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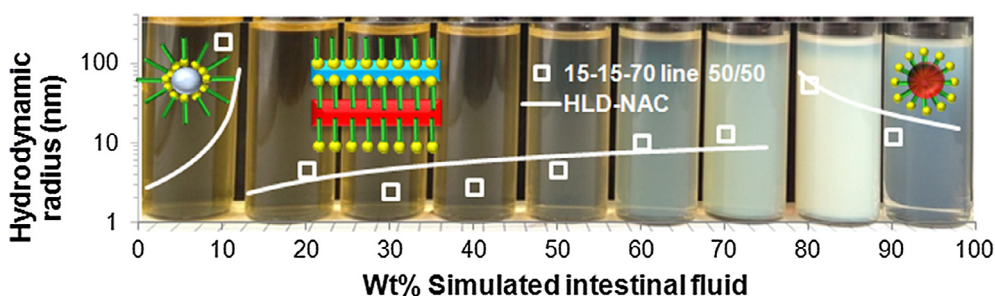
Predicting solubilisation features of ternary phase diagrams of fully dilutable lecithin linker microemulsions



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GRAPHICAL ABSTRACT



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ABSTRACT

Fully dilutable microemulsions (μ Es), used to design self-microemulsifying delivery system (SMEDS), are formulated as concentrate solutions containing oil and surfactants, without water. As water is added to dilute these systems, various μ Es are produced (water-swollen reverse micelles, bicontinuous systems, and oil-swollen micelles), without the onset of phase separation. Currently, the formulation dilutable μ Es follows a trial and error approach that has had a limited success. The objective of this work is to introduce the use of the hydrophilic-lipophilic-difference (HLD) and net-average-curvature (NAC) frameworks to predict the solubilisation features of ternary phase diagrams of lecithin-linker μ Es and the use of these predictions to guide the formulation of dilutable μ Es. To this end, the characteristic curvatures (C_c) of soybean lecithin (surfactant), glycerol monooleate (lipophilic linker) and polyglycerol caprylate (hydrophilic linker) and the equivalent alkane carbon number (EACN) of ethyl caprate (oil) were obtained via phase scans with reference surfactant-oil systems. These parameters were then used to calculate the HLD of lecithin-linkers-ethyl caprate microemulsions. The calculated HLDs were able to predict the phase transitions observed in the phase scans. The NAC was then used to fit and predict phase volumes obtained from salinity phase scans, and to predict the solubilisation features of ternary phase diagrams of the lecithin-linker formulations. The HLD-NAC predictions were reasonably accurate, and indicated that the largest region for dilutable μ Es was obtained with slightly negative HLD values. The NAC framework also predicted, and explained, the changes in microemulsion properties along dilution lines.

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1. Introduction

Fully dilutable microemulsions (μ Es) have been a subject of research because of the role that aqueous dilution plays in oilfield chemistries, drug delivery and other applications [1–5].

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The most common use of dilutable μ Es is as self-micro emulsifying delivery systems (SMEDS), where a drug is dissolved in the oil + surfactant “pre-concentrate” to be diluted by body fluids [1,5,6]. SMEDS may concisely be defined as concentrated μ Es or latent μ Es [7]. A microemulsion system can be defined as a thermodynamically stable, transparent/translucent dispersion of an aqueous and/or oil phase, stabilized by an interfacial film of surfactants [8–12].

The first challenge in formulating dilutable μ Es has been the choice of safe and effective surfactants and oils. Linker-based lecithin μ Es have been shown to have a desirable phase behavior and excellent solubilisation capacity, and to be non-toxic [13–16]. In a lecithin-linker formulation there are three surface active components, namely the lecithin surfactant, the lipophilic and the hydrophilic linkers. The lipophilic linker is a surface active species that segregate near the surfactant tails, increasing the lipophilic interactions between the surfactant (lecithin) and the oil [13]. The hydrophilic linker is a short chain surfactant-like molecule that co-adsorbs with the surfactant at the oil/water interface, increasing the interfacial area [13,14]. The choice of oil, linkers, lecithin, and their concentrations are among the decisions the formulator needs to make. This multi-variable problem is similar for other μ E formulations, which can require the evaluation of thousands of combinations to find a fully dilutable system.

Currently the development of fully dilutable μ Es requires the use of a trial and error approach [17]. There is a shortage of models to design, formulate and predict the phase behavior of surfactant-oil-water systems (SOW) such as dilutable μ Es. Indicators, such as the hydrophilic lipophilic balance (HLB), critical micelle concentration (CMC), critical packing parameter (CPP), interaction energy ratio (Windsor's R ratio) and phase inversion temperature (PIT), have only served as guidelines [18]. Thermodynamic models have been explored to predict the phase behavior, including Helfrich's membrane free energy approach, however, the lack of model parameters have hindered further practical applications of those approaches [19–22]. Statistical and data mining models have attracted the interest in the pharmaceutical industry for predicting phase boundaries of ternary phase diagrams (TPDs), however these models require gathering experimental data for similar systems to train the model [23,24].

