Molecular Design of Micelles for Drug Delivery Purposes

Maria Velinova[1], Y. Tsoneva[1], D. Sengupta[2], A. Ivanova[1], S. J. Marrink[2], A. Tadjer[1]

[1] Faculty of Chemistry, University of Sofia, 1126 Sofia, Bulgaria.
E-mail: maria.velinova@chem.uni-sofia.bg;
[2] Faculty of Mathematics and Natural Sciences, University of Groningen,
9747 Groningen, the Netherlands.

The cell membrane is largely resistant to most of the present chemotherapeutics and to all alien proteins and DNA; therefore, the utilization of the endocytic pathway for intracellular transfer seems unfeasible. The design of reliable, effective and risk-free artificial systems for transport through the cell membrane will overlay the road to new pharmaceutical approaches for treatment of presently incurable diseases. Suitable candidates for such systems are micelles formed by ethers of oligo(ethyleneglycol)s and fatty alcohols (C_xEO_y) [1]. A change in the ratio of ethyleneglycol units and methylene groups modifies the hydrophilic-hydrophobic balance in the molecule and thereof the propensity to formation of supramolecular aggregates.

One of the purposes of the present study is to derive from first principles calculations and test molecular mechanics parameters for such ethers to be used in subsequent all-atom simulations of micelles formation. Monomers and dimers with two different types of periphery, which are short-chain prototypes of the amphiphilic surfactant $C_{12}(EO)_5$, were used as model systems. The geometry of low-energy conformers are obtained with modified OPLS and optimised with PBEPBE/aug-cc-pVTZ in vacuum and in implicit solvent. Convincing validation of the derived parameters provided the comparison between the density, molecular volume, enthalpy of solvation and vaporisation obtained from molecular dynamics (MD) simulations (Amber99/NPT/300 K) of diethyl ether and the existing experimental data.

On the other hand, the water solution of nonionic surfactants $C_{12}(EO)_5$ and their capacity to pack antimicrobial peptides (AMPs) and transport the latter across a bilayer are investigated on coarse-grained level with MARTINI coarse-grained (CG) force field [2]. The structural aspects of the amphiphilic organization in explicit aqueous medium is obtained from the simulation data for model micelles built of various number of $C_{12}(EO)_5$ molecules. Micelle shape, stability and water penetration into the hydrophobic core is acquired thereof. Examination of the results for the selected micelle permits the establishment of size-stability relationship. Finally, a small AMP is incorporated in one of the stable micelle and subject to CG MD simulation. Alongside with analysis of structural features, the stability of the formed $(C_{12}(EO)_5)_n$/peptide complex is evaluated by means of binding energy assessment.

References

1. E. Mileva, P. Tchoukov, D. Exerowa, *Adv. Colloid & Interface Sci.* 47 (2005) 114.
2. H. Lee, A. H. de Vries, S. J. Marrink, R. W. Pastor, *J. Phys. Chem. B* 113 (2009) 13186.