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Extended Abstract

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Innovative surfactants as stabilizers of membrane proteins for structural studies in solution

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Membrane proteins (MPs) account for 25-30% of proteomes and present over 70% of the pharmaceutical targets. MPs play key roles in the transport of a large panel of compounds through the cell membrane. The presence of MPs in the hydrophobic cell membrane makes them difficult to be isolated in their functional forms and to be crystallized for further steps to a 3D-structure resolution and ultimately to be used as targets in the structure-based drug design approaches. As a consequence, membranes proteins account for less than 5% of the 3D-structures resolved. In this context, surfactants (detergents) are used as key components during the extraction and structural studies of MPs. Detergents are required for maintaining MPs in solution for crystallography needs. Unfortunately, major detergents tend to unfold these proteins as they are in fast-exchange equilibrium with micelles, weakening the compactness of the membrane region and leading to a partial-to-severe loss of functionality. Based on the concept that the vast majority of membranes proteins share a net enrichment in basic residues at the interface between membrane and cytoplasm, a property known as the positive-inside rule, we conceived a new class of detergents based on this feature, which, in addition to their capacity to interact with membranes proteins through hydrophobic interactions, will have the additional capacity to generate a network of salt bridges around the membrane region with these basic residues. Our main focus will deal with the design, the chemical synthesis and the outcome of new generation of detergents for the extraction, stabilization and crystallization of membrane proteins. Macromolecules are essential cellular components in biological systems responsible for performing a large number of functions that are necessary for growth and perseverance of living organisms. Proteins, lipids and carbohydrates are three major classes of biological macromolecules. To predict the structure, function, and behaviour of any cluster of macromolecules, it is necessary to understand the interaction between them and other components through basic principles of chemistry and physics. An important number of macromolecules are present in mixtures with surfactants, where a combination of hydrophobic and electrostatic interactions is responsible for the specific properties of any solution. It has been demonstrated that surfactants can help the formation of helices in some proteins thereby promoting protein structure formation. On the other hand, there is extensive research towards the use of surfactants to solubilize drugs and pharmaceuticals; therefore, it is evident that the interaction between surfactants with macromolecules is important for many applications which includes environmental processes and the pharmaceutical industry. In this review, we describe the properties of different types of surfactants that are relevant for their physicochemical interactions with biological macromolecules, from macromolecules–surfactant complexes to hydrophobic and electrostatic interactions. Surfactants are amphiphilic molecules capable of reducing the surface tension between two immiscible phases. These molecules are either chemically produced (synthetic surfactants) or based on biological materials (biosurfactants). The reduction of surface tension is due to their amphiphilic properties, as their molecules consist of both hydrophilic and hydrophobic moieties. The hydrophilic part contains heteroatoms such as oxygen, sulphur, nitrogen and phosphorous, which appear in functional groups such as alcohol, thiol, ether, ester, acid, sulphate, sulfonate, phosphate, amine, amide, etc., while the hydrophobic part is typically a paraffin, cycloparaffin or aromatic hydrocarbon, which may contain halogens. Due to their dual affinity, amphiphilic molecules are not stable either in polar or in organic solvents. To meet both types of affinities, the hydrophilic moiety must be surrounded by a polar solvent, while the hydrophobic moiety must be in contact with an organic solvent. Such conditions exist only between two immiscible phases. The boundary between a condensed phase and a gaseous phase is referred to as a surface, and the boundary between two condensed phases such as two liquids or a liquid and a solid, is referred to as an interphase. Many properties of surfactants depend on this strong affinity for surfaces or interphases. Chemical surfactants are derived from non-biodegradable components, and in some cases can cause serious problems to the environment, the formation of foams which inhibit or paralyze natural (or artificial) purification processes, concentrate impurities and can spread bacteria or viruses, the increase of phosphate content in basins, from polyphosphates that are used in combination with surfactants.Given the problems caused by synthetic surfactants, different studies have been carried out over the past years, seeking to find alternative products compatible with the environment and have demonstrated the feasibility of producing these compounds from microorganisms. Most microbial biosurfactants are typically biodegradable, biocompatible and have stable activities under extreme environmental conditions. Hence the interest to study their production from fungi and bacteria, among which the genera *Bacillus* and *Pseudomonas* stand out. Many of these biosurfactants produced by *Pseudomonas aeruginosa* have been characterized and studied as agents capable of removing hydrophobic compounds from soil, antimicrobials and biofilm disruptors. Although the physicochemical properties of (bio) surfactants have been well documented through the years, their interaction with biological components has had less focus. This review therefore focuses on the properties of surfactants that are relevant for their physico-chemical interactions with biological systems, and when possible compare them with their biological counterparts.

The study of the interactions between surfactants, both synthetic and microbial (biosurfactants), with proteins is of great interest in various biotechnology fields and industries such as food, cosmetics, pharmaceutical, biomedical, and environmental. In the biomedical industry, protein–surfactant systems are used for the production of hydrogels The hydrogels form the base of fibrous proteins such as fibroin, which are used for tissue regeneration and drug delivery. There are three main forces that drive the protein–surfactant interaction: (1) electrostatic, (2) hydrophobic and (3) Van der Waals. The dominant interaction is determined by the nature of both molecules and their concentration. These molecular interactions have an influence on the native structure of proteins promoting or preventing denaturation, aggregation and loss of enzymatic activity among other factors. Surfactants of biological origin have an advantage over synthetic surfactants in terms of their ability to prevent denaturation of proteins and a reduction in their aggregation. The protein–surfactant systems mainly studied are those that contain globular proteins such as bovine serum albumin (BSA), α-lactoglobulin and β-glucosidase. In contrast, very few studies have been performed exploring the fibrous protein–surfactant systems. Type I collagen, silk fibroin, and keratin are fibrous proteins that have been studied in combination with ionic and non-ionic surfactants. A few studies suggest that the molecular interactions presented by fibrous proteins (collagen, fibroin, keratin) in combination with ionic and non-ionic surfactants are similar to the globular protein–surfactant systems.

Bottom Note: *This work is partly presented at* 6th World Congress on NATURAL PRODUCT & SYNTHETIC CHEMISTRY June 24-25, 2019 | New York, USA.