This means that the amorphous regions are reactive 'hot spots' in which physical changes and/or chemical degradation (especially hydrolysis) can be initiated. The amorphous content can be formed either during crystallisation or subsequent processing. It is argued that the processing induced disruption is mostly at the powder surface, which means that a small amount of disorder (by weight of the sample) can be a very substantial amount of the powder surface. If the powder surface is essentially all amorphous, then the interaction between the powder and other phases will change. Alterations in interfacial interactions can affect many aspects during the production, storage and use of products. As processing induced disruption is seldom a deliberate and controlled event, it tends to lead to batch-to-batch variations. As the disruption is unstable, recovery to the crystalline form will result in a change in properties with time after processing. Overall there is an urgent need to characterise materials for amorphous content and to understand how this relates to the functionality of the material in the subsequent processes and in the product for which it is to be used.

Bulk analytical techniques, such as differential scanning calorimetry, powder X-ray diffraction and even IR spectra, will measure the properties of the sample as a whole. The detection limits for amorphous content with such techniques can vary, but will generally have a lower cut off of 5–10% [4]. Vapour sorption is a powerful way by which amorphous materials can be studied. Firstly, amorphous samples tend to absorb substantial quantities of water, which can be used (by comparison with the response for a crystalline sample) to show that amorphous material is present. Recently [5–8] isothermal microcalorimetry has been used to study the process by which amorphous material converts to the stable crystalline form. The transition from the amorphous to the crystalline form will depend upon the mobility of the molecules. When below the glass transition temperature (T_g) the molecules lack sufficient mobility to allow spontaneous (within the time scale of a standard laboratory experiment) crystallisation. The difference between T_g and T can be adjusted either by adding a plasticiser to lower T_g, or by heating the sample to raise T. Many amorphous structures absorb water, which then acts as a plasticiser in order to lower T_g. However, certain hydrophobic materials may require alternative small molecules to absorb and lower T_g (these could include the vapours of ethanol or chloroform for example Ahmed et al. [9]).

An advantage of calorimetry is that it is a non-specific monitor of heat changes that occur within the measuring site of the instrument. The disadvantage is that the response of interest may well be masked by, or associated with, responses which are not of interest. The skill of the operator is therefore needed to devise experiments that limit artifacts due to parallel reactions. Perhaps the simplest and most used calorimetric method to study amorphous material in powders, is to seal the powder in a glass ampoule with a small tube containing a saturated salt solution (Fig. 2). The saturated salt solution will yield a defined relative humidity (RH) at any set temperature [1]. A typical response for amorphous lactose equilibrated at 25°C 75% RH (saturated sodium chloride solution) is shown in Fig. 3. Fig. 3 can be seen to have two distinct sections, there is an initial small protracted response followed by a large sharp peak. It is possible to delay the onset of the large sharp peak, to a certain extent, by either increasing the sample mass or by decreasing the RH (to a lower critical point, which is that RH which will allow sufficient absorption to cause crystallisation in a measurable time). Aso et al. [8] have shown that the temperature and humidity used in the calorimetric experiment alter the rate of crystallisation, and they concluded that this was due to changes in matrix viscosity affecting the molecular motion of the drug under study (nifedipine).

Fig. 2. Sealed glass ampoule containing a sample of powder and a tube with a saturated salt solution (reproduced with permission of Thermometric). The salt solution generates a specific humidity in the air tight ampoule. The heat flow due to any changes in the powder as a consequence of the humidity are recorded.

For samples with lower amorphous contents the large sharp peak is often seen to split into two separate regions. There is considerable debate concerning the significance of the different sections of the response and if logical decisions are to be made on how to interpret the data it is important to consider the processes which occur.

The initial slow peak (Fig. 3) is not crystallisation, as it is possible to stop the experiment at the end of this

