Intranasal Powder Administration of a Spray Dried Tuberculosis Vaccine Candidate Characterized using the Alberta Idealized Nasal Inlet

Brynn Murphy[1], Maximilian Aisenstat[2], Mani Ordoubadi[2], Scott Tavernini[1], Kelvin Duong[1], Jing Zheng[3], Randy Whittal[3], Dominic Sauvageau[4], Christopher Fox[5], Warren Finlay[1], Reinhard Vehring[2], Andrew Martin[1]

[1]Aerosol Research Laboratory of Alberta, University of Alberta, Edmonton, AB, CA
[2]Particle Engineering Research Group, University of Alberta, Edmonton, AB, CA
[3]Mass Spectrometry Facility, University of Alberta, Edmonton, AB, CA
[4]Chemical and Materials Engineering, University of Alberta, Edmonton, AB, CA
[5]Infectious Disease Research Institute (IDRI), Seattle, WA, United States

KEYWORDS: spray drying, vaccine, deposition, in vitro, idealized geometry

INTRODUCTION

Intranasal vaccine delivery is advantageous for generating an immune response as it is non-invasive, and may provide effective protection by mimicking the natural entry route for many pathogens [1]. The objective of this study was to characterize intranasal powder delivery of a novel spray dried tuberculosis vaccine candidate using the Alberta Idealized Nasal Inlet (AINI). *In vitro* methods were developed to coat the internal surfaces of the AINI to control particle bounce.

METHODS

Powder Preparation: Trehalose and vaccine powders were spray dried using a custom research dryer [2]. The vaccine powder adjuvant was a synthetic TLR4 agonist glucopyranosyl lipid adjuvant (GLA) formulated in a squalene-in-water emulsion (SE). No antigen was included in the first round of testing in this study. The GLA-SE adjuvant vaccine powder feedstock concentrations and spray drying process parameters were modified from a previous inhalable version [3] to target nasal delivery. An energy and mass balance model [4] was used to choose spray drying parameters to maximize production rate while preserving the inhalable version's wet glass transition temperature. The trehalose powder was spray dried with similar conditions. Feedstock and particle compositions are shown in Table 1, and spray drying process parameters are shown in Table 2.

Table 1. Feedstock concentrations and particle compositions of trehalose and vaccine powders.

Component	Vaccine Powder Composition		Trehalose Powder Composition	
	Feedstock (mg/ml)	Particle (% w/w)	Feedstock (mg/ml)	Particle (% w/w)
Trehalose	200	81	200	100
Tris (Buffer)	2.42	1	0	0
Squalene	34.4	14	0	0
DMPC	7.6	3	0	0
GLA	0.1	0.04	0	0
Vitamin E	1.0	0.4	0	0

Table 2. Process parameters used for spray drying vaccine and trehalose powders.

Parameter	Setting
Drying gas flowrate (SLPM)	700
Inlet Temperature (°C)	70
Twin-fluid Atomizer Gas Pressure (kPa)	138
Liquid Feed Flowrate (ml/min)	3.1
Predicted Outlet Temperature (°C)	48.2
Predicted Outlet RH (%)	6.9
Predicted Powder Moisture Content (%)	1.3
Predicted Wet Glass Transition Temperature (°C)	96
Predicted Evaporation Rate ($\mu m^2/ms$)	4.0

Device Filling: The Aptar Pharma Unidose Powder System (UDSp), a single use, primeless nasal drug delivery device, was used for testing. Devices were filled with 10 mg, 20 mg, or 40 mg trehalose powder, or 20 mg vaccine powder, according to manufacturer instructions.

Experimental Apparatus: Regional deposition and the fraction of powder penetrating the AINI were measured using the experimental setup displayed in Figure 1. To mitigate particle bounce, two AINI coatings were tested [5]: 20% Tween 20 in glycerol (v/v), and 1 ml of a Brij solution (3 g Brij:20 ml Ethanol) in 5 g glycerol. A mixing inlet and pre-separator (Copley Scientific, UK), and breathing filter (AG Industries, USA) were positioned in series downstream of the AINI.

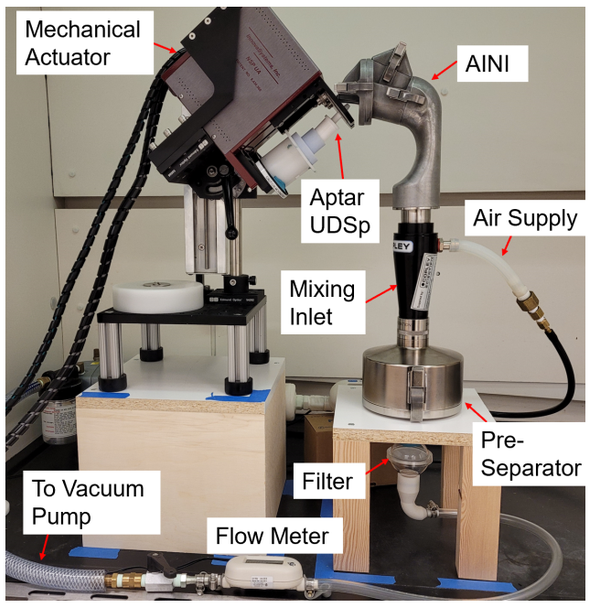

Figure 1. Annotated image of the experimental setup.

