

Characterisation of Particles Emitted from Beclomethasone Dipropionate Solution Metered Dose Inhalers

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Summary

QVAR[®] is a highly efficient beclomethasone dipropionate (BDP) solution metered dose inhaler (MDI) that employs ethanol as a co-solvent to dissolve BDP in hydroxyfluoroalkane (HFA) 134a. The aim of this study was to design a novel method of capturing particles generated from the actuation of the solution MDI which would allow the solid-state properties of the material to be evaluated. The material ejected from the QVAR[®] inhaler appeared to be a BDP solvate. Desolvation upon heating induced the crystal lattice to collapse and, depending upon the heating rate employed during differential scanning calorimetry experimentation, the material either recrystallised spontaneously to the anhydrous crystalline state or converted into a metastable amorphous form. Powder x-ray diffraction measurements confirmed that QVAR[®] produced material that did not correspond to anhydrous crystalline BDP.

Introduction

Beclomethasone dipropionate (BDP) is one of the most commonly used corticosteroids in the treatment of asthma. Several formulations have been developed to deliver BDP to the pulmonary system including, nebulisers (Darwis and Kellaway, 2001), dry powder inhalers (DPI) (Weda *et al.*, 2000) and metered dose inhalers (MDI) (LeBelle *et al.*, 1996). However at present, regardless of the means by which BDP is delivered, its pulmonary 'targeting' is typically poor. The solubility of BDP in aqueous solutions is very low ($< 0.1 \mu\text{g ml}^{-1}$; Sakagami *et al.*, 2001) and as a consequence particulate based systems are typically used to administer BDP to the airway epithelium. In order to act locally in the tissues a particle must first dissolve within the airway lining fluid, which is primarily aqueous. This process dictates pulmonary targeting with an optimum pulmonary dissolution profile existing for locally acting compounds. Instant dissolution is not ideal because if the drug is instantly soluble in the airway lining fluid it will be rapidly taken up into the systemic circulation. Slow dissolution velocity of hydrophobic compounds can limit absorption, however, if particles do not dissolve they will be removed from the lung by mucociliary clearance. .

QVAR[®] is a solution MDI that employs ethanol as a co-solvent to dissolve BDP in hydrofluoroalkane (HFA) 134a propellant. The size of the aerosolised material emitted from QVAR[®] is significantly smaller than the particle size of traditional chlorofluorocarbon (CFC) MDI formulations and this results in much greater lower airway deposition. However, despite its world-wide clinical use, very little is known about the solid-state characteristics of the particles/droplets emitted from the QVAR[®] formulation. Therefore, the aim of this study was to design a novel method of capturing the particles generated from the actuation of solution formulations which would allow the solid-state properties of the material emitted from the inhalers to be evaluated.

Materials and Methods

The second stage of the twin-stage impinger (TSI, Copley Instruments, UK) was modified to allow the direct collection of emitted material. The dose collector was lined with either aluminium foil (for subsequent thermal analysis studies) or a Mylar polymer sheet (for subsequent powder x-ray diffraction (PXRD) studies) to capture material. The QVAR[®] (3M Ltd, UK) formulation was actuated into the TSI a sufficient number of times to ensure a measurable output for the analytical procedures. The TSI was disassembled and the collection device removed, consolidated and analysed by differential

scanning calorimetry (DSC) or PXRD. For the DSC experimentation, the samples were heated to 350°C at 20°C per min using a DSC821c (Mettler Toledo, USA) DSC or at 300 °C per min using a Pyris 1 DSC (Perkin Elmer) equipped with an Intracooler 2P chiller unit, and the resulting heat-flow response monitored. Oxygen free nitrogen was used as the purge gas at a flow rate of 110 ml min⁻¹ in order prevent thermally induced oxidation upon heating. Temperature and heat-flow calibration of the equipment was performed prior to analysis using an indium reference standard as per the manufacturer's instructions. PXRD data were recorded with a Bruker D8 Advance diffractometer using the following operating parameters; [λ(Cu-Kα) = 1.5418 Å, voltage 40 kV, filament emission 40 mA] with 1 mm divergence slit, 1 mm receiving slit and 0.2 mm scatter slit. Samples were scanned under ambient conditions from 3-40° (2θ) using a 0.01° step width and a 1 s count time. Prior to analysis, the sample was enclosed in a modified Mylar film powder holder to minimise moisture absorption during the experimental analysis.

Results and Discussion

Anhydrous BDP powder (crystalline reference) displayed a single endothermic transition onset 208°C, which corresponds to the melting transition (T_m) of the steroid (Figure 1; previously reported as 213°C by Nachengtung, 1999). The absence of an exothermic re-crystallisation transition or a glass transition (T_g) suggests that this material was predominantly crystalline and contained little or no amorphous content.

