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Use of heat of adsorption to quantify amorphous content in milled pharmaceutical powders

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ABSTRACT

Isothermal calorimetry operated in gas perfusion mode (IGPC) is often used to quantify the amorphous content of pharmaceutical powders. Typically, the calibration line is constructed using the heat of crystallisation as the sample is exposed to high levels of a plasticising vapour. However, since the physical form to which the amorphous fraction crystallises may be dependent on the presence of any crystalline seed, the calibration line is often seen to be non-linear, especially as the amorphous content of the sample approaches 100% w/w. Redesigning the experiment so that the calibration line is constructed with the heat of adsorption is an alternative approach that, because it is not dependent upon crystallisation to a physical form should ameliorate this problem. The two methods are compared for a model compound, salbutamol sulphate, which forms either a hydrate or an anhydrate depending on the amorphous content. The heat of adsorption method was linear between amorphous contents of 0 and 100% w/w and resulted in a detection limit of 0.3% w/w and a quantification limit of 0.92% w/w. The heat of crystallisation method was linear only between amorphous contents of 0 and 80% w/w and resulted in a detection limit of 1.7% w/w and a quantification limit of 5.28% w/w. Thus, the use of heat of adsorption is shown to be a better method for quantifying amorphous contents to better than 1% w/w.

1. Introduction

Pharmaceutical powders are frequently milled to reduce their particle size distribution and improve their physical properties (for instance, to enhance blending, dissolution or pulmonary delivery). One unintended consequence of milling is that the high energies imparted to the sample can result in generation of crystal defects and amorphous regions, particularly on surfaces. This mechanical activation increases surface energy and means that milled powders are frequently highly cohesive/adhesive (Brodka-Pfeiffer et al., 2003). Additionally, their properties may change with time, temperature and/or relative humidity (RH) as any amorphous material present relaxes and/or crystallises with time. The amorphous fraction generated by milling may often be small (around 1% w/w) but occurring primarily on surfaces its impact on the properties of the bulk powder can be significant. This is especially true for dry-powder inhaler formulations, where aerosol performance is contingent upon forces of adhesion and cohesion (Sharma et al., 2013), but may also affect flow and blending of bulk powders. As a consequence it is important that methods to quantify small (<1% w/w) amorphous contents are available.

Of the many techniques that show potential for such an assay, isothermal gas perfusion calorimetry (IGPC) is particularly useful (Gaisford, 2012) because it requires a relatively small (typically 10–50 mg) mass of sample and can be applied to any pharmaceutical powder if a suitable plasticising vapour is available. The plasticiser (often water or ethanol) is perfused over the sample in an inert carrier gas (nitrogen); as the amorphous material absorbs the plasticiser, its glass transition temperature (T_g) is reduced, eventually resulting in crystallisation (and so an exothermic heat). The heat of crystallisation is quantitatively proportional to the mass of amorphous material; reference to a calibration line prepared by blending appropriate mass ratios of crystalline and amorphous material allows quantitative analysis. The quantification limit (QL) is often better than 1% w/w because the heat of crystallisation is usually substantial.

The method has some limitations however. Because the crystalline fraction of the sample will act as a seed, as the amorphous content of the sample increases, the number of crystalline seed particles reduces (and in the case of the 100% amorphous sample, there is no seed). One manifestation of this is that the calibration line is often seen to deviate from linearity as the amorphous content approaches 100% w/w (O Neill and Gaisford, 2011). Another is that some samples may undergo solid-state conversion post-crystallisation (Gaisford et al., 2010), making determination of the heat of crystallisation difficult.

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An alternative approach is to measure the heat of wetting of the sample before and after crystallisation. While the sample is partially amorphous, water will be both adsorbed and absorbed. Once crystalline, only water adsorption will be measured and so the difference gives the heat of absorption. This approach was first used by Mackin et al. (2002) in an assay for amorphous content using dynamic vapour sorption, but has not been previously applied to IGPC. Hence, the specific aim of this work is to explore the feasibility of heat of absorption measurements as a method of quantifying small amorphous contents and to compare its use with (conventional) heat of crystallisation measurements. Salbutamol sulphate (SS) was selected as a model compound because it shows complex crystallisation.

2. Materials and methods

Crystalline SS was supplied by Micron Technologies Ltd. (UK) and was used as received. Amorphous SS was prepared by spray-drying an aqueous solution (10% w/v) using a B-290 mini spray-dryer (Buchi Labortechnik Ag). The following settings were used; inlet temperature 140 °C, outlet temperature 60 °C, aspirator 100%, pump 20%. The spray-dried sample was seen to be amorphous by X-ray powder diffraction (data not shown). SS hydrate was prepared by holding SS on a watchglass in a humidity chamber (100% RH) for 24 h.

Experiments were performed with a gas perfusion accessory housed in a 2277 thermal activity monitor (TAM, TA Instruments Ltd., UK) operated at 25 °C. Samples (10 ± 0.1 mg) were weighed directly into the stainless steel ampoule (5 mL volume). Partially amorphous samples were prepared by dry-mixing appropriate mass ratios of crystalline and spray-dried SS.

