Rationalizing the Design of Pluronics–Surfactant Mixed Micelles through Molecular Simulations and Experiments


ABSTRACT: Aqueous systems comprising polymers and surfactants are technologically important complex fluids with tunable features dependent on the chemical nature of each constituent, overall composition in mixed systems, and solution conditions. The phase behavior and self-assembly of amphiphilic polymers can be changed drastically in the presence of conventional ionic surfactants and need to be clearly understood. Here, the self-aggregation dynamics of a triblock copolymer (Pluronics L81, EO$_3$PO$_{43}$EO$_3$) in the presence of three cationic surfactants (with a 12C long alkyl chain but with different structural features), viz., dodecyltrimethylammonium bromide (DTAB), didodecyldimethylammonium bromide (DDAB), and ethanediyl-1,2-bis-(dimethyldodecylammonium bromide) (12-2-12), were investigated in an aqueous solution environment. The nanoscale micellar size expressed as hydrodynamic diameter ($D_h$) of copolymer−surfactant mixed aggregates was evaluated using dynamic light scattering, while the presence of a varied micellar geometry of L81−cationic surfactant mixed micelles were probed using small-angle neutron scattering. The obtained findings were further validated from molecular dynamics (MD) simulations, employing a simple and transferable coarse-grained molecular model based on the MARTINI force field. L81 remained molecularly dissolved up to $\sim$20 °C but phase separated, forming turbid/translucent dispersion, close to its cloud point (CP) and existed as unstable vesicles. However, it exhibited interesting solution behavior expressed in terms of the blue point (BP) and the double CP in the presence of different surfactants, leading to mixed micellar systems with a triggered morphology transition from unstable vesicles to polymer-rich micelles and cationic surfactant-rich micelles. Such an amendment in the morphology of copolymer nanoaggregates in the presence of cationic surfactants has been well observed from scattering data. This is further rationalized employing the MD approach, which validated the effective interactions between Pluronics−cationic surfactant mixed micelles. Thus, our experimental results integrated with MD yield a deep insight into the nanoscale interactions controlling the micellar aggregation (Pluronics-rich micelles and surfactant-rich micelles) in the investigated mixed system.

INTRODUCTION

Surfactants are extensively used in scientific, technical, and industrial applications due to their superior adsorption and micellization properties in an aqueous solution environment and so have received considerable attention for several decades. In particular, poly(ethylene oxide, EO)−poly-(propylene oxide, PO)−poly(ethylene oxide, EO)-based triblock copolymers, known as Pluronics, constitute a class of commercially available non-ionic surfactants offering a wide hydrophile−lipophile balance (HLB) range that have found interest in the biomedical field as quality conveyance vehicles, sensitizers, and part of pharmaceutical formulations, besides being used in personal care products, textiles, inks, and

Received: November 22, 2022
Revised: January 31, 2023

© XXXX American Chemical Society

https://doi.org/10.1021/acs.langmuir.2c03176
Langmuir XXXX, XXX, XXX−XXX

See https://pubs.acs.org/sharingguidelines for options on how to legitimately share published articles.
coatings, among others.1−4 Pluronic are highly surface-active macromolecules that undergo self-assembly, thereby forming nanoscale aggregates (micelles) above the critical micelle concentration (CMC) or critical micelle temperature (CMT), whose hydrophobic core is shaped by solvated poly(propylene oxide) (PPO) blocks and encompassed by an external shell of completely hydrated poly(ethylene oxide) (PEO) end chains.5−8

Other surfactants are often added to Pluronics to tune their solution properties and to improve their colloidal stability.7−11 Mixed Pluronics−surfactants systems have been examined for understanding their synergistic/antagonistic interactions that give rise to some beneficial properties such as an increase in the cloud point (CP), enhanced solubilization of hydrophobic substances, or inducing charge on mixed micelles.7−10 The mixed micellar systems offer better interfacial and colloidal properties in comparison to their individual counterparts and are often beneficial in practice. Several reports have proved that the cleansing properties of Pluronics can be modulated with the addition of other surfactants.5,12−14 Consequently, the total amount of the surfactant necessary for a desired application can be reduced, which leads to a decrease of both the environmental and the economic impacts. Hence, binary aqueous mixtures of non-ionic amphiphilic Pluronics and ionic surfactants have attracted significant attention in applied research.1,3,5,8,15 Reported results show that the strong interaction between ionic surfactants and uncharged Pluronics leads to the formation of charged mixed micelles with decreasing size that finally transform into very small ionic surfactant-rich micelles at high surfactant concentrations. However, the nature and strength of this synergy rely upon a delicate balance between the charge and hydrophobicity of both the polymer and surfactant.5,11,15 Prior studies have revealed that among all the ionic surfactants, the anionic surfactants displayed the strong synergistic interaction modifying the colloidal behavior of Pluronics solutions.8,16−19

Also, the Pluronics and cationic surfactant blended micellar systems are getting a lot of consideration in the area of surfactant science and technology.8,20−23 The formation of mixed micelles and their dependence on environmental factors (temperature, pH, additives, etc.), counterion binding, and thermodynamic and other parameters must be investigated to achieve a deep understanding of their physicochemical behavior with implications for their application prospects.

In recent years, computer simulation methods have emerged as a powerful and efficient tool to study the aggregation behavior of surfactants. The molecular dynamics (MD) simulation approach has been extensively used to explore the dynamics and morphology dependence of surfactant architecture in varied frameworks.24−29 A detailed knowledge of the molecular scale interactions governing the self-assembly is of great importance to design an effective Pluronic−surfactant mixed system. Thus, the present work reports the self-assembly and aggregation behavior in Pluronic−cationic surfactant mixed systems employing phase separation study and small-angle neutron scattering (SANS). The L81 Pluronic was chosen because it forms vesicle structures, and we are particularly interested in analyzing the effect of a surfactant on these aggregates. Here, the selected cationic surfactants contain alkyl chains with 12 carbon atoms (12C) with a bromide counterion but differ in the structure and degree of hydrophobicity, i.e., single chain dodecyltrimethylammonium bromide (DTAB), double chain didodecyl-dimethylammonium bromide (DDAB), and dimeric (gemini) ethanediyl-1,2-bis(dimethyldecyl-ammonium bromide) (12-2-12), as illustrated in Scheme 1.

