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Investigation of dry powder aerosolization mechanisms in different channel designs

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ABSTRACT

Aerosolization efficiency is the key characteristic of dry powder inhaler (DPI). However, lack of knowledge about powder dispersion and deposition is still a major obstacle to further improve inhaler. In the current work, both the *in vitro* deposition experiments and numerical simulations were employed to investigate the performance of three different DPI channel designs. The powder model was commercially available Seretide® Accuhaler®, which contains carrier lactose and drug mixture of fluticasone propionate (FP) and salmeterol xinafoate (SX). The *in vitro* results, such as the mass mediate aerodynamic diameter (MMAD), fine particle fraction (FPF) and fine particle dose (FPD), were obtained by the Next Generation Impactor (NGI). The values of MMAD were significantly ($p < 0.05$) affected by channel design. However, based on the FPF result, the three channel designs had similar capabilities of aerosolization. It was demonstrated that particle–wall collision was the dominant mechanism for the detachment and de-agglomeration at these conditions. Furthermore, good linear correlations were found between the FPD values on the first 4 stages of NGI and the outlet velocities of their corresponding particles, which would be used for a potential on-line approach to the evaluation of DPI efficiency.

1. Introduction

Pulmonary drug delivery to treat chronic respiratory diseases has been proven as a potential delivery route to complex drugs that cannot be delivered orally (Stegemann et al., 2013). Pressurized metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs) are the main techniques for dispersing and aerosolizing solid drug particles, which is paramount for pulmonary delivery. Due to the concern about ozone depleting effects of chlorofluorocarbons used in pMDIs, the DPIs are emerging as an important noninvasive delivery approach in the new decade and beyond (Calvert et al., 2009; Behara et al., 2011; Heng et al., 2012). The need to utilize drug particles smaller than 5 μm in order to obtain a local deposition within the lower parts of the lung leads to a variety of challenges (Cordts and Steckel, 2012). For DPI formulations, micronized drug powders are commonly mixed with relatively larger coarse lactose carriers to facilitate powder handling during the manufacturing and powder aerosol delivery (Zhou and Morton, 2012; Le et al., 2012). Upon aerosolization of inhaler, the carrier particles would deposit in the mouth and throat regions. It is essential for the drug particles that are attached to the carrier particle surface to be able to detach from it so that they do not deposit together with the carrier particles, but instead deposit in the targeted lower respiratory airways (Kho and Hadinoto, 2013).

DPI efficiency is decided by three factors: properties of particles (carriers and drug powders), device design (geometrical structure) and inspired flow rate. Young et al. (2011) studied the influence of drug loading and carrier size on drug aerosol performance using homogeneous spherical model carriers. The results showed that as carrier size increased, fine particle fraction (FPF) decreased, while as drug loading increased, there was no change in FPF until a critical threshold was exceeded. Adi et al. (2011) obtained an inverse linear relationship between the agglomerate strength and the dispersion performance which provided direct information on them. Das et al. (2012) calculated distributions of powder strength of a cohesive bed by Monte Carlo simulations and analyzed the de-agglomeration

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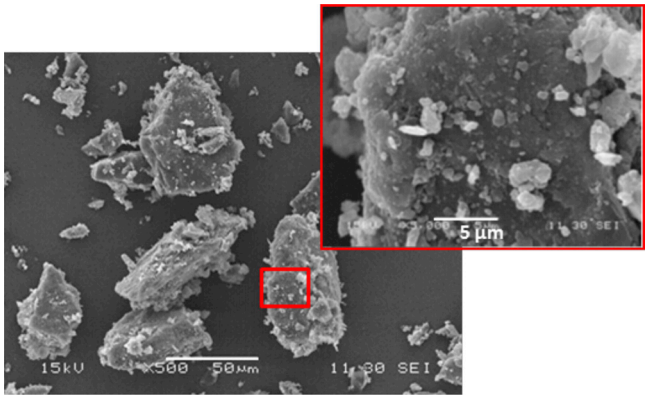

Fig. 1. Scanning electron micrographs of model powders. The lower scale bar is 50 μm and the upper one in the zooming picture is 5 μm.

properties of lactose particles. Dispersion by acceleration in a uniform flow field was also studied, which seemed to be effective when the relative particle–fluid velocity is beyond a certain value (Calvert et al., 2011). Coates et al. (2004, 2005, 2006, 2007) studied the design of Aerolizer®, such as mouthpiece geometry, air inlet size and grid structure, by the combination of computational fluid dynamics (CFD) and experiments, which indicated that even minor modifications of the DPI features could have a significant effect on the overall inhaler performance. Tong et al. (2009, 2010, 2011, 2012) used CFD or CFD coupled with discrete element method (DEM) to study the dispersion performance of mannitol loose agglomerates, where the results indicated that the breakage of the agglomerate was mainly attributed to the mechanical impaction and less affected by the shear effect from the flow–particle interaction. These results may be more useful for dispersion analysis of carrier-free powders, while DPIs are often made up of carrier and drug particles. Lack of knowledge about carrier based particle dispersion mechanisms is still a major obstacle to further improve inhaler performance.

