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The solid-state and morphological characteristics of particles generated from solution-based metered dose inhalers: Influence of ethanol concentration and intrinsic drug properties

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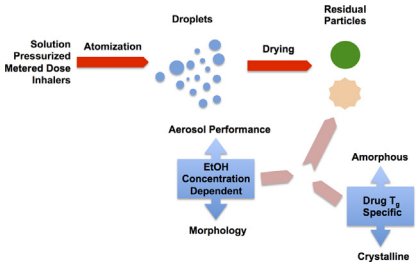
HIGHLIGHTS

- Particle size of solution pressurized metered dose inhaler is affected by initial droplet diameter and drug concentration.
- Aerosol performance is governed by droplet drying time.
- Solid state of produced aerosols is determined by glass transition temperature of a drug.
- Final structure of the aerosol is dependent on ethanol concentration and droplet drying kinetics.

GRAPHICAL ABSTRACT



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ABSTRACT

The aerosol performance, physical properties and formation process of two corticosteroids (beclomethasone dipropionate and fluticasone propionate) and caffeine (active pharmaceutical ingredients: APIs) from ethanol-based pressurized metered dose inhaler solution formulations, containing various ethanol fractions, were evaluated using cascade impaction, thermal analysis and scanning electron microscopy. In general, the final aerosol particle size distribution (post USP induction port) was unaffected by ethanol concentration (mass median aerodynamic diameter and geometric standard deviation values for each formulation were independent of ethanol concentration (%, w/w) in the initial formulation). However, ethanol concentration directly affected the percentage of particles that passed the USP induction, resulting in a significant decrease in fine particle fraction, across all formulations, as ethanol was increased. Thus it can be concluded that particle size is governed by initial droplet diameter and API concentration, while performance is governed by drying time. The physico-chemical properties and morphology of the dried API particles, collected from cascade impactor stages, showed that the solid state was related to the glass transition temperature (T_g) and, to some extent, the saturated hydrofluoroalkane propellant (HFA)/ethanol solubility of the APIs. The low T_g API caffeine, with high HFA solubility resulted in crystalline particles, while the high T_g corticosteroids were amorphous. Furthermore, the final structure of the particles was dependent on the ethanol concentration and drying kinetics after initial droplet formation. This study has shown that the solid-state physico-chemical properties and morphology of particles is intrinsically linked to the API properties and drying kinetics of the propellant/co-solvent. These variations in aerosol efficiency, particle morphology and solid-state characteristics may have direct effects on drug efficacy and bioavailability after deposition in the lung.

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1. Introduction

Pressurized metered dose inhalers (pMDI) contain an active pharmaceutical ingredient (API) either suspended or solubilized in a propellant, with stabilizing excipients and/or co-solvents [1]. Solution-based pMDIs are generally considered advantageous over suspension formulations, since it is easy to control the dose, dose reproducibility and aerodynamic size via alteration of the formulation variables [1,2].

In pMDI solution-based systems that only contain API, co-solvents and propellant, the final particle size distribution (i.e. post induction port aerosols) will be dependent on the propellant choice and concentration of non-volatile component (i.e. API) that affects the residual particle size [3].

The concentration of co-solvent is the primary determinant for the performance of a formulation when metering volume, actuator geometry and API concentration are fixed [4]. For example, it has been reported that the efficiency of solution pMDIs to deliver respirable mass decreases with increasing ethanol concentration; determined using an Aerodynamic Particle Sizer (APS Model 3320) coupled with an APS Model 3306 Impactor Inlet [5]. This previous study demonstrated a 30% decrease in the FPF (fine particle fraction) with considerable increase (approximate 20%) in impactor induction port deposition.

Our previous work studied the effect of ethanol co-solvent on the residual particle size and structure of particles generated from solution-based pMDIs, using budesonide as a model API [6]. In our previous study, the structure of the residual particles was dependent on (1) the initial ethanol concentration and (2) the ability of the rapid drying droplets to recover from internal cavitation and propellant/ethanol evaporation, relating this to molecular mobility and viscosity at the surface of the drying droplet.

The current study aims to expand on our previous report by investigating the influence of the non-volatile API components on the residual particle size and morphology. Since the generation of irregular shaped particles is dependent on molecular mobility in the rapidly drying droplet, it is proposed that the intrinsic solubility of API in both ethanol and HFA will have a significant impact on particle morphology. Three APIs were chosen as model compounds used in this study due to their relative differences in solubility in HFA and ethanol: beclomethasone dipropionate (BDP), fluticasone propionate (FP) and caffeine (Table 1).

