Importance of Powder Residence Time for the Aerosol Delivery Performance of a Commercial Dry Powder Inhaler Aerolizer®

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Abstract

Background: The performance of dry powder aerosol delivery systems depends not only on the powder formulation but also on the dry powder inhalers (DPIs). Effects of turbulence, grid, mouthpiece, inlet size, air flow, and capsule on the DPIs performance have been investigated previously. Considering powder dispersion in DPIs is a time-dependent process, the powder residence time in DPIs is supposed to have a great impact on DPIs efficiency. This study sought to investigate the effect of powder residence time on the performance of a commercial DPI Aerolizer®.

Methods: A standard Aerolizer® (SD) and five modified devices (MD1, MD2, MD3, MD4, and MD5) were employed for this research. Computational fluid dynamics analysis was used to calculate the flow field and the powder residence time in these devices. Recombinant human interleukin-2 inhalation powders and a twin impinger were used for the deposition experiment.

Results: The powder mean residence time in the secondary atomization zone of the devices was increased from 0 ms for SD to 0.33, 0.96, 1.42, 1.76, and 2.14 ms for MD1, MD2, MD3, MD4, and MD5, respectively. At a flow rate of 60 L/min, with an increase in the powder residence time in these devices, a significant gradual and increasing trend in the powder respirable fraction was observed from 29.1% ± 1.1% (MD1) to 32.6% ± 2.2% (MD2), 37.1% ± 1.1% (MD3), and 43.7% ± 2.1% (MD4). There was no significant difference in the powder respirable fraction between SD and MD1 or between MD4 and MD5.

Conclusions: Within a certain range, increasing the powder residence time could improve the performance of Aerolizer® by increasing the powder–air interaction time (the main reason) and increasing the powder–device compaction (the secondary reason). Combination of high turbulence level and sufficient powder residence time could further improve the device performance.

Key words: powder residence time, Aerolizer®, respirable fraction

Introduction

Dry powder inhalers (DPIs) are commonly used for treatment of systemic diseases (such as diabetes) and respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease, and tuberculosis). Within the airway branching system of lung, the alveoli have an enormous surface area compared to the airway and consequently play the most important role in pulmonary drug absorption.(1) For treatment of systemic diseases, following deposition in the alveoli, ideally the powder systems can dissolve speedily and then the drug (with molecular weight <40 kDa) can penetrate into the lungs and appear in the blood rapidly.(2) Based on the principle that for some drugs the therapeutic effect is related to the plasma drug levels, the therapeutic effect is related to the drug deposition in the alveoli and consequently to the DPIs performance. For treatment of respiratory diseases, the drug effect can also be improved by increasing the alveoli drug deposition.(3,4) So an improvement of DPIs deposition performance is required for a greater therapeutic effect of dry powder inhalations. A correct inhalation technique in patients is required for a better DPI performance, and upon a same inspiratory flow,
the deposition performance of dry powder aerosol delivery systems depends on the performance of DPIs as well as the powder formulations. Over the past decades, extensive researches have advanced the aerosol delivery systems by control of powder formulations.\(^5\)\(^-\)\(^10\) At the same time, several previous studies have described the underlying principles governing DPIs design.\(^11\)\(^-\)\(^13\) Voss and Finlay\(^14\) showed that turbulence played a significant role in fine particle dispersion, and Coates et al.\(^15\)\(^-\)\(^19\) investigated the effect of grid structure, mouthpiece length and geometry, inlet size, air flow, and capsule on the DPI performance.

Considering powder dispersion in DPIs is a time-dependent process; apart from the factors mentioned above, the powder residence time in DPIs is supposed to have a great, although perhaps not the most important, impact on DPIs performance. When drug powder clusters are released into the air flow, it’s hard for all powder contacts to be broken at the same time due to forces from the air acting only upon the aggregate surface exposed to the air. Therefore, a sufficient length of time is required for powder aggregate absolute dispersion. If the powder deagglomeration time provided by the device is inadequate, the undispersed powders will deposit in the throat and upper airways, decreasing the total pulmonary drug deposition. To the best of our knowledge, until now no literature published previously demonstrated the effects of powder residence time on dispersion performance of a DPI.

The aim of this study was to examine the effect of powder residence time on the performance of a commercial DPI Aerolizer\(^\circ\) (SD) and five modified devices (MD1–MD5) were used in this study, and the performance of these devices was investigated using computational fluid dynamics (CFD) simulation coupled with experimental powder dispersion analysis. The powder residence time was determined using CFD.