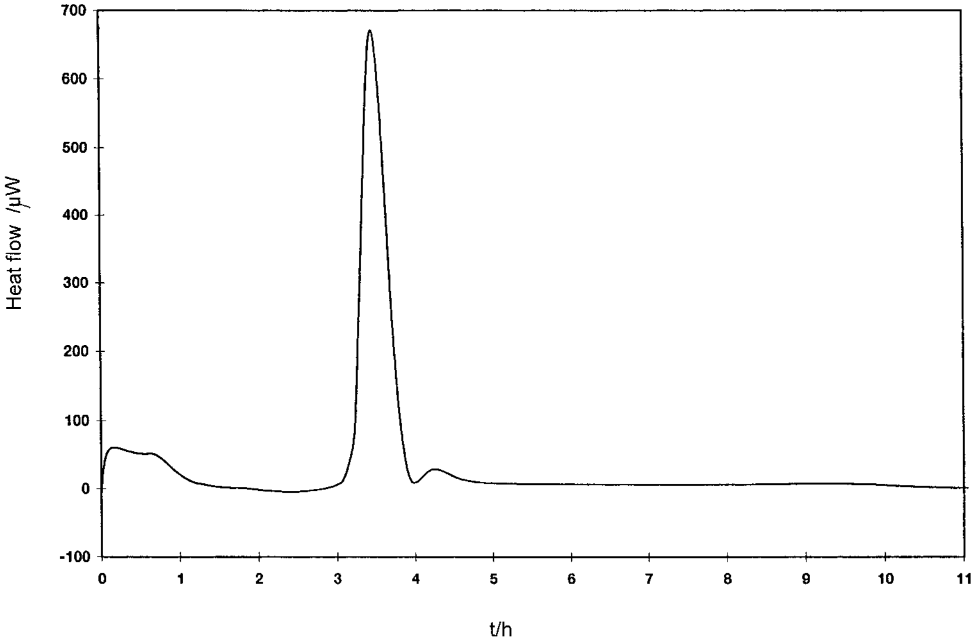

Fig. 3. Typical crystallisation response for amorphous lactose (75% RH, 25°C, tube internal diameter=4.6 mm, surface area of salt solution 16.76 mm^2).

phase and show that the sample is still amorphous (by X-ray diffraction, and DSC). It has been argued that this region represents a vapour phase wetting of the powder (exotherm) minus a response for the generation of the humid air from the saturated salt solution (endotherm), such that the net response is small.

It is necessary to be aware of the form of response that is generated from the saturated salt solution. Blank experiments (no powder load) do not mimic the real experiment exactly, as more humidity will be needed when water is absorbed into the solid, however, it is valuable to know what kind of response is generated during humidification. In Fig. 4 responses for freshly sealed glass ampoules containing different saturated salt solutions are shown. The reference in Fig. 4 is a freshly sealed empty ampoule. From the data in Fig. 4 it can be seen that changes in the salt solution have a significant contribution to the shape of the initial peak. These changes may reflect wetting of the cell, evaporation from the salt solution, and crystallisation of the salt following evaporation. It is interesting that the net blank response can be exothermic or endothermic depending upon which salt is used. If it is assumed that the initial water sorption to the powder of a real experiment will always be exothermic, then with some salt solutions the wetting response should be a sum of two exotherms (the wetting and the blank response for the salt solution), whereas for other experiments the initial response will be a sum of a net endotherm (blank response) and an exotherm. This discussion shows that for any calibration and control between different laboratories it is essential to know which salt solution has been used and what has been sealed in the reference cell. (NB sealing the same salt solution in the sample and reference cell will give a zero baseline displacement if there is no powder in either ampoule, but will not mask the salt solution effects completely if powder is present in one cell. This is because the powder will absorb water and thus more evaporation will be needed, which will not occur in the blank cell).

The kinetic aspect of water evaporation must also be considered. The rate of evaporation from a saturated salt solution will depend upon the surface area available. If results are to be identical in different laboratories then this aspect of experimental design must also be standardised (as a minimum reported).

