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RESEARCH PAPER

Does the United States Pharmacopeia Throat Introduce De-agglomeration of Carrier-Free Powder from Inhalers?

Patricia Tang • Philip Chi Lip Kwok • Zhenbo Tong • Runyu Yang • Judy Agnes Raper • Hak-Kim Chan

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ABSTRACT

Purpose We hypothesize that the USP induction port may de-agglomerate carrier-free powder emitting from dry powder inhalers (DPIs).

Methods Aerosols emitting from a range of DPIs (Spinhaler®, Turbuhaler® and Osmohaler™) and induction ports (USP throat, straight tube, Alberta idealized mouth-throat geometry (AG)) were sized by laser diffraction. Total drug recovery was obtained by HPLC and fine particle fraction computed. Air flow patterns were simulated using Computational Fluid Dynamics (CFD).

Results The straight tube did not de-agglomerate emitted powder. However, the USP throat and AG further de-agglomerated powders from the Spinhaler, but not the Turbuhaler and Osmohaler. While budesonide powder deposited similarly in all induction ports, deposition was significantly higher in the AG for both DSCG and mannitol. CFD revealed agglomerates impacting on the USP throat with higher localized velocity compared with the straight tube. CFD further showed a more complex flow pattern with high-velocity air jets in the AG, which explains the higher FPF for DSCG and the lower FPF for mannitol using the AG.

Conclusion The USP throat further de-agglomerated the emitted powder from the DPI when it did not sufficiently disperse the powder. Other tools such as laser diffraction may be used for cross-examining to avoid artifacts in the results.

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KEY WORDS de-agglomeration · dry powder inhaler · powder aerosol · USP throat

INTRODUCTION

For measurement of aerosol particle size distribution, the United States Pharmacopeia induction port ('USP throat') is used as a standard to connect the pharmaceutical inhaler device to a cascade impactor. The induction port is a 90-degree bend (1). Recently we found that, for dry powder aerosols, impaction could cause powder de-agglomeration depending on the angle of the bend (2). While a shallow angle of 15-degree had a minimal effect, 90-degree impaction produced significant de-agglomeration. These results triggered the present investigation into the potential effect on powder dispersion by the USP induction port which is also a 90-degree bend. We hypothesize that the induction port may introduce de-agglomeration of powder emitting from dry powder inhalers (DPIs). In this study, powder de-agglomeration refers to the breakup of the drug agglomerates into smaller agglomerates or individual particles. As the induction port is widely used for pharmaceutical aerosol research and DPI product development, the study is of potential significance from both the regulatory and scientific view points.

Drug particles for pulmonary administration (typically < 5 μm in size) have a high specific surface area. These small particles will form agglomerates due to cohesive forces which include van der Waals force, electrostatic attraction, and forces due to solid or liquid bridges. For respiratory delivery, the powder must be able to de-agglomerate into individual primary particles upon dispersion, or into smaller agglomerates suitable for inhalation. There are three main mechanisms of de-agglomeration (or dispersion), namely (3):

1. Dispersion by agglomerate impaction onto a wall;
2. Dispersion by shear or acceleration flow;

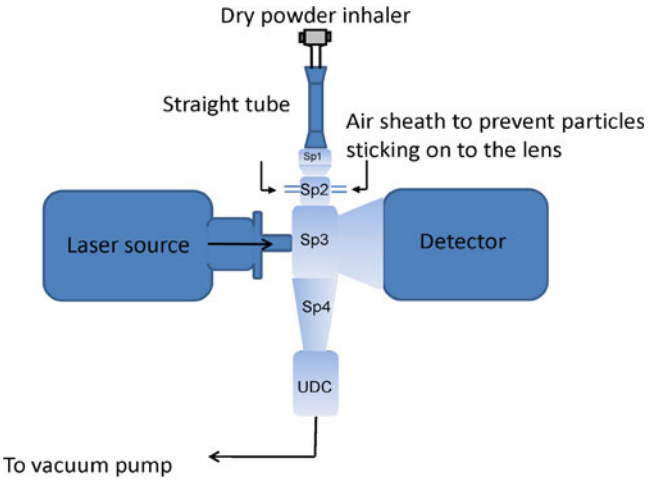

Fig. 1 Schematic diagram of the experimental set-up for particle size measurement of aerosol exiting the induction port. Four Spraytech parts (Sp1 to Sp4) and the unit dose collector (UDC) were connected in series. Different Spraytech parts were required to provide an airtight connection for the setup. UDC was used to collect powder from the dry powder inhaler. Different induction ports will sit on Sp1.

3. Dispersion by mechanical forces, e.g. fluidization, scraping and vibration

The first step of dispersion involves fluidisation of the powder which takes place when air, drawn through the dry powder inhaler, has sufficient energy to disperse the powder inside (and out of) the inhaler making the powder airborne. Then dispersion by shear flow, due to the turbulence of the air stream, and dispersion by impaction with the inhaler's interior wall will disperse the powder into smaller agglomerates (fragments) or individual particles. If the flow velocity is high, the chance of these discrete particles to form agglomerates or for small agglomerates to form large agglomerates is small. This is because: 1) at high velocity, there will be a decrease of residence time which implies that the de-agglomerated airborne particles or fragments will have minimum interactions between each other (4,5); 2) particles (or fragments) are more likely to follow the flow stream at high velocity, thus reducing the possibility of collisions; 3) new agglomerates are formed only when the relative kinetic energy of particles are dissipated, so they are less likely to form with collisions at high velocity. In our present study, de-agglomeration by impaction will be the main mechanism with respect to the effect of the USP throat. Drug agglomerates, emitted from a dry powder inhaler at high velocity, upon impaction with the throat may further de-agglomerate if the inter-particulate cohesion holding the agglomerates together is overcome by the stress induced by the impact against a hard surface (3).

