Development of a spray-dried inhalable dry powder presentation of a Tuberculosis vaccine candidate with demonstrated long term physical stability at high temperatures for use in developing countries

Mellissa Gomez[1], Joseph McCollum[2], Hui Wang[1], Mani Ordoubadi[1], Nicholas B. Carrigy[1], David Barona[1], Shital Bachchhav[1], Isobel Tetreau[1], Michelle Archer[2], Alana Gerhardt[2], Chris Press[2], Ryan M. Kramer[2], Christopher B. Fox[2], Reinhard Vehring[1]

[1]University of Alberta, Edmonton, Canada; [2]Infectious Disease Research Institute, Seattle WA, USA

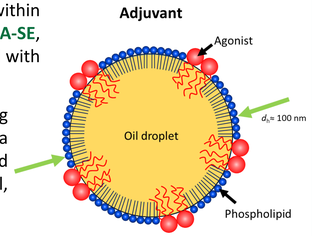
Introduction

Two key issues hindering the ability to safely and effectively distribute vaccines in the developing world are the cold chain maintenance required by many vaccines and the problems associated with needle delivery. Complex vaccine formulations can be encapsulated and stabilized within thermostable microparticles suitable for pulmonary delivery through spray drying. An adjuvanted tuberculosis vaccine, ID93+GLA-SE, was spray dried into a dry dosage form designed for administration with a dry powder inhaler. This presentation was placed on a stability study and assessed for aerosol performance and vaccine integrity after one year of storage.

Materials & Methods

Powders suitable for inhalation must be within respirable range and highly dispersible. **ID93+GLA-SE**, formulated as a nanoemulsion, was spray dried with a **trehalose-trileucine** excipient system.

Trehalose was chosen as the main stabilizing excipient and trileucine was chosen as a dispersibility enhancing agent. A low feed concentration was used to generate small, respirable particles.



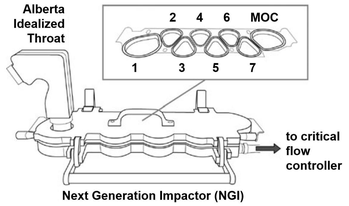
$$d_a = \sqrt[6]{\frac{\rho_P}{\rho^*}^3}\sqrt{\frac{c_F}{\rho^*}}d_D$$

An inlet temperature of 65 °C and drying gas flow rate of 200 SLPM was chosen to achieve a low outlet temperature of 36 °C and low outlet relative humidity of 7%. These previously developed spray drying parameters targeted minimized processing loss and maximized long-term physical stability at room temperature storage [1].

Resulting powder consisted of 78%, 3% trileucine, 2% Tris buffer and 17% ID93+GLA-SE, by mass.

Particle morphology, aerosol performance, and adjuvant and antigen stability was assessed over one year at various storage temperatures.

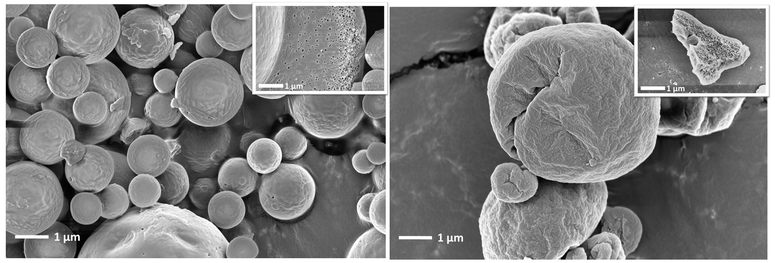
Aerosol performance of the powder was measured using a commercial low resistance dry powder inhaler (Seebri Breezhaler®), with a throat model attached to an impactor [2].