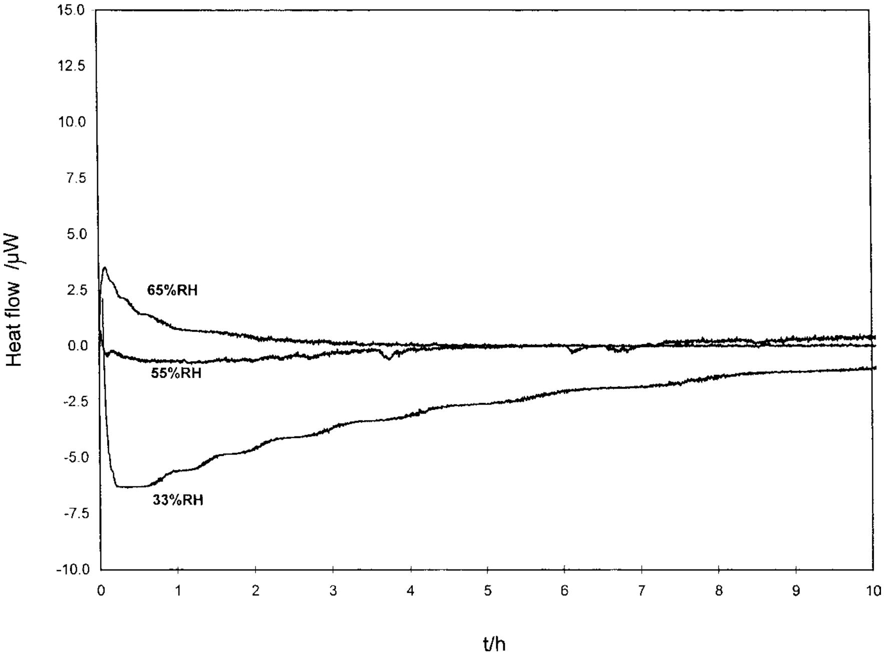

Fig. 4. Examples of blank responses for different saturated salt solutions.

As well as contributions from wetting of the powder and the blank response in the cell, it is probable that transitions in the powder also make a contribution to the early part of the response. Buckton and Darcy [10] have shown that collapse occurs during this early stage. Indeed a sample which had been collapsed (by exposure to 50% RH) did not show a response during this early period. Unfortunately, the process by which collapse was induced will result in retained absorbed water, and as such it cannot be proved as to whether this initial response is due to the collapse process, the water sorption or (most probably) both. In conclusion, the initial response is a composite of wetting, collapse, and changes in the saturated salt solution. Thus, an apparently simple thermal event is in fact a complex mixture of numerous different responses.

The large peak in Fig. 4 includes the response for crystallisation. This can be proved by showing that the powder in the bottom of the ampoule is amorphous before, and crystalline after, this peak. This peak is a composite of (at least) two main events, which are the crystallisation (exotherm) and water desorption (endotherm). It is probable that there will be further contributions from within the salt solution reservoir, and potentially some condensation of the desorbed water in the ampoule.

The fact that the measured crystallisation response is often split into two regions causes further confusion. For example, Sebhatu et al. [7] show a schematic version of the calorimetric response for the crystallisation of lactose (Fig. 5) and state that Part II is crystallisation and Part III may be mutarotation from β to α-lactose. They assess crystallinity by using the area under the curve for Part II, which equates to ca. 32 J/g. However, Briggner et al. [5] and subsequent publications from our group, use the area under what would be Parts II and III to describe the heat change for the crystallisation process. This gives a measured value of ca. 48 J/g for the crystallisation of amorphous lactose. Work in our laboratory is currently directed to measuring the extent of mutarotation during crystallisation to ascertain what contribution this makes to the measured response. It should be noted that for samples that do not exhibit mutarotation, there is very clear evidence for two distinct peaks during crystallisation. This is very obvious during the crystallisation of salbutamol sulphate [6], where a distinct endotherm

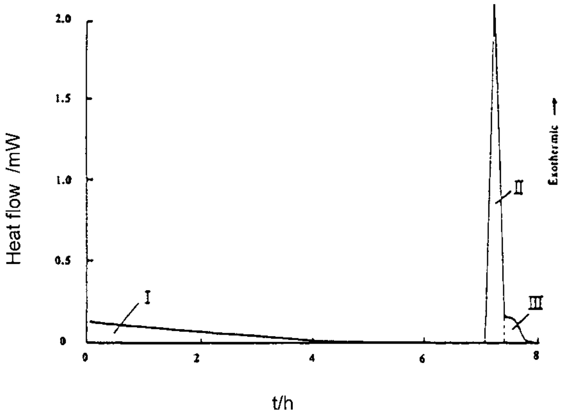

Fig. 5. Schematic microcalorimetric heat flow curve for crystallisation of amorphous lactose reproduced from [7] with permission from International Journal of Pharmaceutics.

is seen in the first half (before the peak reaches a maximum) of the crystallisation exotherm.

