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A study of the crystallisation of amorphous salbutamol sulphate using water vapour sorption and near infrared spectroscopy

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Abstract

The crystallisation of amorphous salbutamol sulphate prepared by spray drying was monitored using a humidity controlled microbalance (Dynamic Vapour Sorption apparatus, Surface Measurement Systems) combined with a near-infrared probe. Amorphous salbutamol sulphate was prepared by spray drying from a solution in water. The particles were then analysed using scanning electron microscopy, thermogravimetric analysis, differential scanning calorimetry, powder X-ray diffraction, isothermal microcalorimetry and water vapour sorption analysis combined with near-infrared spectroscopy (NIR). Isothermal microcalorimetry and water vapour sorption combined with NIR spectroscopy were able to detect the transition from the amorphous to crystalline state. However while the isothermal microcalorimeter showed only a classic crystallisation exotherm when the material was exposed at 75% RH, the DVS-NIR results at the same humidity highlighted a more complex process. When exposed at 75% RH, the uptake of water was followed by crystallisation that was detected using NIR. The expulsion of water after crystallisation was very slow and at a constant rate whether the material was exposed to 75 or 0% RH. The NIR and DVS studies indicated that the material had crystallised very soon after exposure to high RH. The water that was expelled during crystallisation was not displaced from the particles and remained associated with the particles for many days. This study showed that the use of gravimetric analysis together with NIR spectroscopy provided valuable information on the dynamics of the crystallisation of salbutamol sulphate. The retention of water within recently crystallised salbutamol is potentially important to the behaviour of dosage forms containing the amorphous (or partially amorphous) form of this drug. © 2002 Published by Elsevier Science B.V.

Keywords: Salbutamol sulphate; Amorphous; Crystallisation; Calorimetry; Water sorption; Near-infrared spectroscopy

1. Introduction

The amorphous state of a solid is characterised by the absence of the three-dimensional long-range order that exists in a crystalline material.

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The four most common ways to induce amorphous character in a solid are condensation from the vapour state, supercooling of the melt, mechanical activation of a crystalline mass (milling) and rapid precipitation from solution (freeze-drying or spray-drying) (Hancock and Zografi, 1997).

Amorphous regions in crystals are generally thermodynamically unstable and therefore they show some tendency to crystallise spontaneously. The transition from amorphous to crystalline form will depend on the mobility of the molecules. Once incorporated into an amorphous region, water can increase the free volume and lead to enhanced molecular mobility of the solid causing a reduction in the glass transition temperature (T_g). As the T_g drops below the experimental temperature T, the amorphous material will collapse under gravity and subsequently will crystallise (a recent demonstration of this long established process is given by Buckton and Darcy (1999)). During crystallisation, water that was present in the amorphous regions is expelled from the solid.

In the pharmaceutical industry amorphous or partially amorphous material can be formed during many processes, for example milling or spray drying. As the amorphous state can be critical in determining the solid-state physical and chemical properties of many pharmaceutical dosage forms, it is important to be able to accurately quantify it. Differential scanning calorimetry or powder X-ray diffraction, are able to measure the amorphous content of samples, but they have a limit of detection of between 5 and 10% (Saleki-Gerhardt et al., 1994). However, material with low amorphous content, where the amorphous state is process induced, is generally characterised by a high level of disruption that is mainly concentrated at the surface (i.e. a region of material of undetermined depth from the surface into the bulk) and consequently in these cases it may be inappropriate to use X-ray diffraction or differential scanning calorimetry. A powerful method to investigate properties of the surface of powders is vapour sorption analysis, where a microbalance in a temperature and humidity controlled environment allows the study of uptake and release of water (Saleki-Gerhardt et al., 1994). Such gravimetric sorption experiments are well suited to the study of amorphous forms, as the amorphous material will often sorb water very readily.