Material and Methods

Materials

The drug recombinant human interleukin-2 (rhIL-2) was purchased from Four Rings Biopharmaceutical Co., Beijing, China. Human serum albumin was purchased from Jiangsu Chuangnui Biotechnology Co., Nanjing, China. Mannitol and threonine were obtained from Huixing Biochemical reagents Co. Ltd., Shanghai, China. High-performance liquid chromatography (HPLC) grade acetonitrile was obtained from Shanghai Lingfeng Chemical reagent Co. Ltd., Shanghai, China. NaClO\(_4\) (99.9% assay) and HClO\(_4\) (99.9% assay) were purchased from Nanjing Chemical reagent Co. Ltd., Nanjing, China.

Geometries of the modified devices

To investigate the importance of powder residence time for the powder dispersion performance of the device, a standard device Aerolizer\(^\circ\) (SD) and five modified devices (MD1–MD5) were adopted in this study. Geometries of the devices adopted are shown in Figure 1. The standard device consisted of a primary turbulent atomization zone, two air inlets, a mouthpiece tube, and a mesh at the entrance to the mouthpiece tube. Compared with SD, secondary turbulent atomization zones with various heights and additional meshes with a large voidage on the secondary turbulent atomization zone were added to the modified devices, and the structure of mesh at the entrance to the mouthpiece tube remained the same as that of SD. The height of the secondary turbulent atomization zone was 2, 4, 6, 8, and 10 mm for MD1, MD2, MD3, MD4, and MD5, respectively. With each having a different secondary turbulent atomization zone height, various powder residence times could be achieved, and the effect of powder residence time on the device

![FIG. 1. Geometries of the standard device Aerolizer\(^\circ\) (SD) and the five modified devices (MD1–MD5). a: geometries of SD; b: geometries of MD1–MD5 with the additional secondary turbulent atomization zone; c: the additional secondary turbulent atomization zone of MD1–MD5 with height (H) of 2, 4, 6, 8, and 10 mm, respectively; d: the primary turbulent atomization zone of all devices; e: the additional mesh on the secondary turbulent atomization zone.](image-url)
performance could be determined by comparing the powder dispersion performance from devices with different powder residence time.

**CFD numerical method**

To simulate the flow fields generated in devices, a CFD package Fluent 6.2.16 was employed. The computational geometries and their boundary conditions were created using Gambit 2.2.30. The structured grids contained approximately 130,000 hexahedric elements. Three different grid sizes (65,000, 130,000 and 260,000 elements) were tested for each device. Analysis of grid convergence concerning mean velocities and turbulence kinetic energy indicated the size of adopted grids (about 130,000 elements) to be adequate. The boundary conditions of air inlets, outlet of mouthpiece and other walls in the computational models were set as velocity-inlet, outflow and wall, respectively. To simplify conditions in the model, it was assumed that: (1) air in the model was incompressible, (2) flow in the inlets was steady and parallel to the axis, (3) the friction heat was negligible in this process. Flow in the device was transitional or turbulent.

For determination of turbulence level in the DPI, a low Reynolds number (LRN) k-ω model was selected, based on its ability to accurately predict pressure drop, velocity profiles, and shear stress for transitional and turbulent flows. All transport equations were discretized to be at least second order accurate in space. Convergence of the flow field solution was assumed when the global mass residual was reduced from its original value by five orders of magnitude and when the residual reduction rates for the equations were sufficiently small. To ensure that a converged solution was reached, residual and reduction-rate factors were decreased by an order of magnitude and the results were compared. The stricter convergence criteria produced a negligible effect on the flow field.

As the performance of DPIs could be influenced by the acceleration of the air as much as the steady flow, the flow fields were simulated for both accelerating and steady inlet flow. For the steady flow simulation, a flow rate of 60 L/min was adopted. For the accelerating flow simulation, an inlet flow as a sine function of the physical flow time as shown in Equation (1) was adopted using the User-Defined Function in Fluent 6.2.16:

$$v = 60 \sin \left( \frac{t \Pi}{10} \right)$$  \hspace{1cm} (1)

where $v$ is the inlet velocity magnitude (L/min), $t$ is the flow time (s), and $\Pi$ is the circumference. Although this formula could hardly reflect the complicated breath of human, by acting as a representation of accelerating inlet flow it could be used to compare the flow fields generated in different devices. The unsteady simulation of the volume weighted average flow velocity and turbulence kinetic energy was performed for all devices during the flow time of 10s.

To estimate the powder residence time in devices, a Transport and Reaction model was adopted. Powders with a density of 0.2 g/mL and air were selected as the mixture species, and the powder–air mixture density followed the volume weighted mixing law. Following addition of powder–air mixture with a powder mass fraction of 100% for 0.0001 ms, a mixture with a powder mass fraction of 0 was selected to flow in the device. The residence time distribution of powders was achieved by monitoring changes of the powder mass fraction in the outlet of the primary turbulent atomization zone, the secondary turbulent atomization zone, and the device. The mean residence time ($t$) was calculated using Equation (2), where $C_i$ was the powder mass fraction in the outlet of device at the time of $t_i$.

$$t = \frac{\sum t_i C_i}{\sum C_i}$$  \hspace{1cm} (2)

**Formulation and aerosolization method**

The dispersion experiment was performed using rhIL-2 inhalation powders prepared by spray drying with a Buchi 191 mini spray drier (Buchi Labortechnik AG, Flawil, Switzerland). The composition of rhIL-2, mannitol, threonine, and human serum albumin in a weight ratio of 0.1/750/250/0.25, and the conditions of spray drying were set as follows: inlet temperature, 110°C; outlet temperature, 69°C; spraying air flow rate, 600 L/h; solution feed rate, 2 mL/min; solid concentration, 2%.

