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Isothermal calorimetry: A predictive tool to model drug-propellant interactions in pressurized metered dose systems

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ABSTRACT

The purpose of this work was to evaluate gas perfusion isothermal calorimetry (ITC) as a method to characterize the physicochemical changes of active pharmaceutical ingredients (APIs) intended to be formulated in pressurized metered dose inhalers (pMDIs) after exposure to a model propellant. Spray dried samples of beclomethasone dipropionate (BDP) and salbutamol sulphate (SS) were exposed to controlled quantities of 2*H*,3*H*-decafluoropentane (HPFP) to determine whether ITC could be used as a suitable analytical method for gathering data on the behavioural properties of the powders in real time. The crystallization kinetics of BDP and the physiochemical properties of SS were successfully characterized using ITC and supported by a variety of other analytical techniques. Correlations between real and model propellant systems were also established using hydrofluoroalkane (HFA-227) propellant. In summary, ITC was found to be suitable for gathering data on the crystallization kinetics of BDP and SS. In a wider context, this work will have implications on the use of ITC for stability testing of APIs in HFA-based pMDIs.

1. Introduction

Since the introduction of the first commercially available hydrofluoroalkane (HFA) pressurized metered dose inhaler (pMDI) in 1994 (Leach, 1997), significant progress has been made in understanding the fundamental interactions between active pharmaceutical ingredients (API) and hydrofluoroalkane propellants, namely HFA 134a and HFA 227. Understanding the relationship between HFAs and active pharmaceutical ingredients (APIs) used for inhalation formulations is pivotal to the design and performance of the final formulation. Many techniques have been employed in the past to study API stability in HFAs in terms of aerodynamic diameter and geometric particle size; including visual inspection of flocculated particles (Wu et al., 2008; Tzou et al., 1997), *in vitro* cascade impaction (Phillips et al., 1990) and *in situ* laser diffraction to study particle growth (Jones et al., 2005). High performance liquid chromatography (HPLC) methods have also been utilized to observe chemical stability of APIs exposed to propellants (Tzou et al., 1997). Although previous studies have provided some insight into the interactions of APIs in this medium, zeta potential, micelle formation and other physicochemical tests are more challenging to conduct, due to the volatile nature of HFAs at ambient pressure. To compensate for this shortfall, a model propellant substitution 2*H*,3*H*-decafluoropentane, namely HPFP, which is liquid at ambient pressure, has been proposed to mimic the physiochemical properties of HFA 227 (Rogueda, 2003).

This model propellant has previously been employed to study drug-HFA interactions. For example, atomic force microscopy techniques (Traini et al., 2005; Traini et al., 2006a,b; Rogueda et al., 2011) have been conducted in which HPFP was utilized as a medium to further investigate cohesive drug–drug, drug–surfactant, drug–propellant and drug–canister interaction forces. A recent study by Bouhroum et al. (2010) has measured the adhesive forces between beclomethasone dipropionate (BDP) clathrates formed by trichlorofluoromethane and pMDI components in the presence of HPFP. HPFP has also been used as a surrogate for HFA to study particle stability of chitosan–sodium tripolyphosphate nanoparticles intended for the pulmonary delivery of nucleic acids (Sharma et al., 2008).

Isothermal calorimetry (ITC) is a quantitative physical technique used to determine reaction thermodynamics and kinetics. Being invariant to sample physical form, it can be used to study solutions,

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solids and heterogeneous mixtures and has been applied to many areas of pharmaceutical development, including pre-formulation stages of inhalation device development, determination of solubility (Castronuovo et al., 1998), enthalpy of solution (Chadha et al., 2003), percentage crystallinity (Gaoand and Rytting, 1997) or amorphicity (Gaisford, 2012) and interactions between drug and carrier (Lloyd et al., 1999). The high sensitivity of the technique means that ITC has potential to study complex drug-propellant interactions, suited to API stability studies (Charlebois et al., 2003).

Building on previous research (Ahmed et al., 1996), this study is designed to expand the use of ITC beyond using water or organic vapours. Specifically, ITC was used to investigate physiochemical changes in API particles after exposure to HPFP. Spray dried samples of BDP and salbutamol sulphate (SS), two common drugs for inhalation with distinctively different properties and solubilities in HFA-227, were eluted with controlled volumes of HPFP to determine whether ITC is suitable for establishing information regarding the crystallization kinetics of inhalation powders in real-time. In a wider context, the studies will have implications for the use of ITC for stability testing in HFA-based pMDIs.

2. Materials and methods

2.1. Materials

Beclomethasone dipropionate was supplied by Ai Radhe Sales (Gujarat, India). Salbutamol sulphate was supplied by Interchem (Chongqing, China). Water was purified by reverse osmosis (Milli-Q, Molsheim, France). All solvents were analytical grade and supplied by Sigma (Sydney, NSW, Australia). Propellant HFA-227 was supplied by Ineos Fluor Ltd. (Cheshire, UK). Metering valves (DF 31, nominal metered volume 50 μL) and actuators with orifice diameters of 0.3 mm, were supplied by Bespak Europe Limited (Norfolk, UK). Glass pMDI containers were supplied by Saint Gobain plc (London, UK). Aerosol formulations were pressure filled using a Pamasol Laboratory plant 02016 (pamasol W. Mäden AG, Pfäffikon, Switzerland).