Besides the USP induction port, we included a straight tube (to avoid impaction) as the control and the Alberta idealized mouth-throat geometry for comparison. Numerical simulations and aerosol deposition experiments have been extensively done for the idealised mouth-throat geometry (6–10). When 500 μg terbutaline was dispersed via the Turbuhaler®, the drug deposition in the coated USP throat (57.3±4.5%) was lower than the coated idealized mouth-throat geometry (67.8±2.2%) (11). It was postulated that deposition will mainly take place in oral cavities due to jet impingement, since the jet speed and swirl emitted from the device is relatively high (11). In the present study, we did computational fluid dynamic (CFD) simulations to compare the velocity, turbulence kinetic energy, integral scale strain rate, and agglomerate trajectories in the three different induction ports employed. More importantly, powder de-agglomeration was measured by laser diffraction on a Spraytech (Malvern Instrument, Worcs, UK). An impactor was not used because it may cause further de-agglomeration due to turbulence through the nozzles and impaction on the collection surfaces. This can complicate the data interpretation as it would be difficult to differentiate the potential de-agglomeration effect of the throat from that of the impactor. Currently, marketed DPI products are formulated as either

Table I Experimental Conditions of the HPLC Analysis for DSCG, Budesonide, and Mannitol

Parameters	DSCG	Budesonide	Mannitol
Column	5 μm NH2 100 Å 250×4.60 mm (Phenomenex Luna, Torrance, CA, USA)	Novapak C18 (Waters, Massachusetts, USA)	Resolve C18 5um 3.9×150 (Resolve™ C18, Waters, Massachusetts, USA)
Mobile phase	65% acetonitrile: 35% phosphate buffer (pH 3.2)	60% methanol: 40% de-ionized water	De-ionized water
Flowrate (mL/min)	2.0	1.0	1.0
Method of detection	UV detection at 320 nm	UV detection at 240 nm	RI detection
Run time per injection (min)	10	10	10
Injection volume (μL)	20	100	100
Solvent for rinsing the inhalers, induction ports, different parts of Spraytech, and unit dose collector.	De-ionized water	80% methanol: 20% de-ionized water	De-ionized water

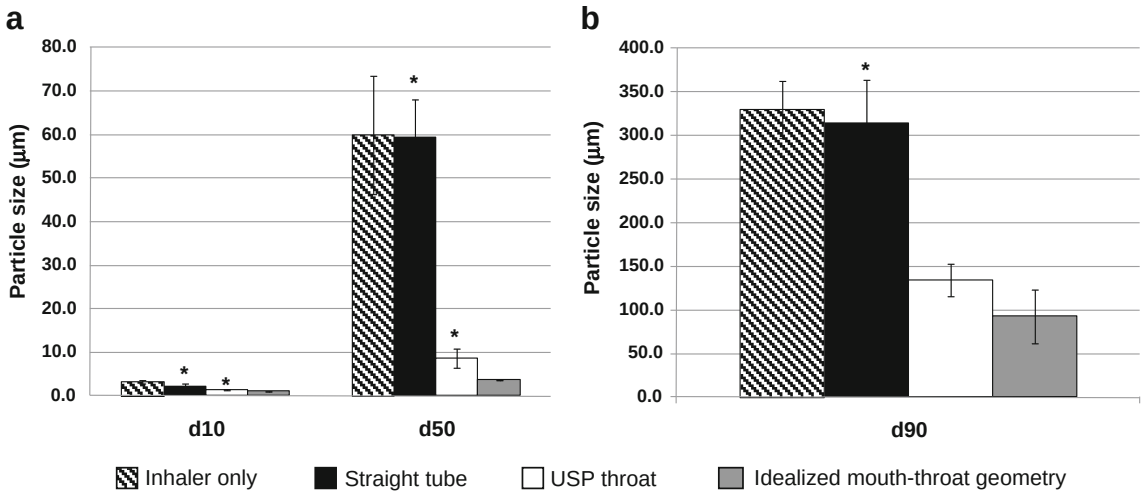

Fig. 2 Particle size distribution of DSCG powder emitting from the inhaler device directly and via different induction ports, measured by the Spraytech, when dispersed using the Spinhaler at 100 L/min.

a powder blend with lactose carrier or a carrier-free powder. Three carrier-free commercial products were used for testing, namely, Intal Spinhaler®, Pulmicort Turbuhaler® and Aridol Osmohaler™. Carrier-based products were not measured because i) Spraytech cannot differentiate between carrier and drug particles, ii) the scattered light signal from the drug particles is too low to be detected, and iii) carrier systems would necessitate a preseparator which would cause impaction hence complicate interpretation of the results.

MATERIALS AND METHODS

Powder

Three commercial inhalation products were used, including Intal Spinhaler® (Douglas Pharmaceuticals Australia Ltd, Sydney, NSW, Australia) with capsules containing 20 mg pure DSCG, Pulmicort Turbuhaler® (Astra Zeneca Pty Ltd, Sydney, NSW, Australia) containing 400 μg pure budesonide, and Osmohaler™ (Pharmaxis Ltd, Sydney, NSW, Australia) with capsules containing 10 mg of mannitol. Prior to the dispersion, the Intal capsules were pierced manually with a 1.35 mm drill bit. This was necessary as the piercing mechanism in the Spinhaler generated inconsistency in the hole size [1.35 ± 0.24 mm (n=10)], leading to variable powder emptying hence masking the effect of different induction ports on powder de-agglomeration.

For mannitol, HPMC capsule was used to load the powder, as gelatin capsules were found to shatter with high flowrate (100 L/min) in our study. Spinhaler and

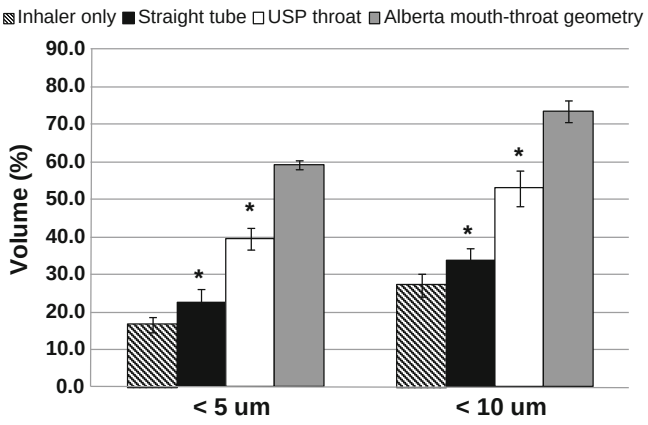

Fig. 3 Amount of DSCG powders with particle size smaller than 5 and 10 μm, as measured by the Spraytech, when dispersed using the Spinhaler at 100 L/min.

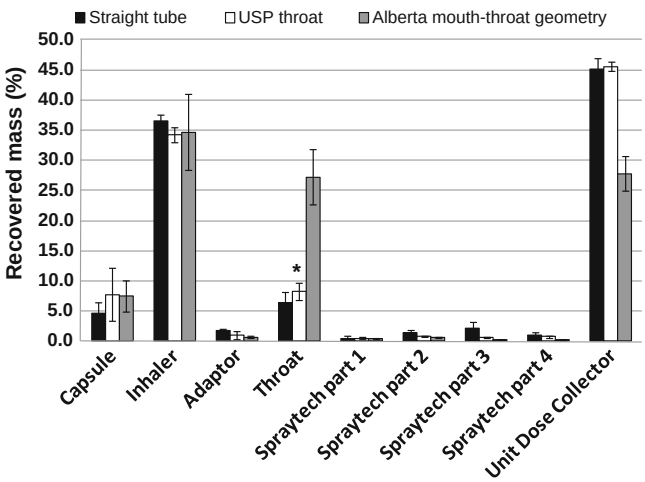

Fig. 4 Mass deposition of DSCG in capsules, inhaler, adaptor, induction ports, different parts of the Spraytech (1 to 4) and unit dose collector when dispersed using the Spinhaler at 100 L/min.

