

Thermal Characterisation of Beclometasone Dipropionate (BDP) From Dry-Powder Inhalers

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Introduction

Formulation of drugs for pulmonary delivery is an increasingly popular strategy, because the lungs present a huge surface area for absorption, first pass metabolism is avoided and there is good patient compliance. Formulation presents some challenges however. To penetrate the lungs, the particle size of the drug must lie between 2-5 μm . Particles of this size distribution are typically obtained by milling, so may be partially amorphous, cohesive and difficult to flow and aerosolise. To ameliorate this, the drug is often blended with a coarse carrier, typically lactose, prior to formulation. Lactose 'fines' are also often included to aid product performance. The blend is metered into capsules and delivered with a dry-powder inhaler (DPI). The inspirational effort of the patient creates a turbulent air-stream that separates the drug from the carrier.

DPI performance is critically dependent upon both the force of adhesion between the drug and the coarse carrier and the turbulence of the air-stream and is extremely difficult to quantify in-vivo. Hence, a number of in-vitro models have been developed to enable at least comparative performance of DPI formulations. The simplest model is the twin-stage impinger (TSI), in which stage 1 represents the upper airways and stage 2 the lower lung (and so the target site in-vivo). In use, it is recommended that both stages of the TSI contain a small reservoir of solvent, to trap aerosolised powder and enable quantitative analysis. This approach has the drawback of dissolving the sample, and so any information on sample physical form is lost.

Here, we develop a simple attachment for the TSI to trap the particles prior to entry to stage 2, allowing physical form to be determined by analysis with differential scanning calorimetry. Additionally, we investigate the importance of having the solvent reservoir in stage 1.

Aims

The specific aims of the project were to;

- Develop an attachment for the TSI to trap solid particles entering stage 2 and allow recovery for analysis
- To use DSC to identify the material entering stage 2
- To evaluate the role of the solvent reservoir in stage 1



Figure 1: The TSI system (left) and the modified dose collector (right)

Methodology

BDP and α -lactose monohydrate were purchased from Sigma-Aldrich (UK). Easyhaler[®] BDP inhalers were purchased from Orion Pharma Ltd (UK). All materials were used as received. The TSI apparatus (Figure 1 left) was purchased from Copley Scientific Instruments Ltd (UK). For each actuation of the DPI (200 μg BDP) air was flowed through the TSI at a rate of 60 L/min for 5 s. A particle collector was designed and machined from acrylic (Figure 1 right) – the collector was lined with aluminium foil, when enabled entrapped particles to be removed and analysed with DSC. For some experiments, a solvent reservoir (7 mL of 25:75 water:methanol) was placed in stage 1 of the TSI.

Characterisation of physical form was performed with DSC (Q2000, TA Instruments Ltd) operated at 20 $^{\circ}\text{C}/\text{min}$ from 0-300 $^{\circ}\text{C}$. Samples were contained in aluminium Tzero pans and the instrument was calibrated with indium prior to use.