Experimental Procedure: An automatic actuator (NSP UA, InnovaSystems Inc., USA) was used with actuation parameters supplied by Aptar Pharma. The actuator was adjusted to achieve a 45-degree angle between the device tip and the inlet plane of the vestibule. The height of the actuator was adjusted so that the device would insert 2.5 to 5.0 mm into the vestibule on actuation. Quiet inhalation of 7.5 ± 0.1 L/min through the AINI [6,7] was simulated by drawing 30.0 ± 0.1 L/min through the pre-separator using a vacuum pump while supplying 22.5 ± 0.1 L/min of room air to the mixing inlet. At this 30 L/min flow rate, the cut point for the pre-separator is 15 µm [8]. A crystallization dish and cotton swab were used to collect any fraction of the dose that escaped out of the nostril during testing, described below as the residual fraction. The tip of the device was wiped with the cotton swab after actuation, and each sampling region was washed thoroughly with 80:20 deionized water: methanol. The amount of trehalose deposited in each region was determined using LC-MS/MS (MRM). The limit of quantification (LOQ) for this assay was 1 ng/µl.

RESULTS AND DISCUSSION

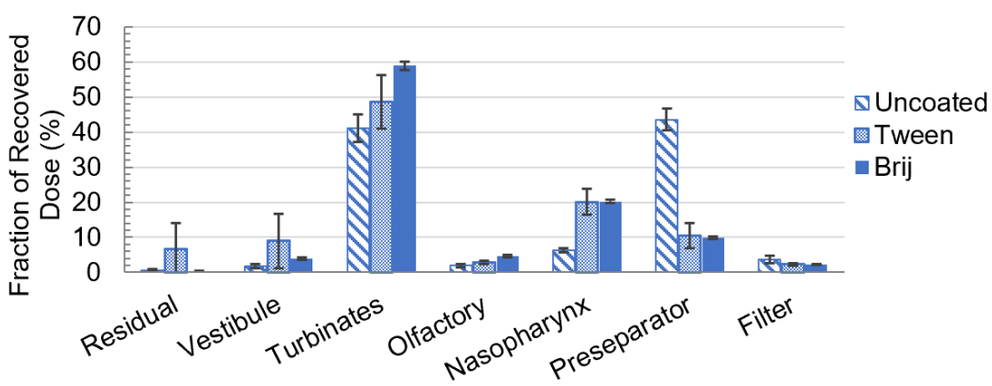

Figure 2. Mean recovered trehalose from 40 mg doses of trehalose powder actuated into the uncoated, Tween coated, and Brij coated AINI. Error bars represent one standard deviation of three repeated experiments.

Figure 2 displays a comparison of coated and uncoated deposition results for the 40 mg dose. Notably, high pre-separator recovery for the uncoated case indicates large particles (>15 μm in aerodynamic diameter) penetrated the AINI, likely due to particle bounce off AINI surfaces. Coating the AINI surfaces reduced recovery from the pre-separator. Similar results were observed at 10 mg and 20 mg doses.

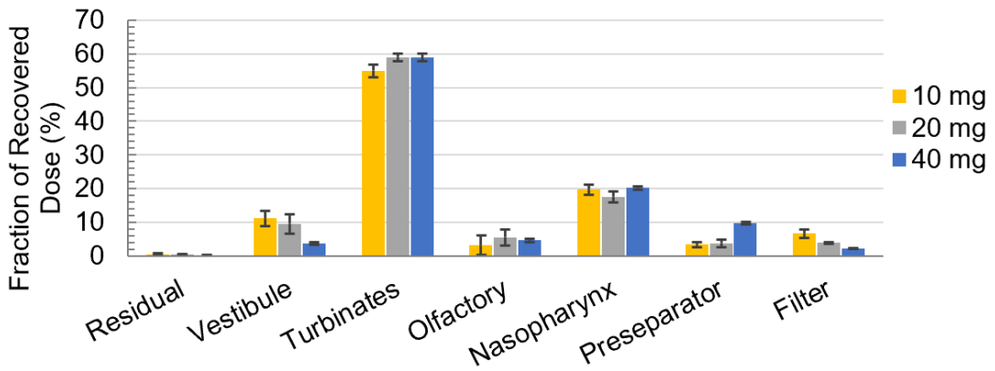

Figure 3. Mean recovered trehalose for 10 mg, 20 mg, and 40 mg doses of trehalose powder actuated into the Brij-coated AINI. Error bars represent one standard deviation of three repeated experiments.