The model propellant 2*H*,3*H*-decafluoropentane was supplied by Apollo Scientific, Cheshire, UK. This was subsequently purified with chromatographic grade acidic and basic aluminium oxide (Fluka, Gillingham, UK) to remove impurities that could potentially alter measurements (Traini et al., 2005). Approximately 400 g of acidic aluminium oxide was added to a sealed flask containing 2 L HPFP and agitated using the Ultrasonic Cleaner (Unisonics, Australia) for 45 min. The resultant supernatant was vacuum filtered over a 0.2 μm PTFE to remove the aluminium oxide. The filtrate was then added to an additional flask containing approximately 400 g of basic aluminium oxide. This secondary mixture was again agitated using the Ultrasonic Cleaner for 45 min and the filtrate removed by vacuum filtration. HPFP was stored in capped laboratory bottles (Boeco, Germany), which contained approximately 100 g of 2 mm diameter molecular sieves (Sigma-Aldrich, Australia) to prevent moisture ingress.

2.2. Preparation of BDP and SS micro-particulates

Beclomethasone diproprionate and salbutamol sulphate particles were prepared using a Mini Spray Dryer in closed loop configuration (Büchi, B-290, Switzerland). An ethanolic BDP solution (5% w/v) was spray-dried using the following parameters: inlet temperature 60 °C, outlet temperature 43 °C, feed rate 10% (2.5 mL min^{-1}), 100% aspiration (40 m^3 h^{-1}) and an atomizing pressure of 742 kPa. An aqueous salbutamol sulphate solution (10% w/v) was spray dried using the following parameters: inlet temperature 150 °C, outlet temperature 95 °C, feed rate 2% (0.5 mL min^{-1}), 100% aspiration (40 m^3 h^{-1}) and atomizing pressure of 742 kPa. The spray dried powders were stored at <10% RH and 25 °C, in tightly sealed containers, for >1 week prior to testing.

2.3. Size distribution

The particle size distributions of both BDP and SS were measured by laser diffraction (Malvern Mastersizer 2000, Malvern, Worcestershire, UK). Approximately 5 mg of dry powder was introduced through a Scirocco dry feeder (Malvern, UK) and dispersed using 4-bar pressure. Samples were measured in triplicate at an obscuration between 3% and 10% with a refractive index of 1.564 and 1.553 for BDP and SS, respectively.

2.4. Scanning electron microscopy and focused ion beam milling

The BDP and SS micro-particulates were imaged using FEI Quanta 200F (Oregon, USA), field-emission scanning electron microscopy (SEM) prior to and after being suspended in HPFP and HFA-227, respectively. Samples were deposited on sticky carbon tabs, mounted on SEM stubs and sputter coated (Quorum Q150, Kent, UK) on a tilt-rotating stage to achieve a 10 nm gold coating prior to SEM analysis and focused ion beam (FIB) milling. Spray dried particles were then imaged at 5 kV. Focused ion beam milling of the samples was performed with a FIB–SEM dual beam system (Quanta 200 3D, FEI, USA). Micro-particulate samples were milled at an accelerating voltage of 30 kV and a beam current of 25 pA. Milling times for all samples were kept under 5 min. The samples were then examined using the SEM at 5 kV and tilted at 30° for visualization of the cross section.

2.5. Specific surface area

The specific surface areas of the BDP and SS micro-particulates were measured using a Micromeritics Tristar II 3020 (GA, USA). Prior to surface area analysis, the samples were degassed with N_2 for 48 h at 50 °C. Approximately 200 mg of sample were used for each experiment. Nitrogen adsorption isotherms were performed at relative pressures between 0.05 and 0.3 at 77.3 K and the surface area calculated according to the Brunauer–Emmett–Teller equation.

2.6. Differential scanning calorimetry

Thermal analysis of the BDP and SS micro-particulates, prior to and after 6 h exposure to HPFP vapour, was performed using differential scanning calorimetry (DSC Q2000, TA Instruments, Delaware, USA). Approximately 4 mg of sample powder was weighed into non-hermetic T-zero Aluminium pans. All experiments were subject to a heating rate of 10 °C min^{-1}. The cell constant and enthalpy calibrations were performed with indium (Certified Reference Material LGC2601, Batch E1, LGC, London, T_m = 156.61 °C, ΔH_f = 28.70 J g^{-1}) in accordance with the manufacturer's instructions. The measured values were in excellent agreement with those of the reference material ($T_m \pm 0.03$ °C, $\Delta H_f \pm 0.1$ J g^{-1}). Nitrogen (50 mL min^{-1}) was used as a purge gas and data were analyzed with Universal Analysis 2000 software (TA Instruments, Delaware, USA). Approximately 4 mg of each micronized drug was used as a standard to calculate crystalline percentages.

2.7. Isothermal calorimetry using HPFP

Calorimetric data was recorded using a 2277 Thermal Activity Monitor (TAM, Thermometric AB, Järfälla, Sweden) at 25 °C. Samples of each micro-particulate powder (20 ± 0.01 mg) were