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Colloids and Surfaces A: Physicochemical and Engineering Aspects

Effect of surfactant structure on the mixed micelle formation of cationic gemini–zwitterionic phospholipid systems
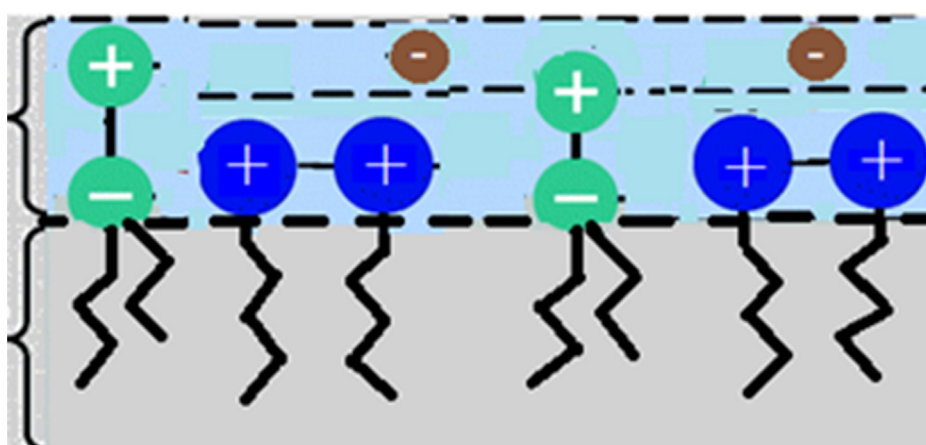
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HIGHLIGHTS

- Mixing of zwitterionic phospholipid (PL) with cationic geminis have been studied.
- PL participates more than geminis in mixed micelles.
- PL contributes more in mixed monolayer than in mixed micelles.

GRAPHICAL ABSTRACT

ABSTRACT

The micellization behavior of mixed zwitterionic/cationic solutions, that is, of zwitterionic phospholipid, 1,2-dioctanoyl-sn-glycero-3-[phospho-L-serine] (sodium salt) (PL) and cationic gemini surfactants, alkanediyl-α,ω-bis(dimethylalkylammonium bromide (alkyl: 14 or 16 and alkane: butane, pentane or hexane) (m-s-m), have been studied by surface tension measurements. Various physicochemical properties, viz., critical micelle concentration (cmc), surface excess concentration (Γ_{max}), minimum area per molecule (A_{min}), interaction parameters (β^m, β^σ), and thermodynamic parameters such as standard Gibbs energy of micellization ($\Delta G_{mic}°$), standard Gibbs energy of adsorption ($\Delta G_{ads}°$), and excess free energy of mixing (ΔG_{ex}^m, $\Delta G_{ex}°$), have been evaluated. The obtained results indicate that the mole fraction of PL in the mixed micelles, calculated on the basis of Rubingh's model, is different from stoichiometric mole fraction of PL (α_1). The negative values of $\Delta G_{mic}°$ and $\Delta G_{ads}°$ show that the micelle formation and adsorption of surfactants at the air/solution interface is energetically favorable with the magnitude of $\Delta G_{ads}°$ greater than that of $\Delta G_{mic}°$. The negative values of ΔG_{ex}^m and ΔG_{ex}^σ indicate better stability of the mixed systems. The insights presented herein on the gemini-phospholipid mixed micelle properties may find use towards their applications in the relevant areas of solubilization/drug delivery/etc.

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1. Introduction

Upto 40% of the pharmaceutical entities discovered today are hydrophobic in nature and hence are of low aqueous solubility. This low solubility often presents many *in vitro* and *in vivo* hurdles, like decreased bioavailability, incomplete release from dosage form, and limited choices of delivery technologies. Various strategies, like complex formation with cyclodextrin, liposomes, surfactant micelles and microemulsions, have been developed [1–4]. However, some of these options are not good as they may be harmful to liver and kidney [5,6]. Also, surfactants usually have high cmc values and are not stable after administration.

From the research on liposomes it is clear that phospholipids are the amphiphiles which offer unique benefits as excipients. Phospholipids with two short chains of four to eight carbons readily form micelles in aqueous medium [7] with cmc's lower than those of conventional surfactants and form monolayers at the air/water interface [8]. They are non-toxic, parenterally well tolerated and have high biocompatibility.

Phospholipids interact with surfactants and form mixed micelles [9–11]. Being essential constituents of biological membranes, phospholipids are involved in various biological activities in living organisms [12,13]. The knowledge of phospholipid-surfactant systems is important for many reasons, e.g., solubilization and reconstitution of biological membranes, isolation of membrane protein [14] and design of drug delivery systems [15]. For this purpose a number of investigations have been carried out [16,17]. These studies showed the breakdown of lamellar structures and the formation of lipid-surfactant mixed micelles. Litchenberg [18] postulated that the effective surfactant to lipid ratio producing liposome saturation and solubilization depends on the cmc of surfactants. Mixed micelles of surfactants and phospholipids have advantages as drug carrier over other carrier systems: they have hydrophobic core which can encapsulate hydrophobic drugs; have small size due to which they show an increased vascular permeability and accumulation in pathological areas with leaky vasculation. Mixed micellization of phospholipids with conventional surfactants is fairly well studied [9–11,18,19] but with gemini surfactants, the reports are scarce [20].

