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The Use of Organic Vapor Sorption to Determine Low Levels of Amorphous Content in Processed Pharmaceutical Powders

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ABSTRACT Organic dynamic vapor sorption (organic-DVS) was used to characterize amorphous content in known amorphous-crystalline mixtures of lactose and salbutamol sulfate. N-octane was chosen as an apolar probe and measurements were carried out by exposing mixtures of each sample to partial pressures 0–90% p/p_0. A linear relationship between amorphous content and n-octane partial pressure was observed for both lactose and salbutamol sulfate with R^2 values of 0.992 and 0.999, respectively. In addition, the influence of sequential mechanical processing in a ball mill on the amorphous content in crystalline lactose was investigated. Cumulative milling times resulted in an exponential increase in amorphous content (using the linear relationship obtained for lactose), with a maximum amorphous content of 14% being induced after 60 min milling. In comparison, analysis of the 60 min mill time samples after exposure to 85% relative humidity suggested 0.00% amorphous content.

KEYWORDS Lactose, Salbutamol sulfate, Amorphous, Ball milling, Organic dynamic vapor sorption

INTRODUCTION

Many drug delivery systems are based on active pharmaceutical ingredients (API) and/or excipient systems that are crystalline in nature. The final dosage form is often required to exhibit a specific functionality that requires the API/excipient to undergo specific manufacturing processes, such as milling or micronisation. The consequence of such high energy processes is that various degrees of disorder in the form of crystal defects and/or amorphous regions may be generated (Ahmed, Buckton, & Rawlins, 1996; Krycer & Hersey, 1991; Schellinger, 1950; Schultz, 1995; Ward & Schultz, 1995).

Although amorphous powder may be desirable due to increased solubilization rate and bioavailability, the amount of amorphous material present after processing of a bulk crystalline powder is often unpredictable and can generate many formulation performance, processing, and storage challenges. Furthermore,

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process induced amorphous material may have lower physical and/or chemical stability (Buckton, Butler, Thielmann, & Williams, 2001; Kawakami, Numa, & Ida, 2002; Newell, Buckton, Butler, Thielmann, & Williams, 2001; Ward & Schultz, 1995), with the amorphous content continually being thermodynamically driven to revert to a more stable crystalline form. Indeed, if thermodynamic constraints are met, amorphous material will spontaneously recrystallize when the glass transition temperature (T_g) is exceeded. In addition, with increasing humidity, the glass transition temperature is reduced (through plasticization) (Buckton & Darcy, 1999; Stubberud, Arwidsson, Hjortsberg, & Graffner, 1996). For example, materials, such as amorphous lactose, will spontaneously crystallize when water content in the amorphous component is ≥7.25% w/w, equivalent to a relative humidity (RH) of 57% RH (Burnett, Thielmann, & Booth, 2004; Shalaev & Franks, 1995).

Clearly, for pharmaceutical products, which may routinely be subjected to conditions conducive to amorphous recrystallization, variations in the degree of amorphous content in primarily crystalline samples may have serious implication with regards to formulation performance. Since amorphous content induced during processing will be primarily located on the surface (Begat, Young, Edge, Kaerger, & Price, 2003; Price & Young, 2005; Schultz, 1995; Young & Price, 2004), there is potential for the amorphous material to form bridges and 'fuse' to other particles during the recrystallization process (Schultz, 1995). Indeed, recent investigations of dry powder carrier-based blends, used for inhalation, have suggested variation in amorphous content of the API to play a major role in the efficacy and delivery performance (Young & Price, 2004).

