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Research Paper

Influence of Mouthpiece Geometry on the Aerosol Delivery Performance of a Dry Powder Inhaler

Matthew S. Coates,[1,2,3] Hak-Kim Chan,[2,4] David F. Fletcher,[1] and Herbert Chiou[2]

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Purpose. To investigate the influence of mouthpiece geometry on the amount of throat deposition and device retention produced using a dry powder inhaler (Aerolizer®), along with the subsequent effect on the overall inhaler performance.
Materials and Methods. Computational Fluid Dynamics analysis of the flowfield generated in the Aerolizer® with various modified mouthpiece geometries (including cylindrical, conical and oval designs) was used in conjunction with experimental dispersions of mannitol powder using a multi-stage liquid impinger to determine how the overall inhaler performance varied as the mouthpiece geometry was modified.
Results. Geometry of the inhaler mouthpiece had no effect on device retention or the inhaler dispersion performance. In contrast, the mouthpiece geometry strongly affected the amount of throat deposition by controlling the axial component of the exit air flow velocity. The radial motion of the emitted aerosol jet was found to have little effect on throat deposition in representative mouth–throat models. Despite the reduced throat deposition, there was no difference in the overall inhaler performance.
Conclusions. For cases where low throat deposition is a key design parameter, this study demonstrates that the amount of throat deposition can be reduced by making minor modifications to the inhaler mouthpiece design.

KEY WORDS: computational fluid dynamics (CFD); dry powder aerosols; dry powder inhaler (DPI); mouthpiece geometry; pulmonary drug delivery.

INTRODUCTION

Rapidly expanding interest in inhalation drug delivery over the past decade has led to the development of novel dry powder aerosol systems capable of delivering drugs to the respiratory tract for both local and systemic therapeutic effects (1–4). To maximize delivery to the deep lung, and minimize unwanted deposition in the throat and upper airways, recent research has been focused on improving the nature of the dry powder drug formulation (5–8) as well as the design of the delivery device. Today there are a large number of dry powder inhalers available commercially, which vary in dispersion efficiency due to their design characteristics (9–11).

Aside from the dispersion efficiency of dry powder inhalers, another important aspect of the inhaler performance is the amount of throat deposition and device retention produced using the device. Reducing the amount of powder deposited in the patient's throat after inhalation has been shown to increase the total amount of lung deposition (12). Throat deposition is known to be strongly related to the velocity of air flow exiting the device (13–15), which can be readily controlled by varying the design of the inhaler mouthpiece. Additionally, the amount of device retention could theoretically be controlled by varying the internal surface area of the inhaler. Despite this fact, there appears to be little published data examining how the design of an inhaler mouthpiece affects the amount of throat deposition and device retention, and subsequently the overall inhaler performance.

The aim of this study is to examine the effect of mouthpiece geometry on the overall performance of a dry powder inhaler (Aerolizer®). Specifically, how design of the inhaler mouthpiece affects the exit air flow velocity and the internal mouthpiece surface area, and the subsequent effects on throat deposition and device retention. Additionally, the performance of the device with different modified mouthpieces is compared with that of the original Aerolizer® design to examine the possibility of improving the overall performance of a dry powder inhaler by making minor changes to the design of the inhaler mouthpiece.

MATERIALS AND METHODS

Computational Fluid Dynamics (CFD) analysis, using ANSYS CFX5.7.1 software (ANSYS, USA) was performed

[1] School of Chemical and Biomolecular Engineering, The University of Sydney, Sydney, NSW 2006, Australia.
[2] Faculty of Pharmacy, The University of Sydney, Sydney, NSW 2006, Australia.
[3] Pfizer Global R&D, Inhalation and Device Centre of Emphasis, Cambridge Research Centre, Cambridge, UK.
[4] To whom correspondence should be addressed. (e–mail: kimc@pharm.usyd.edu.au)

