Investigating phase behaviour of lipid-water-ethanol systems in lipid nanoparticle (LNP) formation

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Lipid nanoparticles (LNPs) are used as drug delivery systems, attracting much attention after their successful application in nucleic acid therapeutics including mRNA vaccines [1]. LNPs are manufactured through mixing of ethanolic lipid solutions and aqueous solutions containing nucleic acid therapeutic payloads, typically using microfluidic mixers due to their controllable and reproducible mixing conditions. Molecular self-assembly of LNPs results from the complex interplay of constituent material properties and process parameters related to solution composition, temperature, and mixing[2]. However, the process of self-assembly during mixing remains a "black-box" model requiring further research and understanding of this interplay to enable rational process development to enhance scalability and therapeutic advancements.

The aim of this project is to gain insight into the phase behaviour of LNPs by developing phase diagrams for the self-assembly process using a frequently used constituents: SM102, DSPC, Cholesterol, and DMG-PEG2000. Firstly, by establishing lipid constituent solubility in ethanol and binary water-ethanol miscible environments, we map out suitable concentration ranges LNP manufacturing. Secondly, we investigate their phase behaviour as the environment changes (e.g., water-ethanol ratio, pH, and ionic strength) and its impact on self-assembly. Lastly, we develop a phase diagram that identifies environments for stable LNP formation using widely used lipid constituents.

These findings will aid further development of process models for controlling the manufacturing process to tailor manufacturing to desired outcomes enabling faster production, reduced waste, and better control and scalability. This can be applied to enhance development of LNPs as drug delivery systems in therapeutics.

Keywords:
Lipid Nanoparticles, Phase Diagram, Pharmaceuticals, Drug Delivery

References:

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