Scheme 1. Structure Formulae and Properties of the Surfactants Used in This Study

The choice of these cationic surfactants was made based on their different micellization behaviors in an aqueous solution environment, i.e., DTAB forms small spherical micelles (CMC ~15.4 mM at 30 °C),3 12-2-12 forms cylindrical/rod-like micelles (CMC ~0.95 mM at 30 °C),6 while DDAB (CMC ~0.085 mM at 30 °C)6 remains insoluble in water due to its high Krafft point (~16 °C) and forms vesicles/lamellar structures in dilute solution at ambient temperature. In this study, the concentration of the Pluronics L81 solution is taken as 1% w/v and 3% w/v while the surfactant concentration ranged from 0 to 50 mM. The phase behavior of L81 in the presence of cationic surfactants in varying concentrations, expressed as the CP, will be examined and followed by the scattering measurements. MD simulations using a coarse-grained (CG) model were carried out to rationalize our experimental data and provide a platform for screening of potential systems. The employed model is expected to allow us to study how the L81 aggregates transform into mixed micelles, and the consequent changes in the CP, in the presence of the cationic surfactants with different structural and solution properties.
Materials. Pluronics L81 was received as a gift sample from BASF, NJ, USA. The cationic surfactants: DTAB (≥98% purity), DDAB (98% purity), and 12-2-12 (98% purity), used as additives, were purchased from Merck, India. All the compounds were used without any further purification. Solutions were prepared in deuterium oxide (D₂O) for neutron scattering experiments to produce a very good contrast between the hydrophobic core and the solvent, while double-distilled water was used for solution preparation for the remaining experiments.

Experimental Methods. To achieve the study in conditions of the Pluronics-rich micelle or ionic surfactant-rich micelle for our investigated system, we have selected the concentration of Pluronics as 1% w/v while varying the concentration of cationic surfactants. However, as this concentration was too low to form a sufficient number of micelles in mixed Pluronic/surfactant simulated systems within a reasonable amount of computational time, we have also employed a 3% w/v Pluronics solution in the presence of varying concentrations of cationic surfactants to enable a more direct comparison between simulations and experiments.

Phase Behavior. The phase separation (2η) phenomenon expressed as the CP was scrutinized in Pluronics L81 to perceive the impact of cationic surfactants (DTAB, DDAB, and 12-2-12) in triggering the phase changes due to varied aggregation. Here, the CP has been determined by observing an abrupt turbidity appearance in the solution with a concentration of cationic surfactants. However, as this concentration was too low to form a sufficient number of micelles in mixed Pluronic/surfactant simulated systems within a reasonable amount of computational time, we have also employed a 3% w/v Pluronics solution in the presence of varying concentrations of cationic surfactants to enable a more direct comparison between simulations and experiments.

Scattering Silhouette. The hydrodynamic diameter (Dₜ) of micelles and vesicles were obtained from dynamic light scattering (DLS) for the examined mixed systems employing a Zetasizer (Malvern Instruments, UK). The He–Ne, 4 mW laser (wavelength λ₀ = ~635 nm) was used as the incident beam with the scattering angle 90°. The Dₜ was recorded considering three consecutive measurements for each sample.

SANS experiments were performed on the selected 1% w/v and 3% w/v Pluronics L81 solutions to determine the aggregate size and shape using a SANS diffractometer at the Dhruva reactor, BARC, Mumbai, India. The measured scattering data were corrected by SASFIT software, where the coherent differential scattering cross-section (dΣ/dΩ) per unit volume was evaluated as a function of the wave vector transfer Q (= 4πsin θ/2)/λ₀, where λ₀ is the wavelength of the incident neutrons and θ is the scattering angle. The models used for SANS data analysis have been described in detail in the Supporting Information (eqs S1–S18).

Computational Methods. Simulation Details. All simulations were performed using the MD GROMACS 2019 software package by integrating the equations of motion using the leapfrog algorithm with a 20 fs time step (standard for CG simulations). Bonded interactions, i.e., bond stretching and angle bending, were held rigid using the linear constraint solver (LINCS), whereas non-bonded interactions comprised Lennard-Jones (LJ) and Coulomb functions. Long-range electrostatic interactions were computed using the particle mesh Ewald (PME) method. The non-bonded interactions were computed using the Verlet cutoff scheme (potential shift Verlet modifier) and a cutoff of 1.2 nm. Unless otherwise stated, the temperature was set to 333 K using the velocity-rescaling thermostat using a coupling time constant of 1.0 ps. The Parrinello–Rahman barostat was used to maintain the pressure at 1 bar using an isotropic coupling with a time constant of 24.0 ps. The simulation boxes were created using Packmol with all molecules distributed randomly, and NpT ensemble production runs were performed with periodic boundary conditions in all directions. Previously, an energy minimization step was performed for the initial simulation boxes using the steepest descent algorithm to avoid close contacts between molecules. Afterward, two equilibration MD simulations were carried out in the NVT and NpT ensembles to set the proper temperature and density, respectively. The total potential energy, pressure, temperature, and density were monitored along the equilibration and production stages to ensure that the thermodynamic equilibrium was reached. The Visual Molecular Dynamics (VMD) software package was used to visualize the MD trajectories. The formation of aggregates was analyzed using an in-house code based on the Hoshen–Kopelman cluster-counting algorithm.

