

Simulation of non-ionic surfactant micelles for controlled drug release

**Modules used**

Materials Studio® DPD
Material Studio® Discover
Material Studio® COMPASS
Material Studio® Amorphous Cell

Services used:

Contract Research Services

Industry sectors

Drug Delivery

Study made by:

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Franck Pitré, Galderma

Organizations

Galderma, Accelrys

Researchers from Galderma and Accelrys have collaborated to apply a multiscale modeling approach to the study of the stability of micellar systems for the controlled release of a drug.

Galderma is a pharmaceutical company specializing in dermatological treatments. They have significant interest in applying new technologies to better understand the behavior of topical drug formulations. In particular, there is a need to understand the underlying cause of physical and chemical instability of a drug used in a particular type of formulation. This instability is speculated to be attributed to the location of the drug in relation to the interface between micellar microphases present in the system. Since it is not always possible to obtain these data experimentally Galderma R&D leveraged the expertise of Accelrys' Contract Research Services to gain insight into the nature of the molecular distribution of the different species within the micelles.

Background Information:

Surfactants are molecules that have amphiphilic character, i.e., they have both hydrophilic and hydrophobic groups, rendering them soluble in organic solvents as well as in water. When the surfactant concentration in a solution is higher than a critical concentration (CMC), the surfactant molecules form supramolecular aggregates called micelles.

Micelles are commonly used as drug delivery devices to solubilize hydrophobic drug molecules or to protect them from environmental conditions (e.g., gastric acid). For the delivery system to succeed, favourable interactions between the drug and the surfactant are necessary. These interactions, as well as the morphology of the resulting micellar solutions, can be modified by the presence of new molecules as well as by changes in the solvent quality or temperature.

Objective:

The objectives of this work were to gain insight on the localization of different molecules incorporated into the micelles, and on the influence of the formulation on the final morphology of the solutions.

Methodology:

Following the use of atomistic modeling to estimate the thermodynamic properties of the non-ionic surfactant and the drug (Materials Studio® Discover and COMPASS forcefield), a suitable coarse-grained model for the surfactants, the drug molecule and the solvents were generated (Figures 1 and 2). Mesoscale modeling was then performed to study the morphology of five simple systems with increasing complexity (Materials Studio® DPD®):

- Non-ionic surfactant in water solution
- Non-ionic surfactant and hydrophobic drug in water solution
- Non-ionic surfactant, hydrophobic drug and polar solvent in water solution
- Non-ionic surfactant, hydrophobic drug, preservative and polar solvent in water solution
- Non-ionic surfactant, hydrophobic drug and non-ionic polymeric surfactant in water solution

Results:

For the system consisting of the non-ionic surfactant in aqueous solution, a micellar solution was obtained (Figure 3). The size of the micelles was found to be nearly independent of the temperature and of the surfactant concentration in the range 1% to 4%. As the drug was added to the system, the micelle size was reduced, with the drug concentrating at the core-corona interface. Additionally, the impact of the solvent quality was studied and it was found that under worst solvent conditions, the drug diffused out of the micelle. On the other hand, when adding a polar solvent, the solvent molecules remained outside the micelles, whereas the drugs tended to spread throughout the corona-core interface (Figure 4).

The simulation was repeated incorporating a well-known preservative. The results indicated that the preservative migrated to the micellar corona, counteracting the impact of the polar solvent with respect to the drug, which was located slightly closer to the centre of the micelle (Figure 5) compared to the previous systems. Higher concentrations of the preservative led to unstable systems, a fact that was validated experimentally.

When a polymeric non-ionic surfactant was added, no major changes were observed with respect to the drug, with the active ingredient remaining inside the micelle and located at the corona-solvent interface. Additionally however, bridging between the micelles was observed, as strands of the polymeric surfactant showed the capability to extend between adjacent micelles (Figure 6). This is a condition which may lead to flocculation and precipitation.

Solution to the Challenge:

A multiscale modeling approach was used to better understand the behavior of topical

drug formulations. This study demonstrated that molecular simulations performed by an expert can provide insights on the degree of stability of different formulations as well as on the changes in the molecular distribution within the micelles after the incorporation of hydrophobic active principles, aqueous co-solvents and non-ionic surfactants at different temperatures. The Dissipative Particle Dynamics simulation results obtained agreed with the experimental data and in addition provided important molecular information that can not be obtained from experiments.

