drugs containing several hydrogen bonding acceptors and donors uniformly located on these structures but another group of drugs were nimodipine and fenofibrate principally only containing clustered hydrogen bonding acceptors. The PEO-*b*-3PCL including cucurbitacin drugs exhibited substantially improved drug solubility than the PEO-*b*-PCL di-block linear copolymer having a PCL:PEO ratio of 1. Nevertheless, a contrast result was achieved for the nimodipine and fenofibrate drugs. The intermolecular interactions confirmed that much more hydrogen bonds were formed among the cucurbitacin drugs and 3 PCL blocks compared with those of the di-block linear copolymer. Also, as the hydrogen bond donors are absent and the hydrogen bond acceptors are clustered onto the nimodipine and fenofibrate drugs, the hydrogen bonds created within the multi-PCL block milieu were considerably decreased and afforded undesirable solubility values. Thus copolymers with multiple hydrophobic blocks highly increased loading of hydrophobic drug molecules on which several hydrogen bond acceptors and donors were uniformly dispersed.

MD simulations were carried out in water at 1 atm and 298.15 K on a spherical micelle formed using *N*-acetylated poly(ethylene glycol)-poly(γ-benzyl L-glutamate) (PEG-PBLG-Ac) amphiphilic block copolymers, containing 9 BLG and 11 EG units, that were used as drug carriers [135]. Calculations were done on the spherically arranged copolymers and reached the equilibrium indicating somewhat elliptical micelle composed of a PBLG hydrophobic interior core with a PEG hydrophilic external shell. PEG blocks in the micelle showed dense helical conformations and the PBLG blocks revealed R-helical forms. Numerous hydrogen bonds formed by the water solvent molecules led to stabilization of the helix conformations for the PEG blocks so that they became hydrated and this was proved with extended residence times for the water molecules around the oxygen atoms of PEG ether than that of the pure water. Several water molecules were dispersed in the hydrophobic core that displayed constant exchanges by the pure water throughout the simulations. The molecules generally formed clusters in places among the copolymers that created hydrogen bonds with themselves and the hydrophobic core by hydrophilic amides and esters groups. The micelle formed hydrogen bonds with water molecules that greatly stabilized its structure.

Hybrid polymer micelles were designed as drug carriers containing combined corona chains of polyethylene glycol (PEG) and poly(L-glutamic acid) (PLGA) (Fig. 20) [136]. The water-soluble PLGA random coils in acidic solution were changed to water insoluble α-helices that caused micro-phase separated micelle coronas and creating PEG channels. The channels connected the interior core and the external shell that enhanced the drug diffusivity from the micelles into the solution. The PEG-*b*-PPO and PLGA-*b*-PPO-*b*-PLGA formed micelles in water, where PPO was poly(propylene oxide). The PPO blocks in the two block copolymers were aggregated throughout their self-assembly to cores enclosed with corona mixed chains of PEG and PLGA blocks. Such structures were characterized by zeta potential, nuclear magnetic resonance spectra, dynamic light scattering, and circular dichroism spectra. As well, MD simulations were accomplished to investigate the structures of hybrid micelles as DDSs indicating preserved colloidal stability along with adjustable release rates. The release rates were controlled with micelle structures, mixture compositions and other factors like pH.

12. CONCLUSION

Computational modeling methods provide valuable tools to design and develop diverse drug carriers with improved features including nanoparticles, polymers and polymeric nanocomposites, graphene and its analogues, fullerenes, carbon nanotubes and its derivatives, DNAs, proteins, peptides, micelles, and liposomes. The efficacy of these systems is mostly dependent on their drug loading capacities, drug release rates, and blood stability. MD simulations afford very important full data on carriers' structures and interactions occurred among them and with drug molecules under different physical and chemical environments. MD simulations are complimentary to the experimental results because they provide quantitative and microscopic information about the mechanisms of experimentally happened phenomena. Also, then are able to recognize limiting elements in different systems that aid to find the optimized formulations. So far, DPD and CG approaches have been used in MD simulations to investigate the properties of various drug carriers. Atomistic MD procedures have restricted length and time scales of some nanometers and microseconds but the DPD and CG approaches are more appropriate to simulate submicron scales for several hundreds of microseconds that neglect atomistic information for both of carrier and drug. Hybrid CG and atomistic approaches gives a favorable method for the scales problem as they take benefits of the two procedures. Although the carriers' stability and loading are central parameters for their development, another fundamental factor is carriers' interactions with the biological membranes. These investigations offer in-depth