Current methods for quantification of amorphous content in pharmaceutical excipients (with approximate limits of detection indicated in brackets (% w/w)) include differential scanning calorimetry (DSC) (10%), modulated DSC, and hyper DSC (1.5%) (Buckton & Darcy, 1999; Hill, Craig, & Feely, 1998; Saleki-Gerhardt, Ahlneck, & Zografi, 1994; Saunders, Podluii, Shergill, Buckton, & Royall, 2004), density (10%) (Duncanhewitt & Grant, 1986; Suryanarayanan & Mitchell, 1985), powder X-ray diffraction (1–10%) (Buckton & Darcy, 1999; Saleki-Gerhardt et al., 1994), FT-Raman (1%) (Murphy, Prescott, & Larson, 2005), and Near IR (1%) (Gombas, Antal, Szabo-Revesz, Marton, & Eros, 2003; Hogan & Buckton, 2001; Wargo & Drennen, 1996). It is interesting to note that few techniques are capable of quantifying amorphous contents below 1%. These techniques include: solid state NMR (0.5% w/w) (Gustafsson, Lennholm, Iversen, & Nystrom, 1998), solution calorimetry (0.5%) (Hogan & Buckton, 2000), and microflow calorimetry (0.5% w/w) (Briggner, Buckton, Bystrom, & Darcy, 1994; Buckton, Darcy, & Mackellar, 1995; Dilworth, Buckton, Gaisford, & Ramos, 2004; Gustafsson et al., 1998).

One of the most sensitive techniques for the determination of amorphous content is gravimetric vapor sorption (~0.2% w/w) (Buckton & Darcy, 1995; Saleki-Gerhardt et al.,1994). In general, the technique involves measuring the moisture uptake in samples containing mixtures of 100% amorphous and 100% crystalline material to construct a calibration curve. Subsequently, using the same conditions and technique, a sample with unknown amorphous may be calculated. It is interesting to note however, that this method for determination of amorphous content may be flawed, because direct comparison of partially amorphous particles to wholly amorphous and wholly crystalline systems may result in a significantly different outcome as semicrystalline materials will have different molecular mobility compared with wholly amorphous or crystalline material (Craig, Kett, Murphy, & Price, 2001). The difference in mobility may affect the uptake of moisture, where water molecules may not be able to migrate through the system in the same way. However, for many common pharmaceutical systems, this method is generally accepted (Buckton & Darcy, 1999; Saleki-Gerhardt et al., 1994).

The determination of amorphous content via gravimetric measurement can be achieved through a series of different scientific approaches. For example, the approach developed by Saleki-Gerhardt et al., (1994) measured equilibrium moisture uptake of various crystalline and amorphous mixtures at specific humidities. Such an approach resulted in a linear relationship between equilibrium moisture content and crystallinity with a detection limit of least 1%. However, it is interesting to note that with this technique, samples must not be exposed to relative humidity levels that will cause a recrystallization event. Subsequently, the detection limits are limited to mass differences obtained at humidities below the glass transition of the material.

In comparison, the method described by Buckton & Darcy (1995) utilizes a water vapor induced

recrystallization event to determine the amorphous content. By investigating the residual weight change after conducting multiple moisture sorption cycles (0–90% RH), Buckton and Darcy were able to determine variations in amorphous content between samples of amorphous and crystalline lactose (due to the formation of the monohydrate during crystallization of the amorphous form). In comparison, Mackin et al. (2002) compared the relative mass difference at specific partial pressures of polar organic solvents prior to and post organic solvent induced recrystallization. Assuming no hydrate or solvate formation, the difference in uptake between the partially amorphous and recrystallized material is directly related to the amount of amorphous material in the sample.

The present investigation is an extension of the well-known approach developed by (Saleki-Gerhardt et al., 1994). However, instead of using water vapor where the RH range is limited to partial pressures below that of the sample glass transition, an apolar organic probe was used. As with gravimetric water vapor isotherms, it was assumed that amorphous material will have a greater organic vapor sorption capacity than the crystalline material. However, because the probe is relatively large and apolar, the entire partial pressure range may be used without observing a crystallization phenomena (thus potentially allowing higher resolution). As with the previous studies, the relative sorption of amorphous and crystalline samples was investigated using blends of 100% crystalline and amorphous material.

Furthermore, to keep in line with previous investigations on amorphous material, alpha-lactose monohydrate and salbutamol sulfate, were chosen as model systems because they are widely used in pharmaceutical preparations as excipients and medicaments, respectively (Columbano, Buckton, & Wikeley, 2002; Hogan & Buckton, 2001; Saleki-Gerhardt et al., 1994).