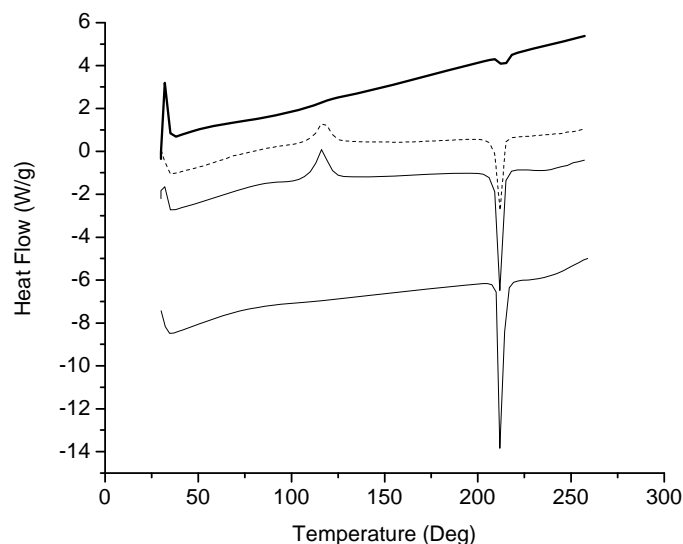


Figure 1. A comparison of the material collected from the QVAR[®] 100 inhaler using 40 (top trace), 60 (dotted middle trace) and 100 (solid middle trace) actuations compared with the original beclomethasone anhydrous material. The samples were analysed using differential scanning calorimetry using a 20 °C per min heating method. Endotherm is down in the trace

The material collected from the QVAR[®] was analysed using a slow DSC heating method and showed a similar endothermic transition in the temperature region corresponding to the melting point of the crystalline anhydrous BDP i.e. onset ca. 208°C. As the number of sprays actuated into the TSI collection unit increased from 40 to 100, the BDP melting endotherm intensity became larger and an exothermic peak at ca. 115°C appeared in the thermograph. Varvaet and Byron (1999) reported a similar profile when analysing a BDP, attributing an exothermic peak at ca. 110°C to CFC 11 solvate and an endothermic melt at 210°C to BDP. The exotherm was explained as concurrent desolvation of the solvate followed by recrystallisation to an anhydrous crystalline lattice, but no additional spectroscopic evidence was provided to support this. Although desolvation may be occurring, this may result in crystal lattice collapse and spontaneous recrystallisation.

The thermal profiles of the material collected from the QVAR[®] inhaler and analysed using hyper-DSC provided additional evidence to support the 'desolvation – recrystallisation' hypothesis used to explain the results obtained under slow heating conditions. The original BDP anhydrous material produced a

single endothermic peak in the hyper-DSC thermal profile at ca. 209°C (figure 2a). The material collected from the QVAR[®] MDI did not exhibit a thermal transition corresponding to the anhydrous BDP melt endotherm, but demonstrated a large endothermic peak onset at ca. 150°C. Removal of the solvate upon heating in the hyper-DSC experiment could again have caused crystal lattice collapse from the solvate to a desolvated form at ca. 130°C, but the rapid heating rate used may have been sufficiently quicker than the kinetics of recrystallisation such that no corresponding BDP melting endotherm was observed. The absence of the BDP melt endotherm suggests that no crystalline anhydrous form is produced during the sample collection process from the QVAR[®] inhaler and that the BDP melt transition observed in the slow scan experimentation is an artefact of the slow-heating rate process.

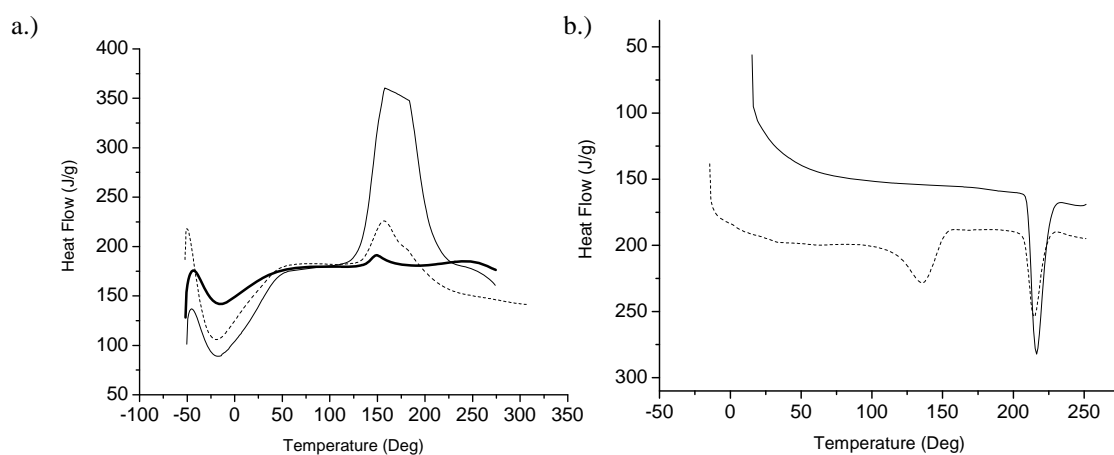


Figure 2. Hyper differential scanning calorimetry profiles of a.) Material collected from the QVAR[®] 100 inhaler after 50 (bottom), 100 (middle) and 200 (top) actuations b.) BDP ethanol solvate re-crystallised from pure ethanol (top trace) and BDP (bottom trace). Endotherm is down in the trace.