Gemini surfactants are, in contrast to single tail/single head surfactants, composed of two tails, two heads and a spacer that connects the two heads. Hydrophobic tails and spacers can be rigid or flexible, short or long. Long tails, although increase their surface activity, decrease their solubility [21,22]. The unusual and improved properties of the gemini micelles in comparison to monomeric surfactant micelles are related to spacer. Spacer decides the distance between the two head groups in a gemini molecule [23]. In micelles of conventional surfactants the process of micellization and micellar properties depends upon the tail length of surfactant and the distance between the two heads. In gemini micelles, in addition to these factors, length and type of spacer is also important [24]. Even stereochemistry of spacer affects their aggregation properties. Aleandri et al. [25] studied mixed cationic liposomes formulated with 1,2-dimyristoyl-sn-glycero-3-phosphatidylcoline and three stereomeric forms of cationic gemini surfactant 2,3-dimethoxy-1,4-bis(N-hexadecyl-N,N-dimethylammonium) butane dibromide, by differential scanning calorimetry, fluorescence, TEM and dynamic laser light scattering. They found that different stereochemistry of these gemini strongly affect their capability of condensing and transfecting a plasmid DNA and of delivering a photosensitizer. Hence, stereochemistry of gemini affects the organization of lipids in the mixed bilayers and affects the biological features of the formulation. The effect of tail and spacer on the micellization of geminis has been studied by various workers [26–28]. Keeping in view the above mentioned points and

better performance of gemini surfactants on all surfactant utilization fronts, in this paper we report a detailed study of mixed micellization of a phospholipid with six cationic *m-s-m* type gemini surfactants.

On the basis of obtained experimental results, various theoretical models of mixed micellization were proposed [29–34]. Out of these models, pseudophase separation approximation with regular solution approximation (RSA) is mainly used. It has been found to model cmc and micellar compositions accurately [35–37]. Although its use is often questioned [38,39], it is used due to its simplicity. In this paper we have applied RSA, Motomura and Rosen's models to analyze the results and to obtain various parameters, like the maximum surface excess at the air/water interface (Γ_{max}), minimum area per amphiphile molecule at the air/water interface (A_{min}), the Gibbs energy of micellization ($\Delta G_{mic}°$), Gibbs energy of adsorption ($\Delta G_{ads}°$) and Gibbs excess free energy of mixing (ΔG_{ex}).

2. Materials and methods

2.1. Materials

Phospholipid, 1, 2-dioctanoyl-*sn*-glycero-3-phospho-L-serine (sodium salt) (abbreviated hereafter as PL) was Avanti Polar Lipids, Inc (Canada) product (cat no. 840031P). The *m-s-m* geminis (m = 14, 16 and s = 4, 5, 6) were synthesized through the interaction of N,N-dimethylalkylamine (alkyl = tetradecyl or hexadecyl) and α,ω-dibromoalkane (alkane = butane, pentane, or hexane) as per the literature method [40]. The reagents were refluxed at molar ratio 2.1:1 in dry ethanol with continuous stirring at 80 °C for 48 h to ensure as much as possible a complete biquaternization. The progress of the reaction was monitored by using thin-layer chromatography (TLC) technique. After completion of the reaction, the solvent was removed under vacuum. An ethanol/ethylacetate mixture was used for recrystallization (at least three times). After recrystallizations, all the six surfactants were characterized by ^{1}H NMR and Fourier transform infrared spectroscopy.

2.2. Method

Aqueous solutions of pure amphiphiles were prepared in double-distilled water whose surface tension varied between 71 and 72 mN m^{-1} (at 30 °C). The equimolar stock solutions were mixed in different ratios to obtain different mole fractions. In few systems solutions of 8:2 and 6:4 were turbid. The surface and micellar properties of the solutions were studied by the ring detachment method using a tensiometer based on Du Nouy principle. Initially, 30 ml of water (used as solvent) was put in the container. It was then equilibrated before starting the experiment. Then a known amount of stock solution of single or mixed surfactants was added with a microsyringe (Hamilton–Bonaduz, SCHWEIZ), mixed properly, and was again equilibrated for 15 min before measuring the surface tension (γ). The error in the measurements was ±0.5 mN m^{-1}. The γ decreased continuously and then became constant along a wide concentration range. The point of break, when the constancy of surface tension began, was taken as the cmc of the system.

3. Results and discussion

3.1. Micellar behavior of gemini:PL mixtures

The cmc values for pure PL and geminis are in good agreement with the literature values, i.e., 0.150 mM for 14-4-14 [41], 0.164 mM for 14-5-14 [41], 0.170 mM for 14-6-14 [41], 0.028 mM for 16-4-16 [42], 0.032 mM for 16-5-16 [42], 0.038 mM for 16-6-16 [42] and 2.28 mM for PL [43]. It can be clearly inferred from the cmc data