

Investigation of design features on the performance of 3D-printed dry powder inhalers. Part 1: grid mesh

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Summary

The study on inhaler performance through modified inhalers with homogeneous aperture size across the full grid structure have been carried out. In our research, the size of each small opening except the four in the corners of inhaler grid was kept constant, and the wire splitting the grid was designed to vary, thus generating grids with same aperture size but different voidage (Figure 1). In addition, instead of injection moulding method, a novel 3D printing technology was employed to fabricate the modified inhalers, which is rarely studied. Therefore, the primary objective for this work is to investigate the influence of grid mesh voidage on inhaler performance, as well as confirming the feasibility of 3D-printed inhalers for pulmonary drug delivery. For the assembled 3D-printed inhaler with a voidage of 68.7%, the Fine Particle Fraction (FPF) was raised to 37.2 compared with the inhaler with a voidage of 13.2% and FPF of 33.8%. There was a rising trend of FPF and delivered dose when grid voidage increased, which attributed to less drug impacting on the meshes of grid and more drug passing through the apertures. The experimental results were also coupled with computational fluid dynamics (CFD) analysis, which provided a complementary understanding of the drug delivery performance differences.

Key Message

Modified inhalers by 3D-printing method, with constant aperture size across the full grid structure, were successfully fabricated and assembled. Inhalers with an increased voidage had higher *in-vitro* drug delivery performance and lower air resistance, which was proved by enhanced powder residues in the devices and more centralized powder jetting verified by CFD.

Introduction

Dry powder inhalation (DPI) system for pulmonary drug delivery has received increasing attention and development since its advent in mid 1960s. To gain a better understanding of the influence of inhaler design on de-attachment and/or de-aggregation for better lung deposition, the mechanism and key design factors on inhalers were comprehensively studied [1]–[3]. Efforts to improve DPI performance has been primarily focused on the modification of device, as well as engineering of powder formulation [4]. In terms of inhalers, the specific design features that have an essential influence on the aerosolization performance were also investigated, including mouthpiece length, mouthpiece diameter, inlet size, and grid structure design [1]–[3]. Among them, grid mesh is commonly found placed at the upstream of a DPI mouthpiece and exists to enhance de-aggregation of powdered dose through mechanical impaction [5]. In most design of DPIs, especially of capsule-based inhaler, the grid structure is present with essential functions on particle deposition in the lungs. Research by Wong *et al.* found grid structure is beneficial to improve break-up and aerosolization of agglomerates [3]. Fletcher *et al.* showed strong jetting flow exiting the device in the absence of grid while reduced jet spreading and tendency to have the particles along the center of the jet with grid at the entry of mouthpiece [6]. Zhou *et al.* designed a cross-grid and showed insignificant drug delivery performance between the full Aerolizer® grid and the modified cross-grid Aerolizer® while studies by Coates *et al.* exhibited better performances with complete Aerolizer® grid than modified grid with higher voidage [1], [2].

Although the study on grid design of inhalers have been carried out, the size of each small opening changed with heterogeneous size across the full grid structure. The work of influence of grids with homogeneous size but different grid voidage still hasn't been done. In our research, the size of each small aperture except the four in the corners was kept constant, and the wire splitting the grid was designed to vary, thus generating grids with same size but different voidage. In addition, the traditional manufacture process of inhalers, inject molding, is complex and time-consuming, and less research is seen on the study of the whole modified inhalers. Recently, additive manufacturing, also well-known as 3D printing, as a novel technology, extended its application to the pharmaceutical field. Yet, limited research on 3D-printed DPIs is found. What we searched is that 3D-printing was employed to fabricate

a single part of DPIs, such as mouthpiece [7], instead of the whole inhalers. Therefore, the objectives for this work are to investigate the drug delivery performance of 3D-printed inhalers with modified grid structure, as well as verifying the feasibility of 3D-printing technology for pulmonary drug delivery.