Irrespective of whether the crystallisation response should be taken as Parts II and III or just Part II for lactose (see Fig. 5 and discussion above), it is clear that the crystallisation response is reduced in size due to the endotherm for water desorption. Recently Buckton and Darcy [11] have shown that the measured calorimetric crystallisation peak, plus the enthalpy of vapourisation for a reasonable estimate of the amount of water desorbed (i.e., the quantity of water needed to plasticise T_g below T minus the quantity of water which is retained as a hydrate) approximates to the combined endotherms for hydrate loss and melting that are measured in a DSC for the crystallised lactose. This balance of heats would indicate that the contributions within the saturated salt solution are relatively small during the crystallisation response. It was concluded [11] that because the net exotherm in the microcalorimeter was the same for each RH studied at 25°C, then the water desorption must have been similar at each RH. This means that the amount of water sorbed at each RH was the minimum quantity needed to cause rapid crystallisation. This would be the case if the supply of water vapour were slow, due to slow diffusion in the cell and the small surface area of the saturated salt solution. It can be shown that if the supply of water vapour is rapid and plentiful, then the amorphous lactose will equilibrate to a different water load at each RH, prior to crystallisation (see gravimetric sorption below). It can be considered fortuitous that the experimental design caused a balance of kinetics, which resulted in the area under the curve at each RH appearing identical[1] at 25°C for crystallisation of both amorphous lactose [5] and amorphous salbutamol sulphate [6]. Buckton and Darcy [11] went on to show that at higher temperatures there was a difference in the net area under the curve for different humidities (Table 1). This is due to the fact that the amount of water needed is less to lower T_g below T when T is higher, and also that the rate of evaporation and diffusion of the water vapour will increase with T. It is extremely important to realise that the calorimetric response for crystallisation contains this substantial balance of exotherm(s) and endotherm(s). If the data are to be used in a quantitative manner it is vital that the impact of changes in environmental conditions (temperature and/or RH) is understood, and that any comparison between data at different temperatures and humidities is undertaken with great care.

Table 1
Net area under the curve (J/g) for the crystallisation of amorphous lactose at different temperatures and humidities (adapted from [11]). Reproduced from International Journal of Pharmaceutics [12] with permission[a]

Temperature (°C)	Sodium chloride	Sodium nitrite	Magnesium nitrite
25	48.9	47.9	48.2
35	53.0	47.1	59.4
45	62.1	63.2	66.5

[a] Sodium chloride: 75% RH at all temperatures studied; sodium nitrite: 65% RH at 25°C, 62% at 35°C and 60% RH at 45°C; magnesium nitrite: 53% RH at 25°C, 50% RH at 35°C and 47% RH at 45°C.

A further difficulty with quantification of the degree of crystallinity is the choice of calibration standard. Calibration is via a sample which is completely amorphous, which when mixed with a completely (within all reasonable limits) crystalline sample gives a linear

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[1] Briggner et al. [5] reported data for crystallisation of lactose at different RH values at 25°C. The small differences in enthalpy changes at each RH were regarded as insignificant. Current work in our laboratory indicates that the small differences in enthalpy change are real, and are most likely related to small differences in water desorption during crystallisation.

relationship between measured area under the crystallisation response and the % amorphous material present. However, real samples will have individual particles that are each partially crystalline and partially amorphous. There are uncertainties as to whether the two state calibration model is the same as the one state mixed particle sample. Indeed there is good evidence to suggest that the responses are different, if one compares the milled samples reported by Briggner et al. [5] to mixtures, the responses are different shapes. With particles which have been processed to make them partially amorphous it seems to be impossible to separate the crystallisation event from the initial response (Part I in Fig. 5). It seems impossible to halt the crystallisation process for the milled samples once collapse has started, whereas there is a clear lag phase between these two for completely amorphous lactose, or mixtures of amorphous and crystalline powders. The merging of the crystallisation response with the initial response for processed samples makes it hard to decide how to measure the area under the curve for crystallisation.

It would be desirable to have a standard reference material which would give a response in a sealed ampoule RH experiment. As the response that is measured is in fact a transformation from a thermodynamically unstable to the stable form, it becomes difficult to imagine a suitable standard. A standard which was physically and chemically stable would not give a response in the sealed ampoule experiment. Almost by definition, a reference standard should be stable, so that it can be transferred between laboratories and arrive in the same physical form. Unless an innovative alternative can be devised as a reference standard, these experiments will need to be defined in exact detail to ensure that they may be reproduced in other laboratories.

6. Conclusion

Water sorption studies on powders are increasing in popularity. They provide a means of characterising a range of powdered samples which are not readily studied by other techniques. It is comparatively simple to calibrate the humidity which is generated in the experiments. However, there are major problems in defining standard reference materials. It would be valuable to attempt to get cross laboratory agreement on some suitable reference materials.

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