The gas perfusion accessory splits the incoming gas into two streams; one is routed directly to the sample ampoule (the 'dry' line) and the other passes through two humidifying chambers, becoming saturated with (in this case) water, prior to entering the sample ampoule (the 'wet' line). Mass flow controllers adjust the proportional flow rates of the gas along the two lines in order to produce any desired RH in the sample ampoule. The total flow rate was 150 mL h^{-1}. A 9-step humidity program was used; 0-30-0-95-0-30-0-95-0% RH. The selection of 30% and 95% RH is arbitrary, but dynamic vapour sorption experiments (data not shown) showed that 30% RH was below cRH and 95% RH was above cRH (the critical relative humidity, above which crystallisation occurs). The time period of each step varied depending on the amorphous content of the sample, ranging from 1.5 to 10 h. The amplifier range was 3000 μW and data were recorded (1 point every 30 s) using the dedicated software package Digitam 4.1. The TAM was calibrated prior to use with the electrical substitution method. Data were analysed with Origin 8.5 (Originlab Corp, USA). Note that while the TAM plots exothermic events as a positive power, by convention exothermic changes in heat are quoted as negative values.

Differential scanning calorimetry (DSC) measurements were made with a Q2000 DSC (TA Instruments Ltd., UK). Samples (5–10 mg) were weighed into hermetic Tzero aluminium pans. An empty pan, matched to the weight of the sample pan, was used as a reference. Samples were heated from 0 to 250 °C at 20 °C/min. The cell constant and enthalpy calibrations were performed with indium (Certified Reference Material LGC2601, Batch E1, LGC, London, T_m = 156.61 °C, $\Delta_f H$ = 28.70 J/g) in accordance with the manufacturer's instructions. The measured values were always in excellent agreement with those of the reference material (T_m ± 0.03 °C, $\Delta_f H$ ± 0.1 J/g). Nitrogen (50 mL min^{-1}) was used as a purge gas and data were analysed with Universal Analysis 2000.

All experiments were conducted in triplicate. Results are reported as mean ± standard deviation.

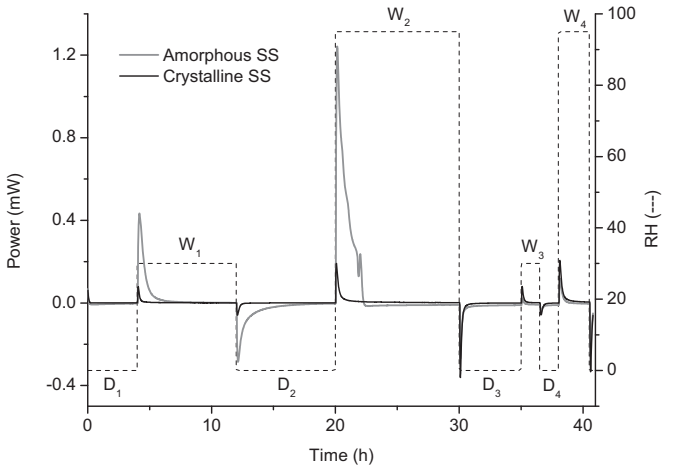

Fig. 1. Power–time data for amorphous (grey line) and crystalline (black line) SS as a function of RH.

3. Results and discussion

Fig. 1 shows the power time data for both crystalline and amorphous SS as a function of RH. A series of exothermic (positive) and endothermic (negative) powers are seen as the RH of the environment surrounding the sample is varied. Periods during which the sample is held under a dry gas are labeled D_{1-4} (noting that the initial period D_1 represents drying of the sample following loading into the calorimeter) and periods during which the sample is exposed to raised humidity (either 30% or 95%) are labeled W_{1-4}. Although the data look complex, interpretation is relatively straightforward, remembering that the area under the curve for each period gives the net change in heat (in mJ).

Starting with crystalline SS, the only process occurring should be adsorption (to a greater extent during W_2 and W_4) during periods W_{1-4} and desorption during D_{2-4} (the changes in heat should be equal and opposite to those of adsorption). Table 1 shows these data and these trends are seen.

Conversely, the amorphous sample shows a much larger power during initial exposure to 30% (W_1) and 95% RH (W_2). This is because several additional processes are occurring during these periods. During W_1 water is adsorbed onto all surfaces while the amorphous fraction absorbs water (but the T_g is not lowered sufficiently to cause crystallisation). During W_2 sufficient water is absorbed that the sample crystallises, resulting in a complex series of exothermic events. Assignment of the processes that give rise to each exotherm is discussed below. It suffices here to note that the response of the amorphous sample is significantly different from that of the crystalline sample and that is the basis of the sensitivity of the method. After W_2 the sample, now crystalline, only adsorbs water during periods of exposure to raised humidity (W_3 and W_4) and consequently the heats are seen to reduce (Table 1). Indeed, the heats of adsorption are actually smaller than that of the crystalline

Table 1
Area under curve (AUC) data for the various dry and elevated RH periods for the crystalline and amorphous SS data shown in Fig. 1.

Period	Crystalline SS AUC (mJ)	Amorphous SS AUC (mJ)
W_1	−63.6 ± 1.4	−989.0 ± 30.3
D_2	64.0 ± 1.9	916.3 ± 10.2
W_2	−270.4 ± 6.7	−3806.9 ± 20.4
D_3	250.2 ± 5.9	232.2 ± 20.5
W_3	−49.9 ± 0.8	−28.1 ± 1.1
D_4	47.5 ± 0.8	29.5 ± 1.1
W_4	−212.4 ± 2.8	−163.9 ± 17.3