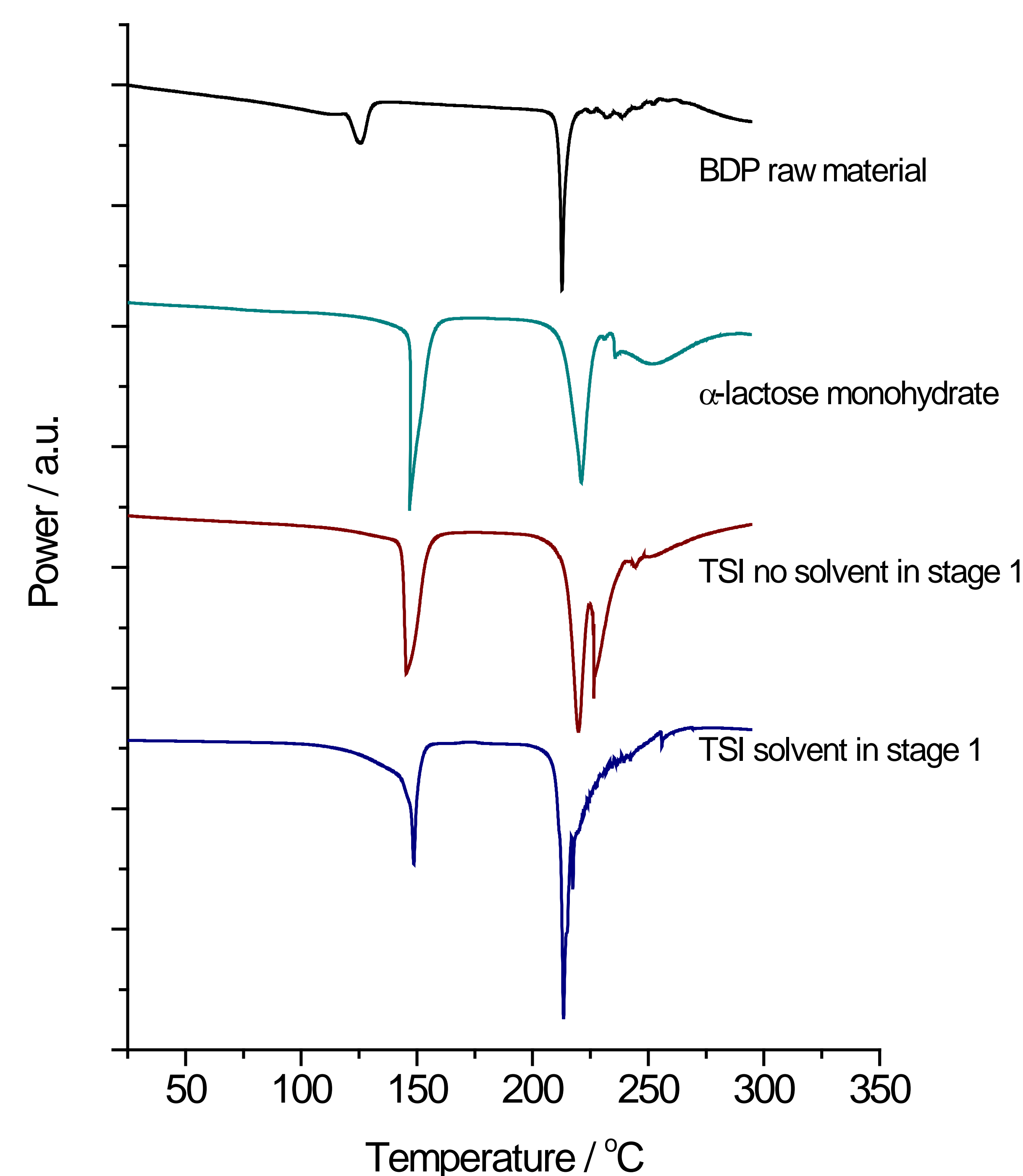


Figure 2: DSC thermal traces for (top to bottom) BDP raw material, α -lactose monohydrate, material from the sample collector with no solvent in TSI stage 1 and material from the sample collector with solvent in TSI stage 1.

Results

The DSC thermal trace of BDP raw material (Figure 2) shows endotherms at 125 and 215 $^{\circ}\text{C}$. The higher temperature peak corresponds to melting. It is not clear what the lower endotherm represents, but it is characteristic for BDP. The thermal trace for α -lactose monohydrate shows loss of water of hydration at 150 $^{\circ}\text{C}$ and melting of the anhydrate form at 220 $^{\circ}\text{C}$. At higher temperatures the baseline becomes noisy, because of thermal degradation.

The solvent collector worked as intended, capturing particles before they entered stage 2. With no solvent reservoir in stage 1 the DSC thermal trace of the recovered material from the collector showed a thermal trace similar to that of lactose – although in this case there is a second higher temperature melting endotherm corresponding to the presence of β -lactose as well as α -lactose. There was no obvious evidence that BDP was in the sample, although the blended formulation is primarily lactose. The data suggest that in this case, the TSI was not a good model for in-vivo behaviour, since separation of the coarse carrier from the BDP had clearly not occurred.

When the solvent reservoir was included in stage 1 the material recovered from the collector showed different thermal behaviour. There is evidence of melting at 215 $^{\circ}\text{C}$, corresponding to BDP, and there is no β -lactose melt, although the dehydration peak at 150 $^{\circ}\text{C}$ is still present, indicating that at least some lactose must have reached stage 2. The difference from the thermal trace of α -lactose monohydrate may indicate that only lactose fines reached stage 2 when the solvent reservoir was used. In any case, the main conclusion is that the solvent reservoir acts to separate the carrier and BDP, so its inclusion results a better model of in-vivo behaviour.

Summary

The particle collector accessory for the TSI allowed solid particles to be isolated and analysed prior to entry into stage 2 which in turn allowed investigation into the role of the solvent reservoir in stage 1. It was clear that to mimic the effects of a turbulent air-stream in-vivo, the solvent reservoir needed to be included. In the next phase of the work, similar tests will be conducted with pressurised metered-dose inhaler (pMDI) formulations of BDP, to determine the physical form of the active upon aerosolisation.

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