Methods and Materials

Onbrez[®] capsules (Novartis Pharmaceutical Company, Switzerland) was obtained from a pharmacy. Each capsule contains inhalable Indacaterol maleate dry powder equivalent to 150 microgram indacaterol. Deionised water was purified by reverse osmosis (MilliQ, MilliPore, Canada). All chemicals used were of high-performance liquid chromatography (HPLC) analytical grade and purchased from Chem-Supply (Canada). Ethanol was purchased from VWR, Mississauga, Ontario, Canada.

Construction of 3D model of inhalers and assembly of inhalers

The 3D models of modified Breezhaler[®] were created using Creo software developed by PTC (USA) and exported as .stl files to be prototyped. The 3D models with grid structures modified were shown in Figure 1. The size of each small square aperture (except the four in the corners) was kept constant, and the mesh splitting the grid was designed to vary, thus generating openings with same size but different voidage. 6'6 was used to define the grids, representing 6 small square apertures horizontally and 6 vertically with same size and voidage as the commercial Breezhaler[®] with a voidage of 48.3%. Similarly, 4'4 represents 4 small square apertures horizontally and 4 vertically with a lower voidage of 13.2% while 7'7 represents 7 apertures horizontally and 7 vertically with a higher voidage of 68.7%. Inhalers were then constructed from photopolymer resin (Tough 1500, ABS) by Form 3 Stereolithography (SLA) 3D printer (Formlabs Inc, USA), with an overall layering thickness of 25 μ m for each single part of the inhalers. 3D-printed mouthpieces with varied grid mesh and assembled 3D-printed inhalers were shown in Figure 2. The 3D-printed parts were assembled for further evaluation.



Figure 1 Front view of grid mesh of modified 3D inhalers

Evaluation of *in-vitro* aerosol performance

The aerodynamic particle distribution of Indacaterol maleate powder through the three modified inhalers was determined using a Next Generation Impactor (NGI, Copley, Nottinghamshire, UK) with a suitable mouthpiece adaptor, setup as described in the US Pharmacopeia. For each dispersion, thirteen capsules containing Indacaterol maleate dry powder formulation were used and dispersed into the NGI system through the modified inhalers (IN-1, IN-2, IN-3), respectively. 50 μ L of glycerol mixture containing ethanolic Brij35 was coated on each of the NGI stages. The system was run at 60 L/min for a total of 4 s with 4 L of air passing through the inhaler with 13 doses of Indacaterol maleate for each run. The cut-off size of NGI stages 1-7 at an airflow rate of 60 L/min were 8.06, 4.46, 2.82, 1.66, 0.94, 0.55 and 0.34 microns, respectively. Indacaterol maleate particles deposited on device, conduction port (CP), pre-separator (PS), stage 1-7, and micro-orifice of collector (MOC), and drug residue in the capsules were collected, then assayed by high-performance liquid chromatography (HPLC) (Waters, MA) using ultraviolet detector.

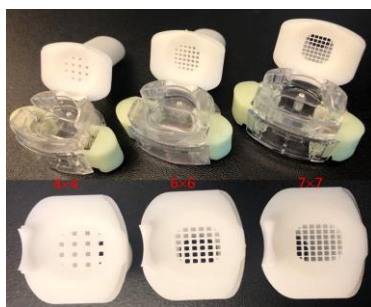


Figure 2 3D-printed mouthpieces with varied grid mesh (upper row) and assembled 3D-printed inhalers (lower row)

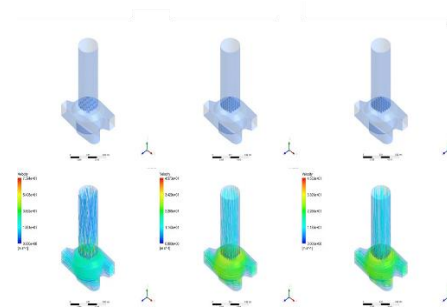


Figure 3 Internal fluid flow areas displayed with corresponding velocity streamlines tracking through the three inhalers with varied voidage

CFD modelling

CFD analyses conducted by ANSYS Fluent 2020R1 were used to provide a complementary understanding of the performance differences among these three configurations, shown in Figure 3. Shear Stress Transport (SST) model together with the constant test flow rate of 60 L/min was chosen to generate the flow field, and particle performances were evaluated via the Lagrangian particle tracking method afterwards [1]. The mesh independent study results reached within an acceptable range of error with the help of Ansys Fluent Meshing. Additionally, pressure drop data collected at different locations along the mouthpiece by Sensirion EK-P4 was used to validate the computational results.