EXPERIMENTAL

Materials and Methods

Materials

Lactose monohydrate (lactose) was supplied by Borculo Domo Ltd. (Lactochem crystals) (Netherlands). Salbutamol sulfate was supplied by Inter-Chemical Ltd. (China). *N*-octane was supplied by BDH (Australia) and was of analytical grade.

Preparation of Crystalline and Amorphous Standards of Model Drug and Excipient

Crystalline salbutamol sulfate and lactose were preconditioned by storing in tightly sealed containers with a saturated solution of potassium chloride. This produced a relative humidity of 84% at 25°C (Richardson & Malthus, 1955). Samples were stored for a period of 7 days to ensure crystallization before being transfered to a desiccator over phosphorous pentoxide (0% RH) prior to analysis. Amorphous samples of salbutamol sulfate and lactose were prepared by spray drying from an aqueous solution using methods described elsewhere (Columbano et al., 2002; Price & Young, 2004).

X-ray Powder Diffraction

In order to confirm the spray drying process and preconditioning methods resulted in amorphous and crystalline forms, the materials were characterized using X-ray powder diffraction (D5000, Siemans, Karlsruhe, Germany). The settings were as follows; 5 to 40 2θ, step size 0.04 2θ, step time 2 s, temperature 25°C.

Organic Dynamic Vapor Sorption

Organic DVS is a relatively novel method for determining the amorphous content of powders by measuring the adsorption isotherm of organic vapors, using an automated gravimetric vapor sorption analyzer. In general, the organic DVS works using the same principle as standard water moisture sorption. In simple terms, the DVS is an ultrasensitive microbalance with a resolution of 1 part in 10 million (Cahn microbalance). The main instrument is housed in a temperature controlled chamber (5–85°C) and required humidities are generated by mixing dry and saturated vapor gases using a mass flow controller before passing over the sample and reference holders (Buckton & Darcy, 1995).

The technique measures the adsorption of an apolar molecule (*n*-octane) into the surface of a sample as a function of partial pressure. Since the relative adsorption of the molecule into amorphous and crystalline samples will vary, a calibration curve may be constructed by comparing the relative adsorption in blends of 100% crystalline and 100% amorphous samples. From this, the amorphous content of an unknown sample may be determined. Measurements

were conducted on a DVS-1 (Surface Measurement Systems, UK), at 25°C, using *n*-octane as the vapor probe. The humidity probes in the instrument were removed and replaced with sealing blanks to protect them from irreversible damage due to the organic vapors, and the vapor outlet was exhausted to a fume extractor due to safety considerations.

Organic vapor sorption isotherms were measured on 100% crystalline, 100% amorphous, and mixtures containing known amounts of each. Approximately, 100 mg of either lactose or salbutamol sulfate mixtures were weighed into the sample pan and exposed to a three step *n*-octane partial pressure (p/p_0) cycle of 0%–90%. Equilibrium at each step was determined by a dm/dt of $0.0002.min^{-1}$.

Preparation of Mechanically Milled Lactose Samples

To further investigate the organic DVS technique a series of milled lactose samples, containing unknown amorphous content, were analyzed. Mechanical activation of the lactose samples were achieved by comminution in a small volume ball mill (1 L) containing 60 ceramic balls (mean diameter of 19.27 ± 0.71mm). Approximately, 100 g samples of crystalline α-lactose monohydrate were weighed into the ball mill which was rotated at 42 $rev.min^{-1}$ for durations of 10, 20, 30, 40, 50, and 60 min. Each sample was collected and stored in tightly sealed containers over phosphorus pentoxide prior to DVS analysis.

As previously described, each sample was analyzed using *n*-octane vapor, and amorphous content was determined based on a mass difference between p/p_0 *n*-octane vapor pressures of 0 and 90% ($n=5$). In addition, approximately 10 g of the 60 min mill time sample was transfered onto a glass Petri-dish and stored in a tightly sealed container with a saturated solution of potassium chloride to produce a humidity of 85%. The sample was stored for three weeks at 85% RH to ensure recrystallization, during which time the sample was regularly stirred to ensure moisture penetration into the powder bed. After three weeks, the sample was removed and transfered into a container with phosphorous pentoxide (0% RH) for a minimum of 24 hr before DVS analysis (using the method described above). Due to cost constraints relative to salbutamol sulfate, the mechanical activation of the model drug samples could not be investigated and the effect of the introduction of amorphous material was limited to the chosen excipient.