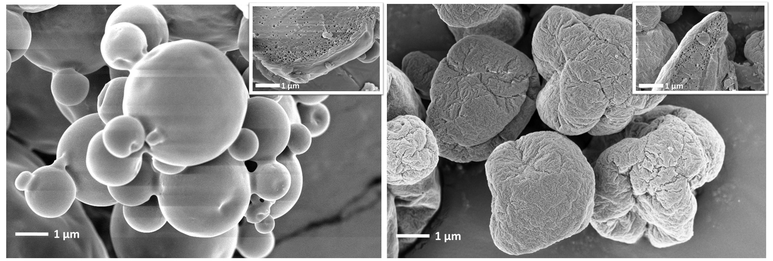
Results

Control (without trileucine) **Spray-dried Vaccine (with trileucine)**

Timepoint 0

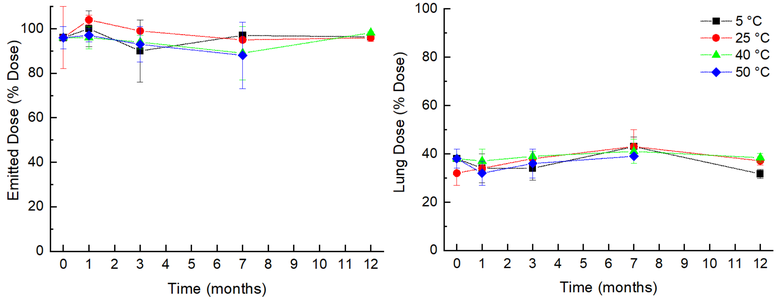


12 months of storage at 40 °C



- **Nanoemulsion droplets were successfully encapsulated within the particle wall**
- **Addition of trileucine to the spray dried vaccine resulted in preservation of particle morphology even after 12 months of storage at 40 °C**

Aerosol Performance



- **Emitted dose (left) and lung dose (right) was maintained for the trileucine-containing spray dried vaccine even after 12 months of storage at 40 °C**

Vaccine Stability

Sample	Storage Length	Storage Temperature	Emulsion Size Change	Oil Retention	Agonist Retention	Antigen Retention
Liquid Vaccine [3]	3 months	37 °C	110%	-	0%	0%
Spray-Dried Vaccine	3 months	40 °C	23%	89%	66%	50%
	1 year	25 °C	31%	95%	85%	44%
		40 °C	33%	81%	0%	49%
		50 °C	71%	55%	0%	43%

- **Stabilization of the vaccine via spray drying greatly enhanced vaccine retention for storage above refrigerated temperatures**

Conclusions

The addition of **trileucine** to the spray dried vaccine powder formulation improved **physical stability**.

The trileucine-containing spray dried vaccine powder demonstrated **excellent aerosol performance** that was maintained even after **long term storage** at **high temperatures**, suggesting reliable administration.

The tested excipient formulation successfully **improved thermostability** of the ID93+GLA-SE vaccine, reducing need for cold temperature storage.

References

1. M. Gomez, M. Archer, D. Barona, H. Wang, M. Ordoubadi, S. Bin Karim, N. B. Carrigy, Z. Wang, J. McCollum, C. Press, A. Gerhardt, R. Kramer, C. Fox and R. Vehring, "Microparticle Encapsulation of a Tuberculosis Subunit Vaccine Candidate containing a Nanoemulsion Adjuvant via Spray Drying," European Journal of Pharmaceutics and Biopharmaceutics, 2021.

2. M. Gomez, J. McCollum, H. Wang, M. Ordoubadi, C. Jar, N. B. Carrigy, D. Barona, I. Tetreau, M. Archer, A. Gerhardt, C. Press, C. B. Fox, R. M. Kramer and R. Vehring, "Development of a formulation platform for a spray-dried, inhalable tuberculosis vaccine candidate," *International Journal of Pharmaceutics*, vol. 593, p. 120121, 2021

3. R. M. Kramer, M. C. Archer, N. Dubois, N. Dubois Cauwelaert, E. A. Beebe, P.-w. D. Huang, Q. M. Dowling, A. M. Schwartz, D. M. Fedor, T. S. Vedvick and C. B. Fox, "Development of a thermostable nanoemulsion adjuvanted vaccine against tuberculosis using a design-of-experiments approach," International Journal of Nanomedicine, vol. 13, pp. 3689-3711, 2018.

Acknowledgements

UNIVERSITY OF ALBERTA
IDRI
NIH National Institute of Allergy and Infectious Diseases