Development and *In Vitro* Testing of a New High Efficiency Dry Powder Inhaler for Carrier-Free Formulations

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SUMMARY

Background: Current DPIs on the market have fine particle fractions (FPF) in the range of 10-70%, produce high mouth-throat (MT) depositional losses of approximately 30-95%, and have relatively low and variable lung delivery efficiencies. A high efficiency dry powder inhaler (DPI) was developed and tested for use with carrier-free formulations across a range of different *in vitro* inhalation flow rates. Methods: The performance of the new design was investigated and reported in terms of aerosolization characteristics. The new design oriented the capsule chamber (CC) at an angle of 90 degrees to the main flow passage, which contained a 3D rod array for aerosol deaggregation. Results: Orienting the CC at 90^{o} to the mouthpiece produced an albuterol sulfate emitted dose (ED) of 73.4%, fine particle fractions (FPFs) less than 5µm and 1µm of 95.1% and 31.4%, respectively, and a MMAD of 1.5µm when tested at a flow rate of 45LPM. The variability associated with both ED and deaggregation was low with the CC_{90}-3D design when tested between 31.8 to 55.1 LPM, respectively. There was no significant change in emitted dose across the range of flow rates. FPF changes of approximately 1% in value and MMAD changes of approximately 0.1 µm in value, were observed. Conclusions: The new inhaler produced an extremely high quality aerosol with little sensitivity to flow rate and is expected to deliver approximately 95% of the ED to the lungs.

INTRODUCTION

There is currently a need for high efficiency dry powder inhalers (DPIs). Current DPIs on the market have fine particle fractions (FPF) in the range of 10-70%, produce high mouth-throat (MT) depositional losses of approximately 30-95%, and have relatively low and variable lung delivery efficiencies. Most DPIs are passive devices, in which the patient's inspiratory effort is required to aerosolize the powder. Variability in inspiration characteristics commonly leads to differences in dose emission and the quality of the aerosol produced. To maximize inhaler performance, some form of feedback to the patient is considered desirable with inhaler usage. A recent review of potential inhalation device innovations emphasized the need for DPI inspiratory independence, high respiratory dose efficiency, and patient friendly devices that may include feedback with correct usage [1].

One potential pathway toward developing a high efficiency DPI is the use of excipient enhanced growth (EEG) technology. With this approach, the inhaler generates an aerosol from a submicrometer combination particle formulation composed of a drug and a hygroscopic excipient. The small size of the aerosol particles minimizes deposition in the device and extrathoracic airways. The particle size increases in the warm and humid lung environment due to the inclusion of a hygroscopic excipient and associated water uptake, resulting in lung deposition of the aerosol. Previous studies with spray generated aerosols and EEG delivery have demonstrated low MT deposition [2], the potential for significant size increase of the aerosol in the lungs [3], deposition of the droplets within airway models [4], and the potential to target deposition to specific regions of the lungs [4]. Son et al. [5] previously developed an optimized EEG formulation for use with DPIs that contained albuterol sulfate (AS; model drug), mannitol (MN; model hygroscopic excipient), and L-leucine (dispersion enhancer).

The objective of this study is to develop a high efficiency DPI that operates with combination particle EEG formulations and maintain performance at different flows and for different delivered medications. The device is designed to maximize emitted dose and increase turbulence in the 3D rod array, which improves deaggregation. Device performance is considered across a range of pressure drops and for two inhaled medications.

METHODS

Materials

Albuterol sulfate USP (AS) and terbutaline sulfate USP (TS) were purchased from Spectrum Chemical Co. (Gardena, CA). Pearlitol® PF-Mannitol was donated from Roquette Pharma (Lestrem, France). Poloxamer 188 (Leutrol F68)

was donated from BASF Corporation (Florham Park, NJ). L-leucine and all other reagents were purchased from Sigma Chemical Co. (St. Louis, MO). Hydroxypropyl methylcellulose (HPMC) capsules (size 3) were donated from Capsugel (Morristown, NJ).

High Efficiency Inhaler Designs

The DPI design considered in this study is illustrated in Fig. 1. The DPI employs the 3D rod array and flow passage geometry previously developed by Longest et al. [6] and implemented in the studies of Son et al. [7] and Behara et al. [8] The new inhaler design employed in this study implements a capsule with the long axis aligned with the incoming airflow. This configuration has the added advantage of placing the capsule in view of the patient and raising the capsule when adequate flow is provided through the inhaler. The new inhaler implements a 90^o (CC_{90}-3D; Fig. 1) angle between the capsule chamber and flow passage. A single air inlet is located above the capsule chamber with a diameter selected to produce a flow rate of 45 LPM at a pressure drop of 4 kPa across the inhaler. The inhaler was created using Autodesk Inventor and exported as .STL files to be prototyped. The files were then prepared for prototyping using 3D Lightyear Software. The parts were built using a 3D Systems Viper SLA System (3D Systems Inc., Rock Hill, SC) using Accura 60 stereolithography resin (3D Systems Inc.).