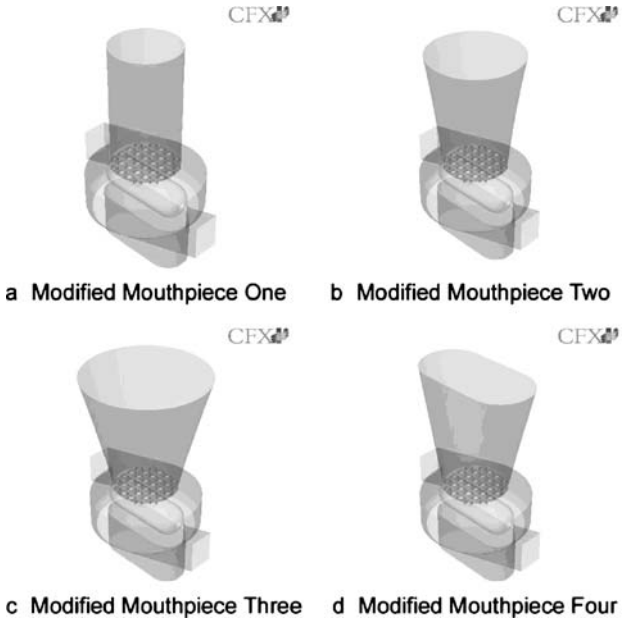

Fig. 1. Schematic of the different modified mouthpiece designs examined in this study.

in conjunction with experimental powder dispersion analysis to determine how the performance of an Aerolizer® (Plastiape S.p.A., Italy) varied as the geometry of the inhaler mouthpiece was modified. The inhaler mouthpiece geometry was studied as this design feature influences the amount of throat deposition and mouthpiece retention, which can significantly affect the overall inhaler performance. Previous studies have shown that up to 20% of the total powder loaded into a capsule can be retained in the Aerolizer® after dispersion, a feature of the inhaler performance with a large potential for improvement (16).

To study the dependence of the inhaler performance on mouthpiece geometry, four modified inhaler mouthpieces were examined, each consisting of a different design. For each case, physical geometry changes were made to the original inhaler to obtain the modified design (performed by Plastiape S.p.A.). Computational fluid dynamics analysis was performed at flow rates of 60 and 100 l min^{-1} to determine the flowfield generated in the device with each modified mouthpiece. The performance of the inhalers was determined experimentally using mannitol powder and a multi-stage liquid impinger. Test flow rates of 60 and 100 l min^{-1} were selected to ensure that the study was performed over a range of inspiratory efforts (1.8–4.0 kPa).

Modified Mouthpiece Geometries

Coates *et al.* have previously reported that reducing the length of the Aerolizer® mouthpiece had no effect on the inhaler dispersion performance, but slightly reduced the amount of powder retained in the mouthpiece after dispersion (16). Therefore in order to minimize mouthpiece retention, the four inhaler mouthpiece geometries examined in this study were designed with a mouthpiece length of 20 mm, as this was deemed the minimum possible length for comfortable use. No modification to the design of the inhaler base was made throughout this study.

Modified mouthpiece one was designed with a cylindrical mouthpiece of the same diameter as the original Aerolizer® design (10.5 mm), but with the shortened mouthpiece length of 20 mm. Only the length of the inhaler mouthpiece varied between the original design (47 mm) and modified mouthpiece one. Modified mouthpieces two and three were designed with circular mouthpiece exits 16 and 21 mm in diameter, respectively (Fig. 1). Modified mouthpiece four was designed with an oval mouthpiece exit with two semi-circular end-pieces of 10.5 mm diameter with a distance between the two end-pieces of 10.5 mm (Fig. 1). In each case, the internal surface area of the inhaler mouthpiece, determined computationally, was significantly reduced from that of the original Aerolizer® design (Table I). No real difference in the specific device resistance was observed between the four modified mouthpiece cases [0.072–0.074 $(cmH_2O)^{1/2}$ $(l\ min^{-1})^{-1}$].

Dispersion Methodology

The dispersion performance of the Aerolizer® with different mouthpiece designs was determined using a spray-dried mannitol powder (particle size d_{50}=3.2 μm, span $[(d_{90} - d_{10})/d_{50}] = 1.3$) and a four-stage (plus filter) liquid impinger (Copley, Nottinghamshire, UK), as described by Coates *et al.* (16). The highly idealised throat (Alberta geometry) described by Grgic *et al.* (17) was used instead of

Table I. Internal Mouthpiece Surface Area and Properties of the Flowfield Generated in the Device for Each Modified Mouthpiece Design

