International Journal of Pharmaceutics 520 (2017) 207–215

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Humidity affects the morphology of particles emitted from beclomethasone dipropionate pressurized metered dose inhalers

James W. Ivey[a], Pallavi Bhambri[a], Tanya K. Church[c], David A. Lewis[c], Mark T. McDermott[b], Shereen Elbayomy[b], Warren H. Finlay[a], Reinhard Vehring[a,*]

[a] University of Alberta, Department of Mechanical Engineering, Edmonton, AB, Canada
[b] University of Alberta, Department of Chemistry, Edmonton, AB, Canada
[c] Chiesi Limited, Chippenham, Wiltshire, United Kingdom

ARTICLE INFO

Article history:
Received 8 December 2016
Received in revised form 28 January 2017
Accepted 28 January 2017
Available online 3 February 2017

Keywords:
Solution metered dose inhaler
Pulmonary drug delivery
Microparticle formation
Morphology
Solid phase

ABSTRACT

The effects of propellant type, cosolvent content, and air humidity on the morphology and solid phase of the particles produced from solution pressurized metered dose inhalers containing the corticosteroid beclomethasone dipropionate were investigated. The active ingredient was dissolved in the HFA propellants 134a and 227ea with varying levels of the cosolvent ethanol and filled into pressurized metered dose inhalers. Inhalers were actuated into an evaporation chamber under controlled temperature and humidity conditions and sampled using a single nozzle, single stage inertial impactor. Particle morphology was assessed qualitatively using field emission scanning electron microscopy and focused ion beam-helium ion microscopy. Drug solid phase was assessed using Raman microscopy. The relative humidity of the air during inhaler actuation was found to have a strong effect on the particle morphology, with solid spheroidal particles produced in dry air and highly porous particles produced at higher humidity levels. Air humidification was found to have no effect on the solid phase of the drug particles, which was predominantly amorphous for all tested formulations. A critical level of air relative humidity was required to generate porous particles for each tested formulation. This critical relative humidity was found to depend on the amount of ethanol used in the inhaler, but not on the type of propellant utilized. The results indicate that under the right circumstances water vapor saturation followed by nucleated water condensation or ice deposition occurs during particle formation from evaporating propellant-cosolvent-BDP droplets. This finding reveals the importance of condensed water or ice as a templating agent for porosity when particle formation occurs at saturated conditions, with possible implications on the pharmacokinetics of solution pMDIs and potential applications in particle engineering for drug delivery.

1. Introduction

Inhaled corticosteroids are widely prescribed for prophylactic asthma therapy (Busse, 2002) and may also benefit patients with moderate to severe chronic obstructive pulmonary disease (Gartlehner et al., 2006). A large proportion of inhaled corticosteroid doses are delivered using pressurized metered dose inhalers (pMDIs) (Lechuga-Ballesteros et al., 2011; Roche and Dekhuijzen, 2016). In modern pMDIs, the drug is either suspended or dissolved in a volatile hydrofluoroalkane (HFA) propellant, with the choice dependent on the solubility of the drug in the propellant (Myrdal et al., 2014); the inhaled corticosteroid beclomethasone dipropionate (BDP) has generally been formulated as a solution (Spahn, 2016) utilizing ethanol as a co-solvent (Gupta et al., 2003). The resulting formulation is contained in a pressurized canister equipped with a metering valve and paired with an actuator (Stein et al., 2014). When a patient administers a dose from a pMDI, the volatile formulation exits the valve via the actuator and is atomized into a fine, rapidly evaporating spray which is inhaled into the patient's lungs (Finlay, 2011).