Results and Discussion

Evaluation of *in-vitro* drug delivery performance

The experimental dispersion of 13 doses of Indacaterol maleate dry powder was performed to study the effect of the grid on the aerosol performance. Figure 4 showed the particle deposition distribution on each part of NGI, with approximate 25% of Indacaterol maleate impacted on the PS and most fine particles deposited on stage 3 and stage 4. As the voidage of inhalers increased, there was also a slightly growth of the fine particle fraction (FPF). With a voidage of 68.73% for the assembled 3D-printed inhaler with modified grids of 7'7, the FPF was raised to 37.2% compared with that of 4'4 with a FPF of 33.8%. The results showed a positively proportional relationship between voidage of inhaler grids and FPF. In addition, the delivered dose (expressed as the percentage of detected drug mass to the labelled mass) through IN-1, IN-2, and IN-3 were $80.4 \pm 0.9\%$, $84.5 \pm 1.3\%$ and $92.7 \pm 0.5\%$, respectively. There was a rising trend of delivered dose when grid voidage increased. Since the width of the mesh splitting the grid was designed to be 0.22 mm, 0.50 mm and 1.63 mm for IN-3, IN-2 and IN-1, respectively, more drug was assumed to be impacted on the mesh instead of passing through the grids with air flow, which means smaller delivered dose. The assumption was verified by Indacaterol maleate retention shown in Table 1. Indacaterol maleate detected in the IN-1 designed with the smallest voidage and widest splitting wire, was 19.6%, larger than that in IN-2 of 15.5% and IN-3 of 7.3 %. More possible reasons were explained by CFD analysis.

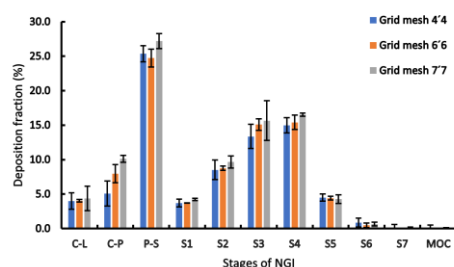


Figure 4 Drug deposition percentage with on each stage of NGI (CP, PS, stage 1-7, MOC) and drug residue in the capsules through three modified 3D-printed inhalers with varied grids

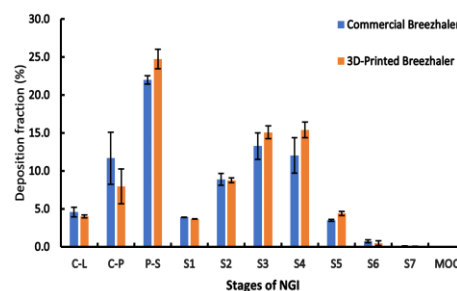


Figure 5 Drug deposition percentage on each stage of NGI (CP, PS, stage 1-7, MOC) and drug residue in the capsules through commercial Breezhaler® and corresponding 3D-printed Breezhaler

Table 1 Summary of experiment results of modified inhalers with varied grids (n=3)

Inhaler No.	Grids	Voidage* (%)	Air resistance (KPa ^{0.5} /(L/min))	Device retention (%)	FPF (%)	FPD (μg)	Delivered dose (μg)
IN-1	4×4	13.16	0.0296	19.58	33.8 ± 3.1	65.92 ± 3.9	120.63 ± 1.28
IN-2	6×6	48.26	0.0228	15.46	35.4 ± 2.5	69.02 ± 5.2	128.31 ± 1.96
IN-3	7×7	68.73	0.0208	7.27	37.2 ± 4.2	72.51 ± 4.8	139.10 ± 0.71
Commercial Breezhaler®	6×6	48.26	0.0130	19.46	29.7 ± 4.4	59.03 ± 3.7	120.81 ± 2.61

*Voidage percentage is a measure of the open area within the grid structure as a percentage of the cross-sectional area of the mouthpiece.