		Turbulence Kinetic Energy[a] (J kg^{-1})		Integral Scale Strain Rate[a] (s^{-1})		Mouthpiece Exit Velocity[b] (m s^{-1})	
	Modified: Original Mouthpiece Surface Area Ratio	60 l min^{-1}	100 l min^{-1}	60 l min^{-1}	100 l min^{-1}	60 l min^{-1}	100 l min^{-1}
Mouthpiece 1	0.43	7.20	20.96	6,110	7,370	11.9	19.9
Mouthpiece 2	0.56	7.24	26.45	5,920	8,650	7.2	13.0
Mouthpiece 3	0.65	7.28	25.80	5,860	7,390	6.3	11.8
Mouthpiece 4	0.54	7.31	27.73	5,810	8,710	7.0	12.8

[a] Volume averaged throughout the inhaler
[b] Area averaged across the inhaler exit plane

the standard USP Throat A, as this has been shown to better represent *in-vivo* throat deposition. The internal walls of the highly idealised throat were left uncoated throughout the dispersion analysis.

For each dispersion performed, three hydroxypropyl methylcellulose capsules (size 3, Capsugel®, USA) were filled with approximately 20 mg of mannitol and dispersed into the impinger running at the test flow rate for a total of 4 s (at 60 l min^{-1}) or 2.4 s (at 100 l min^{-1}). The dispersion times, achieved using a timed-valve (H3CR, Omron, Japan; Type 255, Burkert, Germany), ensured that 4 l of air was drawn through the impinger for each run. The four-pin piercing mechanism currently employed in the Aerolizer® was used to pierce the capsule and all runs were performed in triplicate to obtain mean values. Throughout the dispersion analysis, the temperature and relative humidity of the laboratory were maintained at 22±1°C and 35±5%, respectively.

Mannitol was assayed by high performance liquid chromatography (HPLC) (Waters, USA) using refractive index detection (410 differential refractometer, Waters, USA). Centrifuged samples (100 μl) were injected into a C18 Radial-Pak column (Waters, USA) with de-ionised water as the mobile phase running at a flow rate of 1 ml min^{-1} for 10 min and a retention time of 3 min. A calibration curve was constructed using standard solutions of mannitol which allowed the mass of powder deposited at each location and fine particle fraction to be determined. In this study, the fine particle fraction was defined as the mass fraction of particles smaller than 5 μm, referenced against either the total mass of powder loaded into (FPF_{Loaded}), or the total mass of powder emitted from ($FPF_{Emitted}$), the device. Interpolation of the cumulative undersize plot was used to determine the fine particle fraction. The percentage recovery throughout the dispersion analysis was 98±3%. Analysis of variance (ANOVA) tests followed by pairwise *t*-tests (Tukey's) were carried out with a probability of less than 0.05 considered statistically significant (Minitab 13, Minitab Inc, USA).

Computational Methodology

The flowfield generated in the Aerolizer® with different mouthpiece geometries was obtained by solving the Reynolds Averaged Navier Stokes equations together with the SST (Shear Stress Transport) turbulence model (18) and automatic wall functions using the commercial CFD code ANSYS CFX 5.7.1 (19), as previously described (20). A steady-state simulation was run to solve the device flowfield. The same numerical studies as reported in Coates *et al.* (21) were performed to ensure that the flow properties obtained in this analysis were independent of the computational mesh chosen. The CFD models were validated using Laser Doppler Velocimetry (LDV) techniques by comparing the mouthpiece exit velocities obtained from the computational models with experimental data (16). Good agreement was observed between the computational and experimental results over a range of flow rates and device designs.

Lagrangian particle tracking was performed as a post-processing operation, in which the fate of 1,000 and 5,000 particles with a density of 1,520 kg m^{-3} (22) and particle diameter of 3.2 μm (mono-disperse) were tracked through the fluid after release from the capsule and subjected to drag and turbulent dispersion forces. The particle tracking was initially carried out for the dispersion of 1,000 particles and repeated for 5,000 particles, to determine if the results obtained were independent of the number of particles simulated. Due to the dilute nature of the system, one-way coupling between the solid and fluid phases was assumed. By setting the walls of the mouthpiece to have a zero coefficient of restitution, it was possible to determine the percentage of particles colliding with the internal walls of the different inhaler mouthpiece designs.

RESULTS

Aerosol Characterisation Results

The experimental powder dispersions showed that the geometry of the inhaler mouthpiece had a strong effect on the amount of throat deposition at both test flow rates (Fig. 2a). At 60 l min^{-1}, a statistically significant reduction in throat deposition was observed between modified mouthpiece one (31.8%) and modified mouthpieces two to four (26.0–27.1%).