The particle diameter was measured by laser diffraction (Mastersizer 2000 Particle Size Analyzer, Mastersizer, England). Powder samples were suspended in isopropanol, in which the powders were insoluble. The bulk density was measured in a graduated cylinder (10 mL), and tapped density measurement was performed following 1000 taps, which allowed the density to plateau. Static powder flow was characterized using Carr’s Compressibility Index (CI), determined from the tapped ($\rho_{tap}$) and bulk ($\rho_{bulk}$) densities.

$$CI = \frac{\rho_{tap} - \rho_{bulk}}{\rho_{tap}} \times 100$$  \hspace{1cm} (3)

The deposition behavior of powders from these devices was evaluated using a twin impinger (British Pharmacopoeia 2010, Appendix XII C7, Apparatus A). For each dispersion performed, 10 hydroxypropyl methylcellulose capsules (size 3, Capsugel®, Suzhou, China) were filled with approximately 30 mg of rhIL-2 inhalation powders for each; then the powders were dispersed into the impinger running at a test flow rate of 60 L/min for 10s. The actual flow at the mouthpiece was determined using a rotameter between the pump and the twin impinger. At the end of experiment, the apparatus was disassembled and the inner surface of lower chamber was washed with distilled water. All runs were performed three times to obtain mean values. Throughout the dispersion analysis, the temperature and the relative humidity of laboratory were maintained at 20 ± 2°C and 35 ± 5%, respectively. The drug content was determined using RP-HPLC. A Hypersil 300A C4 column (150 × 4.6 mm i.d.; 5 μm) (Dalian Elite Analytical Instruments Co., Ltd, Dalian, China) was used for the quantification. The column was maintained at a temperature of 30°C. The isocratic mobile phase consisted of perchloric acid buffer (containing 0.1 M NaClO4 and 0.01 M HClO4), acetonitrile (20:80, v/v), and was run at a flow rate of 1 mL/min. Absorbance was monitored at 205 nm. The respirable fraction was defined as the Stage 2 deposition fraction, numerically expressed as the percentage of powders collected in the Stage 2 impinger.
referenced against the total mass of powders loaded in the capsules.

Statistical analysis

Statistical analysis of the experimental data for different devices was performed using Student’s t-test when two groups were compared. Each experiment was repeated three times for all devices. Differences in the experimental results were considered to be statistically significant when \( p < 0.05 \) and highly significant when \( p < 0.01 \).

Results

Computational fluid dynamics results

Figure 2 shows that although differences in the flow field generated in secondary turbulent atomization zone and mouthpiece of the modified devices were observed, the inherent nature of flow field generated in the primary turbulent atomization zone was the same for all devices. Increasing the height of secondary turbulent atomization zone slightly decreased the overall level of flow field velocity generated in the secondary turbulent zone. Although the velocity of flow field generated at the bottom of mouthpiece was decreased with an increase of the height of secondary turbulent atomization zone, there was no difference in the velocity of flow field generated at the top of mouthpiece. It is shown in Figure 3 that a similar level of turbulence was generated in the primary turbulent atomization zone of all devices. With the height of secondary turbulent atomization zone being increased, the turbulence level generated in the secondary turbulent atomization zone was slightly decreased. The turbulence level generated in the middle and outlet of mouthpiece was the same, although a slight difference at the bottom of mouthpiece was observed.

As the accelerating inlet flow could also influence the DPIs’ performance, the unsteady simulation of the flow field generated in all devices was performed when adopting an inlet flow as a sine function of the flow time. During the physical flow time, changes in the volume weighted average flow rate and turbulence kinetic energy in all devices were determined. Similar change processes of turbulence level and flow rate in all devices are shown in Figures 4 and 5, demonstrating that the devices employed in this study could create the same shear and turbulence for an accelerating air flow as well as a steady flow (60 L/min).

Following addition of powder–air mixture with the powder mass fraction of 100% at a flow rate of 60 L/min for 0.00001 ms, the changes of powder mass fraction in the outlet of the primary turbulent atomization zones, the secondary turbulent atomization zones and the devices were monitored (Fig. 6). As shown, the additional secondary turbulent atomization zone did not change the powder residence time distribution in the primary turbulent atomization zone of devices MD1–MD5. By monitoring the powder mass fraction in the outlet of secondary turbulent atomization zone, the powder residence time distribution in the device part containing the primary and secondary turbulent atomization zone was achieved. With an increase of secondary turbulent atomization zone height, the powder residence time in this part was increased significantly. The powder residence time distribution in the whole device was obtained by monitoring the powder mass fraction in the outlet of device, and with the secondary turbulent atomization zone height being increased, the powder residence time was increased significantly.

