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NanoCluster budesonide formulations enable efficient drug delivery driven by mechanical ventilation

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ABSTRACT

Agglomerates of budesonide nanoparticles (also known as 'NanoClusters') are fine dry powder aerosols that were hypothesized to enable drug delivery through ventilator circuits. These engineered powders were delivered via a Monodose® inhaler or a novel device, entrained through commercial endotracheal tubes, and analyzed by cascade impaction. Inspiration flow rates and other parameters such as inspiration patterns and inspiration volumes were controlled by a ventilator. NanoCluster budesonide (NC-Bud) formulations had a higher efficiency of aerosol delivery compared to micronized budesonide with NC-Bud showing a much higher percent emitted fraction (%EF). Different inspiration patterns (sine, square, and ramp) did not affect the powder performance of NC-Bud when applied through a 5.0 mm endotracheal tube. The aerosolization of NC-Bud also did not change with the inspiration volume (1.5–2.5 L) nor with the inspiration flow rate (20–40 L/min) suggesting fast emptying times for budesonide capsules. The %EF of NC-Bud was higher at 51% relative humidity compared to 82% RH. The novel device and the Monodose® showed the same efficiency of drug delivery but the novel device fit directly to a ventilator and endotracheal tubing connections. The new device combined with NanoCluster formulation technology allowed convenient and efficient drug delivery through endotracheal tubes.

1. Introduction

Inhaled drugs are delivered to the lungs via three kinds of aerosol generators; nebulizers, pressurized metered-dose inhalers (pMDIs), or dry powder inhalers (DPIs). Nebulizers and pMDIs are often not efficient in delivering liquid aerosols to patients on mechanical ventilation. A common barrier of drug delivery is the loss of drug aerosols in the humid ventilator circuit and on the endotracheal tube. DPIs have become a popular option for asthma therapy and have been adapted to deliver dry powder formulations to ventilated patients. Optimization of dry powder aerosols and devices, however, is still required to realize the potential of this drug delivery scheme for ventilated patients.

Nebulizers and pMDIs have been historically used during mechanical ventilation. The relative lung deposition efficiencies of different nebulizers and pMDIs have been conducted in many in vitro and in vivo studies (Ari and Fink, 2010). In vitro studies have been highly inconsistent showing highly variable quantities of inhaled drug dose when delivered using either nebulizers or pMDIs. Most liquid formulations have shown poor efficiency because of inertial impaction or gravitational sedimentation of droplets resulting in loss of drug in the ventilator circuit and the endotracheal tube. For example, a study showed a considerable percent of drug was deposited in the spacer chamber, the ventilator circuit and the endotracheal tube when a pMDI was applied (Dhand, 2007). In addition, the humid environment of the ventilator circuit can cause liquid aerosol droplets to increase in size or condense on tubing.

Dry powder inhalers (DPIs) offer an alternative for delivering drugs into ventilated patients. Although many DPIs are available for the treatment of asthma and chronic obstructive pulmonary disease (COPD) (Dolovich and Dhand, 2011), few of them have been successfully applied to mechanical ventilation. Everard et al. used a modified Turbuhaler with the ventilator circuit. The outer covering of the Turbuhaler was removed and the inner cylinder was enclosed to provide spiral disaggregation channels in a chamber. Once the device was loaded, air flowing through the chamber carried the

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Table 1
Dimensions of the Monodose® inhaler and the novel device.

Device	Device geometry	Mesh size (mm)	Inlet opening (mm)	Outlet opening (mm)
Monodose® inhaler	Cylinder	1.28 ± 0.03	4.00 × 5.66	10.72
Novel device	Cylinder	0.15 ± 0.05	2.5	15

aerosol to the endotracheal tube. They reported that approximately 20% of the nominal dose was delivered to a filter placed at the distal end of the tube (Everard et al., 1996).

DPIs on the market are passive devices. The fluidization and aerosolization of drug powder in DPIs depends on the inspiratory effort of patients. Some studies indicated that higher airflow dependence might result in higher dose variability due to differences in the patients' inspiration effort (Martonen et al., 2005). In ventilated patients, however, a patient's inspiration is mainly controlled by the ventilator. Since breathing can be tightly controlled, drug formulations and devices are primary design metrics that would influence DPI performance.

The size and geometry of drug particles play an important role in aerosol performance. To improve deposition in the central airways and peripheral areas in the lungs, drug particles should be in the size range of 1–5 μm. Since cohesive and adhesive forces influence the dispersion of particles in these size ranges, drug formulations should be engineered to reduce interactions between particles and interactions with the surface of the inhaler. NanoCluster budesonide (NC-Bud) was previously shown to enhance drug delivery through endotracheal tubes (Pornputtapitak et al., 2011). The preliminary success of NC-Bud formulations compelled additional studies to assess performance when inspiration is controlled by a ventilator.

