Optimizing the Magnetic Field Mechanism of a Novel Dry Powder Nebulizer for High Dose Delivery

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INTRODUCTION

Development of a novel dry powder nebulizer presents many technical challenges to understand, optimize and control the aerodynamic delivery performance from the device. The novel DryNeb dry powder nebulizer has been designed based on MREs interacting with a main magnet that rotates at a defined speed to create chaotic motion and disperse the medicament inside the drug dosing chamber. This new technology has the potential to deliver pure, excipient-free, micronized drug powders into the lungs with several-fold higher efficiencies than conventional dry powder inhalers (DPIs) and independent of patient inspiratory profile. At the technology's heart is a simple active dispersion engine that utilizes MREs to aerosolize the formulation [1,2]. This new technology serves a dual function solving many of the inherent problems associated with DPIs: (1) it disperses the powder independently from the patient's inhalation force, ensuring reproducible delivery no matter the lung function of the patient; and (2) it is designed to emit powder from the device only when a patient inhales. Importantly, unlike conventional DPIs that require the use of lactose particles as carriers, the DryNeb can use pure drug, allowing the delivery of higher doses [3] and simplification of the formulation development process.

Figure 1 presents the design of the DryNeb that was built and optimized in previous studies. Figure 1a shows the original design where the MREs use chaotic motion to deagglomerate the powder formulations. To date, the performance of the device has been studied using different drugs, with high doses delivered for micronized budesonide (Fine Particle Dose (FPD) >20 mg) and ciprofloxacin (FPD >30 mg). As a secondary dispersion strategy, this study presents the addition of a single-phase coil system intended to generate a magnetic field from the top of the dosing chamber, causing the MREs to oscillate in a vertical plane (Figure 1b). It was hypothesized that a magnetic field applied from the top of the chamber could increase the number of collisions of the MREs with the mesh, thus enhancing re-entrainment and dispersion of material deposited as agglomerates on the mesh surface, resulting both higher ED and FPF.

STUDY AIM

To evaluate the effect of an external single-phase coil intended to generate a magnetic field causing vertical motion of the MREs, promoting additional collisions with the mesh at the top of the drug dosing chamber. The mesh functions to prevent larger agglomerates from exiting the dosing chamber. It was hypothesized that increasing the collisions of the MREs on the mesh can enhance dispersion of the micronized drug and increase delivery efficiency from the device.

NOTE: After completion of the study, issues were identified with the single-phase coil function, which likely explains its limited influence on delivery performance. The elements of the study related to the single-phase coil will be revisited when the coil is fully operational.

EXPERIMENTAL METHODS

The study (DoE) approach to determine the effect of applied magnetic field, frequency of activation and power applied to the coil on drug delivery performance. A third variable, mesh pore size, was also evaluated. Within the bounds of the operating ranges studied, the study was intended to enable prediction of the most effective combination of magnetic field power, field frequency, and mesh size to produce and control delivery of higher Fine Particle Fractions (FPF) from these features of the dry powder nebulizer.

A Box-Behnken Design of Experiments (DoE) approach was used to evaluate the effect of the single-phase coil controllable variables (i.e., frequency of cycles and power applied to the single-phase coil) and the mesh pore size of the mesh on drug delivery performance. The frequency represents how often (i.e., milliseconds) a cycle of north polarity, south polarity, and deactivation of the magnetic field from the single-phase coil occurs. The power represents the percentage of energy applied to the single-phase coil to generate its magnetic field. Finally, different mesh sizes were tested. The mesh is to prevent larger agglomerates being delivered from the dosing chamber.

A fast-screening Impactor (FSI) was used to characterize the aerodynamic delivery performance of the dry powder nebulizer. As responses to the DoE, the FPD, FPF, and ED were calculated and evaluated.

Amphotericin B was used as the drug model for this study, considering its high relevance as a promising treatment for pulmonary fungal infections. The micronized drug was loaded into the device (30 mg) and tested at a flow rate of 60 L/min. The device was actuated 6 times, with each actuation lasting 4 seconds.
The drug deposited on the device and the different sections of the FSI were collected using a 4:1 mixture of Methanol (MeOH)/Dimethyl Sulfoxide (DMSO). Amphotericin B content was assessed using a UV-Vis plate reader (Tecan) at 408 nm wavelength.