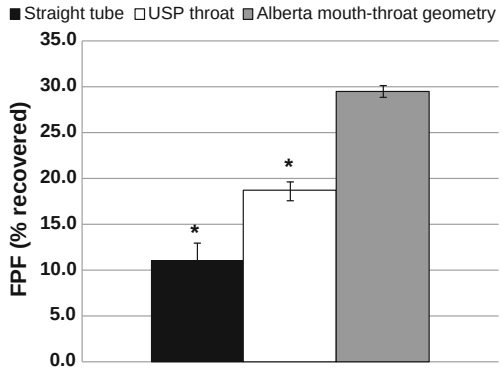

Fig. 5 Fine particle fraction (<5 μm) of DSCG, when dispersed using the Spinhaler at 100 L/min.

Osmohaler were washed at the end of dispersion, while Turbuhaler was not as it is a multi-dose system.

Induction Ports

Three different induction ports were used, including i) the USP throat, ii) a straight tube having the inner and outer dimensions and total length identical to those of the USP throat. The inner surface was polished to 0.4 µm, same as the USP throat, and iii) the Alberta idealized mouth-throat geometry.

Particle Size Measurement

Particle size distribution of the powder coming out from each induction port was measured on a laser diffractometer (Spraytech®, Malvern Instrument, Worcs, UK). The experimental set up is shown in Fig. 1. The flow across the dry powder inhaler was set so that 4 kPa was generated across the DPI, as specified by United States Pharmacopeia (1). Since the flow rate for the Spinhaler (0.051 cm $H_2O^{1/2}$/(L/min)] (12) and the Osmohaler (0.055 cm $H_2O^{1/2}$/(L/min)] (13) were found to be higher than 100 L/min, the maximum flow was set at 100 L/min according to the USP. The duration of suction was set to 2.4 s so that a maximum of 4 L of air was drawn. For the Turbuhaler (0.1 cm $H_2O^{1/2}$/(L/min)] (12), the flowrate at 4 kPa was found to be 56 L/min, as was also reported by Burnell (14) and Wang (15), and the duration of suction was set to 4.8 s. A flowmeter (TSI Inc, Model 4040, Shoreview, MN, USA) was used to set the air flowrate for the dispersion.

The Spraytech measured real-time, *in-situ* particle size distribution of the aerosol passing through a laser beam. Acquisition frequency was 2.5 kHz. The experiments were performed in triplicate for each drug and induction port configuration (device only, straight tube, USP throat, and Idealized mouth-throat geometry). In each experiment, a single dose was dispersed. Particle size distributions were

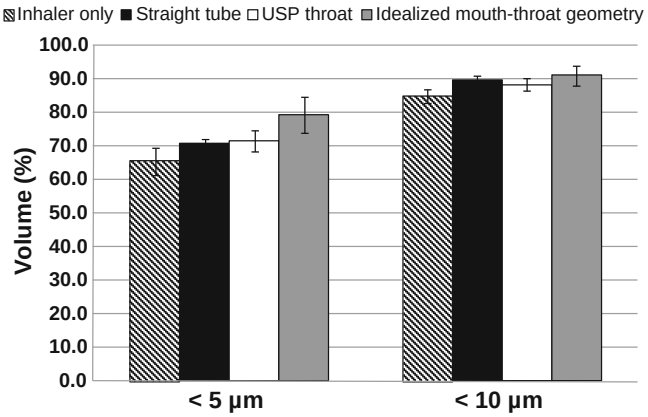

Fig. 7 Amount of budesonide powders with particle size smaller than 5 and 10 μm, as measured by the Spraytech, when dispersed using the Turbuhaler at 56 L/min.

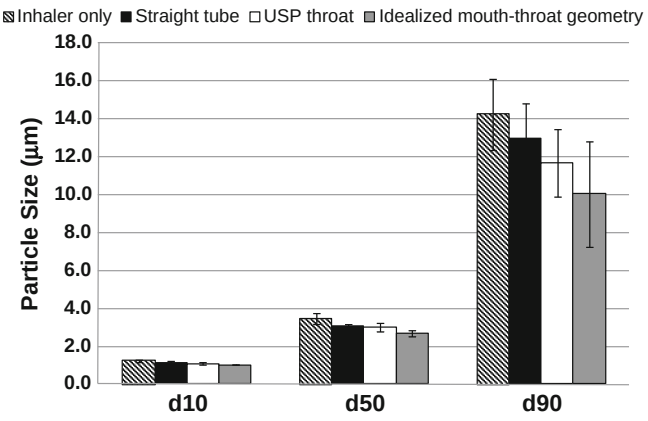

Fig. 6 Particle size distributions of budesonide powder emitting from the inhaler device directly and via different induction ports, measured by the Spraytech, when dispersed using the Turbuhaler at 56 L/min.

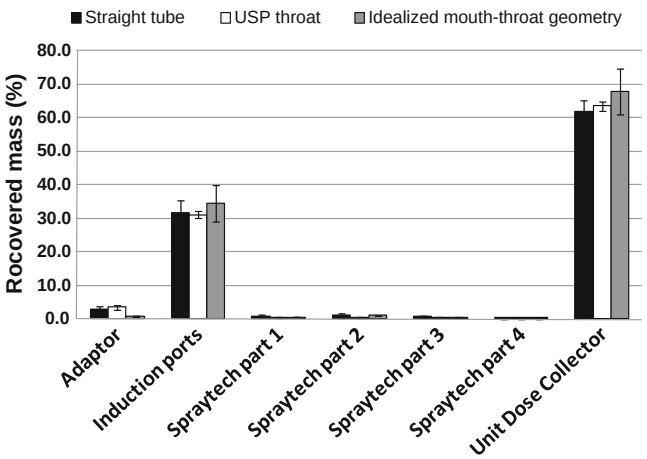

Fig. 8 Mass deposition of budesonide in adaptor, induction ports, different parts of the Spraytech (1 to 4) and unit dose collector when dispersed using the Turbuhaler at 56 L/min.

expressed as d_{10} (volume diameter under which 10% of the sample resides), d_{50} (volume median diameter), and d_{90} (volume diameter under which 90% of the sample resides). In addition to d_{10}, d_{50}, and d_{90}, the percentages of particles with size smaller than 5 and 10 μm obtained from the Spraytech software are included in this work.