The mean residence time of powders in different parts of devices SD and MD1–MD5 is shown in Table 1. According to the results, there was no difference in the powder mean residence time in the primary turbulent atomization zone of all devices. With an increase in the secondary turbulent atomization zone height from 2 mm for MD1 to 4, 6, 8, and 10 mm for MD2, MD3, MD4, and MD5, respectively, the powder mean residence time in the secondary atomization zone was increased from 0.33 ms for MD1 to 0.96, 1.42, 1.76, and 2.14 ms for MD2, MD3, MD4, and MD5, respectively. The powder mean residence time in the mouthpiece was increased slightly from 3.81 ms for SD to 3.85, 3.87, 3.90,
FIG. 3. Turbulence kinetic energy profiles of SD and MD1–MD5 indicating the additional secondary turbulent atomization zone of the modified devices did not affect the level of turbulence generated in the primary turbulent atomization zone and outlet of the device mouthpiece at a flow rate of 60 L/min. a: the primary turbulent atomization zone; b: the additional secondary turbulent atomization zone; c: the mouthpiece.

FIG. 4. Changes of the volume weighted average velocity in SD and MD1–MD5 with an accelerating inlet flow during the flow time, indicating the devices adopted in this study could create the same flow level with an accelerating inlet flow.
4.08, and 4.20 ms for MD1, MD2, MD3, MD4, and MD5, respectively.

Formulation and aerosolization results

In this study, a powder inhalation formulation of rhIL-2 was prepared. The powder volume mean diameter was 2.91 ± 0.10 \text{\mu m}; the bulk density and the tap density were 0.19 ± 0.01 and 0.21 ± 0.01 g/mL, respectively. The Carr’s Compressibility Index of powder was 5.00 ± 0.25, indicating a good flow ability of the powder.

The actual flow at the mouthpiece of twin impinger was set at 60 L/min by the rotameter, and the rhIL-2 inhalation powder dispersion results showed that the additional secondary turbulent atomization zone with various powder residence times (Table 1) had a significant effect on the powder deposition fraction in the impinger (Fig. 7). At a flow rate of 60 L/min, as the powder mean residence time was increased, a gradual statistically significant reduction trend in the mouthpiece deposition was observed from SD (25.5 ± 1.3%) to MD1 (21.0 ± 1.5%), MD2 (17.0 ± 2.9%), MD3 (13.1 ± 2.1%), and MD4 (8.0 ± 1.4%), but no significant difference in the mouthpiece deposition fraction was observed between MD4 and MD5. The increase of the powder residence time led to a significant increase in the Stage 1 deposition fraction from 23.3 ± 2.1% for MD1 to 26.7 ± 1.7% for MD2 and a significant gradual and decreasing trend from 26.7 ± 1.7% for MD2 to 22.9 ± 2.2% and 14.2 ± 2.6% for MD3 and MD4. There was no significant difference in the Stage 1 deposition fraction between SD (20.3 ± 2.3%) and MD1 (23.3 ± 2.1%) or between MD4 (14.2 ± 2.6%) and MD5 (16.2 ± 2.1%). A significant gradual and increasing trend in the Stage 2 deposition fraction was found from MD1 (29.1 ± 1.1%) to MD2 (32.6 ± 2.2%), MD3 (37.1 ± 1.1%) and MD4 (43.7 ± 2.1%). There was no significant difference in the Stage 2 deposition fraction between SD (28.2 ± 1.2%) and MD1 (29.1 ± 1.1%) or between MD4 (43.7 ± 2.1%) and MD5 (44.2 ± 2.3%), although a slight increasing trend was observed. A neglectable capsule retention fraction (< 1.0%) was observed after the deposition experiment. Both SD and the modified devices possessed a large device retention, perhaps because all devices employed in this study were made of acrylonitrile butadiene styrene plastic.
different from the material of commercial device Aerolizer®, which was suitable for carving a device model but perhaps had a large adsorption force for the drug powders. It was supposed that the device drug adsorption could be decreased by selecting the device material. A significant increased device retention fraction was found from MD3 (26.9 ± 1.05%) to MD4 (34.1 ± 1.04%), perhaps because a larger amount of fine particles, easier to be adsorbed than the coarse ones, was generated in MD4.

