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Development of a novel digital breath-activated inhaler: Initial particle size characterization and clinical testing

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ABSTRACT

Background: Delivery of inhaled respiratory medications have been associated with variable delivery of drug due to errors in device operations and have not been designed to monitor true delivery of medication. A fully digital breath-activated inhaled (DBAI) delivery platform has been developed with integrated firmware and software to address these limitations.

Methods: the device was designed to produce similar aerosol particle output to a marketed albuterol MDI and to the albuterol/ipratropium combination in a soft mist inhaler (SMI). Cascade impactor studies were conducted to demonstrate comparable aerodynamic particle size distribution (APSD) metrics. Efficacy was evaluated by pharmacodynamic studies involving spirometry in two separate protocols with adult subjects having COPD (albuterol DBAI vs. albuterol MDI – Study A, albuterol/ipratropium DBAI single arm – Study B).

Results: The total emitted doses (TED) were 81.9 ± 10.3, 109.3 ± 15.0 and 121.9 ± 7.0 μg/actuation for the DBAI, SMI and MDI respectively, and the fine (respirable) particle doses (FPD) were 56.2 ± 6.0, 61.7 ± 5.5 and 79.4 ± 2.7 μg/actuation. MMADs for albuterol sulfate were 1.93 ± 0.11, 1.75 ± 0.19, and 2.65 ± 0.05 μm for the DBAI, Respimat soft mist inhaler (SMI) and MDI respectively. The corresponding GSDs were 1.96 ± 0.16, 2.79 ± 0.25, and 1.48 ± 0.02 μm. The corresponding respirable fractions were 68.7 ± 3.2%, 57.3 ± 10.5%, and 65.2 ± 2.4%. Spirometric study A enrolled 23 subjects (age 64 ± 7.3 years, 39% male, FEV_1 45 ± 14% predicted). Study B enrolled 23 subjects (age 65 ± 8.6 years, 43% male, FEV_1 47 ± 10% predicted). For Study A, FEV_1 at 20 min post-dose improved by 120 (167) mL ($p = 0.002$) for the DBAI device and 109 (183) mL ($p = 0.008$) for the MDI device ($p = 0.86$ for between group differences). For Study B, FEV_1 (20 min post-dose) improved by 216 (126) mL ($p < 0.001$).

Conclusion: The DBAI generated highly respirable aerosols containing albuterol sulfate that were similar to the MDI and SMI in respirable fraction but lower in dose. Subsequent pharmacodynamic studies delivering albuterol sulfate alone and in combination with ipratropium bromide confirmed similar responses for the DBAI compared with the other inhalers, which could possibly be related to a response ceiling. The DBAI breath-activated capability combined with the ability to monitor actual delivery of medication may improve effectiveness by overcoming patient miscoordination.

1. Introduction

Asthma and chronic obstructive pulmonary disease (COPD) affect 235 million and 251 million people globally respectively [1]. Corresponding annual attributable deaths were 383,000 (asthma) and over three million (COPD) in 2015 [2]. The recommended pharmacotherapy for both asthma and COPD is primarily medications delivered by a range of different classes of orally inhaled product (OIP) [3,4]. The current devices available to deliver inhaled medications can be grouped into the following classes: 1) pressurized propellant-driven metered dose inhalers (MDIs) 2) dry powder inhalers (DPIs) 3) nebulizers, 4) breath-actuated MDIs (BA-MDIs), and 4) soft mist inhalers (SMIs). The steps required to use each device correctly are very different. The number of steps and absence of a unified standards contributes the well-

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Fig. 1. PneumaHaler digital breath-activated inhaler (A – version used in the described studies, B & C – current version).

described errors in patient usage, which has been linked to poor disease control [5,6].

MDIs have been considered the gold standard for pulmonary drug delivery for more than 50 years [7]. This class of inhaler requires pairing of the active drug with a propellant. Their main limitation is the need to coordinate the inspiratory maneuver with inspiration that is required for effective medication delivery [7,8]. Additionally, a slow inhalation when using an MDI is as important as co-ordination of inhalation [9] Improper MDI technique has been associated with poor disease control and increased utilization of emergency departments [6]. Add-on devices, such as spacers and valved holding chambers help with technique, but greatly increase the size of the inhaler, a feature that many patients dislike [10,11]. Even with proper technique, approximately 10% of the inhaled dose is deposited in the lower airways [12]. DPIs rely on adequate patient effort to deliver the dose, and efficacy can be affected by environmental conditions such as temperature and humidity [7]. Since higher inspiratory flow is necessary to operate a passive DPI, they are not recommended for children less than five years of age [8]. Unlike the MDI, where the design is relatively uniform for each device, DPIs tend to be complex in construction with a variety of different designs and several more steps are often required for administration of medication. The use of multiple delivery systems may contribute to confusion for patients and health care providers [13].