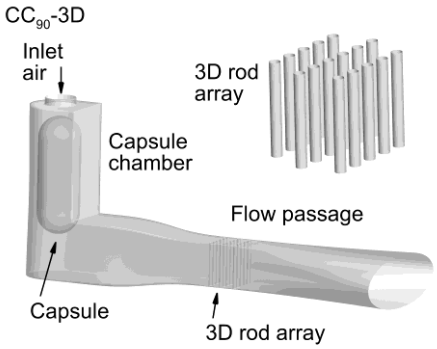

Figure 1. Dry powder inhaler (CC_{90}-3D) with the capsule oriented parallel to the inlet airflow and a 90^o angle between the CC and flow passage.

Preparation of Formulations

Excipient enhanced growth formulation combination particles were engineered as described by Son et al. [5]. Briefly, a 20% ethanol in water solution containing 0.5 mg/ml of total solids concentration consisting of drug (AS or TS), MN, L-leucine and poloxamer 188 in a ratio of 30:48:20:2 (%w/w) was spray dried using a Büchi Nano spray dryer B-90 (Büchi Laboratory-Techniques, Flawil, Switzerland).

Aerosol Particle Size Characterization

To determine aerodynamic particle size of the emitted aerosol, 2 mg of EEG formulation was filled in a hydroxypropyl methylcellulose (HPMC) size 3 capsule and aerosolized into a next generation impactor (NGI; MSP Corp., Shoreview, MN) using the CC_{90}-3D inhaler at an airflow rate corresponding to a 4 kPa pressure drop across each device. The powders were aerosolized until a total air volume of 4 L was drawn through the inhalers at ambient conditions. All measurements were made with at least three replicates. The stages of the impactor were coated with silicone spray to minimize particle bounce and re-entrainment.

RESULTS AND DISCUSSION

Effects of Flow Rate

It is well known that the deaggregation behavior of passive dry powder inhalers relies on the patient's inspiratory effort. The current investigation focused on the changes of deaggregation as a result of changes in air flow rates, which arise from different pressure drops over the inhaler. The deaggregation efficiency of AS with CC_{90}-3D between 31.8 to 55.1 LPM is shown in Table 1. These flow rates correspond to pressure drops in the range of 2 to 6 kPa across the device. The DPI performed well across the range of airflow rates investigated in this study. There was an insignificant difference observed in ED (p=0.582; ANOVA) across the airflow rates studied. Compared to aerosolization at 31.8 LPM, lower $FPF_{<5\mu m/ED}$ and MMAD (p=0.027 and p=0.007; Tukey's Post-hoc) were observed at an aerosolization flowrate of 45 LPM; while decreased $FPF_{<1\mu m/ED}$ and MMAD (p=0.032 and p=0.005; Tukey's Posthoc) were observed when aerosolized at 55.1 LPM. While statistically significant, these differences were extremely small representing FPF changes of approximately 1% in value and MMAD changes of approximately 0.1 µm in value. In general, the variability associated with both ED and deaggregation was low with the CC_{90}-3D design.

Overall, the CC_{90}-3D device demonstrated very low airflow rate dependence on deaggregation and no statistical difference in ED across the airflow rates considered.

Table 1: The effect of airflow rate on aerosolization of AS using the CC_{90}-3D DPI. Standard deviation is shown in parenthesis [n=3].

	CC_{90}-3D		
Air flow rate (LPM)	31.8	45.0	55.1
Pressure drop (kPa)	2	4	6
Emitted dose (%)	71.2 (1.6)	73.4 (4.1)	73.2 (1.9)
$FPF_{<5\mu m/ED}$ (%)	95.5 (0.1)	95.1 (0.2)**	95.3 (0.2)
$FPF_{<1\mu m/ED}$ (%)^	31.4 (0.4)	31.4 (0.1)	30.0 (0.7)**
MMAD (μm) ^	1.54 (0.01)	1.49 (0.00)**	1.48 (0.02)**

^ P<0.05 significant effect for CC90-3D of air flow rate on $FPF_{<5\mu m/ED}$, $FPF_{<1\mu m/ED}$ and MMAD (one-way ANOVA).
**P<0.05 significant difference compared to 31.8 LPM with CC90-3D, respectively (post-hoc Tukey's).

