ITC of mixed micelle systems and micelle-protein interactions

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Detergents are widely used excipients in liquid pharmaceutical formulations. Polysorbates for example are able to stabilize biologicals in their functional state, thus providing enough stability to guarantee an appropriate shelf-life. Further, detergent micelles, formed through self-assembly, are a promising platform to formulate hydrophobic substances in aqueous environments. Clear, thermodynamically stable solutions can be achieved by encapsulation of hydrophobic drugs in the hydrophobic environment of the micellar core. Protein stabilization, as well as micellar solubilization are realized in several licensed pharmaceuticals.

However, for both applications some pivotal mechanisms remain unclear. Different mechanisms of protein stabilization by polysorbates like preferential exclusion, covering of interfaces and surfaces or direct surfactant-protein interactions were hypothesized but the exact processes are unknown. Investigations are complicated by the complex association behavior of polysorbate 20. As a result of the commercial product containing a diverse mixture of polyoxyethylene esthers and esterified fatty acids, it differs essentially from the usual concept of one characteristic type of micelle forming above the CMC. Similarly, little is known about the fate of micellar solutions after intravenous administration. Dilution effects may promote the breakdown of the micellar components and interactions with plasma proteins of both the micellar components and the drug substance are likely to occur. Understanding of the state of these systems in vivo can help to create improved formulations. In particular, this involves (i) comprehension of the association behavior, (ii) micellar breakdown and (iii) the interactions between micelle components and proteins.

Isothermal titration calorimetry (ITC) is a powerful technique to assess the self-assembling properties of those systems, as well as their interactions with proteins. The high sensitivity and resolution of ITC allows to monitor the complete thermodynamic picture of aforementioned processes.

This project aims at understanding the mechanisms of surfactant-protein interactions. Hence, important information on stabilizing mechanisms, as well as likely occurring effects of micellar systems in the human body can be gained. For this purpose, model systems based on buffered protein solutions are created. Micellization, demicellization, as well as surfactant-protein interactions are studied using ITC.