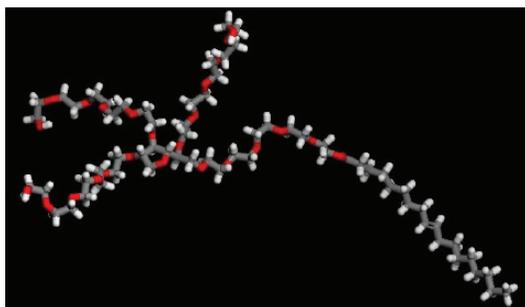


Figure 1. Atomistic model of the non-ionic surfactant molecule.

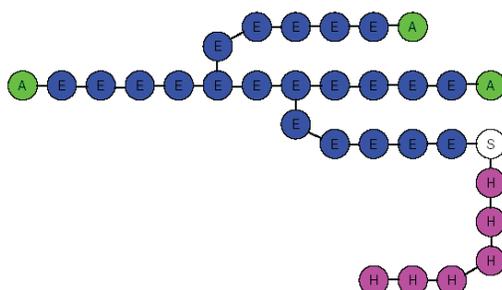


Figure 2. Coarse-grained model of the non-ionic surfactant molecule.

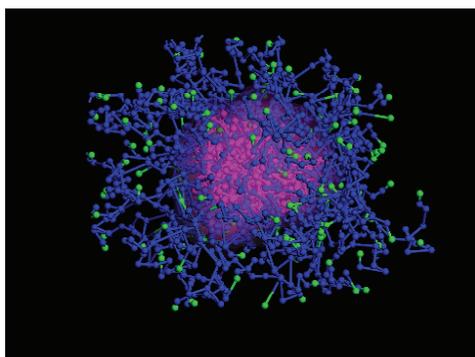


Figure 3. Surfactant micelle in aqueous solution (water not shown).

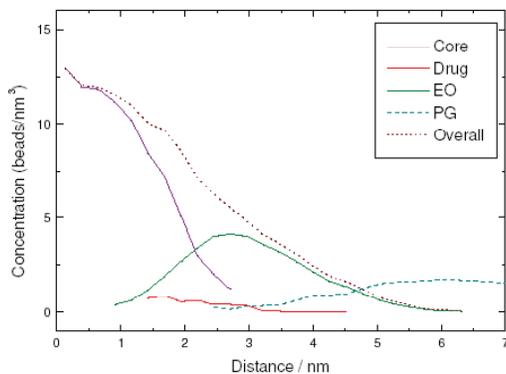


Figure 4. Radial concentration profiles for the system containing non-ionic surfactant, hydrophobic drug, and polar solvent (PG) in water solution. Core and EO stand for hydrophobic tail and polar head of the surfactant respectively.

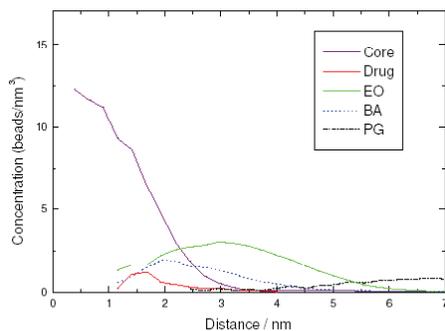


Figure 5. Radial concentration profiles for the system containing non-ionic surfactant, hydrophobic drug, preservative (BA) and polar solvent (PG) in water solution. Core and EO stand for hydrophobic tail and polar head of the surfactant respectively.

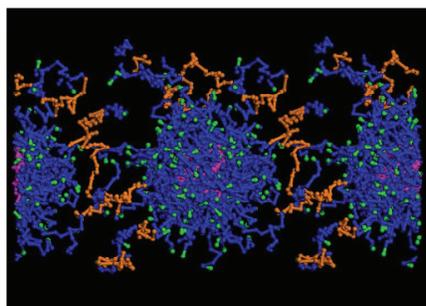


Figure 6. Snapshot of the system containing non-ionic surfactant, hydrophobic drug and non-ionic polymeric surfactant in aqueous solution (water not shown).