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Experimental investigation of design parameters on dry powder inhaler performance

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ABSTRACT

The study aims to investigate the impact of various design parameters of a dry powder inhaler on the turbulence intensities generated and the performance of the dry powder inhaler. The flow fields and turbulence intensities in the dry powder inhaler are measured using particle image velocimetry (PIV) techniques. *In vitro* aerosolization and deposition a blend of budesonide and lactose are measured using an Andersen Cascade Impactor. Design parameters such as inhaler grid hole diameter, grid voidage and chamber length are considered. The experimental results reveal that the hole diameter on the grid has negligible impact on the turbulence intensity generated in the chamber. On the other hand, hole diameters smaller than a critical size can lead to performance degradation due to excessive particle–grid collisions. An increase in grid voidage can improve the inhaler performance but the effect diminishes at high grid voidage. An increase in the chamber length can enhance the turbulence intensity generated but also increases the powder adhesion on the inhaler wall.

1. Introduction

Therapeutic dry powder of an aerodynamic size range of 1–5 μm is found to be the most suitable for pulmonary drug delivery (Edwards, 2002; Newman and Busse, 2002; Hickey, 2004). However, interparticle van der Waals forces are dominating for particles of this size range and the particles tend to be highly cohesive. The aggregated drug particles cause difficulty for particle dispersion, reduce the drug uniformity in the doses and cause drug retention in the inhalers. One solution to improve the drug administration is to physically mix the fine drug particles with coarse carrier particles for combined dispersion. After the dispersion, de-agglomeration of the drug and the carriers is occurred by shear forces and turbulences generated by the airflow in the inhaler and the initial airways (French et al., 1996; Newman and Busse, 2002; Voss and Finlay, 2002; Daniher and Zhu, 2008; Hassan and Lau, 2010a). The liberated fine drug particles are carried deep into the lungs by the airflow for proper clinical outcome. Therefore the specific design of the inhaler is very critical to generate sufficient airflow to disperse the drug formulation and turbulence to break up the aggregates and deliver them into therapeutically effective region of the lung (Newman and Busse, 2002).

Previous research efforts have been focused on the formulation properties (Chan, 2006) and advances in the dry powder formulation are made in controlling the particle size and size distribution (Hinds, 1999; Chew et al., 2000; Chew and Chan, 2002; Gonda, 2004; Heyder, 2004; Louey et al., 2004), particle density (Edwards et al., 1997; Louey et al., 2003; Hadinoto et al., 2006; Giovagnoli et al., 2007; Hadinoto et al., 2007), particle morphology (Edwards et al., 1997; Chew and Chan, 2001; Crowder et al., 2002; Feeley, 2002; Hassan and Lau, 2011), and shape (Chew and Chan, 2001; Shoyele, 2008; Hassan and Lau, 2009, 2010b,c). However, the performance of the dry powder inhalation system depends not only on the dry powder formulation but also the inhaler device. Although a great number of dry powder inhaler (DPI) inventions exist, not many investigate the inhaler performance at a fundamental level (Chan, 2003). Each inhaler manufacturer also has their inhaler designs vastly different from each other.

While experimental and computational studies of various aspects of dry powder inhaler device are reported in the literature, such studies are limited (Friebel et al., 2012). DPI performance is commonly associated with the degree of the particle dispersion, which is closely related to the turbulence level in the DPI. The turbulence level is quantified by the integral scale strain rate (ISSR), determined by dividing the turbulence eddy dissipation rate by the turbulence kinetic energy. Factors affecting the DPI performance can be classified into two main categories, namely the inhalation characteristics and the DPI design parameters. Even though inhalation characteristics have great impact on the performance of DPIs

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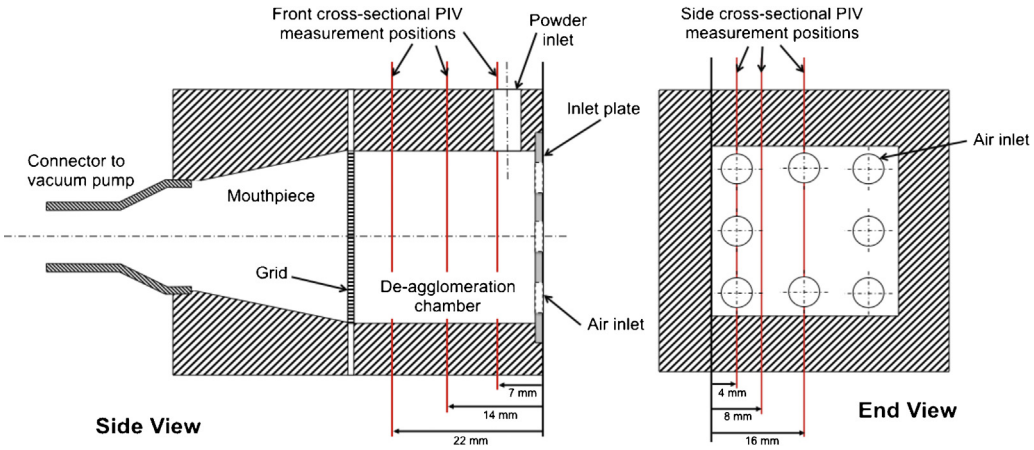

Fig. 1. Schematic diagram of the idealized dry powder inhaler model.