Generally, the methods for constructing inhalers were less researched and reports on device modification were less seen, 3D-printing technology provides a new, fast, convenient, and cost-effective way for inhaler fabrication. This work also did a preliminary investigation on the aerosolization performance of 3D-printed inhalers. Figure 5 showed the particle distribution through commercial Breezhaler® and corresponding 3D-printed Breezhaler, which have an air resistance of 0.0130 and 0.0228 KPa^{0.5}/(L/min)), respectively. The FPF of printed inhaler is 37.2%, significantly higher than that commercial Breezhaler® of 29.7%. This may attribute to unsatisfactory resolution used for 3D-printing. Although a relatively high resolution was used for printing, the inner surface is not as smooth as the commercial inhaler by injection molding from ABS (Acrylonitrile butadiene styrene), thus may generating small vortex and turbulence inside of the air flow field and leading to a higher air resistance. These minor vortex and turbulence may promote de-agglomeration and de-attachment, further enhancing FPF and delivered dose. This could be validated by experiment results, slightly lower device retention of 15.5% through 3D-printed IN-2 compared with 19.5% through the commercial inhalers (Table 1). The other possible reasons for better aerosolization performance of 3D-printed inhalers may attribute to properties of inhaler materials and minor leaking when air is entrained into the system. More characterizations are needed to verify the assumptions.

CFD analysis

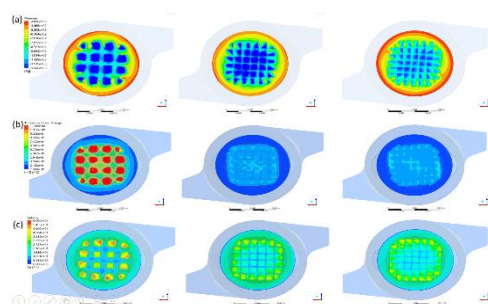


Figure 6 (a) Contour plot of pressure profiles 0.1 mm below the inhaler grid 4×4; (b) Contour plot of turbulence kinetic energy profiles 0.1 mm below the inhaler grid 6×6; (c) Contour plot of velocity profiles 0.1 mm below the inhaler grid 7×7

Velocity streamlines tracking through the three inhalers with varied voidage were shown in Figure 3. With the increase of grid voidage, much reduced air jet spreading and vertexing were observed. The flow fields of devices with intense openings are potentially beneficial because they are likely to focus particles along the centre and reduce the collision of particles on the mouthpiece wall. Figure 6 illustrates how inhaler grid would affect the pressure, the turbulence kinetic energy, and the velocity captured from 0.1 mm below the inhaler grid. Higher values of these parameters indicate an increase of particle de-agglomeration, and the probability of drug carrier detachment [1], [8]. However, more collision between drug and wall, may also be introduced, thus possibly leading to lower FPF. Meanwhile, the drug particles were also likely

to impact on the mesh with wider wire splitting the grid, and then retained in the device. Overall, the FPF depends on all the above factors. Take IN-1(inhaler grid 4×4) as an example, higher velocity and turbulence, theoretically, contributes to a higher FPF, but its experimental FPF was relatively low than inhalers with higher voidage, which results from a predominant factor of large mass impaction and drug retention in the IN-1. The explanation was also verified by the experimental results of drug retention in Table 1.

Conclusions

This work showed the feasibility of constructing inhalers by 3D-printing technology, and assembled inhaler IN-2 had a slightly higher fine particle fraction and delivered dose than the commercial Breezhaler®, which requires further research to figure out the reasons behind. The 3D-printed inhaler with higher grid voidage and constant opening size, was found to show a modest increment on FPF and significant increase on delivered dose because of less drug retention in the device. In summary, the grid structure of capsule-based dry powder inhaler will affect *in-vitro* drug delivery performance but varies based on the design character, and plays an important role on particles centralization.

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