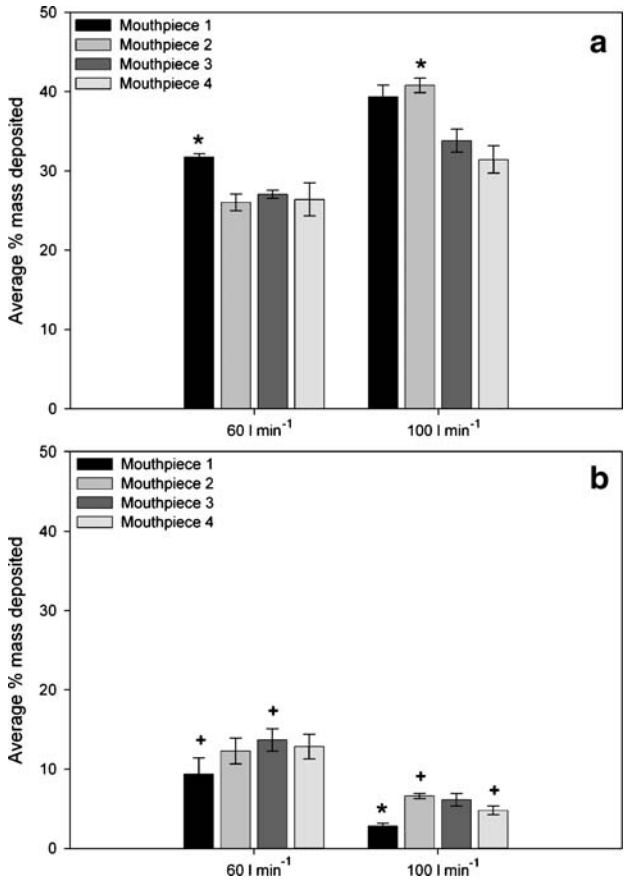

Fig. 2. Percent mass throat deposition (**a**) and mouthpiece retention (**b**) from the dispersion results indicating that the inhaler mouthpiece geometry had a significant effect on throat deposition but little effect on mouthpiece retention (* denotes a statistically significant difference between the indicated and the following results; + denotes a statistically significant difference between the two marked results).

No statistical difference was observed between mouthpieces two to four. At 100 l min^{-1}, throat deposition for modified mouthpieces one (39.4%) and two (40.8%) was statistically different than that of modified mouthpieces three (33.8%) and four (31.5%). No statistical difference was observed between modified mouthpieces one and two or modified mouthpieces three and four.

The inhaler mouthpiece geometry had a less significant effect on the amount of powder retained in the mouthpiece (Fig. 2b). At 60 l min^{-1}, mouthpiece retention varied between 9.4 and 13.7% for the four modified mouthpiece cases. Although less powder was retained in mouthpiece one (9.4%) compared with mouthpieces two to four (12.3–13.7%), a statistically significant difference was observed between modified mouthpieces one and three only. At 100 l min^{-1}, a small but statistically significant difference in mouthpiece retention was observed between modified mouthpiece one (2.8%) and modified mouthpieces two to four (4.8–6.6%) as well as between mouthpieces two (6.6%) and four (4.8%).

Despite variations in the amount of throat deposition and device retention, there was no trend in the overall performance of the inhaler. The FPF_{Loaded} varied between 34.1–40.5% at 60 l min^{-1} and between 33.7–34.5% at 100 l min^{-1}, respectively (Fig. 3a). No statistically significant differences were observed between different mouthpiece geometries at each flow rate. The $FPF_{Emitted}$ varied between 42.4–45.6% at 60 l min^{-1} and between 34.5–39.5% at 100 l min^{-1}, respectively (Fig. 3b). No statistically significant differences in the $FPF_{Emitted}$ were observed at 60 l min^{-1}, but a significant difference was observed between mouthpieces two and four at 100 l min^{-1}.