(de Boer et al., 1997; Chavan and Dalby, 2002; Coates et al., 2005), little control can be achieved. Nonetheless, an increase in the DPI flow rate increases the turbulence generated as well as the intensity and number of impactions between particles and DPI. The de-agglomeration potential and particle dispersion can then be increased. However, the effect of DPI flow rate diminishes as the flow rate is increased beyond 65 L/min (Coates et al., 2005).

A typical DPI includes a drug holder, air inlet, a grid, a de-agglomeration chamber and a mouthpiece (Islam and Gladki, 2008). The size of the air inlet is found to have the most significant effect on the particle dispersion (Coates et al., 2006). A decrease in the air inlet size at the same DPI flow rate increases the inlet velocity and subsequently improves the flow turbulence and particle impaction velocities. However, reduction in the air inlet size is only effective up to a DPI flow rate of 45 L/min. At higher flow rates, a reduction in the air inlet size causes the particles to release prematurely before the flow turbulence and particle impaction velocities are fully developed (Coates et al., 2006). The grid allows the generation of turbulence and particle-grid impaction for de-agglomeration. As the grid voidage increases, there is an increase in the tangential velocity at the grid but the particle-grid impaction decreases. The overall particle dispersion is found to decrease with an increase in the grid voidage (Coates et al., 2004). The design of the inhaler mouthpiece can affect the exit air velocity but no significant effect is found on the DPI performance (Coates et al., 2004, 2007).

From the available reported studies regarding inhaler design, it can be seen that the design of a DPI is vital to the control of drug particle size range that is emitted from the device (Chew and Chan, 1999; Chew et al., 2000). However, no well-established understanding on the effects of device design on the performance of the inhaler are present (Selvam et al., 2010). This study aims to perform a systematic evaluation of the important inhaler design parameter, such as the grid structure, de-agglomeration chamber length and volume. Particle image velocimetry (PIV) technique is applied on an idealized inhaler model to determine the flow field and reveal the key criteria for optimal inhaler design.

Table 2
Inhaler design information.

Inhaler design number	Inhaler 1	Inhaler 2	Inhaler 3
De-agglomeration chamber length (mm)	28	34	40
De-agglomeration chamber volume (mm^3)	23520	28560	33600

2. Materials and methods

2.1. Inhaler model

A schematic diagram of the side and end cross-sectional view of the idealized dry powder inhaler model is shown in Fig. 1. The idealized inhaler model used in this experiment is made of transparent acrylic. Airflow is generated by a vacuum pump (Thomas 2750CGH160, USA) connected to the mouthpiece. Air can enter the de-agglomeration chamber through the inlet plate consisting eight holes of 5 mm diameter. The de-agglomeration chamber has a rectangular cross section of dimension 28 mm by 32 mm. There is a powder inlet at the top of the chamber for the introduction of particles. A grid is present between the de-agglomeration chamber and the mouthpiece. The connector between the mouthpiece and vacuum pump has a funnel shape with a diameter of 16 mm. Seven grid designs are used in the study and the grid design information is shown in Table 1. Three inhaler models with different de-agglomeration chamber lengths are also carried out and the de-agglomeration chamber length information is presented in Table 2.

2.2. Flow measurement

Instantaneous flow field measurements are performed using particle image velocimetry (PIV) technique. The PIV system (TSI, USA) consists of dual Nd:YAG lasers, a PowerView Plus Camera, a synchronizer and an Insight 3G analysis software. The tracer particles can be illuminated by the pair of lasers. The laser has a power of 30 mJ/pulse and 5–7 ns pulses at 10 Hz. The particle images are recorded by the camera at a resolution of 1280 × 1024 pixels and 15 Hz frame rate. The time difference between the two consecutive

Table 1
Grid design information.

Grid number	Grid 1A	Grid 2A	Grid 1B	Grid 2B	Grid 3B	Grid 2C	Grid 3C
Grid side length (mm)	32	32	32	32	32	32	32
Hole diameter (mm)	1	2	1	2	3	2	3
Number of holes	246	45	351	94	39	146	71
Voidage	0.18	0.14	0.27	0.29	0.27	0.45	0.49
Voidage group	A		B			C	