Salbutamol sulphate is a drug that is used in numerous inhalation products. Spray drying could potentially be used as an alternative method to obtain the right particle size distribution suitable for delivery to the lungs in metered dose or dry powder inhalation systems. In these cases however it is important to characterise the amorphous form of salbutamol sulphate, and the process by which the amorphous form crystallises, as this could affect the long-term stability of products containing the spray dried form of the drug. Buckton et al. (1995) have reported that amorphous salbutamol sulphate crystallises when exposed to elevated humidity in an isothermal microcalorimeter at 25 °C. Ward and Schultz (1995) measured the amorphous content of micronised salbutamol sulphate using water vapour sorption analysis and solution microcalorimetry. In the current study we report on the use of isothermal microcalorimetry, near infrared spectroscopy and gravimetric vapour sorption to study the crystallisation of salbutamol sulphate. Near infrared spectroscopy (NIR) is a technique that is becoming more important in the routine analysis of pharmaceutical materials, it has been used in the past to study the transition from amorphous to crystalline lactose (Buckton et al., 1998). NIR is fast (only a few seconds per sample), non-invasive and does not require sample preparation. In this study a NIR probe was housed in a humidity controlled microbalance, so that while the sample was exposed to a specific humidity and the sorption/de-sorption of water recorded, it was possible to obtain NIR spectra. This novel hyphenation of techniques has only been used for studies on the crystallisation of lactose to date (Lane and Buckton, 2000).

2. Materials and methods

2.1. Materials

Crystalline salbutamol sulphate was supplied by Avocado.

Microparticles of salbutamol sulphate were prepared by spray dying from solution in water using a Büchi 190 mini spray drier fitted with a 7 mm pneumatic nozzle. A 10% W/V salbutamol sulphate solution in water was spray dried. The conditions and spray drying parameters were selected based on the work of Chawla et al. (1994): pump speed, 5 ml min^{-1}; air flow rate, 800 l h^{-1}; aspirator level, 5; inlet temperature, 150 °C (± 5°C) and outlet temperature 80 °C (± 5°C). The material was desiccated over phosphorous pentoxide immediately after drying.

2.2. Particle morphology

The morphology and shape of spray dried salbutamol sulphate were examined using a Philips XL 20 scanning electron microscope (Philips, Cambridge, UK).

2.3. Isothermal microcalorimetry

Isothermal microcalorimetry was used to assess the degree of crystallinity of spray dried salbutamol sulphate following the method described by Buckton et al. (1995). Spray dried and feed material were investigated using a Thermal Activity Monitor (Thermometric) at 25 °C. About 50 mg of material, accurately weighed, was placed into a 3 ml glass ampoule together with a tube containing a saturated solution of sodium chloride (75% RH). The ampoule was sealed and equilibrated in the calorimeter for 30 min before lowering into the measuring site. The output from the calorimeter was recorded using a computer as heat flow (dq/dt = power) as a function of time. Spray dried and feed materials were also investigated using powder X-ray diffraction (Siemens D 5000, at the following conditions: Cu Kα ($\lambda = 1.542$ Å) radiation, 2–30° 2θ; step size: 0.02°; time per step: 2 s).

2.4. Thermogravimetric analysis

Thermogravimetric analysis (TA instruments) was undertaken using ca. 6 mg of material in open aluminium pans scanning from 25 to 200 °C at 10 °C min^{-1}.

2.5. Differential scanning calorimetry

Differential scanning calorimetry (Perkin Elmer DSC7) was undertaken using ca. 6 mg of material in non-hermetically sealed aluminium pans and scanning from 25 to 300 °C at 10 °C min^{-1} under an atmosphere of nitrogen.

2.6. Dynamic vapour sorption combined with near infrared spectroscopy (DVS-NIR)

Gravimetric studies of spray dried salbutamol sulphate were undertaken in a humidity controlled microbalance (DVS, Surface Measurement Systems, UK). The dynamic vapour sorption apparatus (DVS) is based on a Cahn microbalance capable of measuring changes in sample mass lower than 1 part per million, placed in an incubator to control the temperature. Mixing dry and saturated vapour gas flows in the correct proportions using mass flow controllers generates the required humidity. The apparatus was computer controlled, allowing a pre-programming of the sorption and de-sorption isotherms. Samples of about 50 mg were loaded on one side of the pan balance and the programme set to control the humidity at 0% for 6 h (drying phase), then at 75% for 15 h (to allow crystallisation) and then back at 0% for at least 3 h (unless otherwise stated). At the same time NIR spectra were recorded using a FOSS NIRSystems spectrometer with the fibre optic probe situated 4 mm below the flat-bottomed pan of the microbalance. Each NIR measurement was the mean of 32 scans over the wavelength range 1100–2500 nm. Spectra were taken every 15 min, recorded and analysed using the Vision software (FOSS NIRSystems).