Due to the low doses of budesonide (400 μg) and mannitol (10 mg), the minimum scattering signals in the Spraytech had to be lowered to 5 and 50, respectively, from the default value of 150 for the measurement to be possible. This, however, resulted in the background noise being more pronounced, causing an artificial peak at 1000 μm (as confirmed by optical microscopy the absence of particles and/or agglomerates of that size captured on a filter paper). Therefore, the signal was filtered to have the peak at 1000 μm excluded.

To investigate any de-agglomeration induced by the straight tube, particle size distribution of the powder emitted directly from the device was also measured by connecting the device directly to the Spraytech part 1 without an induction port.

Chemical Assay

High performance liquid chromatography (Model LC-20AT, Shimadzu, Kyoto, Japan) was used to analyse the drug powder retention in the inhaler, capsules, adaptor, induction port, different parts of the Spraytech, and the unit dose collector. A UV detector (SPD-20A, Shimadzu, Kyoto, Japan) was used to measure DSCG and budesonide while a RI detector (RID-10A, Shimadzu, Kyoto, Japan) was used for mannitol. Table I shows the experimental details of the HPLC methods.

Statistical Analysis

One-way analysis of variance (ANOVA) was used to identify any stastistically significant differences in particle size and mass deposition in the induction ports ($p<0.05$). Significant differences were further analysed with unpaired two-sample *t*-test for a 95% confidence limit. A p value of less than 0.05 was considered statistically significant.

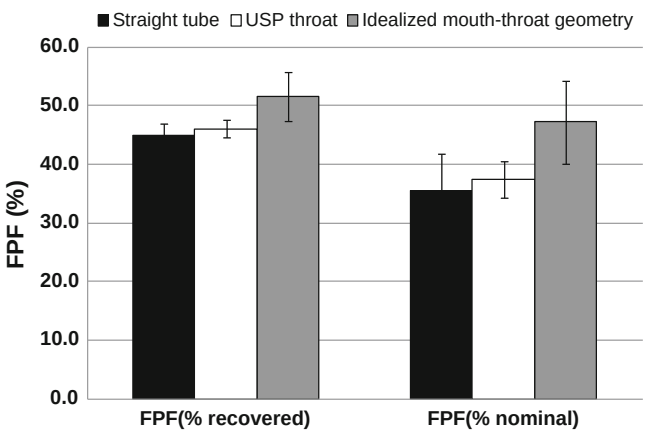

Fig. 9 Fine particle fraction (<5 μm) of budesonide, when dispersed using the Turbuhaler at 56 L/min.

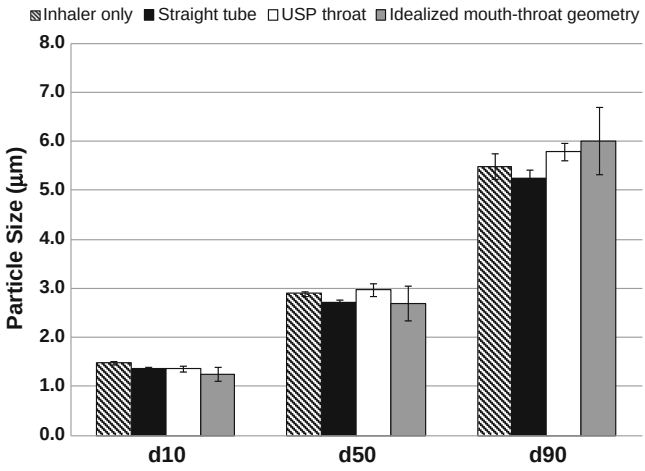

Fig. 10 Particle size distribution of mannitol powder emitting from the inhaler device directly and via different induction ports, measured by the Spraytech, when dispersed using the Osmohaler at 100 L/min.

Data Analysis

The fine particle dose (FPD) was obtained from the % volume of particles < 5 μm from the Spraytech measurement multiplied by the total mass retained in the Spraytech parts 3, 4 and the unit dose collector. The fine particle fraction (FPF) was expressed as the ratio of the FPD to the total recovery obtained from the HPLC assay. Total recovery was the amount of powder collected from the inhaler, capsules, adaptor, induction port, different parts of the Spraytech, and unit dose collector.

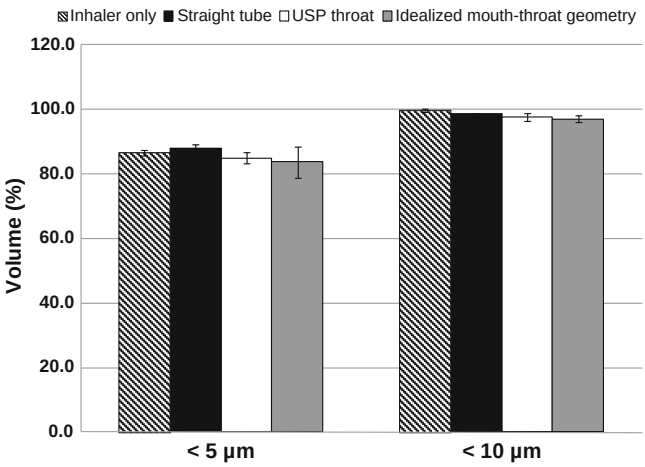

Fig. 11 Amount of mannitol powders with particle size smaller than 5 and 10 μm, as measured by the Spraytech, when dispersed using the Osmohaler at 100 L/min.

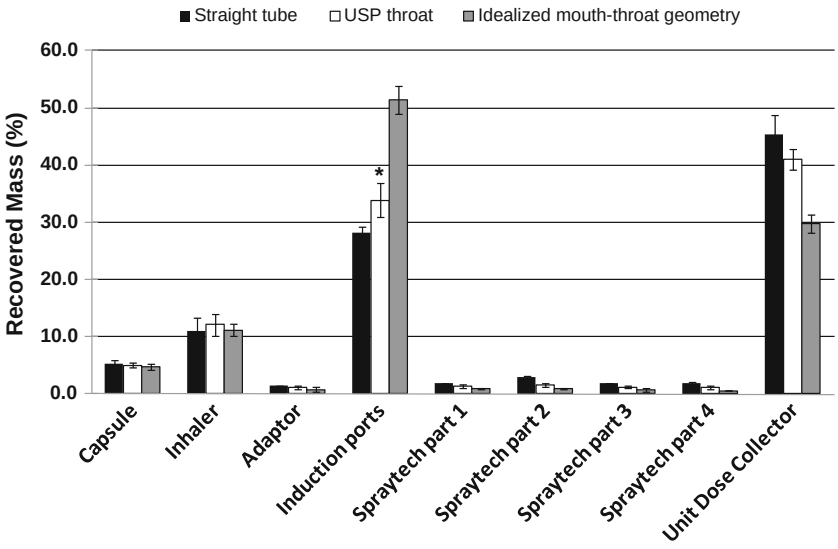

Fig. 12 Mass deposition of mannitol in capsules, inhaler, adaptor, induction ports, different parts of the Spraytech (1 to 4), and unit dose collector when dispersed using the Osmohaler at 100 L/min.

