Molecular Design of Novel Micellar Timed-Release Drug Delivery Systems

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Introduction

Conventional drug delivery methods such as tablets, capsules, or injections administer an immediate large dose of active reagent. The maximum effects of the reagent are observed quickly after the dosage and the efficacy diminishes soon thereafter. Consequently, new drug delivery systems are being studied in which a micelle is formed with the drug to be delivered inside the micellar core. These micellar drug delivery systems are aimed at drugs that are poorly soluble in water. When ingesting a drug that is not water soluble, only a fraction of drug is absorbed into the bloodstream. The rest is excreted through urine. When these insoluble drugs are introduced to surfactants, their solubility increases dramatically. This increase in solubility increases the bioavailability of the drug to the rest of the body. This study aimed to construct a molecular thermodynamic model for the mixed micellization of ibuprofen and surfactants from the polyethylene glycol monoether (C_iE_j) family. The key outputs of the model include: gibb's free energy of micellization and drug solubility as a function of surfactant mole fraction.

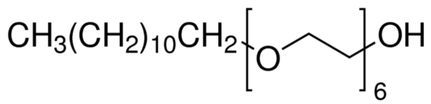

Figure 1 $C_{12}E_8$ Structure

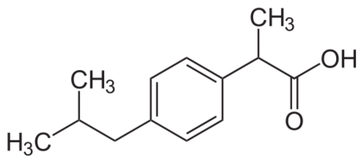

Figure 2 Ibuprofen Structure

Methods

The key property of the molecular thermodynamic modeling approach for self-assembled systems is the gibb's free energy of micellization. For mixed ionic surfactants in water this consists of six contributions: 1) the transfer of surfactant tails or drug molecule hydrophobic areas from bulk water to the micellar core; 2) the creation of a micellar hydrocarbon core-water interface, which accounts for the molecular architecture of the drug molecule; 3) surfactant and drug tail chain packing within the micellar core; 4) surfactant and drug molecule hydrophilic head group steric repulsions; 5) electrostatic effects between charged moieties and counterions; and 6) the entropic effect of mixing various species. The Gibbs free energy of micellization is minimized with respect to core minor radius for different shapes to determine the optimum shape, size and composition of micelle including degree of counterion binding.

Results

$$g_{mic} = g_{trans} + g_{pack} + g_{int} + g_{st} + g_{elec} + g_{ent}$$

As a function of :
Shape (S)
L_c (micellar minor core radius)
α ($n_{C_{12}E_8}/n_{total}$ mole fraction $C_{12}E_8$)
β (Counter-ion Binding)

α = 0.5
Spheres (S = 3)

l_c (Å)	g_{trans}	g_{int}	g_{pack}	g_{st}	g_{ent}	g_{elec}	g_{mic}
12	-18.707	3.381	1.038	0.984	-0.693	1.417	-12.579
12.5	-18.707	3.233	0.971	1.080	-0.693	1.516	-12.599
13	-18.707	3.090	0.898	1.195	-0.693	1.616	**-12.601**
13.5	-18.707	2.952	0.817	1.337	-0.693	1.716	-12.578
14	-18.707	2.818	0.725	1.527	-0.693	1.817	-12.513
14.5	-18.707	2.690	0.620	1.819	-0.693	1.918	-12.352
15	-18.707	2.566	0.500	2.534	-0.693	2.020	-11.780

Figure 3 Optimization of g_{mic} for spheres (S = 3) at $C_{12}E_8$ mole fraction of 0.5

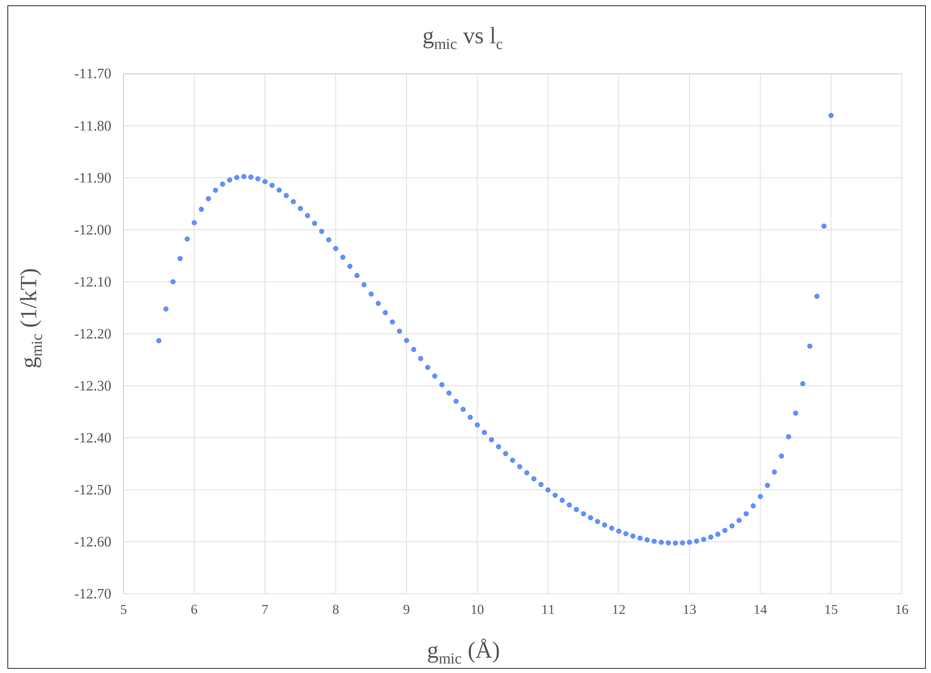

Figure 4 Gibb's free energy of micellization plotted vs minor core radius for spheres (S = 3), and α = 0.5

α	g_{mic} (min)	Solubility (M)	Solubility (g/L)
0.5	-12.60	0.928	191.43
0.51	-12.68	0.909	187.60
0.52	-12.76	0.891	183.77
0.53	-12.84	0.872	179.94
0.54	-12.92	0.854	176.12

Figure 5 Solubility calculations for ibuprofen in $C_{12}E_8$ with composition ranging from α = 0.5 – 0.54. For reference, the solubility of ibuprofen in water is 0.021 g/L

Discussion/Conclusion

The constructed thermodynamic model calculates gibb's free energy of micellization as a function of micelle shape, core radius, composition, and counter-ion binding. Spherical units resulted in the most minimized values of g_{mic} and the most ideal micelle compositions were found to be between α = 0.5 and 0.54. The solubility of ibuprofen in $C_{12}E_8$ was calculated at each of these compositions with values ranging from 0.854 M to 0.928 M, and 176.12 g/L to 191.43 g/L. If the solubility of ibuprofen in water can be increased from 0.021 g/L to 191.43 g/L in $C_{12}E_8$, the bioavailability of the drug can be greatly increased. This holds true for all drugs that are poorly soluble in water and means that the recommended dose of these drugs (~400 mg for ibuprofen) can be reduced.

Further Work

The work done so far shows that micellar drug delivery systems have the potential to be very efficient. Experimental work needs to be done to verify the accuracy of the proposed thermodynamic model. Further work also needs to be done to implement and test a drug release kinetics model.

References

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