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Biocompatible microemulsions of dicephalic aldonamide-type surfactants: Formulation, structure and temperature influence

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ABSTRACT

The temperature effects upon microemulsion systems composed of dicephalic *N*-dodecyl-*N*,*N*-bis[(3-D-aldonylamido)propyl]amines C_{12}-DX (gluconyl GA or lactobionyl LA)/*iso*-butanol/hydrophilic (diethylene glycol monoethyl ether) or hydrophobic (*iso*-octane) oils/water were investigated by evaluating isotropic area magnitudes in the pseudoternary phase diagrams, as well as droplet characteristics by electron paramagnetic resonance (EPR) and dynamic light scattering (DLS) spectroscopies at 25, 40 and 55 °C. We concluded that in the examined systems a cosurfactant, such as middle-chain alcohol, was needed to obtain large mesophase isotropic areas. The phase behavior and structure of the examined systems were temperature insensitive but they were intimately determined by the nature of the C_{12}-DX and the polarity of the oil phase. By adjusting the nature of the oil, as well as the surfactant hydrophilicity, the performed isotropic systems containing low amounts of nonaggressive surfactant could be formulated successfully. Interfacial properties and the dynamic structure of the surfactant/cosurfactant monolayer were studied by the spin probe technique using the 16-doxylstearic acid methyl ester (16-DSE) as the appropriate probe. The polarity of the interface was not affected by temperature but the interface rigidity was dependent upon the nature of the surfactant and oil as well as on temperature. The size of the dispersed domains, evaluated by dynamic light scattering (DLS), was found to be a function of temperature, surfactant content and type of additives. The investigated o/w microemulsions (i.e., ranging from 3.0 to 8.8 nm) constituted promising templates for a variety of syntheses of nanostructures with small size and high-capacity solubilizing media.

1. Introduction

The search for biocompatible, biodegradable and temperature-insensitive microemulsions as various solubilizing and reaction media is of increasing importance for emerging applications in several areas, such as: drug delivery systems, food products, catalysis, transcriptive syntheses and membrane recognition phenomena, new cosmetic formulations and nanotechnologies [1–5]. Among very popular forms of micellar applicable products there are microemulsions – transparent, isotropic, spontaneously formed systems which comprise water and/or oil nano-domains coexisting in thermodynamic equilibrium due to the presence of a surfactant layer at the oil/water interface [2–8]. The unique structural organization of pseudodomains in microemulsions may contribute to additional solubility regions in droplets whose natural radius of curvature is determined mainly by structural and geometrical parameters [9–11], hydrophile–lipophile balance (HLB) [11], and hydrophile–lipophile deviation (HLD) [12,13] as well as thermodynamic aspects [3,7].

As the drug delivery potential of microemulsions needs to be evaluated, the research should mainly be directed towards studies on their temperature stability and insensitivity, as well as to their internal microstructure properties. These features are strictly connected with the solubilization capacity and bioavailability of active molecules, which – together with the microemulsions' safe, biocompatible building blocks – have to be sterilizable, non-irritant to nerves and/or without hemolytic action [2,14–16]. With a change of a control ("tuning") parameter (i.e., temperature, salt concentration and cosurfactant addition) an oil-in-water (o/w) droplet in excess oil phase can be transformed into a water-in-oil (w/o) structure [17]. This phase inversion is commonly connected with a three-phase region (i.e., a bicontinuous microemulsion) in contact with excess oil and water phases. In the case of C_nE_m nonionics the above-mentioned phase inversion can be prompted by raising the temperature [18], which can be disadvantageous in certain application areas. In contrast, almost temperature-insensitive microemulsions can be obtained by applying sugar-derived surfactants (e.g., alkyl glucosides [14], polyglucosides [19], sucrose fatty acid esters [20,21]). It has been observed that weak temperature dependence of the headgroup hydration constitutes to a sort of beneficial property of sugar-derived surfactants. However, to tune

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the spontaneous curvature of the surfactant film by the temperature change, it is difficult to perform, as it can be seen in the case of the well-known C_nE_m systems [22]. Therefore, in literature two approaches are mentioned that have been applied in studies on microemulsions stabilized by sugar surfactants. Firstly, the hydrophilic sugar-derived surfactant was used in a mixture with a hydrophobic alcohol or with a C_nE_m surfactant and the content changes in the mixed interfacial film caused a decrease in the mean curvature from positive in the o/w microemulsion to negative in the w/o. In the other approach polar oils were used. Only in a few exceptional cases, temperature-sensitive ternary microemulsions with sugar surfactants were obtained by employing oils that were more polar than alkanes [17,23].