CFD Modelling

To understand the flowfield generated in the devices, CFD simulations under the same conditions were performed by solving the Reynolds Averaged Navier Stokes using the commercial software Fluent®. The description of CFD model has been detailed in previous papers (16,17). The whole computational domains of USP throat, idealized mouth-throat and straight tube are divided by 90, 506, 132, 650 and 78,256 grids, respectively.

Lagrangian particle tracking was also performed as a post-processing operation, in which the mannitol agglomerate with a density of 800 kg m^{-3} and diameter from 2 μm to 50 μm were tracked through the fluid from centre of inlet and subjected to drag and turbulent dispersion forces. The data provided in this study are not intended to be treated quantitatively, but to illustrate the significant trends in the impaction found computationally.

RESULTS

The straight tube showed similar d_{10}, d_{50}, and d_{90} values to those obtained from the inhaler only (Fig. 2), indicating that the tube did not introduce further de-agglomeration of the powder emitted from the device. In contrast, the d_{10}, d_{50} and d_{90} from the USP throat and the idealized mouth-throat geometry were significantly lower, indicating both of these induction ports caused significant de-agglomeration of powder emitted from the inhaler. Furthermore, the d_{10} and d_{50} obtained from the idealized mouth-throat geometry were significantly lower than those from the USP throat ($p<0.05$).

Since the USP and idealized mouth-throat geometry introduced further de-agglomeration, the amount of DSCG aerosol particles below 5 and 10 μm were, as expected, significantly higher than those obtained without a throat or with a straight tube (Fig. 3). The idealized mouth-throat geometry yielded higher proportions of particles below 5 and 10 μm than the USP throat.

Despite undergoing de-agglomeration in the induction port, powder retention in the USP throat was not significantly different to that in the straight tube ($p=0.23$, Fig. 4). In contrast, the idealized mouth-throat geometry retained significantly more powder than the straight tube and USP throat ($p=0.02$). This resulted in a lower dose captured in the unit dose collector. The powder deposition in the capsule, inhaler, adaptor and Spraytech parts were largely similar between the geometry configurations.

In line with the Spraytech data, using the USP throat the FPF of DSCG was significantly higher and the FPF was further increased with the idealized mouth-throat geometry (Fig. 5).

For Pulmicort Turbuhaler, the d_{10}, d_{50}, d_{90} were not significantly different between the configurations, although there was a size-decreasing trend, especially in the d_{90} (Fig. 6). The amounts of budesonide particles under 5 and 10 μm were also similar in all cases (Fig. 7). Furthermore, powder deposition on all the Spraytec parts and the FPF

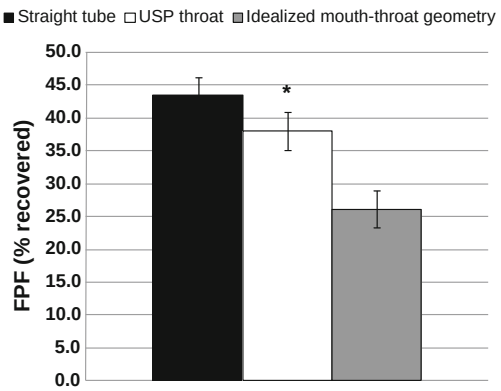

Fig. 13 Fine particle fraction (<5 μm) of mannitol, when dispersed using the Osmohaler at 100 L/min.

were not significantly affected by the throat geometry (Figs. 8 and 9). This indicated that the induction ports had no effect on powder de-agglomeration for Pulmicort.

For the mannitol Osmohaler, the results also showed similar trends as those observed on the Pulmicort Turbuhaler. The d_{10}, d_{50}, d_{90}, and the proportion of particles under 5 and 10 μm were similar in all cases (Figs. 10 and 11). Thus the throat geometry had no effect on the de-agglomeration of mannitol powder dispersed from the Osmohaler. However, drug retention was higher in the USP throat and idealized mouth-throat geometry than that in the straight tube (Fig. 12), with the retention in the idealized mouth-throat geometry being the highest. This increase in throat deposition was associated with a corresponding decrease in the FPF (Fig. 13).

In order to further understand the role of the different induction ports on de-agglomeration, the simulated flow velocity, kinetic energy, integral scale strain rate (ISSR) profiles and agglomerates trajectories for an inhalation flow rate of Q=100.0 L/min are shown in Figs. 14, 15, 16 and 17, respectively. The velocity profiles (Fig. 14) show that the velocity in the idealised mouth-throat geometry is double of that in the USP throat, leading to a higher total kinetic energy (Fig. 15). Furthermore, the ISSR profiles (Fig. 16) reveals much larger ISSR in idealised mouth-throat geometry than in the USP throat and straight tube.

The agglomerate trajectories (Fig. 17) indicated that larger agglomerates (50 μm) impacted more in the idealized mouth-throat geometry, due to its complex internal geometry, than in the simple 90-degree bend USP throat. In contrast, the smaller agglomerates (<10 μm), will follow the airflow with almost no impaction inside all the three induction ports.

