International Journal of Pharmaceutics 514 (2016) 445–455

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Powder dispersion mechanisms within a dry powder inhaler using microscale particle image velocimetry

Xiang Kou[a], Steven T. Wereley[b], Paul W.S. Heng[a], Lai Wah Chan[a], M. Teresa Carvajal[c,*]

[a] Department of Pharmacy, National University of Singapore, Singapore
[b] Department of Mechanical Engineering, Purdue University, USA
[c] Agricultural and Biological Engineering, Purdue University, USA

ARTICLE INFO

Article history:
Received 1 March 2016
Received in revised form 16 July 2016
Accepted 18 July 2016
Available online 4 August 2016

Keywords:
DPI
Dispersion mechanism
Impact
Collision
Image analysis
PIV

ABSTRACT

The goal of this work was to evaluate the ability of Particle Image Velocimetry (PIV) to visually assess dry powder dispersion within an inhaler. Herein, the study reports particle movement characterization of entrained low-micron particles within an inhaler to further scheme of potential mechanisms. Carrier based DPI formulations were prepared and placed in a transparent model Rotahaler® chamber for the aerosolization experiments. Then using the PIV, a high-speed camera, the dried powder dispersion was directly observed and analyzed for all, neat, binary and ternary systems. Powder dispersion mechanisms proposed include drag force, impact with obstacle and particle-particle collision; these different mechanisms depended on the powder flow properties. A revised ratio of aerodynamic response time (τ_A) to the mean time between collisions (τ_C) was found to be 6.8 indicating that particle collisions were of strong influence to particle dispersion. With image analysis techniques, visualization of particle flow pattern and collision regions was possible; suggesting that the various mechanisms proposed did govern the powder dispersion.

1. Introduction

Dry powder inhaler (DPI) is a dosage form for delivering drug as a powder formulation into the respiratory tract. The way DPIs work is by aerosolizing powder to produce airborne particles that will be entrained to travel to the lung. Factors influencing aerosolization performance have been well summarized (Louey et al., 2003; Kou et al., 2012; Handoko et al., 2009; Glover et al., 2008; Musante et al., 2002), some include discharge rate of particles (de Boer et al., 2006; Mendes et al., 2007; Podczeck, 1997; de Boer et al., 2003). However, the mechanism of particle dispersion in DPIs is still unclear despite several studies directed at elucidating this process. Some efforts have been directed on the dispersion and deposition characteristics of dry powder aerosols by modeling approaches using stochastic Lagrangian model (Chew et al., 2002; Li and Edwards, 1997; Mendes et al., 2010; Mendes et al., 2009) and computational fluid dynamic (CFD) (Coates et al., 2005; Coates et al., 2006; Coates et al., 2004; Wong et al., 2010). The configuration of the device and flow field generated was critical in affecting the dispersion process. Turbulence was found to existed in the mouthpiece chamber (Coates et al., 2007). Moreover, the flow turbulence and the induced particle velocity affected the process by particle-particle collision or particle-wall impact (Wong et al., 2010; Gui et al., 2016). This was confirmed by experimental investigations by imaging particle movement in the outlet of the mouth piece (Han et al., 2002a; Han et al., 2002b). Strong counterclockwise rotating flow prevailed due to upstream tangential air injection introduced into the mouthpiece by the holes in the outlet of the mouthpiece. In addition, it was indicated that excess core flow mixing prior to the full formation of the sheath of air caused particle collisions with the mouthpiece wall as a result of the strong tangential air injection. However the study carried out by Han (Han et al., 2002a) focused on the outlet of the mouthpiece chamber, therefore the aerosolization process inside of the inhaler chamber was not observed experimentally. In another study, agglomerates formed and the powder bed was lifted as a plug by the air (Tuley et al., 2008). It was suggested that the plug would be subjected to higher aerodynamic drag forces causing de-agglomeration and reduction of the agglomerate size (Begat et al., 2004; Jones et al., 2008; Podczeck et al., 1997; Podczeck, 1999; Shur et al., 2008; Chamarthy et al., 2007; Otte et al., 2008). However, direct observation for collisions and impact was not reported and the configuration of the device in Tuley's study was different from the Rotahaler® (Tuley et al., 2008). This

* Corresponding author.
E-mail address: tcarvaja@purdue.edu (M. T. Carvajal).

http://dx.doi.org/10.1016/j.ijpharm.2016.07.040
0378-5173/

difference could affect the particle dispersion (Chew et al., 2002). Therefore, their conclusions derived from their reported studies were not directly applicable to DPIs with similar configuration as the Rotahaler®.

Powder dispersion has been associated with not only particle characteristics but also with events such as impact, acceleration, shear stress and turbulent flow (Kousaka et al., 1979). Particle behavior is likely to be affected by interparticle collisions triggered by aerodynamic transport and air turbulence. To date, to the best of our knowledge, direct observation of powder dispersion mechanisms within an inhaler with similar configuration to the Rotahaler® has not been reported. Thus, the aim of the current study is to envision potential mechanisms for powder dispersion using a high speed video to provide direct experimental observation of the powder dispersion process within the DPI mouthpiece, chamber and entrainment of typical DPI formulations discharged from Rotahaler® device.