The aim of this study was to explore the dispersion behaviors of carrier–drug particles from different DPI channel designs by *in vitro* aerodynamic deposition experiments of the model drug, combination of fluticasone propionate (FP) and salmeterol xinafoate (SX), using next generation impactor (NGI). At the same time, an Eulerian–Lagrangian particle tracking mutiphase CFD model was employed to further investigate the potential correlations between particle-wall compaction frequency, turbulent intensity and drug particle outlet velocity and the *in vitro* experimental results, such as the FPF and fine particle dose (FPD).

2. Materials and methods

2.1. Materials

The model dry powders were from commercially available Seretide® Accuhaler® (GlaxoSmithKline, UK), which contains 250 μg FP, 50 μg SX and 12.5 mg lactose per blister as the specification states. The densities of each ingredient were 1.37, 1.11 and 1.53 g/cm^3, respectively. Particle morphology of model powders was visualized (Fig. 1) using a Scanning Electron Microscope (JSM-6360LV, JEOL, Japan). On the lactose surface, there were some smaller agglomerates adhered, which were FP and SX (Fig. 1). Particle size of lactose was obtained using laser diffraction analyzer (MASTERIZER 2000, Malvern Instruments, Malvern, UK). The volume average diameter of lactose was 83.19 μm.

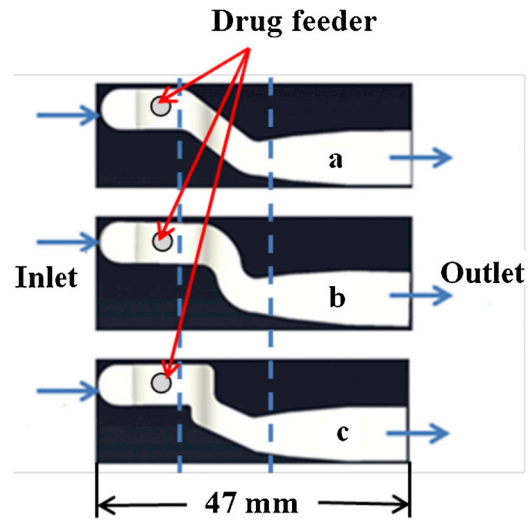

Fig. 2. Top view of the three channels, channel *a*, *b* and *c*.

2.2. Experimental studies

2.2.1. Quantitative sample analysis by high pressure liquid chromatography (HPLC)

Quantitative analysis of the sample was done using HPLC system (Agilent Technologies Inc., CA, USA). The column used was a Hypersil BDS (4.6 mm × 150 mm) which was packed with 5 μm C18 stationary phase (Elite Analytical Instruments Co., Ltd., Dalian, Liaoning, China). The mobile phase was a mixture of methanol and 0.3% (w/v) ammonium acetate buffer in a ratio of 60:40. The buffer was made by dissolving ammonium acetate (AR grade, Sinopharma Chemical Reagent Co., Ltd., China) in reverse osmosis water. The mobile phase was freshly made before each analysis, which was filtered through 0.45 μm nylon filter and degassed. The flow rate was 1.00 mL/min at 40 °C. An ultra violet (UV) detector set at a wavelength of 228 nm was employed. The injection volume of the sample was 20 μL that was determined by means of a loop. Each sample was analyzed in triplicate using a run time of 15 min. All solvents used were HPLC grade. SX standard was obtained from Apeloa Jiayuan Pharmaceutical, Co., Ltd. (Dongyang, Zhejiang, China) and that of FP was obtained from Auriso Pharma. Co., Ltd. (Tiantai, Zhejiang, China).

2.2.2. Deposition test

Three DPI channel designs were used in the *in vitro* deposition tests. The only geometrical differences among them were between the two dashed lines in Fig. 2, where the main turbulence mixing effect was expected. Each blister powders of Seretide® Accuhaler® were filled in the drug feeders before experiment. The channels were installed on a specially designed holder and, via an adaptor, connected to NGI set including the throat and pre-separator (MSP Corporation, Minneapolis, America), testing unit (TPK2, ERWEKA, Heusenstamm, Germany) and vacuum pump (HVP1000, ERWEKA, Heusenstamm, Germany) in sequence (Fig. 3). Each of the connection port was properly sealed. The testing unit is a control system for this setup, which has several functions such as pressure drop measurement, airflow rate adjustment and duration timing.

All the seven NGI stage collection cups were coated using ethyl alcohol solution with 1% Tween80. During the experiments, the pressure drop of each channel was controlled at 4 kPa. The process continued till 4 L air was drawn. Then the pump was turned off. The next dose was loaded and the pump restarted until 10 doses were sampled per experiment. The deposits of the throat, pre-separator and each NGI collection cup were recovered by HPLC