

Towards modern drug carriers: physicochemical characterization of protein using simulation and experiment

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Nanotechnology, especially nanomedicine is a rapidly growing field that has captured worldwide attention. A large number of nanoparticle drug delivery systems have been developed for cancer treatment. Natural biomolecules such as proteins are an attractive alternative to synthetic polymers which are commonly used in drug formulations. Protein nanoparticles are biocompatible, biodegradable, metabolized and are easily amenable to surface modifications to allow attachment of drugs and targeting ligands. Many drugs molecules are known to bind to albumins. This work focusses on bovine serum albumin (BSA), because of its structural homology with human serum albumin (HSA) - their tertiary structures are 76% similar. The understanding of how the protein interacts with model surfaces is of major interest in both fundamental research and applications such as nanomedicine. One of the new promising composite device for protein controlled delivery is silica surface due to its weak interactions with proteins. Despite the constant development of research in biomedicine, there are few systematic reviews about protein adsorption from a molecular point of view.

The use of precise, analytical techniques such as multi-parametric surface plasmon resonance (MP-SPR) and quartz crystal microbalance with dissipation monitoring (QCM-D) allowed us to determine the structure of the layers formed on a nanometric scale under precisely defined and controlled conditions (concentration, ionic strength, pH). A combination of QCM-D and MP-SPR complementary techniques has provided crucial information on the mechanisms behind the protein- silica surface interaction, protein structural changes and biomolecular rearrangements. Both the kinetics of BSA deposition and the maximum surface concentration were determined. The dependence of the maximum coverage on the pH, ionic strength and the experimental kinetic runs were quantitatively interpreted in terms of the Random Sequential Adsorption model. It is shown that using the SPR measurements, one can determine the mechanisms of BSA adsorption, namely the reversibility and orientation of molecules at interfaces. Furthermore, from the comparison of the MP-SPR and QCM-D data we have estimated the hydration of the film on the silica surface.

We combine our experimental measurements with fully atomistic molecular dynamics (MD) simulations to gain new insight into the BSA adsorption on silica surfaces. The simulation work is challenging due to the negative charge on both the BSA and silica under physiological conditions, nevertheless we are able to examine in detail how the protein interacts with surface. In particular, we make strong predictions about the orientation of the adsorbed BSA and its conformational stability. We discuss how the simulations help the interpretation of our experimental observations. These results are essential for designing an alternative scheme for drug delivery systems.

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