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# Effects of Sterol Modified Lipids on Molecular Packing in Lipid Monolayers

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Liposomal drug delivery is a promising, effective therapeutic approach; it has been used for COVID-19 vaccines as well as cancer therapies. However, most liposomal formulations lack the needed stability for long enough circulation prior to reaching the target or getting cleared out of the blood stream. To mitigate this shortcoming, current liposomal formulations use cholesterol as a stabilizing agent. However, cholesterol tends to rapidly exchange out of liposomes, eventually compromising liposomal stability. This study investigates sterol-modified lipids (SMLs) as substitutes for cholesterol for the purpose of improving liposomal stability. Using Langmuir compression isotherms, we compared the packing properties of lipid monolayers rich with SMLs and cholesterol. Therefore, we collected data from two lipid mixtures: (1) 1-palmitoyl-2-oleoyl-glycero-3-phosphocholine (POPC) with cholesterol, and (2) POPC with 1-palmitoyl-2-cholesterylhemisuccinoyl-sn-glycero-3-phosphocholine (PChemsPC). Our results show that both cholesterol and SMLs induce a condensing effect in POPC monolayers, manifested in tighter molecular packing than theoretically predicted. These results are confirmed by Gibb's free energy analysis which shows more favorable interactions in POPC-PChemsPC mixtures compared to POPC-cholesterol mixtures. Combined with our neutron spectroscopy studies of the mechanical properties of liposomes with equivalent compositions, we find a strong correlation between molecular packing and liposomal stability. These findings provide a molecular-level rationale for the use of SMLs as superior candidates in the design of more stable liposomal carriers for drug/vaccine delivery applications.

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