3. Results and discussion

3.1. Scanning electron micrographs

The scanning electron micrographs of spray dried salbutamol sulphate are shown in Fig. 1 (magnification: 3800, bar: 5 μm). The particles were spherical with a diameter of 5 μm or less.

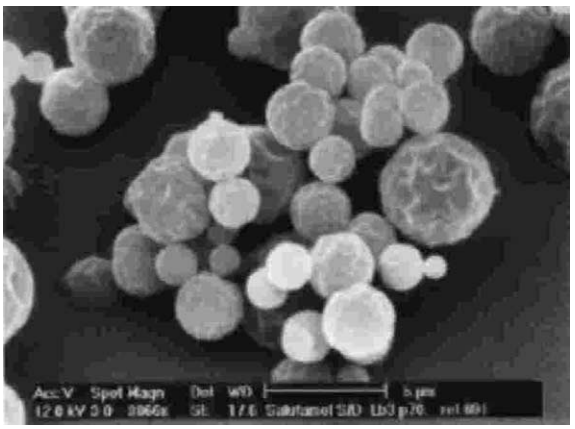

Fig. 1. Scanning electron micrograph of spray dried salbutamol sulphate.

3.2. Isothermal microcalorimeter

The calorimetric data for crystalline and spray dried salbutamol sulphate exposed at 75% RH are shown in Fig. 2. Whereas the feed sample used to prepare the spray dried material (crystalline salbutamol sulphate) resulted, after the initial disruption due to the lowering of the ampoule into the measuring cell, in a flat baseline, the spray dried material produced an exothermic response that corresponds to the crystallisation peak found by Buckton et al. (1995) for the same drug.

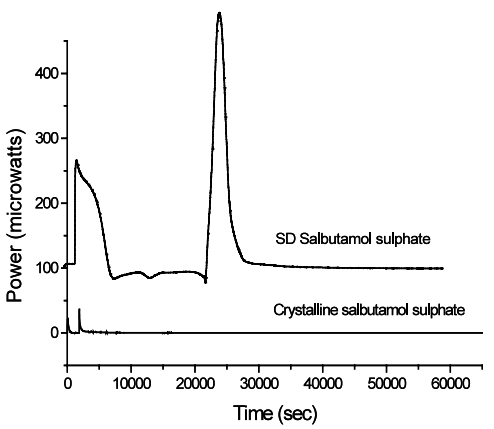

Fig. 2. Microcalorimeter output (power as function of time) of crystalline and spray dried salbutamol sulphate at 75% RH and 25 °C.

The crystallisation response indicates that after a lag time, during which the powder bed absorbs the water vapour, there is a very sudden exothermic output when all the amorphous material in the sample crystallises. As crystallisation occurs, the absorbed water is expelled from the structure, which will be an endothermic process. Therefore the area under the peak, which is the sum of an exothermic and an endothermic event, is considered the apparent enthalpy of crystallisation, which is obviously much smaller than the true enthalpy of crystallisation. Table 1 shows the apparent crystallisation enthalpy of salbutamol sulphate. The average of 22.34 J g^{-1} (SD = 0.645, $n = 4$) is in good agreement with Buckton et al. (1995).

The diffractograms of the feed material (crystalline salbutamol) and of spray dried salbutamol sulphate are shown in Fig. 3. The amorphous nature of the spray dried samples was proved by X-ray diffraction, which revealed no evidence of crystalline structure (The lower detection limit of powder X-ray for crystalline content of salbutamol has not been investigated, these data do not prove total absence of crystalline material, but do show that if any crystalline form is present it is there at a very low level. Generally X-ray is better at detecting a small amount of crystalline form in an amorphous sample than it is at detecting a small amount of amorphous form in a crystalline sample).

