Development and Comparison of New High-Efficiency Dry Powder Inhalers for Carrier-Free Formulations

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ABSTRACT: High-efficiency dry powder inhalers (DPIs) were developed and tested for use with carrier-free formulations across a range of different inhalation flow rates. Performance of a previously reported DPI was compared with two new designs in terms of emitted dose (ED) and aerosolization characteristics using *in vitro* experiments. The two new designs oriented the capsule chamber (CC) at different angles to the main flow passage, which contained a three-dimensional (3D) rod array for aerosol deaggregation. Computational fluid dynamics simulations of a previously developed deaggregation parameter, the nondimensional specific dissipation (NDSD), were used to explain device performance. Orienting the CC at 90° to the mouthpiece, the CC_{90}-3D inhaler provided the best performance with an ED = 73.4%, fine particle fractions (FPFs) less than 5 and 1 μm of 95.1% and 31.4%, respectively, and a mass median aerodynamic diameter (MMAD) = 1.5 μm. For the carrier-free formulation, deaggregation was primarily influenced by capsule aperture position and the NDSD parameter. The new CC-3D inhalers reduced the percent difference in FPF and MMAD between low and high flows by 1–2 orders of magnitude compared with current commercial devices. In conclusion, the new CC-3D inhalers produced extremely high-quality aerosols with little sensitivity to flow rate and are expected to deliver approximately 95% of the ED to the lungs. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:465–477, 2014

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INTRODUCTION

In the field of respiratory drug delivery, there is currently a need for high-efficiency dry powder inhalers (DPIs).[1–3] Current DPIs on the market have fine particle fractions (FPFs) in the range of 10%–70%,[3,4] produce high mouth–throat (MT) depositional losses of approximately 30%–95%,[5–8] and have relatively low and variable lung delivery efficiencies.[9] Considering conventional inhaled medications with wide therapeutic windows, use of these current devices is generally acceptable and provides a clinical benefit that typically outweighs the associated risks.[1,10,11] However, systemic exposure to frequently prescribed corticosteroids has been associated with osteoporosis in the elderly, suppression of growth in children, suppression of adrenal activity, and vocal problems.[4,12] High-efficiency lung delivery of commonly prescribed medications to intended respiratory targets will reduce systemic exposure and decrease the associated side effects. Considering many envisioned next-generation inhaled medications such as antibiotics, gene vectors, pain medications, and chemotherapy, the range of effective dosing is more narrow and side effects are more severe.[1,11,13–15] For these medicines to be safely delivered, most current DPIs are insufficient and new high-efficiency formulation and device combinations are needed.

The development of high-efficiency DPIs faces a number of challenges. 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.[2–4,16] For example, Prime et al.[17] demonstrated a nearly twofold difference in the dose delivered from the Diskhaler (GSK, Raleigh, North Carolina) and Turbuhaler (AstraZeneca, Lund, Sweden) between the flow rates of 30 and 90 liters per minute (LPM). In contrast, the Diskus (GSK) device was less dependent on flow rate and produced a more consistent FPF[17]; however, this device is reported to lose approximately 70% of the dose in the MT region.[6] In volunteers using the Novolizer DPI (Meda Pharmaceuticals, Bishop's Stortford, UK), Newman et al.[18] demonstrated lung delivery efficiencies of approximately 20% and 32% for inhalation flow rates of 45 and 90 LPM, respectively, with MT deposition of approximately 60%. Improved emptying of the DPI device is typically achieved with higher flow rates,[19] which also improves emitted dose (ED) reproducibility. However, higher flow rates are associated with increased MT deposition,[20] which leads to an additional source of variability in the lung delivery.[9] It is noted that the complex relationship among device emptying, deaggregation or detachment from carriers, inhalation velocity, and MT deposition is influenced by the type of particle formulation with carrier-free powders behaving differently from powders with large carrier particles.

Abbreviations used: 3D, three-dimensional or three-dimensional rod array; AS, albuterol sulfate; CAO, capsule aperture orientation; CC, capsule chamber; CFD, computational fluid dynamics; DPI, dry powder inhaler; ED, emitted dose; EEG, excipient enhanced growth; FPF, fine particle fraction; HH, HandiHaler; HPLC, high-performance liquid chromatography; HPMC, hydroxypropyl methylcellulose; LPM, liters per minute; MMAD, mass median aerodynamic diameter; MN, mannitol; MT, mouth—throat; NDSD, nondimensional specific dissipation; NGI, next-generation impactor; PTFE, polytetrafluoroethylene; R^2, coefficient of determination; TB, tracheobronchial; TS, terbutaline sulfate

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To maximize inhaler performance, some form of feedback to the patient is considered desirable with inhaler usage.[2] This can inform the patient that a correct inhalation flow rate was employed and that the dose was received. For example, capsule-based DPIs often provide a rattling sound when sufficient airflow is passed through the device. The Novolizer device has a visual cue to indicate when the dose is successfully delivered, which may have aided in the reduced intersubject variability reported in the *in vivo* study of Newman et al.[18] This feedback may also improve compliance with following the prescribed regime of inhalation treatment.[2] 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.[2]