There is only one design of SMI (Respimat®, Boehringer Ingelheim) that is currently commercially available. Its operation requires the patient to apply significant mechanical force to load a high-rate spring, which is then released at actuation to enable delivery of drug via a two-channel nozzle in which atomization occurs as the two accelerating jets converge near to the exit [14]. The SMI requires multiple steps for correct use and must, like many MDIs, be primed on initial use and if not used for several days [15,16].

All classes of currently available OIPs provide limited feedback to either the patient or the prescribing clinician regarding compliance. The drug delivery devices only document actuation, which is not necessarily an accurate measure of patient use. They do not include feedback to the patient regarding correct device usage, resulting in lost opportunities for making self-improvements in inhalation technique. Other desirable features that are lacking include the ability to record actual medication delivery, the provision of a signal to patients when doses are missed, and an alert for healthcare providers to the presence of non-compliance and symptom worsening. Add-on systems with Bluetooth capabilities already exist, but their drawback is that they are physical attachments contributing to the bulk of the OIP assembly and have a separate cost to the payor [17].

A technical team was formed to provide a solution to the limitations of current devices for the delivery of inhaled medications and to incorporate features that would assist with adherence and healthcare delivery. The result is the first fully digital hand-held portable device for the delivery of inhaled medications, termed a digital breath activated inhaler (DBAI). The DBAI is a novel metered dose inhaler designed to overcome limitations of currently available pulmonary drug delivery devices. The main design components of the Pneuma Inhaler include a vibrating plate piezoelectric spray ejector, a differential pressure sensor, and a microprocessor that controls dose delivery, user notifications, and dose counting. The device is processor controlled, inputs include an on-off switch in the device cover and a differential pressure sensor. The DBAI eliminates the need for patient - device coordination by using the differential pressure sensor to initiate the piezoelectric ejector in response to the onset of inhalation. Outputs on the device include an electronically controlled piezoelectric sprayer, an LED screen, and a microphone. A Bluetooth radio is incorporated in the device construction, which communicates with a smartphone or other device, allowing both data input and output. The device is designed to record and store dosing (date and time stamped) and to serially record and store inspiratory flow throughout the inspiratory maneuver.

The piezoelectric spray ejector optimizes droplet delivery to the lungs by creating droplets in a predefined range with a high degree of accuracy and repeatability. The DBAI eliminates the need for patient - device coordination by using a differential pressure sensor to initiate the piezoelectric ejector in response to the onset of inhalation. Unlike pressurized MDIs, the droplets from the Pneuma Inhaler are generated having little to no intrinsic velocity from the aerosol formation process and are inspired into the lungs solely by the user's incoming breath passing through the mouth tube.

The DBAI is comprised of a separate drug delivery cartridge with a vibrating plate piezoelectric sprayer embedded on the bottom of the drug cartridge, and a handheld unit containing a differential pressure sensor, a microprocessor and three AAA batteries (Fig. 1). When the cartridge is mated to the handheld body, electrical contact is made between the body containing the batteries and the piezoelectric sprayer embedded in the drug cartridge. A horizontal series of three small, user visible LED lights and a small speaker within the handheld base provide user notifications. The LED lights will indicate the following conditions: (a) when the device is on (one green light), (b) when drug is being ejected (three green lights), (c) if the cartridge is empty (three red lights), and (d) if the cartridge is missing (one red light). The device in the current configuration is approximately 3.5 cm high, 5 cm wide, 10.5 cm long and weighs approximately 95 g with an empty drug cartridge (fill volume = 3.5 mL) and with batteries inserted (Fig. 1). For the purposes of the reported studies, cartridges were filled with either albuterol sulfate or the combination of albuterol sulfate and ipratropium bromide. Drug is ejected over 1.5 s, although the version in the clinical protocol ejected the drug over 2.3 s. The timing was changed to be similar to the approved soft mist inhaler (Respimat™, Boehringer Ingelheim).

The initial version of the DBAI has been designed to produce similar