Coarse-Grained Molecular Model. The CG model based on Martini v2.2 for diluted Pluronic aqueous solutions was selected for the L81 Pluronic, whereas the models for DTAB, DDAB, and 12-2-12 surfactants were taken from Prameela et al. It must be noted that some minor changes were implemented, as explained below. For DTAB, we have considered only one C₂ bead acting as a linker between the charged head groups and the alkyl tail, thus adopting a 4:1 mapping rather than the 3:1 mapping used by Wang et al. In this regard, the DTAB CG model is closer to the accepted CG Martini-based mapping that was successfully used in many studies. For 12-2-12, the CG model for 16-2-16 was taken where one C₂ bead was removed from each alkyl tail. Similarly, the DDAB model was constructed based on the above 12-2-12 model but removing one of the charged Q₀ beads. Figure 1 summarizes the CG mapping used in this work.

Figure 1. CG mapping for the L81 Pluronic and DTAB, DDAB, and 12-2-2 cationic surfactants. The black and orange colors in the L81 Pluronic, whereas the models for DTAB, DDAB, and 12-2-12 surfactants were taken from Prameela et al. It must be noted that some minor changes were implemented, as explained below. For DTAB, we have considered only one C₂ bead acting as a linker between the charged head groups and the alkyl tail, thus adopting a 4:1 mapping rather than the 3:1 mapping used by Wang et al. In this regard, the DTAB CG model is closer to the accepted CG Martini-based mapping that was successfully used in many studies. For 12-2-12, the CG model for 16-2-16 was taken where one C₂ bead was removed from each alkyl tail. Similarly, the DDAB model was constructed based on the above 12-2-12 model but removing one of the charged Q₀ beads. Figure 1 summarizes the CG mapping used in this work.
for all compounds, where the L81 CG model consists of SP₁ and SC₃ beads (representing mildly polar and non-polar beads, respectively, both with a 3:1 mapping) to describe the PEO and PPO segments, respectively. The CG model for the cationic surfactants includes Q₀ (representing ionic beads with no hydrogen bond donor/acceptor character) for charged head groups. The alkyl chains were mapped with non-polar C₂ beads for those methyl groups acting as a bridge between the charged head group and the alkyl chain, whereas C₁ beads were selected for the remainder of the alkyl tails. The Qₐ (ionic hydrogen bond acceptor) bead was selected for Br⁻ counter-ions, which implicitly includes the effect of six solvating water molecules, mimicking the first hydration shell. The regular Martini v2.2 water model was chosen where P₄ beads implicitly include four water molecules. 10% of antifreeze “big” BP₄ water beads were added to disturb the lattice packing of equally sized beads since the σ value of the Lennard-Jones potential in BP₄−P₄ interactions is scaled to 0.57 nm rather than the 0.47 nm in P₄−P₄ interactions, thus preventing artificial freezing of the water phase.

Since some changes to the original Prameela et al.¹⁷ CG model were implemented, a validation test was carried out to ensure that the CG model can reproduce the experimental micelle distributions. Thus, a set of four CG-MD simulation tests for the individual compounds (L81, DTAB, DDAB, and 12-2-12) in aqueous solution were performed for 3000 ns of simulation time to ensure that the correct thermodynamic equilibrium is reached. First, a 1% w/v L81 concentration (run 1) was equilibrated in a 30 nm side simulation box. The simulation runs carried out in this work are summarized in Table S1 of the Supporting Information.

Figure 2a shows the final simulation snapshot where all L81 molecules quickly self-assemble into a single large aggregate, reflecting the fact that L81 is highly hydrophobic. This system was run with only 50 L81 because simulating Pluronics at this level of molecular weight and under dilute conditions is highly computationally demanding. Experimental results suggest that no micelles are found even under dilute conditions, but relatively large aggregates are formed instead, exhibiting sizes of around 200 nm and aggregation numbers of \( N_{agg} > 300 \).⁴⁷⁻⁵¹ Our simulations are consistent with this behavior.

Figure 2b shows the spherical micelles obtained in the 1% w/v DTAB aqueous solution (run 2) with average \( N_{agg} = 60 \) and \( \phi = 3.4 \) nm, in good agreement with experimental results found in the literature.⁵²⁻⁵³ Figure 2c confirms the formation of vesicles in the DDAB aqueous solution (run 3), as demonstrated by many experiments.⁵⁴⁻⁵⁷ In fact, after 3000 ns of simulation, the DDAB formed two vesicles with average \( N_{agg} \sim 250 \) and a size of \( \phi \sim 7 \) nm, in good agreement with the light scattering measurements reported by Marques et al.⁵⁸ Finally, Figure 2d shows the formation of poly-dispersed aggregates in the 12-2-12 aqueous solution (run 4), revealing an aggregate size distribution in the range of \( N_{agg} \sim 50/100 \), besides exhibiting some elongated micelles, as also observed in previous computational⁵⁹ and experimental studies.¹⁰,⁶⁰⁻⁶² These validation tests give us the confidence that the CG
model is realistically describing the self-assembly behavior of all the individual components of the system and hence can be used to infer mechanistic information and make predictions about the behavior of more complex mixtures.

## RESULTS AND DISCUSSION

### Phase Behavior

The CP (which is often related to the dehydration of the PEO moiety with the progressive increase in temperature) of 1% w/v L81, i.e., ∼20 °C along with their CMT (<20 °C) is in accordance with the literature data.\(^6,30\) The degree of hydrophobicity exhibited by the three cationic surfactants followed the order: DTAB < 12-2-12 < DDAB.\(^5,63,64\) Studies have also inferred that the clouding phenomenon in these conventional Pluronics can be impacted by the presence of additives, where both a deferral and an improvement were noticed.\(^2,16,31,65–67\) A small amount of an ionic surfactant drastically influences the CP of Pluronics. The temperature-dependent solution behavior for the examined Pluronics–cationic surfactant systems is presented in Figure 3. This clouding behavior compelled us to attempt understanding the phase behavior of L81 (1% w/v and 3% w/v) in aqueous solution.