**Discussion**
From the results of Computational Fluid Dynamics and aerosolization, it was observed that devices with different

| TABLE 1. POWDER MEAN RESIDENCE TIME IN DIFFERENT PARTS OF DEVICES SD AND MD1–MD5 |
|---------------------------------|---------------|---------------|---------------|---------------|---------------|
|                                  | SD/ ms        | MD1/ ms       | MD2/ ms       | MD3/ ms       | MD4/ ms       | MD5/ ms       |
| Primary turbulent atomization zone | 2.71          | 2.66          | 2.70          | 2.67          | 2.72          | 2.80          |
| Secondary turbulent atomization zone | —             | 0.33          | 0.96          | 1.42          | 1.76          | 2.14          |
| Mouthpiece                        | 3.81          | 3.85          | 3.87          | 3.90          | 4.08          | 4.20          |
powder residence times could create various powder dispersion performances. However, because the performance of DPIs is influenced by several factors (such as the flow field and the turbulence level generated in devices), when determining the effect of powder residence time on the DPI performance, it was necessary to exclude the effect of other factors mentioned in the previous studies.

Studying the mechanisms of powder deagglomeration, Voss and Finlay\(^{(14)}\) showed that turbulence plays a significant, although not necessarily the dominant, role on the fine particle dispersion. The fine particle dispersion could be increased by reducing the throat deposition amount,\(^{(22)}\) which was known to be strongly related to the velocity of air flow existing in the device.\(^{(23,24)}\) As shown in this study, when the height of secondary turbulent atomization zone was increased, there was no significant difference in the flow field or the turbulence level generated in the primary turbulent atomization zone of devices SD and MD1–MD5. Although in different devices a slight change in the flow field and the turbulence level generated in the basement of mouthpiece was observed, the flow field and the turbulence level generated in the outlet of mouthpiece were similar, indicating that turbulence generated in the primary turbulent atomization zone and the mouthpiece of different devices had the same impact on powder dispersion. Therefore, it was the different secondary turbulent atomization zones that caused changes in the powder respirable fraction from all devices. As shown in Figures 2 and 3, the flow field velocity and the turbulence level generated in the secondary turbulent atomization zone were decreased from MD1 to MD5 gradually. It was indicated that in this study the turbulence level generated in the secondary turbulent atomization zone was not the dominant factor influencing powder dispersion, for if it had the dominant effect, the powder respirable fraction should have decreased from MD1 to MD5, in contrast to the experimental results observed in this study.

When studying the effect of air inlet size on the DPI performance, it was found that the flow field development time had a significant effect at a flow rate of 60 L/min.\(^{(18)}\) As at the beginning of the flow field development, the inlet flow velocity was increased from 0 to 60 L/min gradually, and a length of time referred to as the flow field development time was required for the flow field and the turbulence level to reach steady state. To study whether the change of powder dispersion performance in different devices was caused by the flow field development time in this research, the volume weighted average flow field velocity and turbulence level development time in SD and MD1–MD5 were evaluated as shown in Figures 8 and 9. According to the results, the flow field velocity and the turbulence level developed in 4–8 ms in SD and MD1–MD5, and there was no significant difference in the development time in these devices. Although before the development time the flow velocity was lower than that generated after the development time, the turbulence level generated in devices before the development time was higher than that generated after that time. For turbulence kinetic energy (\(k\)) is defined as Equation (4):

\[
k = 0.5 (\overline{\nu^2} + \overline{\nu_x^2} + \overline{\nu_z^2})
\]

\[\text{(4)}\]

where \(\overline{\nu}, \overline{\nu_x}, \text{ and } \overline{\nu_z}\) are the average fluctuations of velocity along the x-, y-, and z-axis, respectively. This equation means that turbulence kinetic energy is not dependent on the flow field velocity, but on the average velocity fluctuation. Although the velocity generated in the initial flow field state was low, change in the velocity magnitude and the direction was large, which led to a high fluctuation in velocity and then high turbulence kinetic energy. So if the undeveloped flow field, which was defined as the flow field created in devices before the flow field development time, had a great impact on the dispersion performance, the more powder released by the capsule before the flow field development time, the higher the powder respirable fraction should be. But as shown in Figure 10, no significant difference was found between the results obtained with or without the influence of undeveloped flow field proving the flow field development time had no significant impact on the performance of devices employed in this study.
As mentioned above, the influence of the turbulence level and the flow field development time on change of the powder dispersion performance of devices employed in this study was negligible. Considering powder dispersion is a time-dependent and powder–air-interacting process, the powder residence time could affect the powder dispersion behavior. As the powder residence time increased, more time for interaction between powder and air in the device was available. The increased powder residence time also brought in an increased powder flow path in the device, inducing more opportunities for interaction between powders and the device, which could improve the powder dispersion and increase the powder respirable fraction.