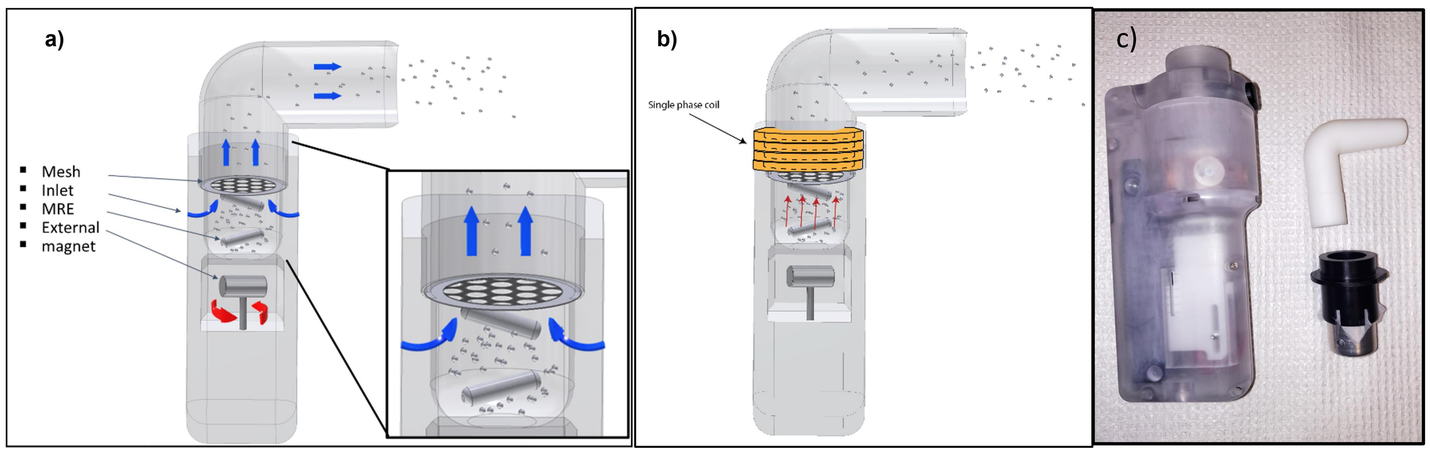

Figure 1. Schematic of the DryNeb Prototype. a) Key components of the device. b) Modified device with external single-phase coil above the mesh c) current DryNeb Prototype.

RESULTS

Both FPF (R^2 = 0.95) and ED (R^2 = 0.91) data exhibited a good correlation with the experimental model enabling prediction of the device input settings that provide optimal delivery. Figure 2 shows the resultant response surfaces obtained for the dry powder nebulizer Emitted Dose performance for the operating ranges studied.

Figure 2 shows the resultant response surfaces obtained for the dry powder nebulizer Emitted Dose (ED) performance for the operating ranges studied.