The addition of the cationic surfactants in varying concentrations (0–50 mM) to 1% w/v Pluronics solution leads to a physical demarcation in the solution, i.e., a single (first) CP when subjected to increasing temperature. However, some mixed Pluronics–cationic surfactant systems even displayed a double CP, which could be due to the growth of micelles at the temperature (as revealed by the bluish region) close to their double CP, as depicted in Figure 3.

For 1% w/v L81 in the presence of 1–10 mM DTAB, i.e., before its CMC (pre-micellar region), the system shows a double CP. The first CP observed is solely due to L81 undergoing phase separation. This suggests the presence of Pluronic-rich micelles with a negligible influence of DTAB on the L81 behavior. A persistent increase in the temperature induces the Pluronic-rich micellar assembly to solubilize more DTAB, forming a colorless solution and then a bluish solution, progressively leading to 2ϕ (double CP). However, 1% w/v L81 in the presence of 15–25 mM DTAB, i.e., at and above the CMC (post-micellar region), the system does not show any evidence of the CP; only the bluish region is observed. This suggests that the presence of 15–25 mM DTAB contributes to the formation of mixed micelles. Upon further increasing the DTAB concentration above 30 mM, no 2ϕ is observed, i.e., CP > 100 °C, which may be due to the presence of a high concentration of the cationic surfactant, thereby forming cationic surfactant-rich mixed micelles.

A similar trend is followed in 1% w/v L81 for [12-2-12] and [DDAB], albeit at different concentration ranges. The CP appears between 1 and 5 mM for 12-2-12 and between 1 and 3 mM for DDAB, while above these respective concentrations, no 2ϕ is observed, i.e., the CP is above 100 °C. However, while the solutions with a low concentration of 12-2-12 show a double CP, the corresponding DDAB solutions show only one CP, which on further heating appears bluish with no evidence of the CP. The behavior of the DDAB solution is most likely due to its very low CMC and enhanced hydrophobicity. As observed for DTAB, an increasing concentration of 12-2-12 and DDAB with 1% w/v L81 leads to the formation of surfactant-rich mixed micelles.

Likewise, the phase behavior was observed for 3% w/v L81 with cationic surfactants (0–90 mM) (Figure 4), which followed a similar trend to that observed in the case of 1% w/v L81 solutions. Here, at low temperature and a lower concentration (5 to 10 mM) of cationic surfactants (DTAB and 12-2-12), the additives do not get solubilized in L81 micelles so that the system displays 2ϕ close to the CP of L81 (first CP). After this, it was observed that the cationic surfactants were found to solubilize in L81 micelles, forming a clear solution. On progressive heating, the solution turns bluish, indicating the presence of some bigger micellar assembly, which finally leads to 2ϕ. As such, although the transition points change with the concentration of L81, the qualitative behavior is the same in both systems.

The scattering data outlined in Figures 5 and 6 illustrate the critical relationship between the Pluronics–cationic surfactant mixed systems, demonstrating the important role of hydrophobic interactions expressed in terms of hydrodynamic diameter (Dₜ), which sheds light on the solubilization of cationic surfactants in L81 micelles.

It was clearly observed that the 1% w/v L81 solution showed a Dₜ of ∼114.8 nm at 30 °C, which first increases with the addition of 1 mM DTAB (∼140.6 nm), likely due to the incorporation of cationic surfactant molecules into polymer-rich mixed micelles. On increasing the concentration of DTAB from 3 to 50 mM, the system shows a drastic fall in Dₜ i.e., it appears as ∼41.0 nm (3 mM), ∼19.1 nm (10 mM), ∼8.9 nm (30 mM), and ∼6.5 nm (50 mM) at 30 °C. This is most likely due to a transition from large polymer-rich micelles to the much smaller cationic surfactant-rich micelles as the cationic surfactant concentration increases (Figure 5a). A similar trend was followed with 12-2-12. Here, too, the Dₜ increases initially in the presence of 1 mM 12-2-12 (∼166.56 nm). However, increasing the concentration of 12-2-12 from 3 to 50 mM, the Dₜ falls drastically, i.e., ∼62.63 nm (3 mM), ∼25.3 nm (10 mM), ∼10.3 nm (30 mM), and ∼7.2 nm (50 mM), at 30 °C (Figure 5a). Unlike DTAB and 12-2-12, no such significant
change in $D_h$ was noticed in the case of DDAB, which again could be due to its more hydrophobic nature (Figure 5a).

The temperature scan in 1% w/v L81 with 10 mM cationic surfactants reveals the influence of temperature on $D_h$ (Figure 5b). The $D_h$ of the mixed micelles is found to increase slightly with temperature, i.e., for DTAB, from $\sim19.1$ nm (at 30 °C) to $\sim27.4$ nm (at 40 °C), $\sim37.4$ nm (at 50 °C), and $\sim39.8$ nm (at 60 °C). For 12-2-12, the $D_h$ values were observed from $\sim25.3$ nm (at 30 °C) to $\sim31.0$ nm (at 40 °C), $\sim55.2$ nm (at 50 °C), and $\sim69.7$ nm (at 60 °C) (Figure 5b). A similar behavior is observed with 10 mM DDAB, but the increase in the $D_h$ is even more distinct than for the former two surfactants. Thus, as the cationic surfactant becomes more hydrophobic, the temperature effect is more pronounced, favoring the micellar

Figure 5. Size distribution profiles expressed in frequency vs hydrodynamic diameter ($D_h$) for (a) 1% w/v L81 with the increasing concentration of different cationic surfactants at 30 °C and (b) 1% w/v L81 with 10 mM cationic surfactants (fixed) as a function of temperature.
growth and the subsequent transition (Figure 5b). This is in qualitative agreement with the phase behavior, as shown in Figure 3.