It is worth to point out that the particle trajectory deviates from the centerline to the side as the particles travel through the induction ports (Fig. 17 a-b). This may lead to a

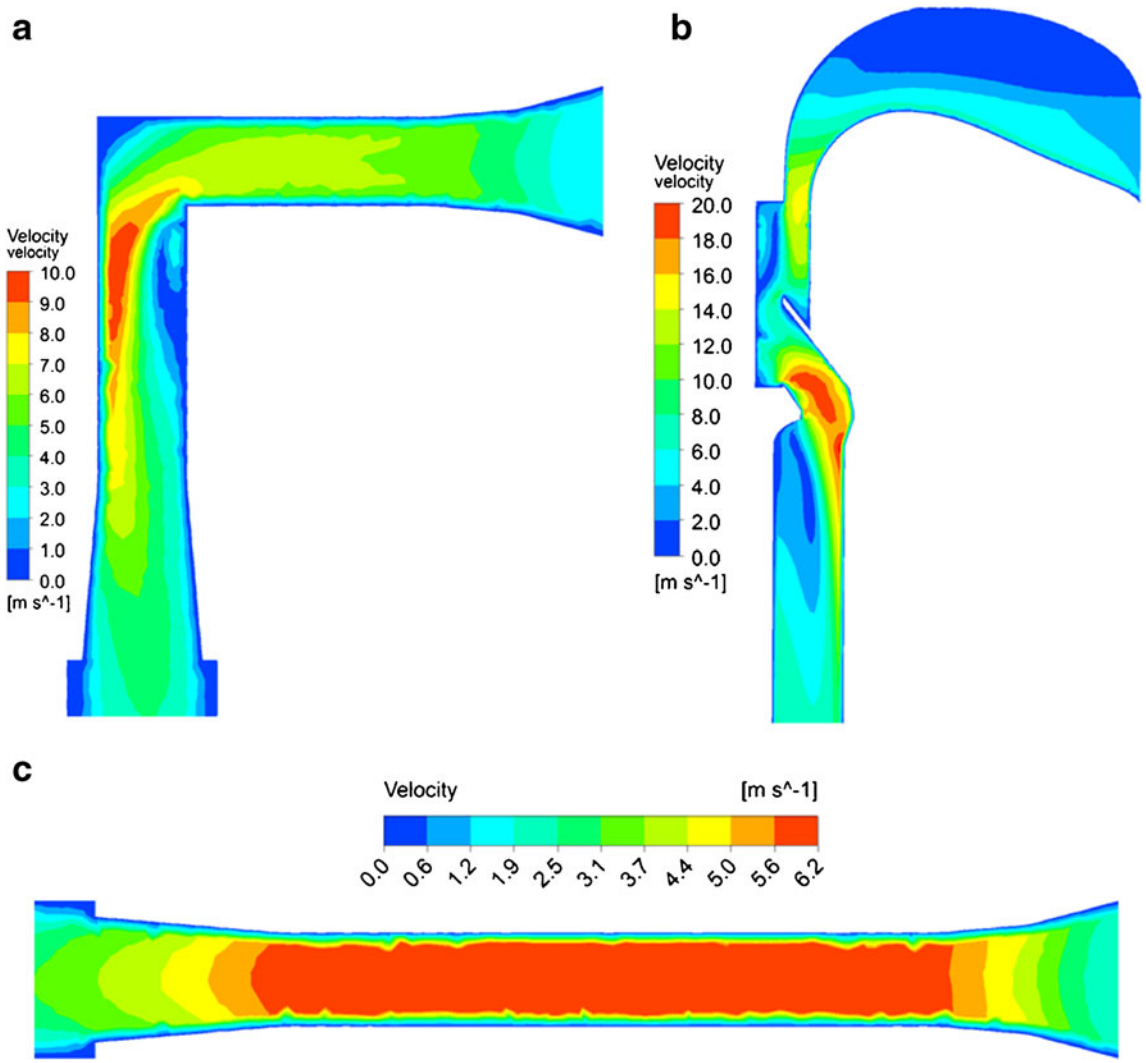

Fig. 14 Flow velocity profile of (**a**) USP throat; (**b**) idealized mouth-throat geometry; and (**c**) straight tube at airflow rate 100 L/min.

concern that not sizing a representative sample in the Spraytech measurement zone. Particles of 10 μm or less deviate more from the centre of USP throat than the 50 μm particles, while particles ≤5 μm deviate more from the centre of the idealised mouth-throat geometry than the 50 and 10 μm particles. If these small particles were outside the measurement zone then the d_{10}, d_{50}, d_{90} obtained using these induction ports will be larger than those obtained using the straight tube and inhaler only. However, this was not the case. For mannitol and budesonide, there was no significant difference ($p>0.05$) between different configurations for d_{10}, d_{50}, d_{90}. For the drugs where they have been sufficiently dispersed in the device, particles emitted from the device were small (d_{50} with device only is 2.89±0.05 μm and 3.44±0.28 μm for mannitol and budesonide, respectively). This shows that even when they deviated from the centre, they were still within the measurement zone. For DSCG, the d_{50} of particles emitted from the device is 59.9± 13.6 μm. These big particles, as shown in Fig. 17 a-b will not deviate from the centre significantly.

DISCUSSION

Regardless of the DPI product, the straight tube did not introduce additional powder de-agglomeration (compared to the inhaler alone) and had lower drug deposition than the other induction ports. These observations corroborated the absence of agglomerate impaction in the straight tube from the simulation results (Fig. 17). Since the straight tube was identical to the USP throat in all respects except for the 90-degree bend, any difference in the results from the USP throat must be due to this angle. Thus the straight tube served as a negative control for throat impaction.

A throat would contribute to ex-inhaler de-agglomeration if the powder is not dispersed sufficiently by the inhaler. This was the case for the Intal Spinhaler, which can be viewed as a low efficiency inhaler. The FPF data (Fig. 5) obtained using the USP throat (18.62±1.06%) is comparable to the literature values of 22.68±2.51% where DSCG was dispersed at 90 L/min using a Twin Stage Impinger coupled to a glass throat (18) and 14.10±1.40% at 100 L/min using a multistage liquid