The parameter $r_{\text{disp}}$ in the model is the minimal turbulence shear stress required for powder dispersion as shown in Equation (5):\(^{(26)}\)

$$r_{\text{disp}} = \frac{0.26 \rho_f (e / \nu_{\text{kin}})^{1/2}}{X_{\text{agg}}}$$

$$r_{\text{disp}} = \frac{0.068 \rho_f (e / \nu_{\text{kin}})^{1/2}}{X_{\text{agg}}}$$

$$r_{\text{disp}} = \frac{0.49 \rho_f (e / \nu_{\text{kin}})^{1/2}}{X_{\text{agg}}}$$

$$r_{\text{disp}} = \frac{1.9 \rho_f (e / \nu_{\text{kin}})^{1/2}}{X_{\text{agg}}}$$

where \(\rho_f\) is the fluid density, \(e\) is the energy dissipation rate, \(\nu_{\text{kin}}\) is the kinematic viscosity and \(I_D\) is the Kolmogorov length scale defined as Equation (6):\(^{(26)}\)

$$I_D = (\nu_{\text{kin}}^3 / \epsilon)^{0.25}$$

where $X_{\text{agg}}$ is the particle size, $\nu_{\text{kin}}$ is the kinematic viscosity and $I_D$ is the Kolmogorov length scale defined as Equation (6).\(^{(26)}\) The transitional region in $3I_D$ to $58I_D$ plays an important role in deagglomeration because the agglomerate sizes are expected to be in that range.\(^{(26)}\) As shown in the model, only in region with turbulent shear stress higher than $r_{\text{disp}}$ could dispersion of a powder layer occur. According to the fluid dynamics principle, the agglomerates should fly from a lower turbulence level region to a higher one, for the higher turbulence level region has a lower pressure. However, when considering the impaction of the agglomerates with each other and

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**FIG. 8.** Development of the volume weighted average flow velocity generated in SD and MD1–MD5 demonstrating that the flow velocity development time was 4–8 ms for all devices.
FIG. 9. Development of the volume weighted average turbulence level generated in SD and MD1–MD5 demonstrating that the flow turbulence level development time was 4–8 ms for all devices, and before the development time the turbulence level generated was higher than that generated after the development time.

FIG. 10. Comparison of respirable fraction of powders obtained with (light shaded columns) and without (dark shaded columns) the influence of the undeveloped flow field. Results influenced by the undeveloped flow field were obtained when buttons of the devices were pressed and released before switching on the pump. Results without the influence of the undeveloped flow field were obtained when buttons were kept being pressed until field flow had been developed (5 s after switching on the pump). No significant difference in the powder respirable fraction was found, indicating flow field development time had no significant effect on powder dispersion performance of devices SD and MD1–MD5 at a flow rate of 60 L/min.
the impaction of the agglomerates with the capsule and the
device, as shown in Figure 11, the flow path of particles in
the devices is confused. The disordered particle flow paths
are shown in Figure 12, indicating there was the possibility
that an agglomerate entered into a region with turbulent
level lower than \( r_{\text{disp}} \) from a higher turbulence level region.
Therefore, dispersion of powder layers was possibly not
continuous. The time required for dispersion process of the
\( i \)th powder layer (the process marked with solid arrow in
Fig. 11) was defined as \( t_i \); the interval time
between dispersion of the \( i \)th and the \((i + 1)\)th powder layer
(the process marked with dotted label arrow in Fig. 11) was
defined as \( t_{i+1} \); and the time required for an agglomerate
dispersion (\( t_{\text{total}} \)) was shown as Equation (7):

\[
t_{\text{total}} = \sum_{i=1}^{n} (t_i + t_{i+1})
\]

where the parameter \( n \) is the number of powder layers in an
agglomerate. Because the flow field distribution and the
mechanism of powder dispersion in the DPI were much
more complicated, it was hard for us to get the real magni-
tude of \( t_{\text{total}} \) but according to results of this study, it was
supposed to be in the millisecond range. At a certain tur-
bulence level, when the powder residence time was lower

**FIG. 11.** The theoretical 2D model to describe the step-by-step and layer-by-layer dispersion of powder agglomerates in the contours of turbulent shear stress. Dispersion process of the \( i \)th and the \((i + 1)\)th layer powder was marked with a solid arrow, and the interval process between dispersion of the \( i \)th and the \((i + 1)\)th powder layer was marked with a dotted label arrow.