The impact of cationic surfactants was also tested on 3% w/v L81 at 30 and 60 °C (Figure 6). The micellar core and corona get dehydrated at higher temperature, and therefore, the $D_h$ of

Figure 6. Size distribution profile ($D_h$) for 3% w/v L81 with 5 and 10 mM cationic surfactant as a function of temperature.
the micelles increases from 30 to 60 °C, probably giving a hint of the micelles undergoing a morphological growth/transition. Furthermore, it was clearly seen that at a very low concentration of cationic surfactants (~5 mM), the system formed polymer-rich micelles, while on increasing concentration of the cationic surfactant to 30 mM, the $D_0$ decreases drastically, suggesting that the copolymer gets solubilized in the cationic surfactant micellar core, thereby hinting at the formation of cationic surfactant-rich micelles. Such a trend in the size distribution profile endorses the effect of dehydration, which may influence the aggregation number ($N_{agg}$) and the micellar core size with a more compact PEO shell.

**SANS Analysis.** The solutions were further investigated using SANS to confirm the changes in the morphology as a result of the incorporation of cationic surfactants within the polymeric micellar aggregates. The scattering curves of individual components, i.e., 1% w/v L81 (multilamellar vesicles, $R_v = 14.57$ Å), 10 mM DTAB (spherical micelles, $R_s = 23.9$ Å), 10 mM 12-2-12 (cylindrical micelles, $R_c = 37.5$ Å, $L > 500$ Å), and 10 mM DDAB (multilamellar vesicles with a thickness of $\sim 20.8$ Å and a vesicle size of $R_v > 500$ Å of the utilizing $Q^{-2}$) in water (on account of SANS, D$_2$O) at 30 °C are presented in Figure 7.

![Figure 7](https://pubs.acs.org/acs.langmuir/2021/fig/7.png)

Figure 7. SANS data pattern for pure 10 mM surfactants: DTAB, 12-2-12, and DDAB, as well as 1% w/v Pluronics L81 at 30 °C.

In the low-$Q$ region of the SANS data for unilamellar vesicles (ULVs), the scattering intensity decreased in a straight line as $1/Q^2$, indicating the presence of large vesicles. At higher $Q$ values, there was increase in the drop of the intensity, and a minimum was observed, which depends on the thickness of the hydrophobic component (monolayer). These ULVs thus were characterized by the monolayer thickness ($t$) as the measurement of the radius of the vesicle ($R_v$) was limited by the $Q_{min}$ of the SANS instrument. The absence of lower cutoffs in the data indicates that the radii of the vesicles could be larger than what could be determined from the present $Q_{min}$ and therefore, the radius of the vesicle was kept fixed at a higher value than to a value of $2\pi/Q_{min}$ i.e., $\sim 500$ Å. On the other hand, in the SANS data from long cylindrical micelles, in the low-$Q$ region of the data, the scattering intensity decreased following a power law as $1/Q$, indicating the formation of long cylindrical micelles. These cylinders were characterized by the cross-sectional radius ($R_s$), while the measurement of their length ($L$) was limited by the $Q_{min}$ of the instrument.

Previous investigations have revealed the thickness of the ULVs to be significantly smaller due to the interdigitation of the hydrophobic tails. The scattering from the head group region is small and can be neglected. It is generally accepted that for the aggregates formed from surfactants, some solvent (D$_2$O) molecules penetrate the head group region to some extent and thus decrease the contrast, thereby reducing the apparent bilayer thickness measured by SANS.

SANS information sheds light on the morphology of L81 micelles upon the addition of cationic surfactants at different temperatures. The results of the SANS experiments revealed that the cationic surfactants greatly impacted the structural features of L81 micelles. Here, we have classified the concentration regimes of cationic surfactants as, low (0–3 mM) and high (10−50 mM) to enable a more systematic analysis, as presented in Figure 8.

To begin with, the formation of multilamellar vesicles in the neat 1% w/v L81 solution was confirmed from the shape of its pair distance distribution function, $p(r)$ (Figure 7). L81–DTAB data show observable changes in the scattering profile of micelles in the low DTAB regime, i.e., the scattering intensity decreases and the correlation peak shifts to a higher Q region (Figure 8a). Looking at the calculated structural parameters (Table 1), we infer that such a reduction in scattering intensity originated from the contraction of the micellar core along with the lowering in the $N_{agg}$ of L81. As a result, the numerical value of scattering length density highlights the contrast existing among the core, shell, and dispersion medium (D$_2$O) during data acquisition. As the cationic surfactant concentration increases, the Pluronics multilamellar vesicles change to ULVs at 1 mM DTAB concentration, with the size of the vesicle ($R_v$) of $> 500$ Å and the thickness of the vesicle ($t_v$) of 13.2, and then convert into cylindrical micelles at 3 mM, with a cross-sectional radius ($R_s$) of 19.3 Å, $L > 500$. As a result, 1 to 3 mM DTAB solutions in 1% w/v L81 show Pluronics-rich mixed micelles. Further increasing the concentration of DTAB from 10 to 50 mM led to the formation of ellipsoidal micelles with an increasing ratio of surfactant/Pluronics aggregation numbers, hence resulting in cationic surfactant-rich mixed micelles (Figure 8a), which is well in accordance with reported studies.