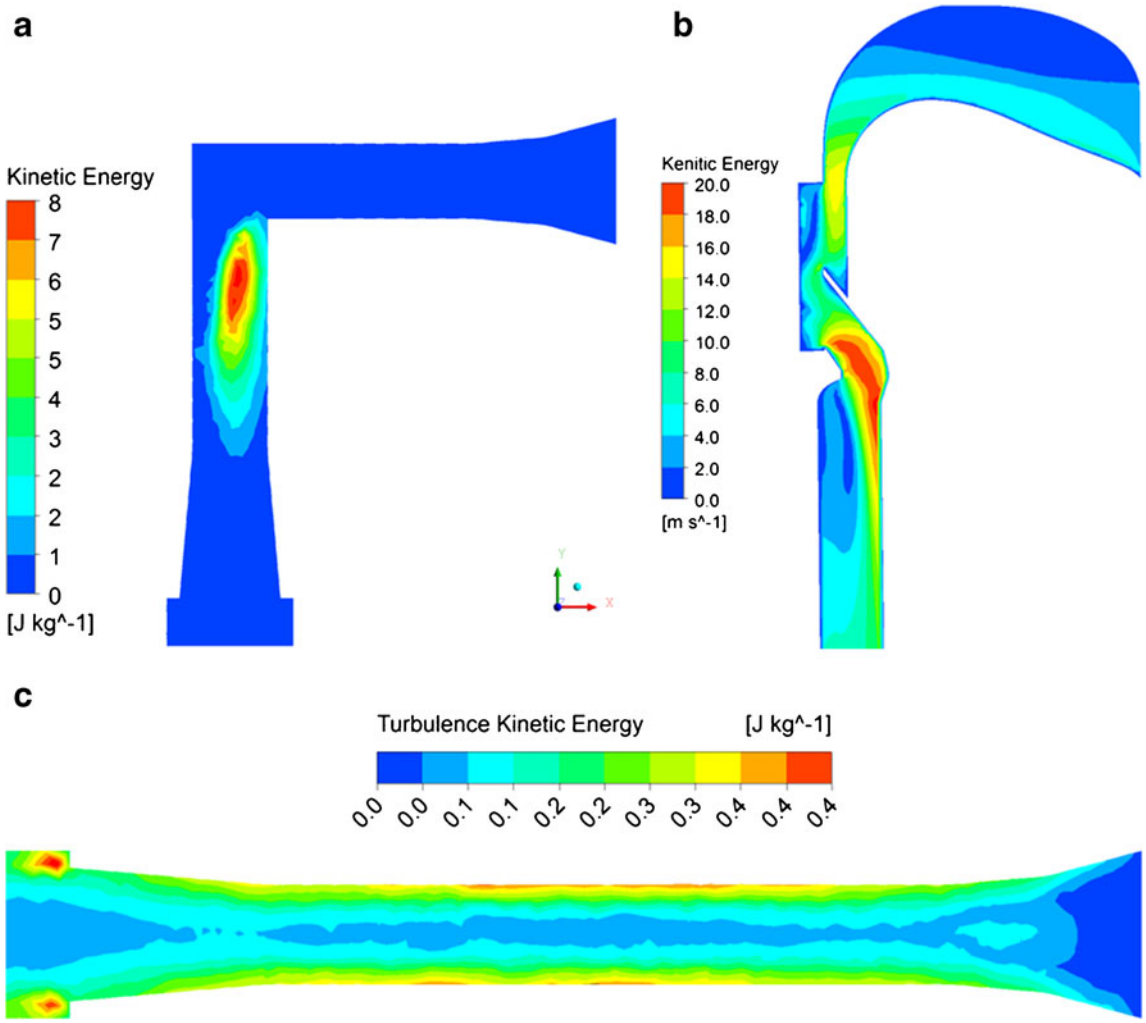

Fig. 15 Flow kinetic energy of (**a**) USP throat; (**b**) idealized mouth-throat geometry; and (**c**) straight tube at airflow rate 100 L/min.

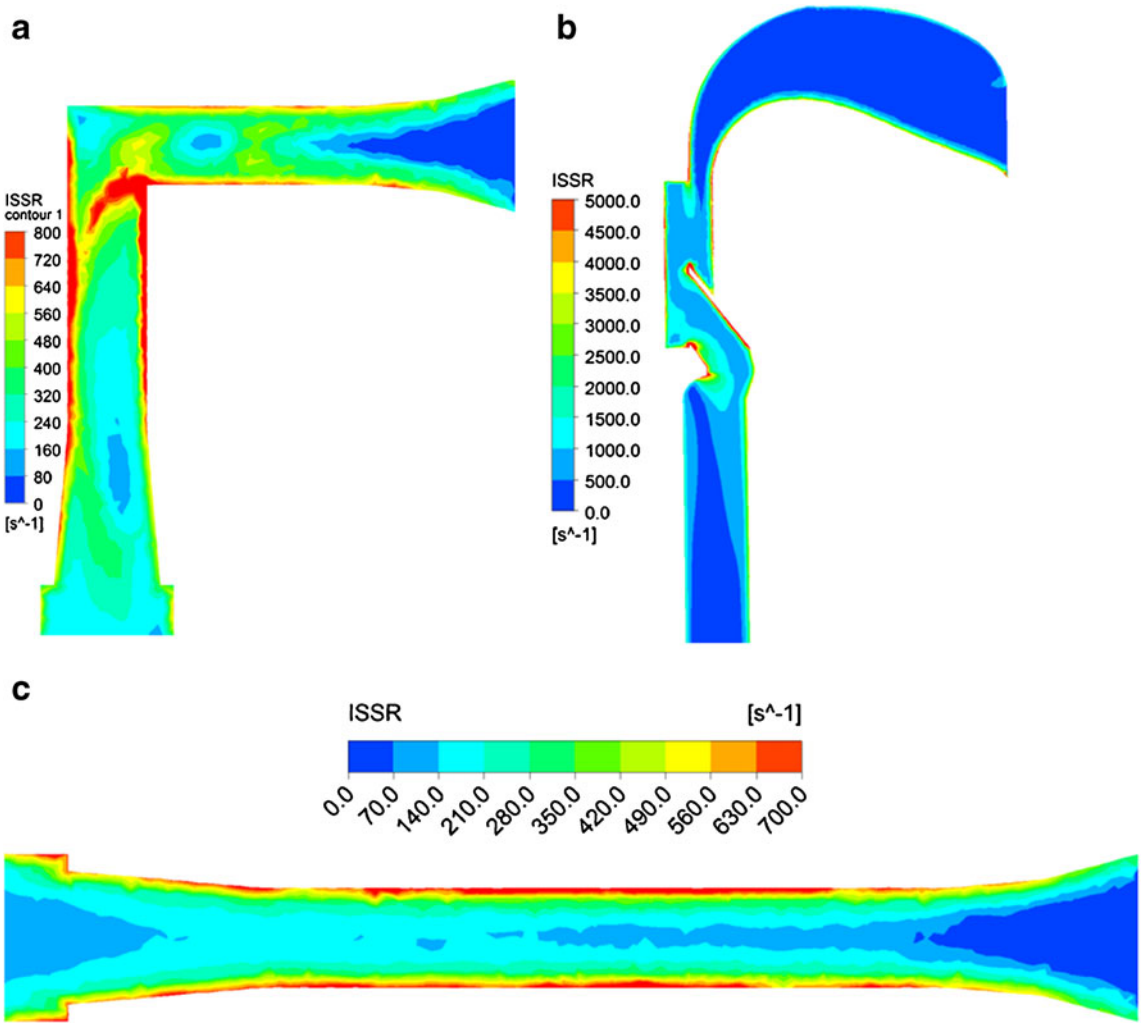

Fig. 16 Flow integral scale strain rate of (**a**) USP throat; (**b**) idealized mouth-throat geometry; and (**c**) straight tube at airflow rate 100 L/min.