Besides drug formulation, device design is another factor that affects drug delivery through a ventilator circuit. A large variability of emitted dose among different DPIs has been reported (Labiris and Dolovich, 2003). The design of DPIs for patients on mechanical ventilation has not been well studied. Here, a novel device was designed in order to enhance drug delivery and be convenient to connect between the ventilator circuit and the endotracheal tube. The combination of engineered dry powders and a novel device design was expected to improve drug delivery efficiency during mechanical ventilation. The effect of other parameters such as humidity, air flow rate and inspiration pattern were also investigated.

2. Materials and methods

2.1. Materials

Budesonide (Bud) was obtained from Sicor de Mexico (Lerma, Mexico). Double-distilled water was provided by an EASYpure® RODI Barnstead International, Dubuque, Iowa. Hi-Lo® cuffed tracheal tubes (PVC) and endotracheal catheter tubes (Kimberly-Clark) were provided by clinical collaborators. The ventilator model was 7200® Series Ventilator System (Puritan-Bennett Corporation, Carlsbad, CA). The details of Monodose® inhaler (Plastiape Monodose Inhaler RS01 Model 7) and the novel device are reported in Table 1 and in Fig. 1.

2.2. Methods

2.2.1. Budesonide NanoCluster fabrication

Budesonide NanoClusters were prepared by milling 5 grams of micronized budesonide in 200 mL distilled water for 20 h. A Netzsch MiniCer Media Mill was operated using YTZ® grinding media (0.5 mm, Tosoh Corp., Tokyo, Japan) under an agitation speed of 2772 rpm. Particle size of the suspensions was determined by dynamic light scattering (Brookhaven Instruments Corp., ZetaPALS) at different time intervals during the milling process. After milling, the collected suspension was frozen at −80 °C and lyophilized for ∼36 h to remove all appreciable water content (VirTis Feezemobile-12XL, The Virtis Company,Gardiner, New York). Lyophilized powder was stored in glass bottles under desiccant at room temperature for further use.

2.2.2. Aerosol characterization

The aerodynamic characteristics of budesonide formulations and commercial budesonide were determined using a Tisch Ambient Cascade Impactor (Tisch Environmental, Inc., Village of Cleves, OH). Approximately 5 mg of each powder was filled in a capsule (HPMC type, size 3, generously provided from Capsugel®, NJ, USA). Powder was introduced to the cascade impactor via a modified Monodose® inhaler or a novel dry powder inhaler. Conditions and parameters such as volumetric flow rate were controlled by a ventilator. The endotracheal tube was placed between the ventilator and the cascade impactor (Fig. 2).

Dry powders deposited on each stage of the impactor were quantified by the difference in weight of the plate on each stage before and after running the experiment. For the

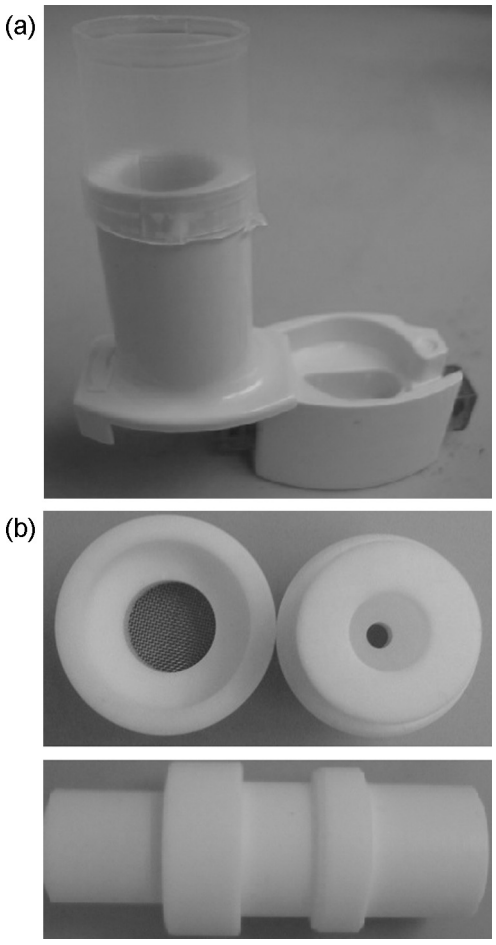

Fig. 1. Photographs of the modified Monodose® inhaler (a) and the novel device (b).