Furthermore, micelles did not associate to form large aggregates, most likely as a result of the surface charge imparted by DTAB molecules at 30 °C. As stated before, aggregation of charged micelles would depend on the relative concentration of the cationic surfactant in the mixed micelles (here estimated via $N_{agg}$ of DTAB) and on the size of the mixed micelles. This implies that a higher $N_{agg}$ of DTAB would be conducive to a more effective charge and greater separation among the micelles. The data shown in Table 1 thus suggest that aggregation of micelles would have been prevented by the appearance of an effective charge. DTAB can be seen to lead to saturation in the solubilization ability of L81 micelles and hence to excessive charge build-up in the shell region. As a result, micelles were stabilized to form Pluronics-rich mixed micelles and cationic surfactant-rich mixed ellipsoidal micelles.

The SANS data of the two other surfactants (12-2-12) and DDAB with L81 followed analogous trends. In (12-2-12), observations include reduction of Pluronic aggregation (327 to 10) and an increase in the aggregation number of surfactants (89 to 242) from 1 to 50 mM (Figure 8b) at 30 °C. For DDAB, there is also a decrease of Pluronic aggregation (190 to 38) and an increase in $N_{agg}$ of the surfactant (52 to 520) from...
Table 1. Fitted SANS Parameters (Semi-Major Axis (a), Semi-Minor Axis (b), Hard Sphere Radius (R_{hs}), Core Radius (R_c), Radius of Gyration (R_g), Cross-Sectional Radius (R_w), Effective Charge (\alpha), Length of the Rod (L), Thickness of the Vesicle (\tau), Size of the Vesicle (R_v), and Aggregation Number (N_{agg})) for 1% w/v L81 with Varying Concentrations of Cationic Surfactants at 30 °C

<table>
<thead>
<tr>
<th>system</th>
<th>morphology and parameter</th>
<th>N_{agg}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1% w/v L81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 unilamellar vesicles, (R_v = 14.6 \pm 0.06 ) Å, (R_c &gt; 500 ) Å</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 unilamellar vesicles, (R_v = 13.2 \pm 0.05 ) Å, (R_c &gt; 500 ) Å</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 cylindrical micelles, (R_v = 19.3 \pm 0.07 ) Å, (L &gt; 500 ) Å</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 ellipsoidal micelles, (a = 87.2 \pm 1.5 ) Å, (b = 40.3 \pm 0.09 ) Å</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 ellipsoidal micelles, (a = 30.0 \pm 0.08 ) Å, (b = 14.3 \pm 0.06 ) Å</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 ellipsoidal micelles, (a = 25.5 \pm 0.08 ) Å, (b = 14.5 \pm 0.06 ) Å</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1% w/v L81 + [DTAB], mM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 spherical micelles, (R_v = 69.6 \pm 1.2 ) Å</td>
<td></td>
<td>327</td>
</tr>
<tr>
<td>3 spherical micelles, (R_v = 60.2 \pm 1.1 ) Å</td>
<td></td>
<td>101</td>
</tr>
<tr>
<td>10 ellipsoidal micelles, (a = 228.1 \pm 1.9 ) Å, (b = 19.2 \pm 0.06 ) Å</td>
<td></td>
<td>59</td>
</tr>
<tr>
<td>30 ellipsoidal micelles, (a = 72.1 \pm 1.3 ) Å, (b = 28.2 \pm 0.07 ) Å</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>50 ellipsoidal micelles, (a = 70.6 \pm 1.3 ) Å, (b = 28.3 \pm 0.07 ) Å</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>1% w/v L81 + [DDAB], mM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 spherical micelles, (R_v = 58.1 \pm 1.1 ) Å</td>
<td></td>
<td>190</td>
</tr>
<tr>
<td>3 spherical micelles, (R_v = 50.4 \pm 1.0 ) Å</td>
<td></td>
<td>114</td>
</tr>
<tr>
<td>10 spherical micelles, (R_v = 28.8 \pm 0.07 ) Å</td>
<td></td>
<td>17</td>
</tr>
<tr>
<td>30 ellipsoidal micelles, (a = 82.8 \pm 1.4 ) Å, (b = 26.4 \pm 0.07 ) Å</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>50 cylindrical micelles, (R_v = 24.6 \pm 0.06 ) Å, (L = 267.2 \pm 2.1 ) Å</td>
<td></td>
<td>38</td>
</tr>
</tbody>
</table>

**Note:** the first \(N_{agg}\) value stands for L81 and the second value stands for the surfactant.

The SANS data of mixed systems composed of Pluronics with 10 mM cationic surfactants are shown in Figure 9 as a function of temperature. The variations in the form of the scattering data of L81 with 10 mM DTAB, as shown in Figure 9a, illustrate that the shape of the aggregates is strongly dependent upon the composition of the solution. As the temperature increases from 30 to 60 °C, we have observed the micellar transition from ellipsoidal micelles to ULVs with increasing micellar thickness (Table 2). Only the ellipsoid model captured the shape of the mixed aggregates in the measured Q range at 30 °C. The scattering data at these concentrations have been analyzed using the ellipsoid model, considering the inter-micellar interactions. This model incorporates the ellipsoidal growth with a minor/major axis ratio, and for aggregation numbers greater than that which will pack into a sphere, the formation of ellipsoids results.

In the case of (12-2-12), the data show micellar transitions from ellipsoidal micelles (at 30 °C) to cylindrical micelles (at 40 and 50 °C) to ULVs (at 60 °C) with the increasing cross-sectional radius (Figure 9b). The fitted parameters obtained from the data analysis are shown in Table 2. In contrast, in 1% w/v L81 with 10 mM DDAB, the analysis of scattering data suggests the presence of spherical micelles, which do not significantly change shape as a function of temperature (Figure

Figure 8. SANS curves with the structure factors and associated conformations for 1% w/v L81 at 30 °C with varying concentrations of different cationic surfactants: (a) DTAB; (b) 12-2-12; and (c) DDAB.