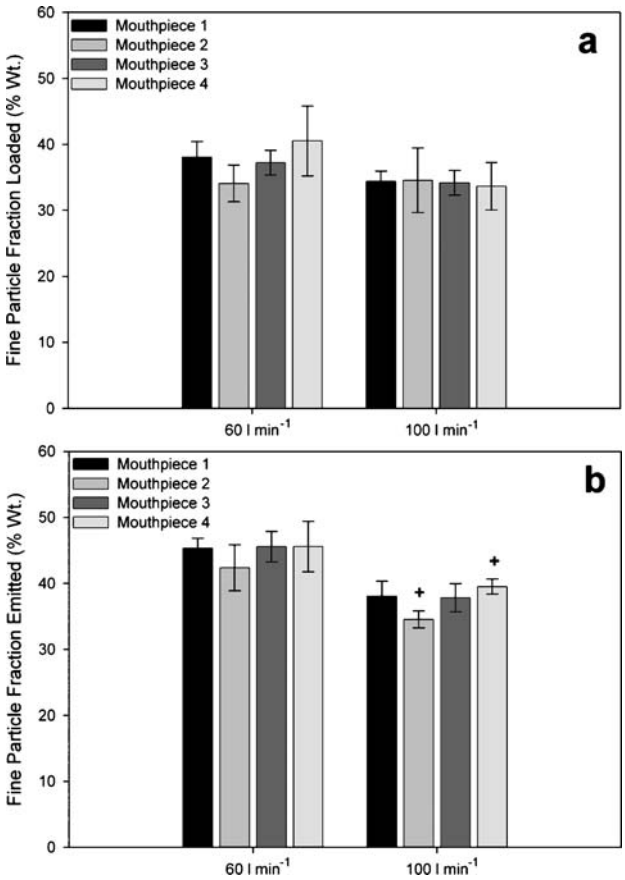

Fig. 3. Percent FPF loaded (**a**) and emitted (**b**) from the dispersion results demonstrating that the geometry of the inhaler mouthpiece had little effect on the overall performance of the inhaler (+ denotes a statistically significant difference between the two marked results).

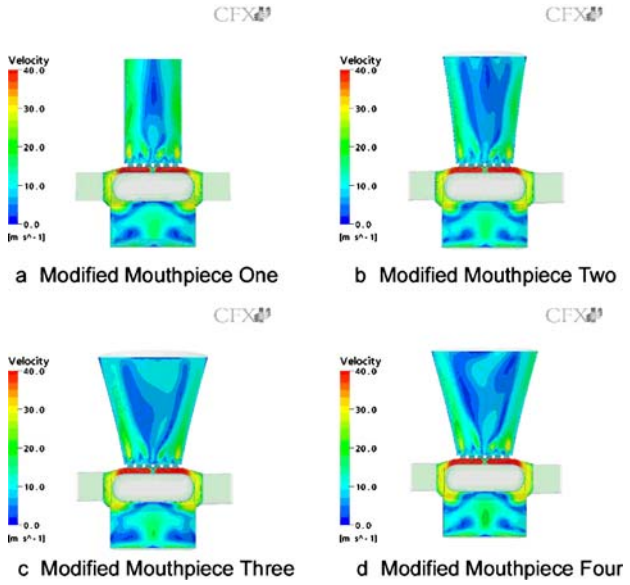

Fig. 4. Velocity profiles of the device flowfield indicating that the geometry of the inhaler mouthpiece had (1) little effect on the flow generated in the inhaler base, but (2) a significant effect on the flow in the inhaler mouthpiece.

Computational Fluid Dynamics Results

Figure 4 shows no noticeable difference in the inhaler base flowfield as the geometry of the mouthpiece was varied at 60 l min^{-1}. Similar trends in the device flow profile were observed at 100 l min^{-1} (data not shown). As the highest turbulence levels occur in the base of the Aerolizer® (21), no major differences in the turbulence kinetic energy and integral scale strain rates were observed (Table I). In contrast, the mouthpiece geometry had a large effect on the flowfield generated in the inhaler mouthpiece (Fig. 4), which strongly affected the velocity of air flow exiting the device (Table I). The inhaler exit velocities (area-averaged over the entire exit plane) decreased from 11.9 m s^{-1} (mouthpiece one) to between 6.3–7.2 m s^{-1} (mouthpieces two to four) at 60 l min^{-1} and from 19.9 m s^{-1} for modified mouthpiece one to between 11.8–13.0 m s^{-1} for modified mouthpieces two to four at 100 l min^{-1}.

