distributions within lipid carriers [125]. Hence, coarse-grained MD simulations were done on a liposome containing more than 2500 lipids indicating various drug loading degrees. Hypericin was used as the drug molecule (commonly applied for the photodynamic treatment) to penetrate the membrane bilayers. Simulations of 10 μs were run on liposomes including 21 − 84 hypericin molecules. The distributions and orientations of hypericin molecules in the lipid bilayers and average force potentials needed to transfer them from aqueous inner droplets across the liposome bilayers were estimated.

11. MICELLES AS DRUG DELIVERY SYSTEMS

Polymeric micelles are amphiphilic block copolymers that are self-assembled structures in aqueous solutions exhibit exceptional characteristics such as large drug loading, biocompatibility, and high in vivo stability which make them beneficial drug carriers [126]. Micelles applied to deliver anticancer drugs illustrated extraordinary properties such as improved targeted drug release, high chemotherapeutic effectiveness, and lower undesirable drug side effects. Hydrophilic and hydrophobic regions in amphiphilic copolymers form diverse micelles for application in delivery of genes, proteins, therapeutics, and drugs [127]. Such copolymers form core-shell nanostructures by inter- and intra-molecular interactions. Polymeric core-shell micelles contain hydrophobic cores covered by hydrophilic shells that are widely used nanobiotechnology and pharmaceutical areas. Micelles can be derived from both natural and synthetic polymers. Usually, natural polymers are more advantageous as they are nontoxic, biodegradable and biocompatible [128].

Polymeric micelles are broadly examined as drug vehicles but it is necessary to understand their detailed morphological changes on drug loading [128]. It has been shown that rods, bilayers, spheres, vesicles and cylinders are created by changing the composition of block copolymer, solvent, interactions of blocks, ionized blocks, pH and temperature [129]. Consequently, investigating mechanisms occurred during formation of micelles as drug carriers are vital because such information assists to recognize their structural and morphological variations at microscopic levels.

To explore structural and dynamical features of polymer micelles, several techniques can be utilized including UV-visible and fluorescence spectra, dynamic light scattering, transmission and scanning electron microscopies [129]. Nevertheless, it is hard to get comprehensive data on the self-assembly and transformation mechanisms of polymer micelles using such analyses as the micelles are formed at nanoscale. Hence, computational simulations are complementary tools to the experimental methods that afford more information to understand the morphology variation, distribution and dynamics of the systems. For example, the mechanism of drug carrier formation within aqueous media is explored with more details by mesoscopic simulations instead of using experimental approaches [130]. However, among typical methods of mesoscopic simulations, the MD simulations provide time scales that are too short to allow micelle formation and simulations at the atomic level is highly costly [131]. Thus DPD allowing very larger length scales and time steps is favorably applied to simulate very complex coarse-grained systems. In fact, the DPD simulations are used as an effective and systematic technique to study the formation mechanisms and microstructures of different polymer micelles [132].

MD simulations were accomplished on the solubilities of hydrophobic drug compounds Cucurbitacin I (CuI) and Cucurbitacin B (CuB) within poly(ethylene oxide)-*b*-poly(α-benzyl carboxylate ε-caprolactone) (PEO-*b*-PBCL) block copolymers indicating diverse tacticities [133]. Particularly, a di-block copolymer of various three tacticities, that is, PEO-*b*-aPBCL, PEO-*b*-sPBCL, and PEO-*b*-iPBCL was utilized. Binary random mixtures containing 10 wt% of drugs were used to calculate the solubility values. The solubilities of the two drugs were highly dependent on the di-block copolymer tacticity. MD simulations exhibited that only PEO-*b*-sPBCL was soluble but the two others did not reveal solubility. As the drugs experimentally indicated solubility into the PEO-*b*-PBCL, the experimentally synthesized di-block copolymer was expected to display syndiotactic tacticity. Such prediction was confirmed by the results obtained from the ring opening polymerizations of cyclic lactones dominantly yielded syndiotactic polymers using stannous octoate catalyst to synthesize PEO-*b*-PBCL block copolymers. MD simulations revealed that the drugs solubilities within the PEO-*b*-sPBCL was dependent on the intramolecular and intermolecular interactions of drugs and di-block copolymer molecules that were investigated by the RDF data.

MD simulations were done on a DDS containing one PEO-b-3PCL block copolymer composed of three blocks of poly(ε-caprolactone) (PCL) with identical lengths attached onto one end of poly(ethylene oxide) (PEO) block that encapsulated two groups of hydrophobic drugs having diverse structures [134]. The first group of drugs was two CuI and CuB cucurbitacin