NanoCluster Budesonide Combined with Novel Devices Optimize Drug Delivery in Mechanical Ventilation.

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ABSTRACT SUMMARY
Agglomerates of budesonide nanoparticles (also known as ‘NanoClusters’) were formulated to optimize drug delivery through ventilator circuits. Budesonide NanoCluster formulations (NC-Bud) were found to navigate endotracheal tubes while micronized drug did not. Novel catheter DPIs were then designed to bypass the variable environment of the ventilator circuit to deliver NanoClusters efficiently and reproducibly.

INTRODUCTION
Inhalation is an attractive route for delivering drug directly to the lungs or systemically¹. However, current formulations (e.g. liquid aerosols) have poor efficiency when delivered through endotracheal tubes². Dry powder formulation was explored as a means to enhance drug delivery in mechanical ventilation.

In previous studies, NC-Bud formulations successfully navigated endotracheal tubes and a traditional dry powder formula failed³. Novel DPIs were developed to optimize NanoCluster powder delivery through endotracheal tubes. Then, these DPIs were fitted to a catheter and explored as a unique system to bypass the highly variable ventilator environment.

EXPERIMENTAL METHODS
Budesonide suspensions were prepared by wet milling. Particle size and morphology of NC-Bud were evaluated by scanning electron microscopy (SEM). Some formulations were selected for ventilation studies. The studies can be divided into 2 parts; formulation development and device design.

For formulation development, 5-10 grams of micronized budesonide was milled in 200 ml distilled water for 20 hours under an agitation speed of 2772 rpm using YTZ® grinding media (0.5 mm, Tosoh Corp.). After milling, the collected suspension was frozen at -80°C and lyophilized. The formulation was delivered via the Monodose® inhaler or novel devices and then entrained through commercial endotracheal tubes and analyzed by cascade impaction. Ventilator-controlled inspiration flow rates, inspiration patterns, and inspiration volumes were investigated.

New devices (DPI with or without catheter) were investigated by using a Fast Screening Impactor (FSI). The effects of mesh size and inlet/outlet opening size were investigated. The devices were operated at a flow rate of 90 L/min for 2.6 seconds by using negative pressure and also investigated when connected with the ventilator circuit (Figure 1).

RESULTS AND DISCUSSION
NC-Bud formulations had a higher efficiency of aerosol delivery compared to micronized budesonide (Bud) when applied using mechanical ventilation. NC-Bud showed a higher percent emitted fraction (%EF) compared to Bud as received (p<0.05) (Figure 2).

The powder performance of NC-Bud was not affected by ventilator inspiration patterns when applied through a 5.0 mm endotracheal
Figure 2. The distribution of budesonide formulations deposited on the cascade impactor when applied through the endotracheal tubes (ID = 5.0 mm) at a flow rate of 30 L/min.

The percent fine particle fractions (%FPF) of NC-Bud were around 80% at the cut off diameter of 5.7 µm and around 50% at the cut off diameter of 3.3 µm. The mass median aerodynamic diameter (MMAD) of NC-Bud under three different inspiration flow patterns (square, ramp and sine waves) was also not significantly different (p<0.05). Moreover, the performance of NC-Bud did not change with the inspiration volume (1.5 – 2.5 L) nor with the inspiration flow rate (20 – 40 L/min). It is likely, therefore, that the time for emptying the capsule was shorter than the time required for delivering 1.5 L of air through the cascade impactor.

The performance of NC-Bud when applied through the novel device was not significantly different from the performance when applied through the Monodose® inhaler (p<0.05). The MMAD of NC-Bud when applied via the new inhaler was 1.7 ± 0.1 compared to 2.2 ± 0.3 when applied via the Monodose®. The %EF of NC-Bud was around 65% for both.

The novel devices were then modified by varying the size of the mesh and the size of inlet and outlet opening. The resistance of the devices was not significantly different although the size of the mesh was increased from 0.15 mm to 1.00 mm. On the contrary, the resistance of the device increased when the inlet opening decreased from 2.5 mm to 1.5 mm. Surprisingly, the %EF of NanoClusters delivered through these devices was not significantly different when the airflow was provided by negative pressure suggesting efficient performance of the NC-Bud powder itself. The %EF of NC-Bud was lower when applied through a catheter tube with a small outlet (DPIMV7) due to NC-Bud loss in the device.

Figure 3. The amount of NC-Bud deposited on the FSI when applied through the catheter tube (ID = 3.0 mm) at a flow rate of 60 L/min for 2 seconds from outside air supply and 20 L/min from a ventilator.

CONCLUSION
NanoCluster budesonide formulations had a higher efficiency of aerosol delivery compared to micronized budesonide as received when applied through endotracheal tubes. The novel device and the Monodose® inhaler showed the same efficiency of drug delivery but the novel device can connect directly to ventilator tubing. The new device combined with NanoCluster formulation technology allowed convenient and efficient drug delivery through endotracheal tubes or through catheters that bypass the endotracheal tube.

REFERENCES

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