3.3. DVS-NIR

The water vapour sorption data of crystalline salbutamol sulphate is shown in Fig. 4. The significant uptake of water when exposed at 75% RH was unexpected, as this drug is not hygroscopic and it does not form hydrates. However, the particle size was small (less than 5 μm, data not reported), which means that the surface area will be substantial, which is the probable reason for the extent of water sorption. The water vapour sorption data for spray dried salbutamol sulphate are shown in Figs. 5 and 6. It possible to observe that as soon as the powder is exposed to 75% RH there is a rapid uptake of water up to 13% w/w, which is then desorbed very slowly. Indeed after

Table 1
Heat output for the same batch of spray dried salbutamol relative to four experiments measured by isothermal microcalorimeter (SD = 0.645)

Material	Weight (mg)	Area	Recrystallisation enthalpy (J g^{-1})
Salbutamol sulphate	50.1	1.08×10^6	21.6
Salbutamol sulphate	50.3	1.16×10^6	23.1
Salbutamol sulphate	50.3	1.13×10^6	22.5
Salbutamol sulphate	50.1	1.11×10^6	22.2

70 h (65 h after the RH was changed to 75%) the water content was still 6%, which is almost half of that which was absorbed (Fig. 6). The rate of desorption of water is almost constant and remains unchanged even if the RH is adjusted from 75 to 0% RH (Fig. 5). The slow diffusion of water from amorphous materials has been observed previously for collapsed amorphous lactose by Darcy and Buckton (1997). It is possible then to imagine that the salbutamol sulphate is in a collapsed amorphous form throughout this slow period of water desorption. However, spectroscopic studies indicate that this is not the case.

The NIR spectra collected from the probe attached to the DVS are shown in Figs. 7 and 8. The data were mathematically treated by use of standard normal variate (SNV) to eliminate the contribution from physical effects such as particle size and were then transformed into the second derivative, in order to make the peaks have greater clarity (in second derivative peaks point downwards). Fig. 7 shows the spectra collected at different humidities for crystalline salbutamol sulphate. The spectra in Fig. 7 are indistinguishable except for small changes in the region related to adsorption of water (1940 nm: O–H stretching and deformation). A selection of NIR spectra of spray dried salbutamol sulphate are shown in Fig. 8 together with the spectrum of crystalline salbutamol sulphate for comparison. The spectra show differences between the amorphous and the crystalline forms in the region 2025–2175 nm; these differences disappear after 2 h at 75% RH. The spectrum of the drug does not then undergo any other changes for the time period from 2 to 55 h exposure to 75% RH, as shown in Fig. 8, with the exception of the water regions at 1450 and 1940 nm, where the NIR peaks decrease slowly in keeping with the slow water desorption observed in the DVS data. It is therefore possible to conclude that after 2 h exposure at 75% RH, immediately after the beginning of the water desorption, the amorphous drug has crystallised in a manner that did not allow rapid desorption of water. It follows that the water is trapped within material in a fused mass, and will only be released after several days. There were however profound differences between the spectra of the feed material (crystalline salbutamol sulphate) and the sprayed material that had crystallised in the DVS (for example, the O–H stretching and intermolecular hydrogen bonds at 1400–1600 nm). These differences may be related to the fact that water molecules were trapped within the particles of the recently crystallised samples.

The isothermal microcalorimetry data for the crystallisation of spray dried salbutamol sulphate

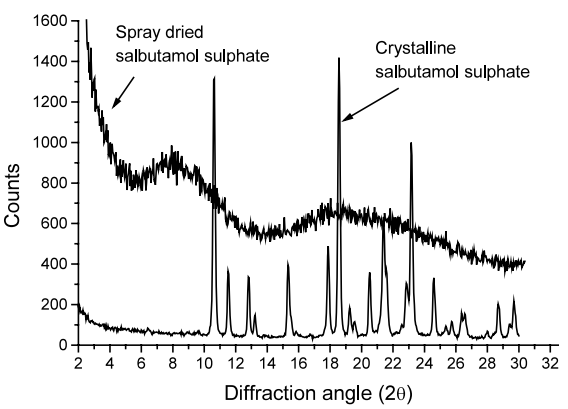

Fig. 3. Powder X-ray diffractograms of crystalline salbutamol sulphate (fed material, Avocado) and spray dried salbutamol sulphate.

