Advancing Inhaled Biologics: Investigating Croda's Excipients for Enhanced Pulmonary Delivery

Tina Baharlou

Newcastle University

Introduction and Objectives

Pulmonary delivery of biologics poses significant opportunities for delivery of a range of therapeutics. Biologics such as monoclonal antibodies and RNA-based therapeutics offer high specificity and potency, but their delivery to the lungs via inhalation is limited by stability issues. Shear stress during nebulisation can cause protein unfolding and aggregation, affecting efficacy and safety. The addition of excipients are typically used to overcome these challenges yet their applicability for these applications have yet to be realised.

The main aims of this project are:

- To evaluate the effect of excipients on Human IgG stability during mesh nebulisation.
- To synthesise and characterise LNPs encapsulating double-stranded RNA (as a model therapeutic) as an alternative delivery platform.
- To assess changes in particle size and stability before and after nebulisation.

Methods

Protein Formulation

Human IgG was formulated in aqueous phosphate buffer with three excipients: Polysorbate 20, Polysorbate 80, and Polyoxyl 35 Castor Oil, at concentrations ranging from 0.01% to 0.1%. Formulations were nebulised using a mesh nebuliser, and samples were collected pre- and post-spray. Particle size and polydispersity were analysed using DLS to assess aggregation.

LNP Formulation

LNPs were prepared using a microfluidic system to encapsulate a model dsRNA. Formulations included cationic and helper lipids dissolved in ethanol and mixed with aqueous dsRNA under controlled flow rates. Post-synthesis, dialysis was performed to reduce ethanol content. Particle size and uniformity were measured before and after nebulisation.