The present contribution mainly addresses aggregation phenomena and potential applications related to biocompatible so-called sugar surfactants [14,24–28], a family which in the presence of water and/or oil forms a rich variety of dynamic self-assembled structures. It has less impact on the natural environment, thus fulfilling green chemistry principles. Owing to our continuous efforts in designing, synthesizing and characterizing aggregation phenomena and performance properties of a variety of saccharide-derived surfactants [29–32], we examined pseudoternary phase systems containing *N*-dodecyl-*N*,*N*-bis[(3-D-aldonylamido)propyl]amines [33,34] (for structures and abbreviations see Scheme 1), water, *iso*-butanol as the cosurfactant, and *iso*-octane, diethylene glycol monoethyl ether (DGME) as the oils. The prepared surfactants C_{12}-DGA and C_{12}-DLA represent a new group of dicephalic aldonamide-type derivatives exhibiting profound surface properties. Fortunately, they can be obtained in a straightforward three-step procedure from readily available, inexpensive reagents. In the literature only Bales et al. [35] performed microenvironment characteristics of micelles of double-headed dodecyl-malono-bis-*N*-methylglucamide in the mixture with SDS.

The main purpose of the present study was to characterize new phase diagrams in view of their temperature sensitivity, properties of isotropic areas and microregion characteristics needed for designing the most appropriate o/w microemulsion-templated processes which we experienced before in other systems [27]. Thus, basing on electron paramagnetic resonance (EPR) we report on the effect of temperature dependent changes in the molecular structure and in the environment around the dicephalic surfactants on their behavior at the liquid–liquid microemulsion droplet interface including spin probe mobility, polarity around the probe, segmental ordering of alkyl chains and rigidity of surfactant film. Additionally to support some spin probe experiments we applied dynamic light scattering (DLS) to evaluate the oil-in-water (o/w) droplets size and diffusion coefficients as a function of the surfactant content and the temperature.

2. Experimental

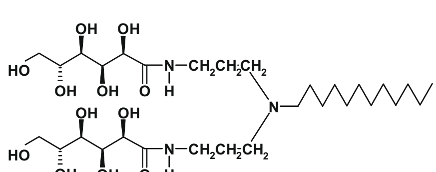
2.1. Materials

N-Dodecyl-*N*,*N*-bis[(3-D-gluconylamido)propyl]amine, and *N*-dodecyl-*N*,*N*-bis[(3-D-lactobionylamido)propyl] amine C_{12}-DX (C_{12}-DGA (HLB = 11.8) and C_{12}-DLA (HLB = 19.4), respectively) were synthesized as previously described [33,34]. The HLB values were calculated according to the McGowan method [11]. *iso*-Octane (from Carl Roth KG Chemicals) and diethylene glycol monoethyl ether (DGME from Merck) were used as oils and *iso*-butanol (from Sigma–Aldrich) – as the cosurfactant. In EPR experiments 16-doxylstearic acid methyl ester (16-DSE), purchased from Sigma–Aldrich, was used as a spin probe. All reagents were of analytical grade and used as provided. Water used for all experiments was doubly distilled and purified by means of Millipore (Bedford, MA) Milli-Q purification system.

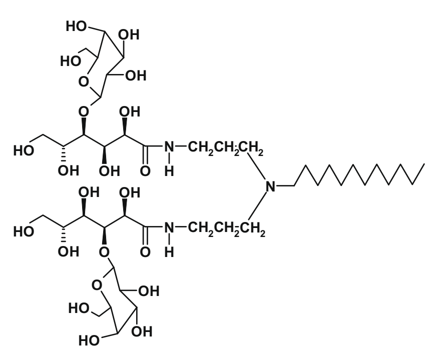
2.2. Pseudoternary phase diagram

Four-component systems can be described with pseudoternary phase diagrams. In the following part we are going to use variables and nomenclature as they have been introduced by Strey and Kahlweit et al. [36,37] who have also precisely described the method. The variables in the mixture are expressed as the mass ratio of oil to water plus oil in the mixture: α = oil/water + oil; the mass fraction of surfactant in the mixture: γ = surfactant + cosurfactant/water + oil + surfactant + cosurfactant; and the mass fraction of cosurfactant: δ = cosurfactant/surfactant + cosurfactant. Oil phase with surfactant/cosurfactant (δ = 0.5) mixture was weighed at various ratios ranging from 0:100 to 100:0. The mixture with the total weight of 0.5 g was placed in a screw-cap glass tube, vortexed vigorously for 30 min, and then titrated

(a)

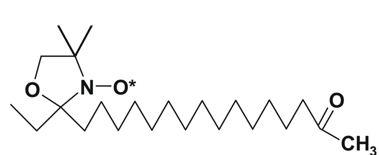


C_{12}-DGA



C_{12}-DLA

(b)



16-DSE

Scheme 1. Structures and abbreviations of (a) *N*-dodecyl-*N*,*N*-bis[(3-D-aldonylamido)propyl]amines – C_{12}-DX, where X = GA and LA; (b) 16-doxylstearic acid methyl ester.