1 to 50 mM (Figure 8c). To compare the cationic surfactants, the same lengths of the hydrophobic tails increase the aggregation number, following the trend DTAB < (12-2-12) < DDAB, due to the increasing hydrophobicity of the surfactant.
Although the overall Nagg increases somewhat with temperature, the relative proportion of L81/DDAB remains constant at approximately 0.37 (see Table 2). This confirms our previous assertion (see Figure 5) that temperature causes a slight increase in the aggregate size for the DDAB/L81 system but does not change the morphology of the aggregates.

Figure 10 shows a higher scattered intensity due to the formation of micelles in the 3% w/v L81 solution. SANS data for solutions of cationic surfactants with varying concentrations are given in Table 3. Lower scattered intensity is attributed to the unimer in solution. The increase in the scattered intensity can be understood in terms of change in the contrast \((\rho_m - \rho_s)^2\) between the micelle and the solvent. However, an increase in neutron scattering intensity is due to an increase in the size of the PPO core. Upon the addition of an increasing concentration of the cationic surfactant (5 to 30 mM), the micelle size decreases as the addition of the cationic surfactant destroys the aggregates of L81. Due to the hydrogen bond and hydrophobic interactions between L81 and the cationic surfactant, surfactant cations align within the L81 micelles to form mixed micelles. On one hand, this enhances the electrostatic repulsion between PEO groups of L81, and on the other hand, due to the preferential partitioning in the hydrophobic region, the surfactants will interact with dehydrated PPO blocks. Therefore, electrostatic repulsion opens up the micelle and the tail chains of surfactant molecules permeate into the PPO block and remove the L81 monomer, thus decreasing the size of micelles. These results are in agreement with the DLS study (Figure 6).

Furthermore, 3% w/v L81 at 30 °C contains ULVs with a thickness of \(t_v = 56.0 \pm 0.1\) Å, while upon increasing the temperature to 60 °C, it aggregates. The intensity of the scattering is reduced in the presence of 5 mM cationic surfactants (DTAB, 12-2-12, and DDAB); the micelles are spherical with \(N_{agg}\) of 230 and 103, spherical with \(N_{agg}\) of 78 and 35, and spherical with \(N_{agg}\) of 104 and 46, respectively, at 30 °C. This means that, interestingly, the surfactant/L81 ratio in the mixed micelles is approximately the same for all three surfactants.

**Table 2. Fitted SANS Parameters for 1% w/v L81 with 10 mM Different Cationic Surfactants as a Function of Temperature**

<table>
<thead>
<tr>
<th>system</th>
<th>(T, (^{\circ}C))</th>
<th>morphology and parameters</th>
<th>(N_{agg})</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mM</td>
<td>30</td>
<td>ellipsoidal, (a = 87.2 \pm 1.5) Å, (b = 40.3 \pm 0.09) Å</td>
<td>112 304</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>unilamellar vesicles, (t_v = 58.7 \pm 1.1) Å, (R_v &gt; 500) Å</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>unilamellar vesicles, (t_v = 101.7 \pm 1.5) Å, (R_v &gt; 500) Å</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>unilamellar vesicles, (t_v = 148.9 \pm 1.7) Å, (R_v &gt; 500) Å</td>
<td></td>
</tr>
<tr>
<td>10 mM</td>
<td>30</td>
<td>ellipsoidal micelles, (a = 228.1 \pm 1.9) Å, (b = 19.2 \pm 0.06) Å</td>
<td></td>
</tr>
<tr>
<td>12-2-12</td>
<td>40</td>
<td>cylindrical micelles, (R_v = 30.7 \pm 0.07) Å, (L &gt; 500) Å</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>cylindrical micelles, (R_v = 34.1 \pm 0.08) Å, (L &gt; 500) Å</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>unilamellar vesicles, (t_v = 38.5 \pm 0.08) Å, (R_v &gt; 500) Å</td>
<td></td>
</tr>
<tr>
<td>10 mM</td>
<td>30</td>
<td>spherical micelles, (R_v = 28.8 \pm 0.07) Å</td>
<td>17 46</td>
</tr>
<tr>
<td>12-2-12</td>
<td>40</td>
<td>spherical micelles, (R_v = 32.7 \pm 0.08) Å, (\alpha = 0.32, R_{hs} = 43.4 \pm 0.09) Å</td>
<td>25 67</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>spherical micelles, (R_v = 34.7 \pm 0.08) Å, (\alpha = 0.29, R_{hs} = 45.9 \pm 0.1) Å</td>
<td>29 80</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>spherical micelles, (R_v = 35.1 \pm 0.08) Å, (\alpha = 0.24, R_{hs} = 47.3 \pm 0.1) Å</td>
<td>30 83</td>
</tr>
</tbody>
</table>

\(^a\)Note: the first \(N_{agg}\) value stands for L81 and the second value stands for the surfactant.
this concentration. Both the 12-2-12 and DDAB systems (but not DTAB) exhibit micellar transitions from spherical to ellipsoidal with increasing $N_{agg}$ with increasing temperature from 30 to 60 °C. It is clearly seen that as the concentration of surfactant increases, the $N_{agg}$ and the micellar size decrease because of the above-mentioned transition from Pluronics-rich to cationic surfactant-rich mixed micelles, which agrees very well with the published study.\textsuperscript{17}

As shown in Figure 10, the addition of a cationic surfactant causes a decrease in the scattering profile, indicating a higher degree of Pluronics/ionic surfactant interaction responsible for demicellization. The decrease in the aggregation number was evidenced, confirming the role of the chain length of the cationic surfactant. Due to preferential partitioning in the hydrophobic region, cationic surfactants will interact with the dehydrated PPO blocks. In other words, long chain incorporation into the micelle core drives out copolymer monomers, which is responsible for the decrease in size.

