Multi-scale Molecular Simulations of Polymer - Ion Pair Amphiphile Complexes

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Ion pair amphiphiles (IPAs), molecular complexes of oppositely charged surfactants, can serve as cost-effective phospholipid analogs for drug delivery. While IPA vesicles exhibit tunable phase behavior, their practical application is often limited by low colloidal stability and complex co-assembly mechanisms with therapeutic payloads. In this study, we integrated coarse-grained molecular dynamics (CG-MD) simulations with refined theoretical models to systematically investigate the structural modulation and stabilization of IPA-based carriers. Our results demonstrate that the colloidal stability of IPA vesicles can be significantly enhanced through polymer incorporation. We identified that polymer charge density, chain length, and rigidity are the primary determinants of vesicle-vesicle interactions; specifically, stiffer and longer polymers promote efficient bridging effects, which can be harnessed to control vesicle fusion kinetics and morphology. Furthermore, our simulations reveal that using explicit charge models is crucial for accurately capturing the realistic self-assembly transitions from micelles to bilayers driven by molecular geometry and IPA cross-interactions. Extending our framework to biopolymer-IPA complexes, we examined the interaction mechanisms of Hyaluronic Acid (HA) and Ribonucleic Acid (RNA). We found that while HA adsorption is sensitive to specific functional group orientations, RNA binding is primarily driven by long-range electrostatic attraction and stabilized by hydrogen bonding between IPA headgroups and RNA nucleobases. Notably, steric hindrance limits the involvement of the RNA backbone in these interactions. Overall, this work provides a comprehensive design framework for engineering robust, polymer-stabilized IPA platforms capable of efficiently delivering diverse biopolymeric therapeutics.

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