**FIG. 12.** The disordered flow paths of the dispersed powders in SD and the modified devices MD1–MD5.
than \( t_{\text{total}} \), only a proportion of powder could be dispersed, and an improvement of dispersion performance could be observed with the powder residence time being increased. When the powder residence time was higher than \( t_{\text{total}} \), the total powder dispersion could occur, and in this condition the DPI performance could not be improved with increased powder residence time. As shown in Table 1, the powder mean residence time in the secondary turbulent atomization zone was increased from 0 ms for SD to 0.96, 1.42, and 1.76 ms for MD2, MD3, and MD4, respectively. This led to the powder respirable fraction being increased from 28.2% for SD to 32.6%, 37.1% and 43.7% for MD2, MD3, and MD4, respectively (Fig. 7). A slight increase of the powder mean residence time from 0 ms for SD to 0.33 ms for MD1 only brought in an increasing trend of powder respirable fraction without statistical significance. Although the powder residence time in the secondary turbulent atomization zone was increased from 1.76 ms for MD4 to 2.14 ms for MD5, there was no significant difference in the Stage 1 or Stage 2 deposition fraction from the two devices. Perhaps this was because the powder residence time in MD4 was sufficient for powder dispersion in conditions of this study (higher than \( t_{\text{total}} \) of the agglomerates), and when the powder residence time was higher than that in MD4, the powder dispersion performance could not be improved.

Conversely, the increased powder residence time brought in an increased powder flow path in the device, and consequently induced more opportunities for powder-device interaction, which could improve the powder dispersion performance and increase the powder respirable fraction. Lagrangian particle tracking was performed using a Discrete Phase Model, in which the fate of 1000 and 10,000 particles with a density of 0.2 g/mL and diameter of 3.0 \( \mu \)m were tracked through the fluid after being released from the capsule region and subjected to drag and turbulent dispersion forces. By setting different walls within the devices to have a zero coefficient of restitution,\(^{15}\) the frequency and location of wall impactions are shown in Table 2. Realistic computational requirements limited the number of dispersed particles to 10,000. No significant difference in the impaction frequency was observed for the 10-fold increase of particles, giving confidence in the models used at capturing the correct trends in particle impactions independent of the number of particles simulated. As shown in Table 2, in different devices percentage of particles impacting on the mouthpiece, grid, and primary turbulent atomization zone were similar. In SD, there was no secondary atomization zone, and in the modified devices with a series of secondary atomization zones, above 70.0% particles impacted on the secondary turbulent atomization zone (Table 2), and the increased particle–device interaction was as expected.

### Table 2. Summary of the Percentage of Particles Impacting on the Different Sections of Different Devices when the Discrete Phase Model Was Used to Simulate the Dispersion of 1000 and 10,000 Drug Particles Introduced in Separate Simulations into Each Section of the Inhaler

<table>
<thead>
<tr>
<th>Percentage of particles impacting on different sections of different devices</th>
<th>Mouthpiece</th>
<th>Grid</th>
<th>Primary turbulent atomization zone</th>
<th>Secondary turbulent atomization zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>10,000</td>
<td>1000</td>
<td>10,000</td>
<td>1000</td>
</tr>
<tr>
<td>SD</td>
<td>46.1%</td>
<td>47.3%</td>
<td>21.3%</td>
<td>17.6%</td>
</tr>
<tr>
<td>MD1</td>
<td>51.5%</td>
<td>48.9%</td>
<td>16.9%</td>
<td>16.2%</td>
</tr>
<tr>
<td>MD2</td>
<td>49.9%</td>
<td>51.2%</td>
<td>22.3%</td>
<td>19.2%</td>
</tr>
<tr>
<td>MD3</td>
<td>44.0%</td>
<td>44.1%</td>
<td>22.5%</td>
<td>17.8%</td>
</tr>
<tr>
<td>MD4</td>
<td>46.1%</td>
<td>41.1%</td>
<td>20.8%</td>
<td>18.7%</td>
</tr>
<tr>
<td>MD5</td>
<td>50.9%</td>
<td>46.5%</td>
<td>20.9%</td>
<td>17.6%</td>
</tr>
</tbody>
</table>

### Table 3. Summary of the Percentage of Particles Impacting on the Top and Side Wall of the Secondary Turbulent Atomization Zones in MD1–MD5 When the Discrete Phase Model Was Used to Simulate the Dispersion of 1000 and 10,000 Drug Particles

<table>
<thead>
<tr>
<th>Percentage of particles impacting on different sections of the secondary turbulent atomization zone in different devices</th>
<th>Top wall</th>
<th>Side wall</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>10,000</td>
<td>1000</td>
</tr>
<tr>
<td>MD1</td>
<td>69.9%</td>
<td>67.7%</td>
</tr>
<tr>
<td>MD2</td>
<td>70.8%</td>
<td>71.9%</td>
</tr>
<tr>
<td>MD3</td>
<td>60.2%</td>
<td>60.5%</td>
</tr>
<tr>
<td>MD4</td>
<td>58.8%</td>
<td>56.4%</td>
</tr>
<tr>
<td>MD5</td>
<td>58.5%</td>
<td>57.0%</td>
</tr>
</tbody>
</table>

**FIG. 13.** Velocity profiles of SD and devices with secondary turbulent atomization zone and decreased inlet size, indicating the decreased inlet size increased flow field velocity generated in the primary turbulent atomization zone of devices.
compaction could possibly bring in a dispersion improvement as reported previously.\textsuperscript{(15,25)} As shown by the impact results, the particle impaction percentage on the secondary turbulent atomization zone was not increased with an increase of secondary atomization zone height. This was because most impaction occurred on the top wall of the secondary atomization zone instead of on the side wall (Table 3), and the area size of the top wall was not changed with an increase of the secondary atomization zone height. As shown in Table 2, in contrast to the trend of the powder deposition results, particle impaction percentage on the devices was not increased from MD1 to MD5, indicating impaction was not the main effect, although it did affect the dispersion performance.