RESULTS AND DISCUSSION

X-ray Powder Diffraction

The XRPD diffractograms of spray dried/crystalline lactose and salbutamol sulfate are shown in Figure 1a and 1b, respectively. In general, the broad, diffuse peaks in the XRPD diffractogram of spray-dried lactose and salbutamol sulfate are indicative of a lack of any significant crystalline long-range order, suggesting amorphous nature. In contrast, the crystalline materials showed characteristic sharp diffraction peaks associated with a highly crystalline material.

Organic DVS

As previously stated, the relationships between *n*-octane vapor sorption and amorphous content, in

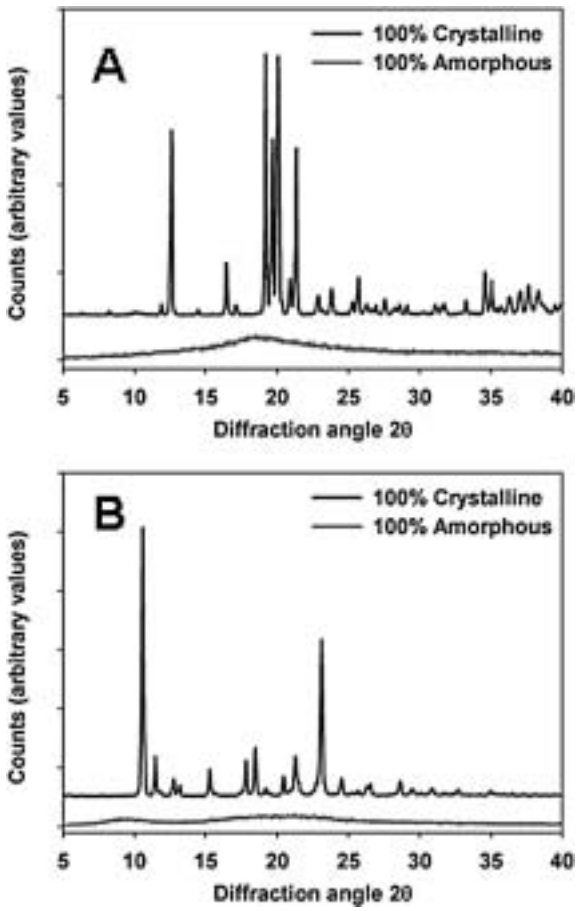

FIGURE 1 XRPD Diffraction Patterns for 100% Crystalline and 100% Amorphous (a) Lactose and (b) Salbutamol Sulfate.

either lactose or salbutamol sulfate, was investigated by exposing samples with different ratios of crystalline-amorphous to p/p_0 0–90%. Data was plotted as a function of % mass change-dry and with cycles being conducted in triplicate. A representative vapor adsorption-desorption cycle for 100% crystalline lactose and 100% amorphous lactose is shown in Figure 2a. As can be seen from Figure 2a, the variation in vapor sorption between the 100% crystalline and 100% amorphous was large with an approximate mass difference of 0.2% at 90% p/p_0. Furthermore, statistical analysis of the data suggested significant differences between p/p_0 at 90% for the crystalline and amorphous samples (ANOVA $p < 0.05$), with mean mass adsorption values of 0.089% ± 0.0004% and 0.2156% ± 0.0112% for 100% crystalline and amorphous lactose, respectively.

Such observations are to be expected because vapor sorption into the crystalline lactose will be preferentially via adsorption, while amorphous sample will be via absorption into the disordered glassy state. To further test the relationship between vapor sorption and amorphous content, a series of mixes of lactose were analyzed using the same cycle conditions. A vapor p/p_0 of 90% was chosen, because it resulted in largest differences between ratios and was used to construct a calibration curve as is shown in Figure 2b. Linear regression of the relationship between vapor sorption (p/p_0=90%) and percentage mass uptake suggested a good correlation with a R^2 value of 0.992.

