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Liposome Sterile Filtration Fouling: The Impact of Transmembrane Pressure on Performance

Authors : Hercules Argyropoulos, Thomas F. Johnson, Nigel B Jackson, Kalliopi Zourna, Daniel G. Bracewell

Abstract : Lipid encapsulation has become essential in drug delivery, notably for mRNA vaccines during the COVID-19 pandemic. However, their sterile filtration poses challenges due to the risk of deformation, filter fouling and product loss from adsorption onto the membrane. Choosing the right filtration membrane is crucial to maintain sterility and integrity while minimizing product loss. The objective of this study is to develop a rigorous analytical framework utilizing confocal microscopy and filtration blocking models to elucidate the fouling mechanisms of liposomes as a model system for this class of delivery vehicle during sterile filtration, particularly in response to variations in transmembrane pressure (TMP) during the filtration process. Experiments were conducted using fluorescent Lipoid S100 PC liposomes formulated by micro fluidization and characterized by Multi-Angle Dynamic Light Scattering. Dual-layer PES/PES and PES/PVDF membranes with 0.2 µm pores were used for filtration under constant pressure, cycling from 30 psi to 5 psi and back to 30 psi, with 5, 6, and 5-minute intervals. Cross-sectional membrane samples were prepared by microtome slicing and analyzed with confocal microscopy. Liposome characterization revealed a particle size range of 100-140 nm and an average concentration of $2.93x10^{11}$ particles/mL. Goodness-of-fit analysis of flux decline data at varying TMPs identified the intermediate blocking model as most accurate at 30 psi and the cake filtration model at 5 psi. Membrane resistance analysis showed atypical behavior compared to therapeutic proteins, with resistance remaining below 1.38×10^{11} m^{-1} at 30 psi, increasing over fourfold at 5 psi, and then decreasing to 1-1.3-fold when pressure was returned to 30 psi. This suggests that increased flow/shear deforms liposomes enabling them to more effectively navigate membrane pores. Confocal microscopy indicated that liposome fouling mainly occurred in the upper parts of the dual-layer membrane.

Keywords : sterile filtration, membrane resistance, microfluidization, confocal microscopy, liposomes, filtration blocking models
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