The aerodynamic particle size distribution of a therapeutic aerosol has a large effect on the efficacy of treatment in pulmonary delivery because of its prominent role in the physical mechanisms of particle deposition in the human airways (Darquenne, 2012). Consequently, a substantial amount of research on pMDIs has focused on measurement and prediction of the drug particle size distribution for solution and suspension formulations. The matter is complicated by the highly dynamic nature of the aerosol

* Corresponding author at: University of Alberta, Department of Mechanical Engineering, 10-269 Donadeo Innovation Centre for Engineering, Edmonton, Alberta T6G 2G8, Canada.
E-mail address: reinhard.vehring@ualberta.ca (R. Vehring).

http://dx.doi.org/10.1016/j.ijpharm.2017.01.062
0378-5173/

generated by pMDIs: as the spray of propellant droplets interacts with the surrounding gas phase, heat, mass, and momentum are transferred (Xu and Hickey, 2014), and thus the velocity, size, and concentration of droplets vary in time and space (Dunbar et al., 1997). Available theory (Finlay, 2001) suggests that the formulation (propellant physical properties, inclusion of co-solvent) and usage environment (air temperature, relative humidity) have the potential to alter these spray dynamics and therefore the deposition in human airways. Indeed, *in vitro* studies summarized in our recent review (Ivey et al., 2015) have demonstrated all of these effects.

As the interaction of pMDI-generated aerosols with humidity is of particular relevance to the present study, a brief survey of research on this topic is merited. Evaporative cooling in pMDI spray plumes can produce temperatures well below 0 °C (Brambilla et al., 2011), and the plume may contain as many as hundreds of millions of microparticles (Stein, 2008). If the air entrained into the pMDI spray plume is sufficiently humid, these conditions might produce supersaturation of water vapor and subsequent nucleated condensation of water (Hinds, 1999). An early evaluation of the effect of humidity on the aerodynamic particle size distribution of nine commercial chlorofluorocarbon pMDIs was conducted by Kim et al. (Kim et al., 1985). Testing was conducted with air conditioned to 22–23 °C and either <1% or 90% relative humidity (RH). A 20 L evaporation chamber was employed upstream of an Andersen cascade impactor to measure the aerodynamic particle size distribution of the fully evaporated aerosols. No significant effect of RH on the aerodynamic particle size distribution for eight of the nine tested inhaler types was observed when the RH was increased from near zero to 90%, and thus it was concluded that for the tested pMDIs humidity did not alter the particle size distribution of the aerosol reaching the impactor. In a later study, Lange and Finlay administered doses from an HFA-propelled suspension pMDI to a model ventilation circuit equipped with a pediatric endotracheal tube coupled to an Andersen cascade impactor (Lange and Finlay, 2000). Ventilation air was supplied at 4.8 L/min with a square wave profile. Ventilation air temperature was varied from 25 °C to 37 °C, and was either unhumidified (RH 8-15%) or humidified to near saturation (RH ≈ 100%). The *in vitro* inhaled dose was observed to depend heavily on the amount of water vapor present in the ventilation air (i.e. the absolute humidity), with the inhaled dose decreasing as the water vapor mole fraction increased. Importantly, Lange and Finlay observed that the aerodynamic particle size distribution of the aerosol passing the endotracheal tube was unaffected by changes in air humidity and that the deleterious effect of humidity on the *in vitro* inhaled dose was mitigated when a spacing device was added to the ventilation circuit prior to the endotracheal tube and impactor. This data suggests that humidity could affect particle sizes in the spacer immediately after droplet production. In a subsequent study designed to further examine the effect of humidity, Martin et al. examined the evaporation rate of millimeter size pendant propellant-ethanol droplets in air with varying humidity levels (Martin et al., 2005). They found no effect of air humidity on droplet evaporation rates.