When using the modified devices, the position that the bolus of drug was placed on the aspiratory flow cycle might be changed by the increased powder residence time. But considering the powder residence time of the modified devices (in the millisecond range) was much less than the typical patient inspiratory flow time (in the second range), the position of drug on the inspiratory flow cycle could not be changed drastically. When using the DPI, the patient was required to hold the breath for about 10 s or longer, this technique could also counteract the slight change of drug position on the inspiratory flow and help the patient to get the full benefit of each dose.

Although the powder inhalation adopted in this study was prepared by spray drying, many commercial dry inhalations are carrier-based formulations blending microsized drug particles with a larger inert carrier material greater than the drug particles ($>50\ \mu m$).\textsuperscript{(28)} In carrier-based formulations, complex multiparticulate agglomerated systems are formed,\textsuperscript{(29)} and upon aerosolization the drug particles should be liberated from the carrier to pass into the respiratory tree. Because the drug particle liberation from the carrier surface was also a time-dependent and powder–air-interacting process, it was possible that the observations in present study could be translated to the carrier-based formulations. But in order to fully understand this issue, it will be necessary to carry out further research.

This study showed that the performance of Aerolizer\textsuperscript{R} was dependent not only on the turbulence level generated in the device but also on the powder residence time of device. The effect of turbulence level and powder residence time on the powder respirable fraction could be combined to

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure14.png}
\caption{Turbulence kinetic energy profiles of SD and devices with secondary turbulent atomization zone and decreased inlet size, indicating the decreased inlet size increased turbulence level generated in the primary and the secondary turbulent atomization zone of devices.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure15.png}
\caption{Aerosol deposition results performed in SD and devices with secondary turbulent atomization zone and decreased inlet size at a flow rate of 60 L/min ($n=3$). *$p<0.05$; **$p<0.01$.}
\end{figure}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
 & SD/ms & Full inlet/ms & 2/3 inlet/ms & 1/3 inlet/ms \\
\hline
Primary turbulent atomization zone & 2.71 & 2.72 & 2.80 & 2.67 \\
Secondary turbulent atomization zone & — & 1.76 & 1.51 & 1.53 \\
Mouthpiece & 3.81 & 4.08 & 3.82 & 3.75 \\
\hline
\end{tabular}
\caption{Powder Mean Residence Time in Different Parts of Devices with the Secondary Turbulent Atomization Zone and Different Air Inlet Size}
\end{table}
improve the DPI performance. The decreased air inlet sizes were adopted, as decreasing the inlet size could enhance the turbulence level in the devices.\(^{138}\) Air inlet of two-thirds or one-third the original area was obtained by adopting an unchanged inlet height and a decreased inlet width equal to two-thirds or one-third the original one. The height of secondary turbulent atomization zone was set at 8 mm. The CFD results (Figs. 13 and 14) showed with a decrease in the air inlet size, the flow field velocity generated in the primary turbulent atomization zone and the turbulence level generated in the primary and secondary turbulent atomization zone were increased significantly, and there was no significant difference in the velocity and the turbulence level generated in the mouthpiece. It is shown in Table 4 that in the modified devices the powder residence time was increased with an additional secondary turbulent atomization zone, while it was not influenced by the decreased inlet size. The deposition experimental results (Fig. 15) shows that, compared with SD, although the adsorption of drug in the devices was increased by 23.1%, the deposition fraction in Stage 2 from the device with the additional secondary turbulent atomization zone and the two-thirds inlet size was increased by 72.3% (\(p<0.01\)). When the inlet size was decreased from two-thirds to one-third the original area, the powder respirable fraction was not increased, perhaps because the turbulence level generated in the device with two-thirds inlet was sufficient for powder dispersion. The results indicated a combination of high turbulence level and a sufficient length of powder residence time could improve the performance of Aerolizer\(^8\).

Conclusions

In this study, a combination of computational and experimental methods was used to investigate the effect of powder residence time on the performance of a commercial DPI Aerolizer\(^8\). The results showed that the powder residence time had a significant impact on the inhaler performance at a constant turbulence level. Within a certain range, increasing the powder residence time could improve the device performance by increasing the powder–air interaction time (the main reason) and increasing the powder–device compaction (the secondary reason). Combination of high turbulence level and sufficient powder residence time could further improve the performance of Aerolizer\(^8\).

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Author Disclosure Statement

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