Flow rate effects on aerosol performance are illustrated in Fig. 2 for the CC_{90}-3D DPI compared with several commercial inhalers. Albuterol Diskus, Diskhaler, and Turbuhaler were previously evaluated by Prime et al.[9] at set flow rates of 28 and 60 LPM. Salmeterol Diskus and Formoterol Turbuhaler were evaluated by Tarsin et al.[10] using flow rates measured from 20 severe asthmatics. Variations in FPF and MMAD as a function of flow rate from these previous studies are compared with results of the CC_{90}-3D DPI. Considering FPF across the range of reported flow rates (Fig. 2a), values change by a percent difference of 30-70% in the Prime et al. [9] data and 70-128% in the Tarsin et al. [10] data. In contrast, FPF between flow rates of approximately 30-60 LPM changes by a percent difference of 0.2% for CC_{90}-3D. MMAD values (Fig. 2b) at low and high flow rates change by 38-56% for the commercial products in the study of Tarsin et al. [10], and were not reported in the study of Prime et al. [9]. MMAD values for the CC_{90}-3D device changes by 4.0%, over a flow range of approximately 30-60 LPM (Fig. 2b). Different flow rates were used in all of the studies described above. However, these flow rates are consistent with inhaler usage and clearly indicate a trend in reduced sensitivity to flow rate with the CC_{90}-3D device. Specifically, the percent difference in FPF and MMAD at low and high flow rates is reduced by 1-2 orders of magnitude with the CC_{90}-3D design. It is noted that FPF was calculated differently in the three studies considered above (based on loaded *vs.* emitted dose). However, this does not alter the relative changes in values considered in these comparisons.

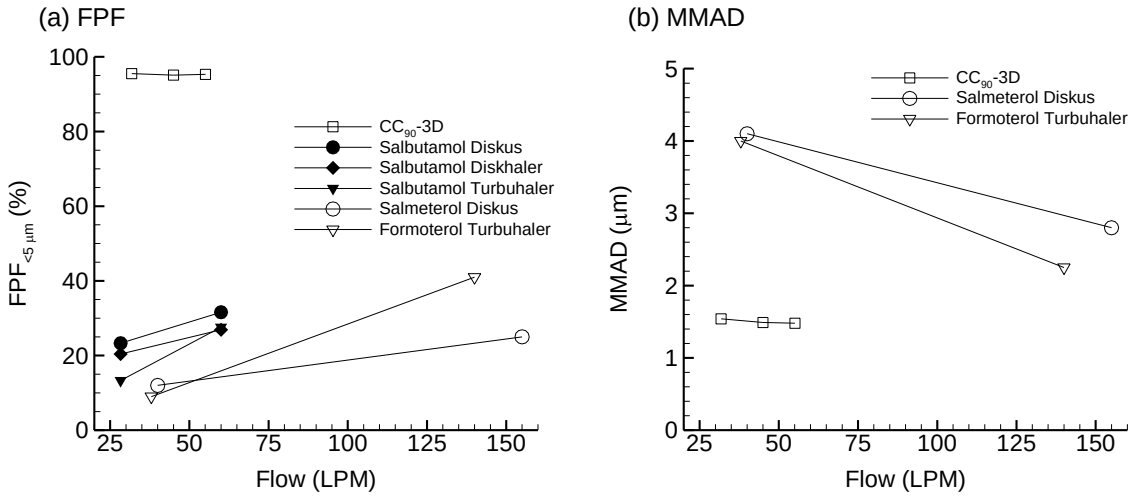

Figure 2. Comparison of flow rate effects for the CC_{90}-3D inhaler and previously reported commercial products in terms of (a) $FPF_{<5\mu m}$ and (b) MMAD. Salbutamol Diskus, Diskhaler, and Turbuhaler were considered in the study of Prime et al. at flow rates of 28-60 LPM. Salmeterol Diskus and Formoterol Turbuhaler were considered by Tarsin et al., and the illustrated line represents the reported linear best fit of the data.

Effects of a New Formulation

It is evident that the CC_{90}-3D DPI performs well and is able to achieve approximately 75% ED. However, these results were demonstrated with only the AS EEG formulation. To expand the analysis, the performance of the CC_{90}-3D DPI was investigated using a terbutaline sulfate EEG formulation at a 4 kPa pressure drop and the results shown in Table 2. Emitted dose values were similar to those observed using the AS formulation. It was observed that the deaggregation values for TS (Table 2) were lower than with the AS formulation (Table 1); which is perhaps a result of differences in physicochemical properties between the drugs.

Table 2 The aerosolization efficiency of the CC_{90}-3D DPI with TS at 4 kPa pressure drop. Standard deviation is shown in parenthesis [n=3].

Description	CC_{90}-3D
Emitted dose (%)	75.2 (0.6)
$FPF_{<5\mu m/ED}$ (%)	89.4 (0.5)
$FPF_{<1\mu m/ED}$ (%)	12.0 (2.3)
MMAD (µm)	2.01 (0.06)

CONCLUSIONS

The new DPI considered in this study achieved high aerosolization efficiency performance with a previously optimized combination particle EEG formulation. The new CC_{90}-3D design met the criteria of producing a high efficiency aerosol. Aerosols produced by the new CC_{90}-3D device were found to be largely independent of flow rate in the range of 2-6 kPa pressure drops. Specifically, the new devices reduced the percent difference in FPF and MMAD between low and high flows by 1-2 orders of magnitude compared with current commercial devices.

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