Perhaps the most effective method to predict the phase behavior of μ Es is through the hydrophilic-lipophilic-difference (HLD) framework [25,26]. The HLD is a semi-empirical correlation that indicates the combination of variables that leads to an “optimal formulation” in a phase behavior scan. A phase behavior scan consists of a series of test tubes containing equal volumes of oil and aqueous phases, typically with a constant total surfactant concentration of less than 10.0% by volume, where one formulation variable is gradually changed. The optimal formulation (HLD = 0)

corresponds to the system where the μ E contains equal amounts of oil and water solubilised in the system, with (Winsor Type III) or without (Winsor Type IV) excess aqueous and oil phases. For negative HLDs (Winsor Type I), the surfactant partitions in the aqueous phase, coexisting with an excess oil phase. For positive HLDs (Winsor Type II), the surfactant partitions in the oil phase, coexisting with an excess aqueous phase. The equations of the HLD framework are [25–27]:

$$\text{For ionic surfactants } HLD = \ln(S) - k \cdot EACN + Cc - \alpha T \cdot (T - 25) \quad (1)$$

$$\text{For nonionic surfactants } HLD = b \cdot S - k \cdot EACN + Cc + c_T \cdot (T - 25) \quad (2)$$

where “S” is the electrolyte concentration (g NaCl/100 ml), “EACN” is the equivalent alkane carbon number; “Cc” is the characteristic curvature of the surfactant, “T” is the temperature of the system ($^{\circ}$ C). Finally, k , α_T , b , c_T are empirical constants for a given surfactant.

The HLD alone has been used to assess trends in formulation properties, including the shape of TPDs. Fig. 1 shows the sign of HLD and the corresponding shape of the TPD [25].

The schematics in Fig. 1 represent only a guideline. The objective of this work is to use the HLD framework to predict the solubilisation features of the TPDs for dilutable lecithin-linker systems in the 2 or 3 phase region obtained near the base of the triangle.

The value of HLD can be used to predict the solubilisation capacity of a μ E system via the net-average curvature (NAC) model [28,29]. The NAC framework uses a mathematical description of the solubilisation of oil and water where any μ E is represented by two coexisting states, one where oil is solubilised as spheres of radius R_o in a continuous aqueous media, and a second one where water is solubilised as spheres of radius R_w in a continuous oil phase. The radius of solubilisation of the dispersed phase (R_{disp}) in the continuous phase is calculated as [28]:

$$R_{disp} = 3 \cdot V_{disp} / A_S \quad (3)$$

where V_{disp} is the volume of the dispersed phase (oil or water) solubilised in the continuous phase, and A_S is the interfacial area provided by the adsorption of the surfactant, calculated as [28]:

$$A_S = \sum n_{S,i} \cdot a_{S,i} \quad (4)$$

where $n_{S,i}$ and $a_{S,i}$ are the number of molecules of surfactant “i” adsorbed at the oil-water interface, and the area per molecule of that surfactant species “i”.

Using the solubilisation radii for oil and water, the NAC model proceeds to define the net (H_n) and average (H_{avg}) curvature, as follows [28,30,27,31]:

$$H_n = (1/R_o - 1/R_w) \quad (5)$$

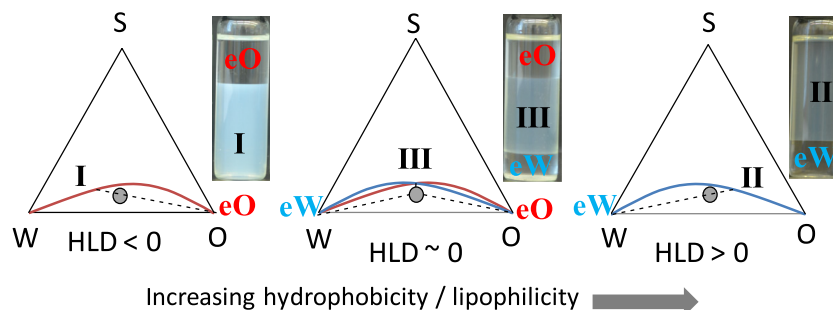


Fig. 1. HLD and its connection with ternary phase diagram (TPD). I, II, III are Winsor Type I, II and III μ Es. eO and eW are the excess oil and aqueous phases. S, O, W correspond to pure surfactant, oil and water, respectively. The circle in the triangle represents the initial composition (volume fraction, based on total volume) of a system with the appearance of the test tubes shown next to each triangle. The dotted line represents a tie line(s) passing through that composition.

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