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Molecular simulation of biosurfactants with relevance to food systems

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ABSTRACT

The application of molecular modelling, and in particular all-atom and coarse grained molecular dynamics simulation, to the study of low molecular weight surfactants with relevance to food systems is reviewed. Two key aspects of surfactant behaviour — their ability to form micelles and their tendency to adsorb to fluid–fluid interfaces (air–water and oil–water) are covered. Since the modelling literature on synthetic amphiphilic surfactants is vast, and much of it not directly relevant to foods, the review concentrates on biosurfactants. Two particular topics are covered in detail: the behaviour of bile salts because of the importance of these in understanding food digestion; the behaviour of novel glycolipid and lipopeptide surfactants derived from microorganisms (bacteria and yeast) due to their increasing importance as functional ingredients in consumer products including foods.

1. Introduction

Surfactants are molecules that have the ability to adsorb at the interfaces between two phases (e.g. air–water, oil–water or liquid–solid), thus lowering the interfacial tension and stabilising the interface. Surfactants are often classified as low molecular weight or polymeric. Polymeric surfactants, such as proteins are out with the scope of this review which will cover only low molecular weight surfactants.

Low molecular weight surfactants are used for a range of applications in the food industry that exploit their surface active and solution properties [1]. These make use of their ability to adsorb to air, oil and solid interfaces to aid in the formation of foams and emulsions or to lubricate solid particles thus altering the flow properties of their solutions, and to form bilayer and micellar structures in foods. Common examples of food grade surfactants are lecithin, mono and diglycerides, sorbitan esters (SPANS) and polyoxyethylene sorbitan esters (Tweens) [1]. The experimental literature on the properties of surfactants is vast. More recently, researchers have made increasing use of molecular simulation methods to complement experiments in an attempt to better relate molecular features to physical properties. Although the literature on simulation of low molecular weight surfactants is extensive, there are few studies that specifically set out to look at surfactant containing model food systems. For this reason, this aspect of the surfactant simulation literature will only be reviewed briefly, with emphasis on indicating where further information can be found. Rather, the review will concentrate on two recent topical areas of study on surfactants that have a relevance to food systems, namely the surface and self-association behaviour of bile salts, and the growing importance of biosurfactants such as glycolipids. Although bile salts are not added directly as food ingredients, they have been studied widely over the past few years due to their importance in food digestion. Microbial biosurfactants are a novel class of surfactants that are receiving lot of attention due to their "natural" sustainable nature. This means that they are an appealing alternative to synthetic surfactants in food systems.

2. Micellization and adsorption of surfactants

The solution and adsorption properties of surfactants are an obvious target for simulation studies. The molecules are easy to represent in simplified algorithm form due to their amphiphilic structure and the two-component nature of surfactant solutions is highly amenable to the simulation approach. Low molecular weight surfactants are able to form a number of self-association structures depending on the physicochemical conditions and concentration. Micelles are important in food systems, but not the only structure formed, with bilayers and liquid crystalline phases being the main structures formed by many low molecular weight surfactants in foods. However, for bile salt modelling covered in a later section, the micelle is the most important solution structure, and so emphasis in this section is on the general properties and modelling of surfactant micelles, to serve as an introduction to bile salt micelle modelling in Section 3.1.

Surfactant micelles can be characterised using two parameters; the critical micelle concentration (CMC) and the aggregation number. The concentration in solution at which micellar aggregates just start to form defines the CMC. The aggregation number is the average number

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of surfactant molecules found in the micelle at the CMC. Much of the simulation effort to date has focused on understanding the formation of micelles, characterising the CMC and aggregation number, how this links to micelle structure and relating this back to experimental observation and functional/physicochemical properties. This work has often focused on surfactants that are not relevant in foods or food grade surfactants in systems not directly related to foods. For this reason, and because the amphiphilic surfactant modelling literature is very extensive it will not be reviewed here. Those interested in these systems are referred to recent reviews of simulation studies of surfactant micellization [2,3] and simulation of adsorption of surfactants to interfaces that have recently been reviewed elsewhere [4•].

3. Bile salts

Bile acids are biological surfactants synthesised from cholesterol in the liver and stored in the gall bladder. They are released as their sodium salts in the mixture bile, which is involved in the digestion of triglyceride fats and oils in the gut. There are a number of bile salt structures found in bile. The primary bile acids, cholic acid and chenodeoxycholic acid are synthesised from cholesterol by enzymic oxidation [5]. Secondary bile salts deoxycholic acid and lithocholic acid are formed when intestinal bacteria dehydroxylate the primary bile acids. Some of these four bile acids are re-adsorbed into the blood stream, and returned to the liver where they can be re-secreted to the gall bladder or conjugated with either the amino acid glycine or the amino sulphonic acid taurine. Bile salt molecules are comprised of a fused five and six membered tetracylic ring steroid core. In cholesterol the sterol ring is flat. In bile salts the presence of a hydroxyl group where two of the six-membered rings fuse, leads to bending of the steroid core due to extra steric strain. The bile salts of the human gut differ in two ways. Firstly, they can be dihydroxy or trihydroxy derivatives, based on how many hydroxyl groups are found on the sterol ring. The position of the attached hydroxyl groups can also vary. Secondly, they can be conjugated to glycine or taurine, or no conjugation is present. In addition to the hydroxyl substituents methyl groups are also attached to the steroid core. The hydrophobic methyl and hydrophilic hydroxyl groups are oriented such that the two different substituent types are on opposite sides of the steroid rings, thus giving the bile salts a bi-facial amphiphilic structure, with a hydrophilic (OH) and hydrophobic (CH_3) face.