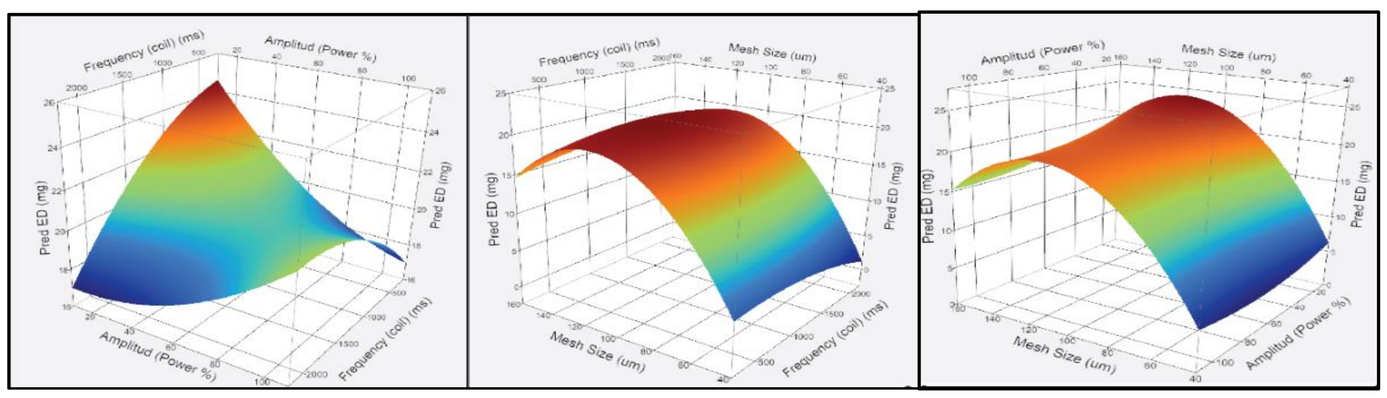

Figure 2. Aerodynamic characterization of Amphotericin B using FSI. The surface response graphs showed (in red) the maximum Emitted Dose (ED) predicted at each combination of variables.

For ED, the mesh size had a strong effect on the overall performance of the device. However, due to the performance issues of the single-phase coil, limited impact on delivery performance was observed related to input power, and magnetic field cycle frequency applied to the coil.
Corresponding response surfaces for the FPF are shown in Figure 3.

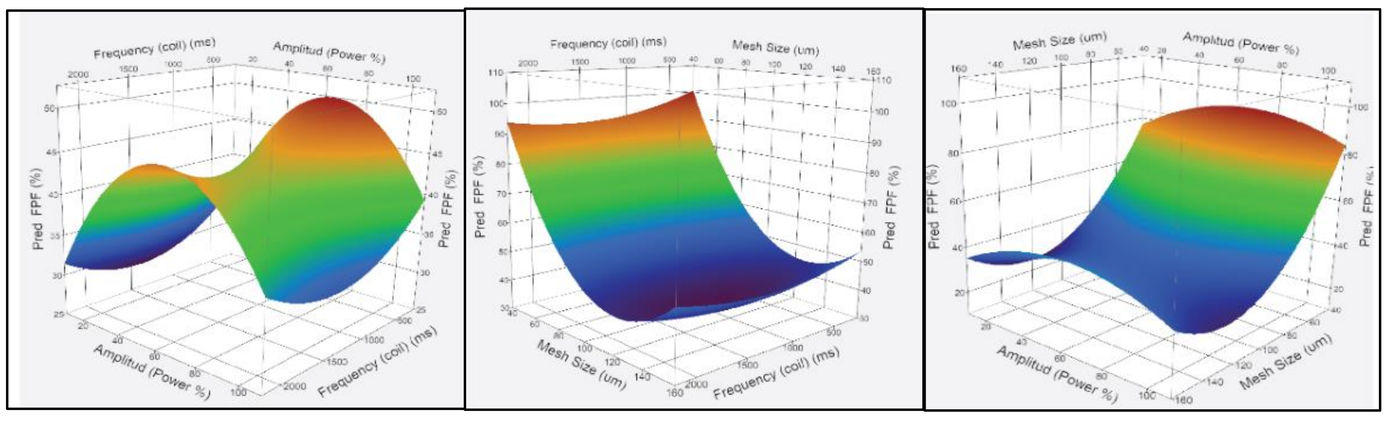

Figure 3. Aerodynamic characterization of Amphotericin B using FSI. The surface response graphs showed (in red) the maximum Fine Particle Fraction (FPF) predicted at each combination of variables.

Overall, the mesh size had a strong effect on increasing the FPF while the power and frequency of the magnetic field cycles applied to the coil had less influence on performance.

Data presented in this study reveals the importance of the pore size of the mesh during the operation of the dry powder nebulizer (DryNeb). The response surfaces from the DoE suggest an optimal design space between 60 and 100 µm for the device when tested with “neat”, excipient-free, micronized Amphotericin B. Higher FPFs, of up to approx. 80%, were predicted for the 60 µm pore size whereas higher EDs were predicted with larger pore sizes. This is likely explained by a balance between the larger pores allowing agglomerate release from the dosing chamber (i.e., increasing the ED), versus the smaller pore size preventing larger agglomerates from being emitted. Limited influence was observed from the introduction of the single-phase coil; however, this will be studied in more detail in subsequent embodiments of the device.

CONCLUSIONS

The mesh pore size had a significant effect on the device delivery performance with predicted FPFs of up to approx. 80% achieved with the DryNeb when tested with “neat”, excipient-free, micronized Amphotericin B.

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