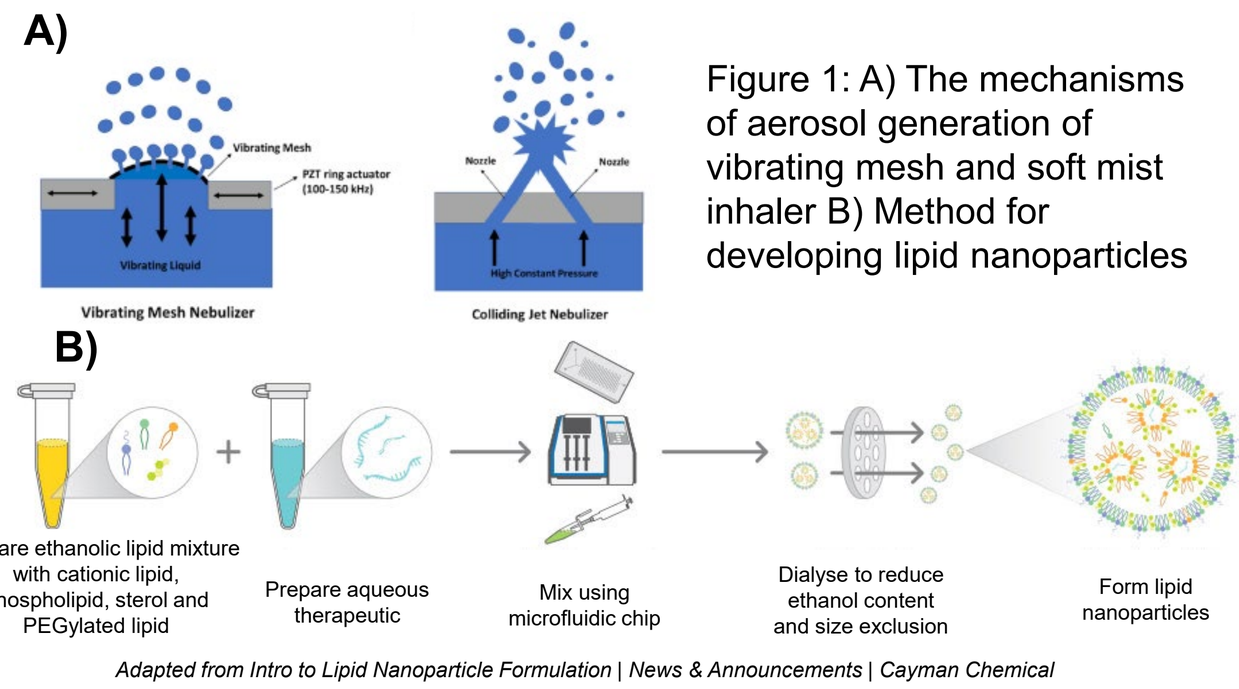


Figure 1: A) The mechanisms of aerosol generation of vibrating mesh and soft mist inhaler B) Method for developing lipid nanoparticles

Adapted from Intro to Lipid Nanoparticle Formulation | News & Announcements | Cayman Chemical