Evidence that humidity can alter the aerodynamic particle size distribution from pMDIs was published by Mitchell and colleagues, who utilized an Andersen cascade impactor with an endotracheal tube fixed to the inlet to evaluate the effect of air humidity on the aerodynamic particle size distribution of BDP solution pMDIs paired with valved holding chambers (Mitchell et al., 2003). They found that increasing the absolute humidity of the testing air resulted in a large increase in the mass median aerodynamic diameter (MMAD) for an HFA BDP pMDI and concluded that the effect was due to growth by condensation of the aerosol particles generated by the inhaler. Martin and Finlay sized salbutamol sulfate suspension pMDIs actuated into valved holding chambers in 37 °C air using an Andersen cascade impactor; to evaluate any effects related to aerosol maturation, they varied the distance between the holding chamber and the impactor by using different lengths of connecting tubing (Martin and Finlay, 2005). They found that increasing the RH from 8% to near 100% resulted in significant increases in holding chamber deposition and MMAD for a conventional formulation containing ethanol and surfactant as well as for an excipient-free formulation. Furthermore, in humidified air the MMAD was observed to decrease significantly as the spacing tubing length was increased. Martin and Finlay's results suggest that significant condensational growth of pMDI drug particles occurs at high air relative humidity, and that this growth is followed by secondary evaporation of the condensed water. This idea is consistent with the prior results: if the aerosol is given sufficient time to mature (as with the large volume evaporation chamber of Kim et al. or the low sampling flow rate employed by Lange and Finlay), any transient size increases will be undetectable by typical particle sizing techniques, as secondary evaporation will have taken place prior to sizing. On the other hand, if the sizing occurs while condensational size changes are still underway (as with the studies of Mitchell et al. and Martin and Finlay), the measured aerodynamic particle size distribution will depend on how far along the aerosol maturation process has progressed. Thus, although condensational growth and secondary evaporation of pMDI-generated aerosols have not been observed directly, the available research provides indirect evidence that these phenomena do indeed occur.

Recently, researchers studying solution pMDIs have focused attention on particle properties other than the aerodynamic particle size distribution. Notably, the solid phase and the particle morphology become important after particle deposition in the airways (de Souza Carvalho et al., 2014), as they may affect particle wettability, dissolution rate, and susceptibility to the lungs' particle clearance mechanisms (Ruge et al., 2013). The solid phase of inhaled drugs has been shown to affect pharmacokinetics and pharmacodynamics in animal models (Sakagami et al., 2002; Sakagami et al., 2001). This is a relevant consideration since unlike in suspension formulations, the drug in a solution pMDI undergoes a rapid transition from a solute to a solid during dosing, with the resultant solid phase potentially dependent on the formulation and usage environment. Therefore, some recent research has evaluated the effects of formulation variables (ethanol content, presence of excipients) on the solid phase and the resultant dissolution and transport characteristics of the drug particles. Grainger and colleagues evaluated two commercially available BDP pMDIs, distinguished by ethanol content and use of the excipient glycerol (Grainger et al., 2012). They found that the glycerol-containing formulation differed significantly from the glycerol-free formulation in its extent of crystallinity, dissolution rate, and *in vitro* transcellular absorption. Similar findings were reported in work by Lewis, Haghi, and colleagues (Haghi et al., 2014; Lewis et al., 2014). Further studies with BDP solution pMDIs (Buttini et al., 2014) and with model propellant systems (Bouhroum et al., 2010; Ooi et al., 2014) indicate that BDP may form solvates or clathrates with ethanol or propellants during drug particle formation.

The morphology of a drug particle may alter its fate after deposition in the lungs as well. Specifically, particle density (Tsapis et al., 2002) and wettability (Schürch et al., 1990) have the potential to affect the rate of particle dissolution or clearance in the airways. Zhu et al. investigated the effect of ethanol content on the morphology of particles generated from budesonide solution pMDIs (Zhu et al., 2013). Utilizing field emission scanning electron microscopy (FE-SEM) and focused ion beam milling-scanning electron microscopy (FIB-SEM), they found that ethanol content had a large effect on the particle morphology. Particles produced from pMDIs with a low ethanol content tended to have an irregular envelope shape and a porous morphology, while those produced from pMDIs with more ethanol were generally smooth, solid,