2. Materials and methods

2.1. Materials

Salbutamol sulphate (Fine Drugs and Chemicals, Hyderabad, India) was used as a model drug. Micronized salbutamol sulphate was obtained using a fluidized bed opposed jet mill (AFG 100, Hosokawa, Augsbur, Germany) at a pressure of 0.4 MPa and a classifying wheel speed of 15000 rpm before use. Coarse carrier was produced by air jet sieving (Hosokawa Micron, Summit, NJ, USA) lactose 125 M (Pharmatose, DMV, The Netherland) to obtain a powder fraction in the size range of 45–100 μm. Micronized lactose (fines) was obtained by jet milling (AFG 100, Hosokawa, Augsbur, Germany) lactose 125 M (Pharmatose, DMV, The Netherland) at a pressure of 0.4 MPa and a classifying wheel speed of 15000 rpm.

2.2. Particle size analysis and surface morphology assessment

Powders under study were sized using the small volume module of the laser diffraction sizer (Coulter LS 230, Coulter Corporation, Hialeah, FL, USA). Except for measurement of agglomerates (neat salbutamol sulphate and neat fine lactose), the powders were sonicated for 0.5 min to break up the agglomerates before measurement (Adi et al., 2007a, 2007b). The $D_{v(10)}$, $D_{v(50)}$ and $D_{v(90)}$ values (representing the 10th, 50th and 90th percentiles of the cumulative size plot respectively) of the samples were determined. The spread of the size distribution was represented by the span $[(D_{v(90)} - D_{v(10)}/D_{v(50)}]$, where a larger span value indicates a broader size distribution. Confirmatory off-line sizing determined by scanning electron microscopy (SEM) was also carried out. The particles were gold-sputter coated under a vacuum before viewing under SEM (JSM-5200, JEOL, Japan). Photomicrographs of the particles were obtained using an image capture software (SemAfore, Version 4.02, Finland) and Feret's diameter of more than 1000 particles per sample were recorded using an imaging software (Image-Pro, Version 6.3, Media Cybernetic, USA). The resulting data were further analyzed to render cumulative size plot using a self-written Matlab program (Version 7.0.1, The Mathworks, USA). Size ($D_{(90)}$, $D_{(50)}$, $D_{(10)}$) and span $[D_{(90)}\text{-}D_{(10)}/D_{(50)}]$ were then derived from the cumulative size plot. Standard deviation was also obtained from this analysis using different samples. The Matlab code is attached as supplemental material. Surface morphology of the particle was assessed by examination of the respective SEM photomicrographs.

2.3. Formulation systems

Three different formulation systems were prepared: 1) Neat micronized salbutamol sulphate; 2) Binary mixture of micronized salbutamol sulphate and coarse carrier; 3) Ternary mixture of micronized salbutamol sulphate with a mixture of coarse carrier and fines. Ten samples from each model formulation were used for the measurements investigated in this study.

For the binary mixture, micronized salbutamol sulphate was mixed with coarse carrier in a ratio of 1:67.5 (w/w). A portion of the coarse carrier was weighted into a 20 mL sample vial containing the micronized salbutamol sulphate. The vial was closed with a stopper and the contents blended using a Vortex mixer for 5 s. More coarse carriers were added into the vial and blended. This process was repeated until all the coarse carriers had been incorporated. The whole mixture was finally blended for additional 10 min to offset any mixer order sequence effect.

For the ternary mixture, first a coarse carrier was mixed with 10% of the fines. Then, a portion of this coarse carrier with fines mixture was weighted into a 20 mL sample vial. The vial was closed with a stopper and the contents blended using a Vortex mixer for 5 s. More coarse carrier powder was added into the vial and blended again. This process was repeated until all the coarse carrier material had been incorporated. The whole mixture was finally blended for an extra 10 min to offset any mixing order sequence effect. Micronized salbutamol sulphate was then blended with the above mixture in a ratio of 1:67.5 (w/w) according to the blending procedure described before.

2.4. Powder flow

Powder flow was expressed by the Hausner ratio, which was the ratio of tap density and bulk density. Bulk density was obtained by pouring powder into 100 mL graduate cylinder. The excess powder was then scraped off. Bulk density is determined by the weight of the powder divided by 100 mL. Tap density was determined by tapping this cylinder containing the powder 1000 times. The final volume was recorded and the tap density is the powder weight divided by the final volume.

2.5. Experimental set-up for observation of powder dispersion

A transparent acrylic tube made according to the Rotahaler® configuration was used to mimic an inhaler device (Fig. 1). The formulations prepared were placed into the transparent device to visualize the aerosolization process. The aerosolization test was carried out using a next generation impactor (MSP Corporation, MN, USA) at aerosolization speed of 28.3 L/min. Each formulation was repeated 10 times. A microscope connected to a high speed camera (PCO, The Cooke Corporation, USA) through a boom microscope stand (Diagnostic Instrument, USA) was employed for real time observation of small regions within the inhaler device. This allowed surveillance of individual particle movement. A

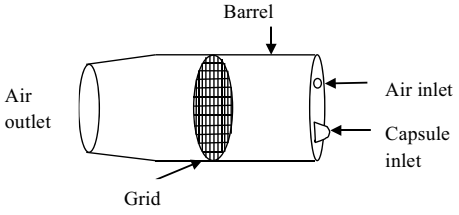

Fig. 1. Schematic diagram of the Rotahaler®.