2. Materials and methods

2.1. Materials

Beclomethasone dipropionate and fluticasone propionate were used as supplied (EP grade, Yicheng Chemical Corp., Jiangsu, China). Anhydrous caffeine (≥99.0%, HPLC grade), anhydrous ammonium acetate (≥99.99%) and mono-potassium phosphate (≥99%) were purchased from Sigma–Aldrich (Castle Hills, New South Wales, Australia). Ethanol (100%), methanol and other solvents (HPLC grade) were obtained from Biolab (Clayton, Victoria, Australia). Water was purified by reverse osmosis (MilliQ, Millipore, France).

Table 1
Solubility values for BDP, FP and caffeine in HFA 134a and ethanol.

API	Solubility in HFA 134a (μg/g)	Solubility in ethanol (mg/mL)
BDP	81 [40] [a]	20 [41] [b]
FP	Below detection limit	1.7 [13] [c]
Caffeine	1280 [40] [a]	5.7 [42] [b]

[a] Room temperature.
[b] 25 °C.
[c] 22 °C.

The propellant, 1,1,1,2-tetrafluoroethane (HFA 134a) was supplied by Ineos Fluor Ltd. (Cheshire, UK).

2.2. Preparation of solution-based pMDIs

A formulation matrix was designed to investigate the effect of API and ethanol concentrations on aerosol performance and maturated particle morphology. The formulation matrix is outlined in Table 2. Each formulation was prepared in pressure resistant glass pMDI canisters (Saint Gobain, Courbevoie, France). For all formulations, the API and ethanol were weighed directly into the canister, which was immediately crimped with a 50 μL metering valve (Bespak Europe Limited, Norfolk, UK), and pressure-filled with HFA 134a using a Pamasol Laboratory plant P2016 (Pamasol Willi Maäden AG, Paffikon, SZ). After filling, each canister was sonicated for 5 min and visually examined to confirm complete miscibility. All canisters were stored for a minimum of 24 h at 25 °C prior to further studies. In general, the formulation matrix reflected the intrinsic solubility of each API in HFA and ethanol. For example, caffeine could be formulated to deliver 50 μg from a HFA system with 0 and 30% (w/w) ethanol, while the same dose of FP could only be formulated with ethanol concentrations above 15% (w/w).

2.3. Evaluation of aerosol performance

The Marple Miller impactor (model 150) (MSP, Minnesota, USA) was used to study the aerosol performance of each solution-based formulation. This impactor was chosen since it had a reduced number of stages, compared to other pharmacopoeia impactors, allowing for easy particle recovery and subsequent physico-chemical analysis. A United States pharmacopeia (USP) induction port was mounted onto to the impactor and pMDIs were sampled at a flow rate of 30 L/min. Actuators with an orifice diameter of 0.33 mm (Bespak Europe Limited, Norfolk, UK) were used throughout the study. Prior to analysis, five shots of each canister were fired to waste. The primed pMDIs were inserted into a custom-made mouthpiece adaptor connected to the USP induction port. After equilibrating the pump for 5 s, four shots were delivered, with a 10 s pause between shots.

Each part of the assembly, including the mouthpiece and the filter, were thoroughly rinsed with mobile phase (Table 3) into suitable volumetric flasks for chemical quantification using high performance liquid chromatography (HPLC). The MMAD (mass median aerodynamic diameter) was calculated from log-probability plots of cumulative percentage versus cut-off diameters and the GSD (geometric standard deviation) was calculated as the square root of the 84th/16th percentile. The FPF was defined as the percentage of mass deposited from stage three to filter (corresponding to the cut-off size ≤5 μm), as a function of the ex-valve dose. The impaction study was carried out in triplicate for each formulation.

2.4. High performance liquid chromatography

API content from cascade impactor measurements was quantified using a Shimadzu UPLC system consisting of a LC20AT pump, an SIL20AHT autosampler and an SPD-20A UV–VIS detector (Shimadzu, Sydney, NSW, Australia). The chromatographic conditions for each API are presented in Table 3. Standard solutions were freshly prepared with mobile phase daily and the linearity was confirmed between 0.1 and 100 μg/mL ($R^2 > 0.999$). Quantification was calculated based on peak area integration.