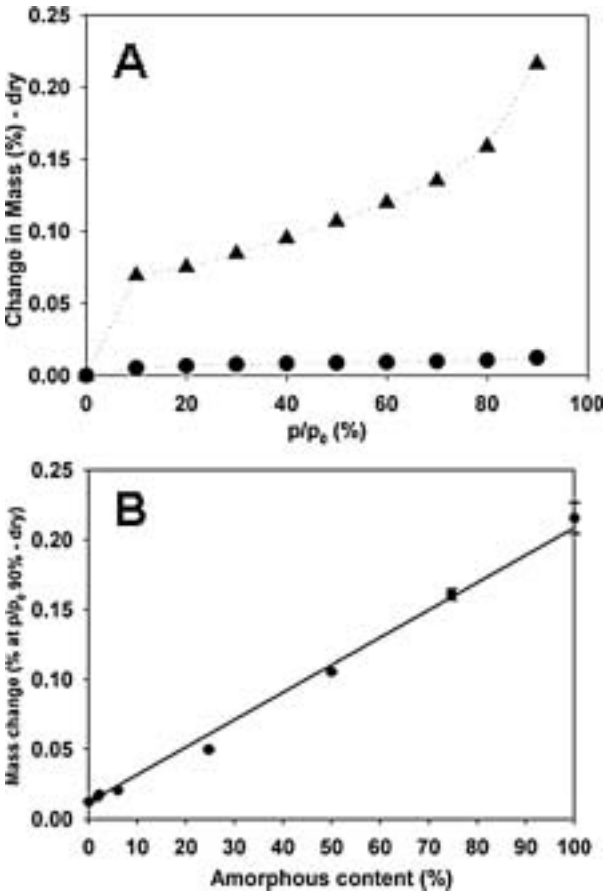

FIGURE 2 (a) DVS Isotherms for the Adsorption and Desorption of *N*-Octane Into 100% Crystalline and 100% Amorphous Lactose Samples (p/p_0 0–90%). (b) Calibration Curve for Moisture Sorption Into Blends of 100% Amorphous and Crystalline Lactose (R^2=0.992).

Similarly, the influence of *n*-octane vapor sorption into mixtures of crystalline and amorphous salbutamol sulfate was investigated. As with the lactose samples, variation in sorption between crystalline and amorphous samples was large with an approximate mass difference of 0.2% at 90% p/p_0. Statistical analysis of sorption isotherms suggested significant differences for all mixes studied (ANOVA $p < 0.05$). Linear calibration data for the sorption of *n*-octane into mixes of amorphous and crystalline salbutamol sulfate resulted in a R^2 value of 0.999. Data are shown graphically in Figure 3.

Measurement of Amorphous Content in Milled Lactose Samples

As previously discussed, the degree of amorphous content present in the milled lactose samples was determined using a novel organic vapor DVS technique. Analysis of the amorphous content with respect to milling time suggested an exponential increase in amorphous content reaching a plateau after 60 min (Figure 4). Such observations are expected, because amorphous content is introduced into the sample by surface molecular damage caused by the milling process. As the particles are reduced in size, the comminution efficiency will follow suit. Such an effect will result in a finite milling efficiency and subsequent amorphous content.

Organic DVS analysis of the 60 min mill time after exposure to elevated humidity suggested a completely crystalline material (0.00%).

CONCLUSION

A new method was developed for determining low levels of amorphous contents for both drug particulate