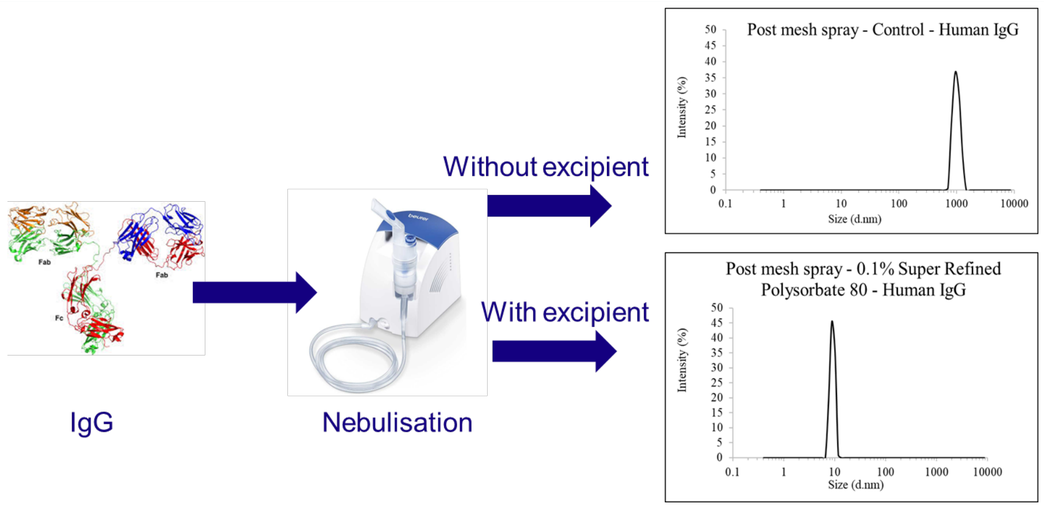
Results

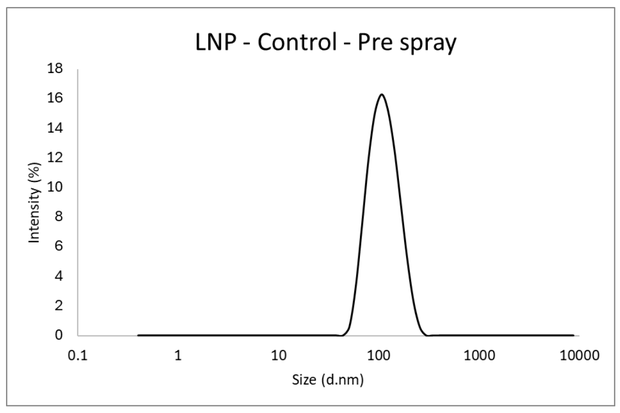
Protein Formulation

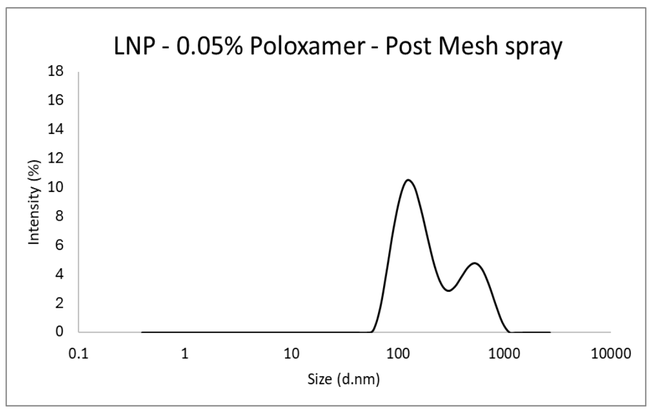
DLS analysis revealed an increase in particle size after nebulisation across all formulations, indicating aggregation. Among the tested excipients, 0.1% Super Refined Polysorbate 80 provided the greatest reduction in aggregation. However, this concentration is at the upper end of the marketed concentration for inhaled therapeutics, limiting its practical application in final formulations.

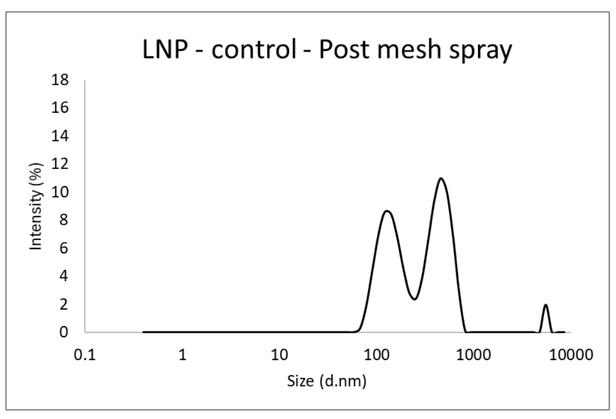
LNP Characterisation

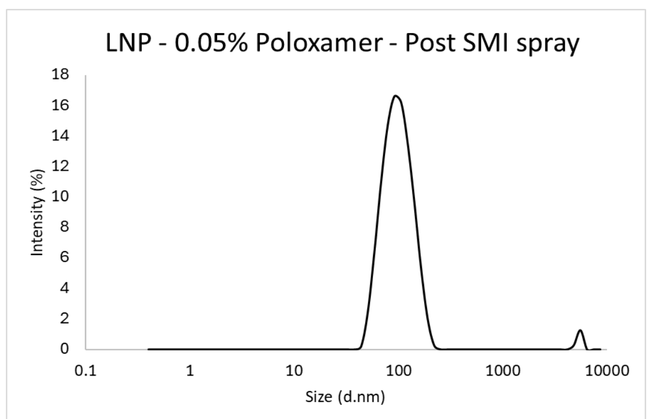
LNPs showed improved particle size uniformity post-dialysis however, nebulisation led to an increase in particle size and visible changes in appearance from opalescent to milky, indicating potential aggregation. This highlights a need for further optimisation to improve LNP stability under shear stress. The addition of surfactant did not stabilise the LNP post-nebulisation using mesh nebuliser but using soft mist inhaler (SMI) there was a consistent particle size.











Conclusion

While excipients showed some ability to reduce aggregation in protein formulations, none were fully protective. The best-performing excipient, Super Refined Polysorbate 80, was limited by toxicity at effective concentrations. Similarly, LNPs were promising in pre-spray stability, but their post-spray aggregation suggests they are sensitive to mesh nebulisation. Formulation and device-related factors both need further refinement.

This study highlights the challenges of delivering biologics via inhalation, particularly protein aggregation during nebulisation. Similarly, excipients in IgG formulations were more effective when used with soft mist inhalers compared to mesh nebulisers. These findings emphasise the importance of both formulation optimisation and device selection to ensure the stability of inhaled biologics.

References

1. J. S. Patton and P. R. Byron, Nature Reviews Drug Discovery, 2007, 6, 67–74.
2. M. Paranjpe and C. Müller-Goymann, International Journal of Molecular Sciences, 2014, 15, 5852–5873.
3. J. Eicher, J. Eicher, B. Zierenberg and R. Dalby, Medical Devices: Evidence and Research, 2011, 145.

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