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Aggregation Behavior of Indomethacin, Cholic Acid and POPC

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Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used class of drugs for the treatment of inflammation, fever and pain. One of their major side effects, especially if used chronically, is ulceration and bleeding of the lower gastrointestinal (GI) tract. It has been reported that NSAIDs cause surface injury by perturbing the integrity of membranes of the intestinal mucosa which can be abrogated by phosphatidylcholine (PC). Moreover, it has been shown that the toxic effect of NSAIDs to the lower gut is related to the presence of bile acid, suggesting that the mixture, not NSAID alone, constitutes the agent that destabilizes lower-gut membranes in a COX-independent manner. Several biochemical studies further indicated that NSAIDs form mixed micelles with bile salts. NSAIDs may also alter the physiological balance of bile acids and phospholipids in the lumen of the small intestine. In order to understand the molecular mechanism by which NSAIDs form mixed micelles with bile salts, and to understand how NSAID-bile salt interaction might be modulated by phospholipids, we studied the binary and ternary mixtures of indomethacin (one of the most commonly used NSAIDs), cholate (a bile salt) and palmitoyloleoylphosphatidylcholine (POPC) lipid in a various molar ratios. Initial results from extensive all-atom molecular dynamics simulations indicate that the binary mixtures have distinct aggregation behaviors and morphology than the ternary mixtures, providing clues about the physical basis for the toxicity of NSAID/Cholic Acid mixtures and how this might be modulated by phospholipids.