## Thermodynamic modeling of aqueous surfactant solutions.

Development and validation of a new modeling framework

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The low solubility of active pharmaceutical ingredients (APIs) in aqueous solutions is a persisting challenge in drug development and design. Surfactants can be used to encounter this challenge. Once the surfactant concentration exceeds the Critical Micelle Concentration (CMC), the formed aggregates serve as vehicles for the hydrophobic APIs increasing their overall solubility. As a first step towards modeling and understanding aqueous surfactant systems, we present a newly-developed and generic thermodynamic framework. Such a thermodynamic framework provides a valuable tool for tailoring surfactants for solubilizing for target APIs.

The new framework assumes that surfactant molecules exist in two different conformations: either singlydispersed in solution (free surfactants) or confined in an aggregate (confined surfactants). These two conformations were treated as different species, each with a distinct chemical potential.

The fractions of the two species are related to the overall surfactant concentration by imposing chemical equilibrium between the two conformations and applying the mass-action law (Figure 1).



**Figure 1.** Equilibrium between the surfactant conformations.  $K_f$  is the equilibrium constant.  $K_{\phi}$  accounts for the influence of interactions.

Application of the chemical-equilibrium condition requires a thermodynamic model to calculate  $K_{\phi}$ . For this purpose, we used the hetero-segmented Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT). By means of this group-contribution model, we generated a minimal set of universal parameters to describe a variety of homologous series including three different non-ionic surfactant classes. The model was validated against vapor-liquid equilibria, solid-liquid equilibria, infinite-dilution properties, as well as octanol/water partition coefficients (Figure 2).



Figure 2. Parity plot of experimental versus correlated partition coefficients between n-alkane/water (circles) and n-octanol/water (triangles) for different poly(ethylene oxide) n-alkyl ether  $(C_iE_j)$  surfactants.

As part of the new framework, we developed a new relationship to calculate CMC. This new relation was applied for members of the n-alkyl- $\beta$ -D-glucopyranosides (C<sub>i</sub>G<sub>1</sub>), C<sub>i</sub>E<sub>j</sub>, and N-alkanoyl-N-methyl-D-glucamides (MEGA-i) classes. Figure 3 shows the results of the CMC modeling for the surfactants C<sub>i</sub>G<sub>1</sub> and MEGA-i.



Figure 3. CMCs in mole fraction of the  $C_iG_1$  (a) and MEGA-i (b) surfactants as function of temperature. Symbols are experimental data. Solid lines are correlations using the newly-developed relation.

Accordingly, the CMCs were quantitatively described over a broad temperature range. The temperature behavior can be fully attributed to the electrostatic characteristics of the surfactant heads and is correctly predicted by our modeling approach.

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## Publications:

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