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Internal liquid crystal structures in nanocarriers containing drug hydrophobic ion pairs dictate drug release

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Hypothesis: Hydrophobic ion pairing (HIP), a solubility engineering technique in which ionic hydrophilic molecules are paired with a hydrophobic counterion, is an attractive strategy for encapsulating ionic water-soluble species into nanocarriers (NC). Drug release from NCs containing HIP complexes is sensitive to ionic strength, pH, and drug:counterion charge ratio, but the exact mechanism for this was unknown, as was the underlying microstructure inside the NC. We hypothesize that HIP complexes arrange into liquid crystalline structures in NC cores and that these structures are responsible for salt- and pH-dependent release.

Experiment: A model hydrophobic ion pair from the cationic antimicrobial peptide polymyxin B sulfate and the anionic counterion sodium oleate is encapsulated into ~100nm NCs formed using Flash NanoPrecipitation (FNP) and stabilized with an amphiphilic diblock copolymer, poly(caprolactone)-b-poly(ethylene glycol). Internal structures are observed by synchrotron small-angle X-ray scattering (SAXS) and transmission electron microscopy (TEM) following NC formulation and are found to vary with polymyxin:oleate charge ratio. In vitro drug release is also measured at two pHs and two charge ratios.

Findings: For a formulation containing a four-fold charge excess of oleate relative to polymyxin, internal structures rearranged from a lamellar phase into an inverse hexagonal phase. The hexagonal phase formation corresponds to a greatly reduced rate of polymyxin release, suggesting that the polymyxin was incorporated into the center of hexagonally-packed rods. When release tests are repeated using phosphate-buffered saline (PBS) at pH 2.0 to ensure protonation of the oleic acid, all internal structures are eliminated and release occurs much faster than at neutral pH, regardless of charge ratio. These findings shed light on the mechanism behind stimulus-responsive drug release from systems containing hydrophobic ion pairs and enable the rational design of controlled-release formulations by manipulating the formation and dynamics of liquid crystalline phases inside NCs.

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