Table II summarizes the percentage of particles impacting on the internal walls of the different inhaler mouthpiece designs when the CFD model was used to simulate the dispersion of 1,000 and 5,000 drug particles. No noticeable difference in the particle tracking results was observed for the five-fold increase in the number of particles, demonstrating that the models had captured the collision frequencies independent of the number of particles simulated. At both flow rates, a significant difference in the percentage of particle-mouthpiece impactions was observed (Table II),

Table II. Average Impact Velocity and Frequency of Particle Collisions with Different Sections of the Aerolizer® when the Computational Model was Used to Simulate the Dispersion of 1,000 and 5,000 Drug Particles

	Percent (%) Particle Impactions with the Inhaler Mouthpiece			
	60 l min^{-1}		100 l min^{-1}	
	1,000	5,000	1,000	5,000
Mouthpiece 1	32	31	28	39
Mouthpiece 2	48	49	52	54
Mouthpiece 3	50	50	53	52
Mouthpiece 4	43	41	45	42

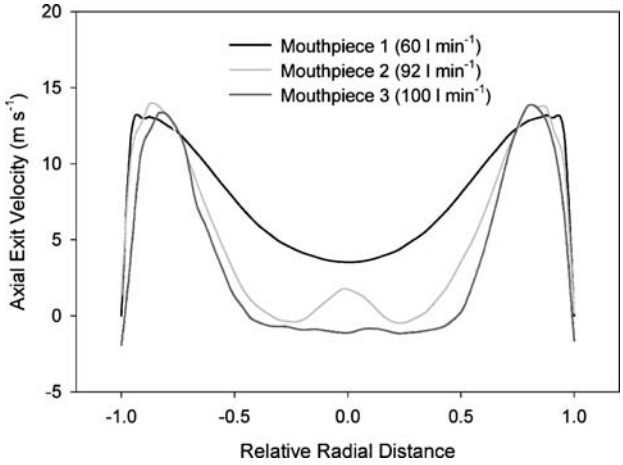

Fig. 5. Comparison of the axial exit velocities plotted across the centre-line of the inhaler mouthpiece, demonstrating that no difference in the maximum values of the axial exit velocity was observed between the three mouthpiece cases.

with mouthpiece one (cylindrical) experiencing the fewest impactions, followed by mouthpiece four (elliptical exit) and then by mouthpieces two and three (circular exit).

DISCUSSION

This study showed that the geometry of a dry powder inhaler mouthpiece can have a significant effect on the amount of throat deposition produced using the device by controlling the exit air flow velocity. At 60 l min^{-1}, reducing the exit velocity from 11.9 m s^{-1} (mouthpiece one) to between 6.3–7.2 m s^{-1} (mouthpieces two to four) led to a significant reduction in the amount of throat deposition (Fig. 2a). At 100 l min^{-1}, a reducing trend in throat deposition was observed as the exit air flow velocity was reduced from 19.9 m s^{-1} (mouthpiece one) to between 11.8–13.0 m s^{-1} (mouthpieces two to four). This demonstrates that the amount of throat deposition produced using a dry powder inhaler can be reduced by varying the design of the inhaler mouthpiece. Low throat deposition is highly desirable when inhaling steroid formulations as this minimizes fungal infection in the throat.

Studies performed by Stahlhofen *et al.* (15) and more recently by Grgic *et al.* (14) and DeHaan and Finlay (13) have shown that in the presence of a constant throat geometry, the amount of *in-vitro* throat deposition is dependent on the velocity of air flow entering the throat and the aerodynamic particle size. However in these studies, the effect the geometry of the emitted aerosol jet has on throat deposition was not examined. When the design of the inhaler mouthpiece was changed from a cylindrical geometry (mouthpiece one) to a conical geometry (mouthpieces two and three), the radial component of the emitted aerosol jet motion (determined from the CFD model) was found to increase significantly. At 60 l min^{-1}, the average radial velocity for mouthpiece one was 0.1 m s^{-1}, which increased to 2.2 and 4.0 m s^{-1} for mouthpieces two and three, respectively. Increasing the radial motion of the emitted aerosol may have a significant effect on throat deposition by initially forcing powder towards the sides of the patient's mouth.