Figure 3 compares the deposition profiles for different powder doses in the Brij-coated AINI. Mean mass recovery was good for 40 mg and 20 mg doses, at 96.1 ± 8.4% and 93.8 ± 5.1%, respectively. However, recovery was lower for the 10 mg dose, at 86.5 ± 1.4%, likely due to the small amount of powder. One of three 10 mg runs was outside the 100 ± 15% recommendation by the Food and Drug Administration [9]. Low pre-separator recovery indicates bounce was well controlled at 10 mg and 20 mg doses. Higher pre-separator recovery for the 40 mg dose may be due to surface overload (in the vestibule region) despite coating. Increased filter deposition at lower doses may reflect more efficient powder deagglomeration for lower device fill weights.

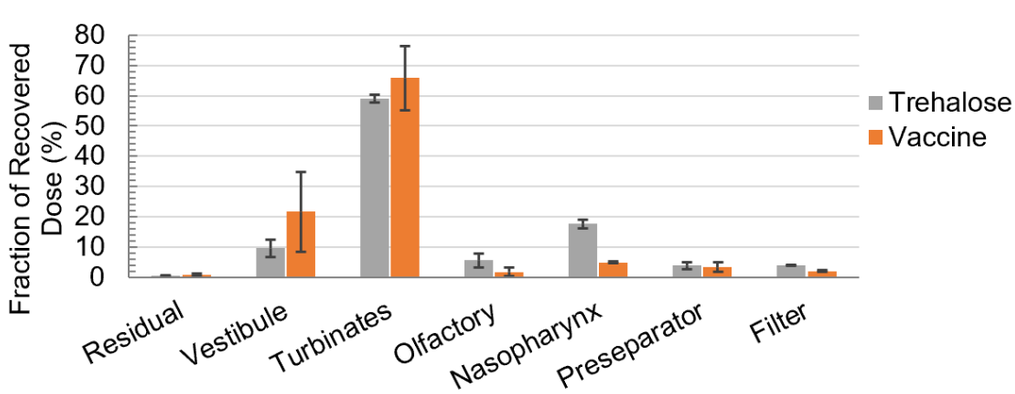

Figure 4. Mean recovered trehalose from 20 mg doses of trehalose powder and vaccine powder actuated into the Brij-coated AINI geometry. Error bars represent one standard deviation of three repeated experiments.

Figure 4 compares the mean trehalose recovery for the trehalose powder and the vaccine powder. Higher deposition in the anterior of the AINI and lower filter recovery suggest that the vaccine powder is more cohesive than the trehalose powder, which aligns with observations made during testing.

CONCLUSIONS

Coating AINI surfaces using the methods examined here appears to provide effective mitigation of particle bounce. Delivery of spray dried powders for intranasal vaccine administration shows promise for the tuberculosis vaccine candidate studied here and merits further exploration.

ACKNOWLEDGMENTS

This study was funded by the National Institutes for Health and supported by the Infectious Disease Research Institute. The authors also thank Aptar Pharma for donating the UDSp devices used in this study.

REFERENCES

1. Wilkins JV, Golshahi L, Rahman N, Li L: Evaluation of Intranasal Vaccine Delivery Using Anatomical Replicas of Infant Nasal Airways. *Pharmaceutical Research* 2021, 38: 141–53.

2. Ivey, J.W., Bhambri, P., Church, T.K., Lewis, D.A., Vehring, R.: Experimental Investigations of Particle Formation from Propellant and Solvent Droplets Using a Monodisperse Spray Dryer. *Aerosol Science and Technology* 2018, 52(6), 702-16.

3. Gomez M, McCollum J, Wang H, Bachchhav S, Tetreau I, Gerhardt A, Press C, Kramer RM, Fox CB, Vehring R: Evaluation of the stability of a spray-dried tuberculosis vaccine candidate designed for dry powder respiratory delivery. *Vaccine* 2021, 39(35): 5025-36.

4. Ivey JW, Vehring R: The use of modeling in spray drying of emulsions and suspensions accelerates formulation and process development. *Computers and Chemical Engineering* 2010, 34(7): 1036-40.

5. Mitchell JP: Practices of Coating Collection Surfaces of Cascade Impactors: A Survey of Members of the European Pharmaceutical Aerosol Group (EPAG). In *Drug Delivery to the Lungs* 2003. The Aerosol Society. London, UK: 2003: 75–8.

6. Chen JZ, Kiaee M, Martin AR, Finlay WH: In vitro assessment of an idealized nose for nasal spray testing: Comparison with regional deposition in realistic nasal replicas. *International Journal of Pharmaceutics* 2020, 582: 119341.

7. Chen J, Martin AR, Finlay WH: Recent in vitro and in silico advances in the understanding of intranasal drug delivery. *Current Pharmaceutical Design* 2020, 27: 1482–97.

8. Marple VA, Olson BA, Santhanakrishnan K, Mitchell JP, Murray SC, Hudson-curtis BL. Next Generation Pharmaceutical Impactor (A New Impactor for Pharmaceutical Inhaler Testing). Part II: Archival Calibration. *Journal of Aerosol Medicine* 2003,16: 301–24.

9. U.S. Food and Drug Administration. Guidance for Industry Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action [Internet]. 2003. Available from: http://www.fda.gov/cder/guidance/index.htm