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 because of 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,[21] the potential for significant size increase of the aerosol in the lungs,[22–24] deposition of the droplets within airway models,[25] and the potential to target deposition to specific regions of the lungs.[25] Son et al.[26] 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). Use of a commercial capsule-based DPI with this formulation produced a FPF (%, <5 μm; $FPF_{<5\,\mu m/ED}$) of 95.3% and MT deposition in an established *in vitro* characteristic model of less than 5%. The study of Son et al.[27] implemented this optimized formulation and evaluated the effects of DPI design on the formation of submicrometer aerosols and deposition in the MT model. The best performing device employed the capsule chamber (CC) of the HandiHaler (HH; Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany) and a novel three-dimensional (3D) rod array to enhance deaggregation of the powder. The resulting HH-3D device produced an ED of 74.2%, a mass median aerodynamic diameter (MMAD) of 1.1 μm, and less than 3% MT deposition.

Behara et al.[28] recently evaluated the effects of a new CC design on DPI performance for an EEG formulation. This study defined a high-efficiency DPI for use with the EEG delivery approach as having an ED of ≥75%, an aerosol MMAD of ≤1.5 μm, which is expected to produce <5% MT deposition,[26,27] and a $FPF_{<5\,\mu m/ED}$ ≥90%. By introducing a new CC design along with the 3D rod array flow passage,[29] improved deaggregation of the EEG formulation was observed. Coating of the capsule with low surface energy polytetrafluoroethylene (PTFE) was also shown to improve ED. The resulting new high-efficiency inhaler had an ED of greater than 80% and produced an aerosol with an MMAD = 1.3 μm with $FPF_{<5\,\mu m/ED}$ >90%.

As described, the optimized EEG formulation of Son et al.[26] coupled with modified and new devices have produced high-efficiency DPIs.[27,28] However, further improvements are possible and additional testing is necessary. The high-efficiency device developed by Behara et al.[28] required coating with PTFE to achieve >80% ED. Previous studies have only tested high-efficiency EEG DPI devices at a pressure drop of 4 kPa and flow rates of approximately 45 LPM.[26–28] Furthermore, only one EEG formulation was previously considered for DPI administration. Ideally, a high-efficiency DPI should perform well over a range of inhalation flow rates and for multiple formulations. The inclusion of visual feedback during correct usage would also be advantageous.

The objective of this study is to develop high-efficiency DPIs that operate with combination particle EEG formulations and maintain performance at different flows and for different delivered medications. Three devices are initially considered, which are the previous CC_1-3D design of Behara et al.[28] and two versions of a new high-efficiency DPI. This new design is intended to maximize ED and increase turbulence in the 3D rod array to further improve deaggregation. Comparisons of the three devices are initially performed using computational fluid dynamics (CFD) simulations and a previously developed parameter that correlates with deaggregation of carrier-free formulations.[29] CFD estimates of inhaler performance are then verified with *in vitro* experiments and one of the two new devices is selected. The CC_1-3D device and new prototype are evaluated for aerosolization performance and ED without and with PTFE coating. Device performance is then considered across a range of pressure drops and for two inhaled medications. Results are intended to further establish the viability of high-efficiency DPI aerosol delivery using the EEG approach. Furthermore, the designs and analysis presented may also improve the performance of existing DPIs that employ conventional-sized aerosols.

MATERIALS AND METHODS

Materials

Albuterol sulfate USP and terbutaline sulfate (TS) USP were purchased from Spectrum Chemical Company (Gardena, California). Pearlitol PF-MN was donated from Roquette Pharma (Lestrem, France). Poloxamer 188 (Leutrol F68) was donated from BASF Corporation (Florham Park, New Jersey). L-Leucine and all other reagents were purchased from Sigma Chemical Company (St. Louis, Missouri). Hydroxypropyl methylcellulose (HPMC) capsules (size 3) were donated from Capsugel (Morristown, New Jersey).

High-Efficiency Inhaler Designs

The three DPI designs considered in this study are illustrated in Figure 1. Each DPI employs the 3D rod array and flow passage geometry previously developed by Longest et al.[29] and implemented in the studies of Son et al.[27] and Behara et al.[28] This flow passage design was shown to maximize the nondimensional specific dissipation (NDSD) parameter, which was proven to quantitatively correlate with deaggregation for a combination particle formulation across a series of eight inhalers evaluated at multiple flow rates.[29] Briefly, the NDSD parameter captures the relative effects of turbulent energy, inverse of the turbulent eddy length scale, and exposure time to turbulence, which each play a role in the deaggregation of carrier-free powders.[29]

The inhalers considered in this study differ based on the CC design. The first device was developed in the study of Behara et al.[28] and orients the long axis of the capsule perpendicular