To examine the importance of this effect, additional dispersions were performed using the highly idealised throat (Alberta geometry) to determine the amount of throat deposition produced from mouthpieces one to three at a constant axial, but varying radial, exit velocity. To obtain the same axial exit velocity observed for mouthpiece one at 60 l min^{-1}, flow rates of 92 and 100 l min^{-1} were required for mouthpieces two and three, respectively, which corresponded to average radial velocities of 0.1, 4.2 and 7.2 m s^{-1} (Table III). Figure 5 shows a comparison of the axial velocity profiles plotted across the centre-line of the mouthpiece exit, demonstrating comparable axial exit velocities between the three mouthpiece cases. Although the minima of these profiles differed, the maximum values

Table III. Throat Deposition, $FPF_{Impinger}$ and Total Emitted Dose Values from Additional Dispersions Performed at a Constant Axial Exit Velocity

	Test Flow Rate (l min^{-1})	Average Radial Exit Velocity (m s^{-1})	Throat Deposition (%wt.)	$FPF_{Impinger}$ (%wt.)	Total Emitted Dose (mg)
Mouthpiece 1	60	0.1	31.8 (0.4)	59.9 (0.9)	54.9 (1.5)
Mouthpiece 2	92	4.2	33.2 (1.9)	62.1 (1.2)	55.4 (0.1)
Mouthpiece 3	101	7.2	33.8 (1.5)	62.0 (1.4)	53.8 (0.2)

The standard deviation of these values (n=3) are provided in parentheses.
The lack of any significant difference in the $FPF_{Impinger}$ and total emitted dose demonstrates that the particle size and mass of aerosol emitted from the inhaler was comparable in each case.

(which have the most significant effect on throat deposition) were identical in each case.

The results from the additional dispersions showed no significant difference in throat deposition between the three mouthpiece cases (31.8–33.8%), indicating that at a constant axial exit velocity of 11.9 m s^{-1} (area-averaged) increasing the radial component of the emitted aerosol jet from 0.1 to 7.2 m s^{-1} had no effect on the total amount of throat deposition (Table III). This demonstrates that in the highly idealised throat geometry the axial, and not the radial, component of the emitted aerosol jet controls the amount of throat deposition.

Interestingly, when the additional dispersions were performed with a standard USP throat A, a significant difference in the amount of the throat deposition was observed between mouthpiece one (15.1%) and mouthpieces two and three (21.1 and 21.4%, respectively). However it is important to note that the USP throat A is known to be generally poor at predicting human throat deposition (23). Whilst the experimental method employed was unable to determine the regional location of oropharyngeal deposition in the different throat geometries, an increase in the radial aerosol motion is expected to have the most significant effect in the mouth, as any radial motion may have been dissipated before the throat is reached. The fact that no difference in throat deposition occurred when the radial exit velocity was increased using the highly idealised throat suggests that any radial aerosol motion may have been dissipated in the throat before the throat walls were reached. Although it has been reported that the majority of inhaled aerosols deposit in the laryngeal area and upper trachea (17), powder deposited in the mouth region has also been found to significantly contribute to the total amount of throat deposition (24).

The less significant effect of mouthpiece geometry on the amount of mouthpiece retention suggests that the small difference in the degree of particle-mouthpiece contact (reflected by the difference in the percentage of particle-mouthpiece impactions) was not sufficient to affect the total amount of mouthpiece retention. Additionally, a comparison of the mouthpiece retention observed with modified mouthpieces one to four at 60 l min^{-1} (26.0–31.8%) with that of the original Aerolizer® design containing the 47 mm mouthpiece (29.8%), shows no difference in mouthpiece retention despite the large difference in the internal mouthpiece surface area (Table I). This suggests that the majority of mouthpiece retention does not occur in the upper section of the inhaler mouthpiece but rather in the lower mouthpiece region, in the section containing the inhaler grid. The computational model used in this study is currently unable to accurately determine the amount of device retention in the different sections of the inhaler.

The study also showed that the geometry of the inhaler mouthpiece had no significant effect on the inhaler dispersion performance. The lack of a significant difference in the FPF_{Loaded} between the different mouthpiece cases indicates that the reduction in throat deposition was not sufficient to have a significant effect on the overall inhaler performance.

CONCLUSIONS

This study showed that the geometry of a dry powder inhaler mouthpiece can have a significant effect on the amount of throat deposition by controlling the axial component of the exit air flow velocity. The radial motion of the emitted aerosol jet was found to have little effect on throat deposition in representative mouth–throat geometries. Despite significant reductions in throat deposition, the lack of difference in the FPF_{Loaded} between the modified mouthpiece designs suggests that the Aerolizer® dispersion performance would not be significantly improved by modifying the design of the inhaler mouthpiece. However, for cases where low throat deposition is a key design parameter, this study demonstrates that scope exists for reducing the amount of throat deposition by making minor modifications to the inhaler mouthpiece design.

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