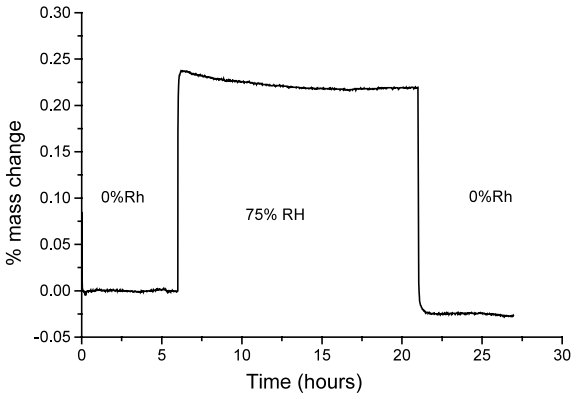

Fig. 4. Water vapour sorption analysis of crystalline salbutamol sulphate as % weight change versus time: 6 h at 0% RH, 15 h at 75% RH and 6 h at 0% RH.

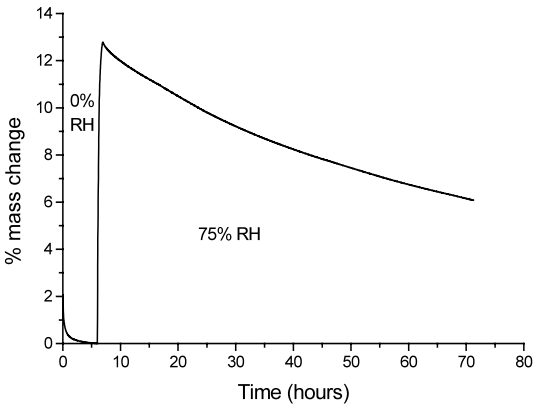

Fig. 6. Water vapour sorption analysis of amorphous salbutamol sulphate as % weight change versus time: 6 h at 0% RH and 55 h at 75%.

gave a classic exothermic peak after exposure to 75% RH with no evidence of the complex situation observed in the DVS-NIR study, probably because the rate of change of heat for the very slow desorption of water was not noticeable on the scale of scrutiny (and during the time of study) used for the calorimetric measurements. In order to check the status of the drug immediately after the crystallisation peak, the microcalorimeter experiment was stopped as soon as the peak reached the baseline and the material analysed using powder X-ray diffraction (same conditions used to analyse crystalline and spray dried material, see description above), DSC and TGA. The XRD trace of spray dried salbutamol sulphate after exposure to 75% RH is illustrated in Fig. 9, which shows that the material had completely crystallised under these conditions. The DSC response for the sample removed from the microcalorimeter showed a broad endotherm (peak between 120 and 140 °C) which is likely to correspond to evaporation of water that is trapped within the particles, followed by a melting endotherm. There was no evidence of a crystallisation exotherm, indicating that the material had already crystallised in the microcalorimeter. Simi-

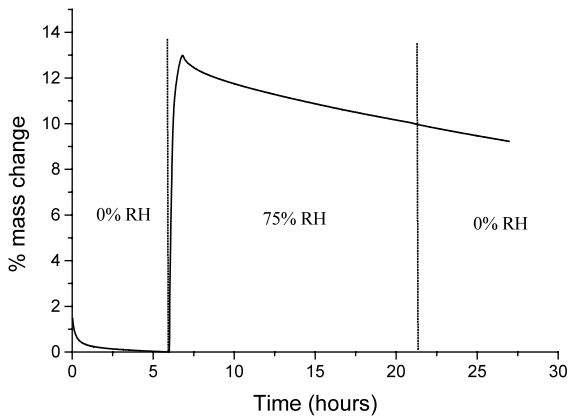

Fig. 5. Water vapour sorption analysis of amorphous salbutamol sulphate as % weight change versus time: 6 h at 0% RH, 15 h at 75% RH and 6 h at 0% RH.