In the human gut the majority of fat is digested in the duodenum, and this is where bile is secreted through the bile duct. The bile salts have an important function in the digestion of fat [6]. As surfactants bile salts are able to emulsify fat, thus increasing the surface area available for digestion, whilst at the same time displacing proteins from the surface of the fat droplets [7••,8•]. The latter aids the adsorption of lipases to the oil–water interface, thus facilitating triglyceride hydrolysis. After fat hydrolysis, the bile salts form so-called dietary mixed micelles (DMMs) with cholesterol and phospholipids [9]. The DMMs act as carriers of free fatty acids formed from the lipolytic digestion of triglycerides in the gut along with other fat soluble molecules. They achieve this by solubilising the products of lipolysis in the hydrophobic core of the micelle, and then transporting these to the intestinal wall where release of the fatty acids and their adsorption into the cells of the intestinal wall occurs [6].

3.1. Micelle formation in bile salts

The structure of the micelle is important in controlling both solubilisation of fatty acids and facilitating adsorption, but the detailed structure and the mechanism by which micelles form are still under discussion. Bile salt micelles are not considered to be spherical like those of amphiphilic surfactants [10]. The reason for this is believed to be the structure of the bile salt molecules. The bifacial amphilicity that they possess plays a significant role in the self-assembly of bile salts into micelles and the structure of the micelles. It is more difficult to pack bile salts into a micelle compared to amphiphilic surfactants. This limits the size of bile salt micelles due to restrictions in the number of hydrophobic contacts that the individual molecules can make, and thus the micelles are smaller than the spherical micelles of amphiphilic surfactants. There is much debate over the mechanism of micelle formation and in particular over whether bile salts have a single CMC, show a two-stage self-association process with two CMC's or lack a CMC altogether and have a continuous self-association at all concentrations [11]. Early models of self-association, such as that proposed by Carey & Small [12] put forward the hypothesis that at low concentrations bile salts form small, primary micelles held together by hydrophobic interactions, followed by subsequent self-association through hydrogen bonding of the primary micelles into larger secondary micelles once the concentration exceeds a second CMC (Fig. 1). It has proven difficult to rationalise the self-association mechanisms experimentally, but recent simulations have thrown some light on the situation. For some time the favoured mechanism has been the two-stage association process. Evidence for this has been cited as the observation that hydrogen bonds are found in bile salt micelles [13]. All atom-molecular dynamics simulations have been carried out that support this mechanism [14–16]. Partay, Jedlovszky & Sega [14,16] simulated sodium cholate (NaC) and sodium deoxycholate (NaDC) micelle formation at three concentrations, 30 mM (close to the CMC), 90 mM and 300 mM. The NaDC simulations are in full agreement with the two-stage association model. At low concentration (30 mM) only small oligomeric primary aggregates form with these primary aggregates held together by only hydrophobic interactions. At higher concentrations the primary aggregates associate into secondary micelles held together by hydrogen bonds. With NaC, on the other hand, simulations suggest that hydrogen bonded oligomers as well as hydrophobic oligomers can form at low concentration, and these associate into mixed secondary micelles at higher concentration. The secondary micelles have the same basic structure in both NaC and NaDC systems, but only the NaDC micelles appear to form via the mechanism suggested by Carey & Small [12]. Partay, Sega & Jedlovszky [15] extended this study to look at the detailed morphology of the primary and secondary micelles and the relationship to bile salt structure. The primary aggregates of cholate micelles were found to be disk-like, flat or oblate, whilst NaDC primary micelles were predominantly spherical [15]. This was explained in terms of the differences in amphilicity of the two molecules. The hydroxyl groups are arranged on the edge of the ring in the NaDC molecule thus giving a hydrophilic edge to the tetracyclic ring. In NaC on the other hand these are arranged on one face of the tetracylic ring. This means that face to face conformations of NaDC are less favourable than those of two NaC molecules, and this modifies the primary micelle structures. The NaDC primary micelles have an open structure, and there is sufficient space in the core for a further NaDC to bind [15]. This binding pocket in the primary micelles may have consequences for the binding of other hydrophobic molecules within NaDC micelles or even DMMs. The primary micelles of both cholate and NaDC associate further into secondary micelles at higher concentration that have an irregular structure and varied shapes [15].

The structure and morphology of bile salt micelles have been debated for many years. It is well established that bile salt micelles do not conform to the classical spherical shape seen with amphiphilic surfactants. Three models for bile salt micelle structure have been put forward. Apart from the primary/secondary micelle model proposed by Carey & Small [12] there are also the disc model [10] and the helical model [17–19]. Kawamura et al. [10] carried out stearic acid spin probe immobilization studies using electron spin resonance to deduce the structure of trihydroxy and dihydroxy bile salt micelles. Their results suggested that the micelles adopted the same shape irrespective of bile salt type, although the structure may differ. For dihydroxy bile salts a signal for both strong and weak immobilization of the spin probe is observed, suggesting two types of micelle structure. For trihydroxy bile salts, on the other hand only a single weak binding signal is seen in the spectra. Kawamura et al. [10] interpreted their results as