impinger (19), verifying our method used to approximate the FPF in the present study. The FPF obtained was affected by two opposing factors, namely (i) break-up of agglomerates (caused by agglomerates impacting on the throat) thus producing smaller particles and (ii) powder deposition (retention) in the throat. Since the deposition of DSCG in the straight tube and the USP throat were similar, this powder was not particularly adhesive to the metal surface, and/or the air flow was sufficiently strong to remove the majority of deposited powder from the throat. Despite the deposition of DSCG in the idealized mouth-throat geometry being much higher than that in the USP throat, the FPF was increased by the idealised mouth-throat geometry due to the higher amount of particles <5 μm in the aerosol. Hence, powder break-up had a more pronounced effect on FPF than retention for the Intal Spinhaler. The higher de-agglomeration was attributed to the more complex flow pattern with localized high-velocity air jets (Figs. 14, 15 and 16). Based on our recent work, mechanical impaction had a significant effect on agglomerate breakage (20,21). As the size of emitted DSCG powder was large (Fig. 2a, d_{50}=60 μm), the de-agglomeration resulted from impaction (Fig. 17) with the USP and the idealized mouth-throat geometry had a significant effect on the fine particle fraction (Fig. 5). Furthermore, since our throats were uncoated, the higher velocity (Fig. 14) and kinetic energy (Fig. 15) in the idealised mouth-throat geometry can promote further de-gglomeration of the emitted powder if it has not been sufficiently broken up in the device, as for the Intal Spinhaler.

Throat geometry had no effect on ex-inhaler de-agglomeration for the higher efficiency inhalers, such as the Tubuhaler and the Osmohaler. These inhalers sufficiently broke up the agglomerates before the powders impacted in the throats. For the Pulmicort, powder retention in the idealized mouth-throat geometry was 34.63±5.47% (Fig. 8), which is comparable to the literature value of 27.5± 5.4% reported by Wang *et al.* when Pulmicort 200 μg was dispersed at 60 L/min (15). Due to the similar throat

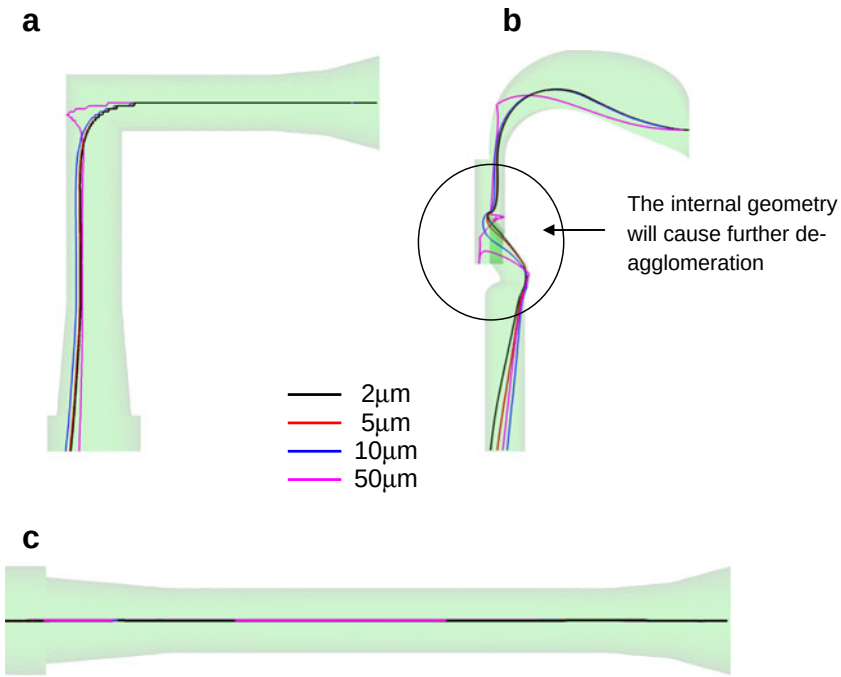

Fig. 17 Agglomerates trajectories of (**a**) USP throat; (**b**) idealized mouth-throat geometry; and (**c**) straight tube at airflow rate 100 L/min.

deposition and lack of further de-agglomeration in the throats, there was no significant difference in the FPF for the Pulmicort between the USP and the idealized mouth-throat geometry (Fig. 9).

On the other hand, mannitol deposition (Fig. 12) in the idealized mouth-throat geometry (51.45±2.38%) was higher than that in the USP throat (33.88±3.01%). A similar observation has been reported before. Zhang and Finlay investigated the deposition of 500 μg terbutaline sulfate from the Bricanyl Turbuhaler on the USP throat and the idealised mouth-throat geometry at 60 L/min (22). The idealized mouth-throat geometry was found to have higher deposition (67.8±2.2% *vs* 57.3±4.5%). As a result of the increased throat retention (i.e. less drug retained in the Spraytech Parts 3, 4, and the unit dose collector), the FPF obtained using the straight tube, USP throat, and idealized mouth-throat geometry was decreased in that order (Fig. 13). Thus throat deposition had a more pronounced effect on the FPF of mannitol. It should be noted that drug retention in the throats may be compound-specific. This is because although both Pulmicort and Bricanyl use the Turbuhaler, the throat geometry only affected retention for terbutaline sulfate (22).

CONCLUSION

USP throat can introduce further de-agglomeration of powder emitted from the inhaler when it has not sufficiently broken up the agglomerates in the powder. This was shown with the DSCG powder dispersed using the Intal Spinhaler.

With other less cohesive powder formulations (budesonide and mannitol) and/or higher performance DPI studied in this work (Turbuhaler and Osmohaler), there was no significant throat-induced powder deagglomeration since the inhalers have sufficiently broken up the agglomerates. In the mannitol case, the powder retention in the idealized mouth-throat geometry was significantly higher than that of USP throat which, consequently, resulted in a lower fine particle dose.

This study has shown that the USP throat could potentially create an artifact in the results, depending on the powder formulation and the inhaler. Therefore, it is important to measure the particle size distribution of powder emitted from the inhaler using other tools such as laser diffraction, with and without the presence of a USP throat to confirm if the USP throat does not contribute to powder de-agglomeration.

Extrapolating the current data to carrier-based formulations has to be done cautiously because both the agglomerate strength and the dispersion mechanism of the carrier-based powder systems can be different from those of the carrier-free systems. For carrier-based DPI products, detachment of the drug particles from the carrier may take place when the powder impacts on the USP throat, provided the inhaler has not sufficiently done so. The fine particle fraction will then be overestimated. With high resistance DPIs, such as the Turbuhaler which operates at approximately 60 L/min, the device would be more likely to disperse the powder sufficiently. Therefore, the emitted powder would not undergo further de-agglomeration when impacted on the USP throat. However, further study is required to confirm this hypothesis.

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