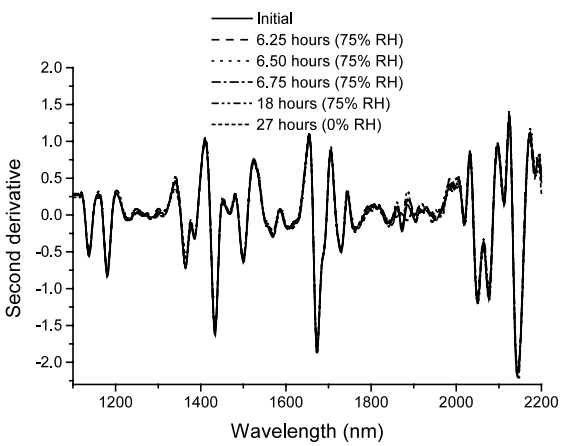

Fig. 7. Second derivative of NIR spectra for crystalline salbutamol sulphate.

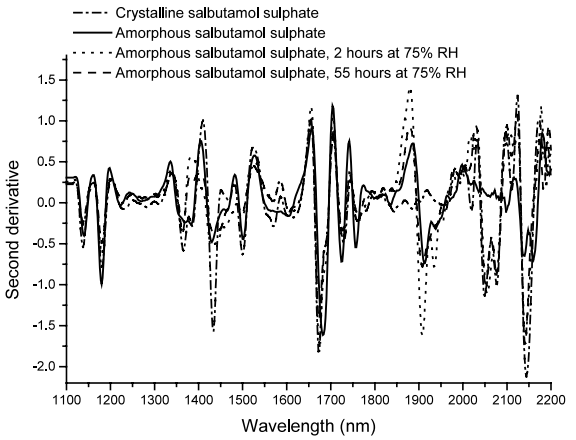

Fig. 8. Second derivative of NIR spectra for spray dried and crystalline salbutamol sulphate.

lar results were obtained using TGA where the samples showed 9.3% weight loss (± 0.04) between 80 and 160 °C. (The DSC and TGA traces have not been reproduced here.)

The results showed that the changes in amorphous salbutamol sulphate were much more complex than those observed by isothermal microcalorimetry. Isothermal microcalorimetry is a very useful technique that enables the process of crystallisation of amorphous material to be evaluated. However, it is quite often difficult to separate the different components of the response, in this case the absorption and de-sorption of water from the crystallisation itself. As a consequence, the area under the peak, which is the sum of the exothermic crystallisation and the endothermic expulsion of water, is considered to be the apparent enthalpy of crystallisation, which is obviously smaller than the true enthalpy of crystallisation. By using the dynamic vapour sorption technique combined with NIR it was however possible to study the way the amorphous material absorbs and de-sorbs water during crystallisation and the crystallisation itself, and this enabled a much more thorough characterisation of the material under investigation.

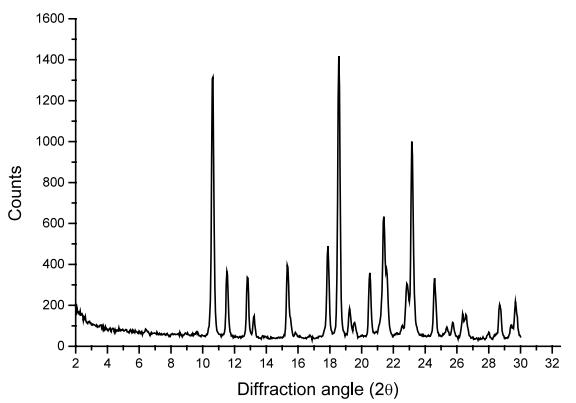

Fig. 9. Powder X-ray diffraction trace of spray dried salbutamol sulphate after exposure to 75% RH.

4. Conclusion

This study showed that the use of gravimetric analysis together with NIR spectroscopy was able to rapidly provide information on the dynamics of the crystallisation of salbutamol sulphate. The results showed that the changes in amorphous salbutamol sulphate during crystallisation were complex and not easily observed by isothermal microcalorimetry.

The retention of water following crystallisation is a surprise and is of potential significance in the cases where the spray dried form of salbutamol sulphate could be employed, for example in dry powder inhalation systems.

Acknowledgements

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