In an attempt to try and mimic the solvate formation, BDP was recrystallised from an ethanolic solution and analysed using the hyper-DSC methodology. The recrystallised BDP displayed one endothermic peak onset ca. 105°C, probably a result of the thermally induced desolvation of ethanol from the crystal lattice, and a second transition with a melting onset temperature of ca. 208°C (figure 2b). The differing behaviour of the BDP-ethanol solvate produced by recrystallisation to the material collected from the QVAR[®] inhaler suggests that the particles formed from the solution are not simply an ethanol-solvate of BDP.

The PXRD analysis of the anhydrous sample (crystalline reference) showed a typical BDP diffraction pattern with strong peaks at ca. 10, 12, 15 and 20 2θ values (figure 3). The Mylar sheet which was used in the collection apparatus did not give any reading in the PXRD trace and was therefore considered suitable for QVAR[®] material collection. The material emitted from the QVAR[®] inhaler appeared to show some degree of crystallinity, but the diffraction pattern contained a number of different peaks compared to the anhydrous BDP. Two of the strongest peaks in the QVAR[®] material at ca. 2θ values of 7 and 14 were absent in the original crystalline material. Although evidence of pure solvate formation cannot be gained from this qualitative data alone, it does demonstrate that the crystalline material that was generated from the QVAR[®] formulation has different solid-state properties compared to the raw material. Previous work by Nachengtung (1999) has shown that BDP can form several crystal structures including solvates and polymorphs. In a similar manner to the data presented in the current work, the studies by Nachengtung (1999) showed that solvent removal at ca. 115°C resulted in the BDP converting into alternative, crystal forms.

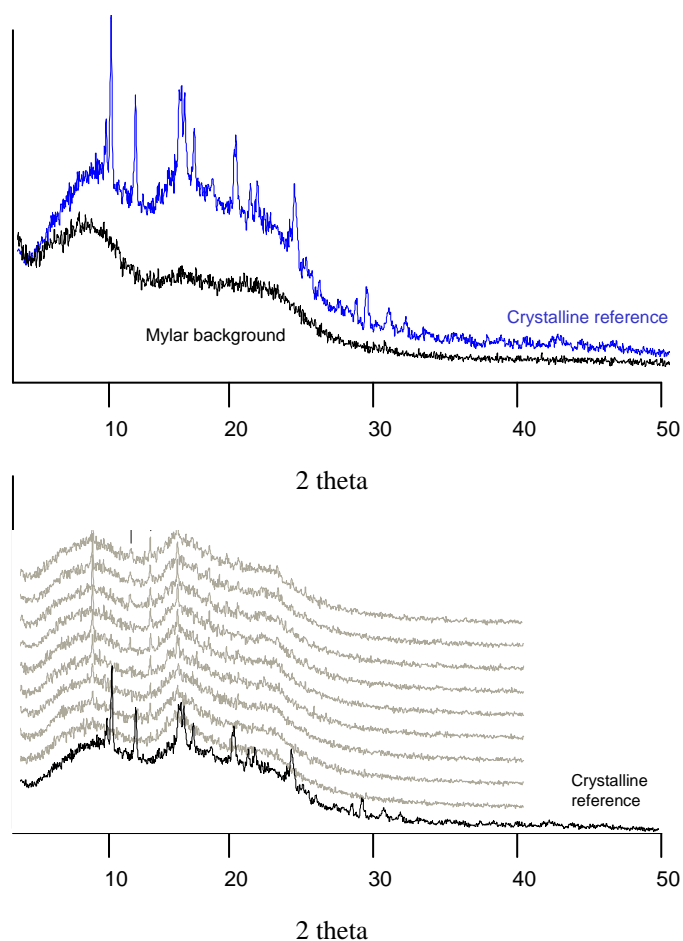


Figure 3. A powder x-ray diffraction profile of a.) anhydrous beclomethasone (top trace) and the Mylar sheet used for collection of the material, i.e. a background (bottom trace) b.) material collected from the QVAR[®] 100 inhaler after 160 actuations.

Conclusions

The modification of a TSI apparatus allowed successful capture of sample emitted from the QVAR[®] solution metered dose inhaler for solid-state characterisation. It appeared that the anhydrous BDP, when released from the QVAR[®] inhaler, produced a solvate or partially solvated crystal structure. The identification of the solvate (i.e. ethanol or hydrofluoroalkane) was not possible using PXRD measurements, therefore further x-ray diffraction experiments are required to further assess the material's crystalline structure.

References

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