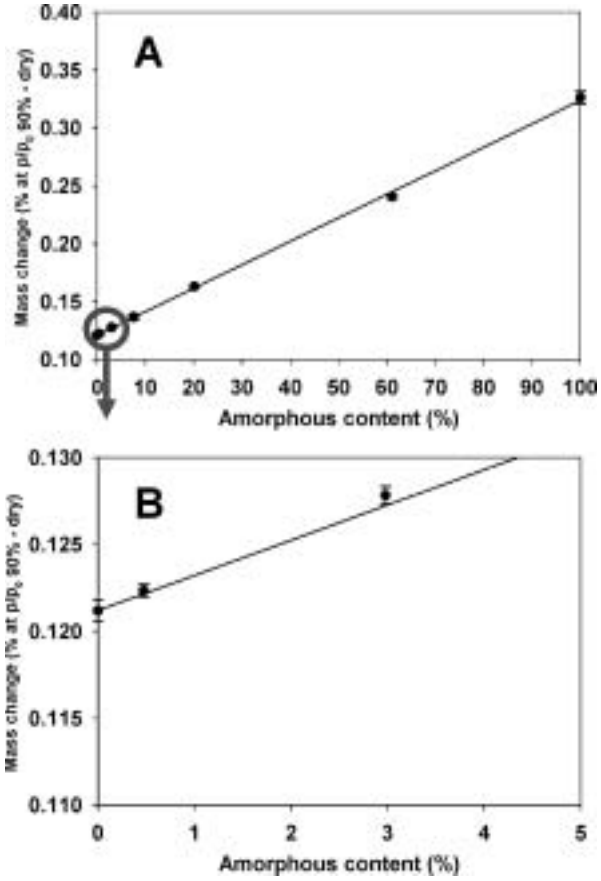

FIGURE 3 **Relationship Between Moisture Sorption of *N*-Octane Into Crystalline-Amorphous Ratios of Salbutamol Sulfate at a p/p_0 of 90%. R^2 value=0.999.**

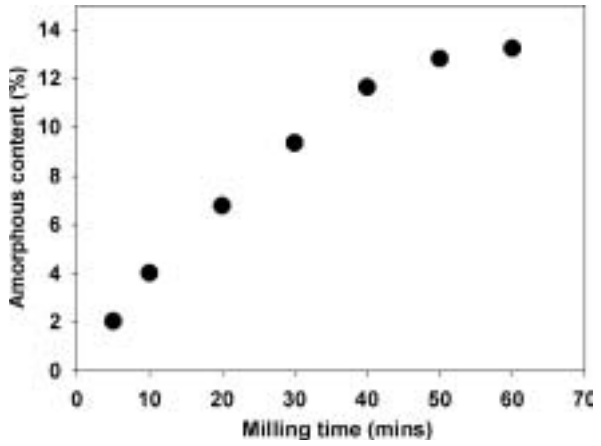

FIGURE 4 **Influence of Mill Time on Amorphous Content of 100% Crystalline Lactose.**

and carrier material. Using known amorphous and crystalline lactose and salbutamol sulfate standards, *n*-octane vapor isotherms were used to create an amorphous content calibration curve. From this curve, samples with unknown amorphous contents could be determined with an accuracy of approx. 0.05%.

The method used to determine amorphous content for this investigation has some distinct advantages over previous gravimetric techniques. First, differently from the methods previously described in literature (Buckton & Darcy, 1995; Mackin et al., 2002), this technique does not require a solvent-induced recrystallization. Additionally, this method does not require the formation of a hydrate/solvate with a known stoichiometry (Buckton & Darcy, 1995). *N*-octane vapor does not typically induce any morphological transformations in the sample, so the entire partial pressure range may be studied, unlike water vapor-based methods (Saleki-Gerhardt et al., 1994). Finally, the kinetics for *n*-octane adsorption is relatively fast (compared to water), so experimental throughput can be faster. Clearly, this technique is applicable to a wide range of pharmaceutical powders without the limitations of previous gravimetric methods. Furthermore, although this particular study investigated two hydrophilic compounds (used in inhalation-based medicaments) the use of this technique to determine amorphous content in hydrophobic material may also be of interest. In such samples it would be envisaged the affinity of the dispersive probe to hydrophobic material would be greater than in the hydrophilic systems, thus, resulting in a further increase in resolution.

Industrial processing of drug particulates and carrier materials used in dry powder inhaler systems may induce changes in the physical properties of the particles. Here the authors confirmed a simple ball milling process introduced amorphous material in the carrier sample. Moreover, storage of the processed α-lactose excipient under high humidity was shown to induce changes in amorphous content.

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