CFD Analysis of the Aerosolization of Carrier-based Dry Powder Inhaler Formulations

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Abstract. This study applied computational fluid dynamics (CFD) analysis to investigate the role of device design on the aerosolization of a carrier-based dry powder inhaler (DPI). The inhaler device was modified by reducing the inlet size, decreasing the mouthpiece length and increasing the mesh grid voidage. The flow patterns in the inhaler device were examined. It was observed that there was no significant influence on the aerosol performance with the reduced mouthpiece. When the inlet size was reduced to one third of the original one, the fine particle fraction (FFP), defined as mount of inhalable fine particles below 5μm in the aerosol, was improved significantly from 17.7% to 24.3%. The CFD analysis indicated that the increase in FFP was due to increasing air velocity for the smaller inlet. No significant difference was shown in FFP when the grid voidage was increased, but more drugs deposited in the mouthpiece and throat.

Keywords: CFD, aerosolization, dry powder inhaler, device
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INTRODUCTION

Aerosols generated by dry powder inhalers (DPIs) are among the most promising forms to deliver therapeutic agents by inhalation to the lungs (1). Performance of DPI depends on many variables including formulation design, device selection, environment and patients' inhalation [1]. The design of inhaler devices plays a critical role on the aerosolization of the DPI formulations.

The effect of grid structure, mouthpiece length, air inlet size and mouthpiece geometry of Aerolizer® on the de-agglomeration of mannitol powders from a drug-only formulation has been investigated [2-4]. Computational Fluid Dynamics (CFD) analysis was used in these series of studies to simulate the flow field generated in the device and thus to elucidate the mechanism of the effect of device design on the de-agglomeration.

Previous studies mainly focused on the dispersion of drug-only systems. To improve dispersion efficiency, large excipient particles are often introduced to a powder inhalation system. The so-called carrier-based DPI formulation enables the fine drug particles to adhere to the surface of the coarse carrier particles. Upon aerosolization, the drug particles are liberated from the carrier and delivered into the respiratory tree while the carriers impact in the throat and are swallowed.

In this study, systemic investigation of the effect of device design on the aerosol performance of carrier-based DPI systems with aid of CFD analysis was performed.

METHODS

Aerolizer device was modified to have 1) a cross grid mesh with a higher viadoge; 2) 1/3 air inlet size; 3) 1/3 mouthpiece length. Figure 1 shows the diagram of the original and modified devices.

FIGURE 1. Diagrams of the original and modified Aerolizer devices.
The *in vitro* aerosol performance was evaluated by a multi-stage liquid impinger (Copley, Nottingham, UK) with a USP induction port (throat). Each Foradile® (Novartis Pharmaceuticals Australia Pty Limited, North Ryde, Australia) capsule contains a labeled dose of 12 μg eformoterol fumarate dihydrate. The dispersion time was 4 s at 60 L/min (20 ± 3 °C and relative humidities of 50 ± 3 %). Triplicate measurements were carried out for each device. The emitted dose was calculated as the percentage of the drug emitted from the capsules and inhaler device during the aerosolisation. The fine particle fraction of total load (FPF total) was calculated as the percentage of drug particles with the aerodynamic diameter < 5 relating to the total drug load. The drug content of eformoterol fumarate was assayed using high performance liquid chromatography (Model LC-20, Shimadzu, Kyoto, Japan).

Computational Fluid Dynamics analysis using ANSYS Fluent 13 was performed. A Reynolds stress model was used for the airflow simulation. The inlets were given an area averaged velocity based on the total airflow rate. A velocity inlet and pressure outlet boundary conditions were used in all simulations. Three grid domains were tested in our preliminary computation. The difference was less than 5% for all variables examined, suggesting that the computed results were independent of the characteristics of the mesh size. The normalized Reynolds stress residuals in the range of 10⁻⁴ have been applied as the convergence criteria to ensure full convergence.

Lagrangian particle tracking was performed as a post processing operation with a user defined function (UDF) loaded into ANSYS Fluent. The DPM tracking parameters were set as 50000 for the maximum number of steps and step length factor of 5. As Lagrangian particle tracking was performed, the number of particles inserted into the inhaler would not have much effect on the impaction result as it only tracked each individual particle impacting on the inhaler wall and neglect the particle to particle influence. The wall was set to reflect any particles that may impact on it.

**RESULTS AND DISCUSSIONS**

There was no significant difference in FPF total between the original, 1/3 mouthpiece length and cross grid (p>0.05). There was no apparent difference in air velocity distribution between the original and 1/3 mouthpiece length devices, as shown in Fig.2. On the other hand, the FPF total increased from 17.7 ± 0.5% for the original device to 24.3 ± 0.5% when the air inlet size was reduced to one-third (p<0.05). This was attributed to the increased air velocity inside the inhaler device (Fig.2). Such increase in air velocity enhanced the detachment of drug particles from carriers, therefore, resulting in higher FPF total.

**FIGURE 2.** CFD analysis of air velocity in the inhalers.
Although there was no significant difference in FPF total between the original and the cross grid devices, their deposition patterns were different (Fig. 3). More drugs deposited in mouthpiece and throat for the cross grid device because increasing the voidage of grid created more swirling air flow pattern in mouthpiece and throat (Fig. 4). Such swirling air flow patterns caused more interactions between particles and inhaler as well as throat walls during aerosolization, thus, more drug depositions in these two parts for the cross grid device. However, this did not cause significant changes in the FPF total here. We believe the detachment of the drug particles from the carrier surface mainly occurs inside the inhaler chamber and/or through the grid prior to entering the mouthpiece and induction port. Therefore, the drug particles escaped the deposition from the mouthpiece and induction port of the original device deposited on stages 1 and 2 instead, together with the lactose carriers.

**FIGURE 3.** Drug deposition patterns from multi-stage liquid impinger.
FIGURE 4. Streamlines that are instantaneously tangent to the velocity vector of the flow, show the direction a particle element will travel during the air flow through inhaler device and throat.

CONCLUSIONS

The mouthpiece length had no significant effect on the aerosolization of Foradile from Aerolizer. The CFD results confirmed that there was no observed difference in the air flow patterns when the mouthpiece length was reduced. Improved aerosol performance was shown after the inlet size was reduced. These improvements were attributed to the increases in air velocity inside the device. The cross grid device had more drug deposition in mouthpiece and throat due to the more swirling air flow pattern. This study demonstrates that the design of Aerolizer device has a significant influence on the aerosolization of carrier-based DPIs. CFD is shown to be a useful tool in investigating the air flow pattern in the inhaler device.

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