Expedited Biologic Formulation and Spray Drying Process Development via Mechanistic Modeling

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Introduction

- Spray drying for pharmaceutical production: fast and cost-effective [1].
- Spray dried biologics e.g., protein, bacteriophages: improved thermal stability and shelf-life [2].
- Particle engineering combined with mechanistic models applied and demonstrated to expedite the development of biological formulation

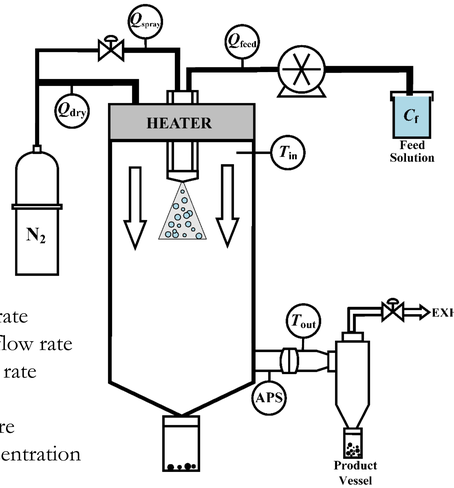
Materials and Methods

❖ Materials:

- ❑ Trehalose: excipient and glass stabilizer
- ❑ Trileucine: surface-active shell former
- ❑ Bacteriophage CP30A: a *Myoviridae* known to be present in the chicken feces that is capable of infecting Campylobacter *jejuni*
- ❑ Tuberculosis vaccine: a recombinant protein ID93 comprised of four *Mycobacterium tuberculosis* (Mtb) antigens and stabilized in the form of a nano-emulsion (~ 90 nm) consisting of squalene oil, DMPC (dimyristoyl-sn-glycero-3-phosphocholine), Tris 7.5, and GLA (glucopyranosyl lipid A).

❖ Methods:

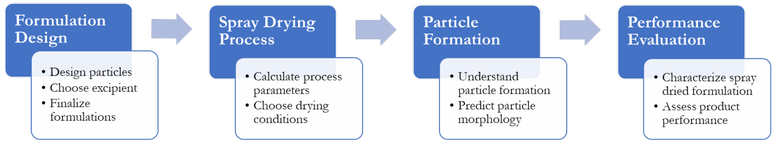
- ❑ Spray drying



- Q_{dry}: drying gas flow rate
- Q_{spray}: dispersing gas flow rate
- Q_{feed}: liquid feed flow rate
- T_{in}: inlet temperature
- T_{out}: outlet temperature
- C_f: feed solution concentration

Results

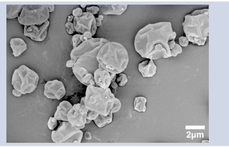
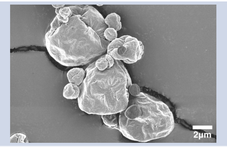
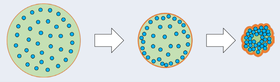
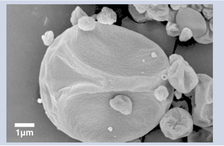
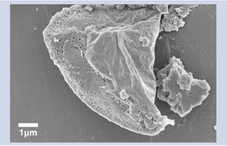
❖ Application of mechanistic models



❖ Formulation and Processing Conditions

Active Biologics	Bacteriophage CP30A	Tuberculosis Vaccine ID93
Formulation Targets	Dry powder phage formulation with low titer reduction and long-term storage stability.	Dry powder vaccine formulation with long-term storage stability and high respirable delivery efficiency.
Spray Dryer	Modified Büchi B-191	Custom-built Dryer
Total Solids Concentration	~ 104 mg/mL	42 mg/mL
Formulation	Trileucine (4 mg/mL) Trehalose (100 mg/mL)	Trileucine (1.3 mg/mL) Trehalose (33.4 mg/mL)
Air-Liquid-Ratio	9	8
Predicted Droplet MMAD	~ 9 µm	~ 8 µm
Dryer Inlet Temperature	70 °C	65 °C
Predicted Outlet Temperature	49 °C	36 °C
Predicted Dryer Outlet Relative Humidity	3%	7%
Predicted Particle Median Volume Equivalent Diameter	3.9 µm	3.2 µm

❖ Performance of spray dried phage and vaccine formulations

Biologic	Phage Formulation	Vaccine Formulation
Spray Dried Particle Morphology		
Particle Formation Schematic		
Particle Surface Structure		
Spray Dryer Condition	Outlet temperatures matched predictions within 2°C during the spray drying processes of both formulations.	
Particle Size	• Consistent with predicted volume equivalent diameter	• Matched particle size prediction • Particles within inhalable range (1-5 µm)
Dry Powder Formulation Performance	• Dispersible powder • High production rate and yield (>53%) • Overall phage titer reduction after formulation, spray drying, 1-month dry room temperature storage, and reconstitution for plaque assay < 1.0 $\log_{10}$(pfu/mL) [3]	• Dispersible powder • High production rate and yield (>70%) • After reconstitution of dried powder o <5% squalene and GLA content loss; o <5% nano-emulsion droplet size change; o Retention of vaccine antigen ID93; • Promising applicability for respiratory drug delivery (> 95% emitted dose, > 30% lung dose, >10% FPF tested in vitro by Next Generation Impactor)
Storage Stability	• Demonstrated physical stability at room temperature (amorphous > 4 months)	• Physical stability at different temperatures after 1 month (5°C, 25°C, 40°C, 50°C)

Conclusions

Mechanistic models proved useful for informed selection of appropriate **excipients**, **formulations**, and **process conditions**, expediting the CMC (chemistry, manufacturing, and control) development process, as fewer experiments were required than would be for an empirical or statistical design approach.

References

[1] Boraey MA, Vehring R. J Aerosol Sci 2014, 67:131-143.
[2] Walters RH, Bhatnagar B, Tchessalov S, Izutsu K-I, Tsumoto K, Ohtake S. J Pharm Sci 2014, 103:2673-2695.
[3] Carrigy NB, Liang L, Wang H, et al. Ann Biomed Eng 2020, 48:1169-1180.

Acknowledgements

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