**CG-MD Simulations.** As described in the previous section, the behavior of L81 in the aqueous phase is considerably affected upon the addition of the cationic surfactants. Thus, the impact of DTAB, DDAB, and 12-2-12 on the L81 aggregation in aqueous solution was further analyzed through CG-MD simulations. It should be noted at the outset that, due to limitations on the size and length scales of the systems accessible to CG-MD simulations with an explicit solvent, it is difficult to quantitatively replicate the conditions of the experimental work (particularly those used in SANS measurements). Hence, we aim primarily to draw a qualitative comparison and gain insights into the physical mechanisms.

![Figure 10](https://doi.org/10.1021/acs.langmuir.2c03176)
Table 3. Fitted SANS Parameters for 3% w/v L81 with 5 and 30 mM Different Cationic Surfactants as a Function of Temperature

<table>
<thead>
<tr>
<th>system</th>
<th>T, °C</th>
<th>morphology and parameters</th>
<th>N_{agg}</th>
</tr>
</thead>
<tbody>
<tr>
<td>3% w/v L81</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>30</td>
<td>unilamellar vesicles, ( \tau_s = 56.0 + 1.0 , \text{Å} ), ( R_g &gt; 500 , \text{Å} )</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3% w/v L81 + [DTAB], mM</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>spherical, ( R_g = 61.8 + 1.2 , \text{Å} )</td>
<td>230</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>103</td>
</tr>
<tr>
<td>60</td>
<td>30</td>
<td>spherical, ( R_g = 31.0 + 0.08 , \text{Å} )</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>64</td>
</tr>
<tr>
<td>60</td>
<td>30</td>
<td>spherical, ( R_g = 30.7 + 0.08 , \text{Å} )</td>
<td>159</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>426</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3% w/v L81 + [12-2-12], mM</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>spherical, ( R_g = 43.5 + 0.09 , \text{Å} )</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>60</td>
<td>30</td>
<td>ellipsoidal, ( a = 130.6 + 1.5 , \text{Å} ), ( b = 48.4 + 0.1 , \text{Å} )</td>
<td>288</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>129</td>
</tr>
<tr>
<td>60</td>
<td>30</td>
<td>spherical, ( R_g = 30.5 + 0.07 , \text{Å} )</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>54</td>
</tr>
<tr>
<td>60</td>
<td>30</td>
<td>ellipsoidal, ( a = 58.2 + 0.09 , \text{Å} ), ( b = 27.5 + 0.07 , \text{Å} )</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3% w/v L81 + [DDAB], mM</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>spherical, ( R_g = 47.9 + 0.09 , \text{Å} )</td>
<td>104</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>46</td>
</tr>
<tr>
<td>60</td>
<td>30</td>
<td>ellipsoidal, ( a = 128.8 + 1.5 , \text{Å} ), ( b = 55.6 + 1.1 , \text{Å} )</td>
<td>375</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>168</td>
</tr>
<tr>
<td>60</td>
<td>30</td>
<td>spherical, ( R_g = 35.7 + 0.07 , \text{Å} )</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>86</td>
</tr>
<tr>
<td>60</td>
<td>30</td>
<td>spherical, ( R_g = 41.7 + 0.08 , \text{Å} )</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>137</td>
</tr>
</tbody>
</table>

“Note: the first \( N_{agg} \) value stands for L81 and the second value stands for the surfactant.”

governing self-assembly and interactions between the different components of the system. Concretely, we used 3% w/v Pluronic instead of 1% w/v since the latter was too diluted to observe a meaningful aggregation within a reasonable computational time. For the same reason, we ran surfactant concentrations between 5 and 90 mM. The L81 aqueous solution at 3% w/v concentration (run 5) was taken as a reference, and it was run for 1000 ns. This system quickly formed a single L81 aggregate, as noticed in the simulation snapshot shown in Figure 11a. The density profile was obtained with the cluster counting code where the density of selected CG beads was displayed from the micelle center of mass (CoM), as shown in Figure 11b. The density profile shows a spherical aggregate with an estimated radius of \( \sim 2.5 \) nm. Given the relatively small size of the simulation boxes (already at the limit of what can be reasonably achieved with present computational resources), we would not expect the L81 solution to form complete vesicles during the simulation. Instead, the outcome simply suggests that the equilibrium aggregation number for this system is larger than 50.

**L81/DTAB/Water Mixture.** A set of four CG-MD simulations were prepared (runs 6, 7, 8, and 9 described in Table S1 of the Supporting Information) considering four DTAB concentrations (5, 10, 30, and 90 mM) to analyze the impact of DTAB concentration on L81 aggregates and to shed light onto the results shown in the experimental section. The systems were equilibrated and run for 1000 ns where the last simulation snapshots for each system are displayed in Figure 12a,c,e,g. At 5 mM DTAB concentration, L81 quickly formed a single aggregate like that in L81 aqueous solution (run 5), reflecting a weak impact of the relatively few DTAB molecules present. Figure 12b displays the density profile of L81 aggregates with adsorbed DTAB and Br⁻ at the surface (see the green and purple DTAB peaks around the L81 PEO peak colored in orange). A similar behavior was found when the DTAB concentration was increased to 10 mM. The DTAB molecules were located at the L81 surface, as illustrated in the simulation snapshot shown in Figure 12c and noticed in the density profile shown in Figure 12d. Conversely, with 30 mM DTAB, the system exhibited smaller L81/DTAB micelles, as shown in Figure 12e. Thus, the increase in available DTAB molecules promoted an increased interaction with L81 in the initial stages of the self-assembly and therefore increased the charge density on the L81 micelle surface. This could be the reason behind the formation of smaller micelles, as also noticed in mixtures of aqueous solutions of Pluronic and ionic liquids.⁵¹,₂⁴,₆¹,₆² According to these results, the observed behavior suggests that repulsive inter-micelle interactions that play the main role in the self-assembly, hindering the formation of larger L81 aggregates. The L81 system with 5 and 10 mM DTAB displayed micelle surface charges of 0.20 and 0.38 nm⁻², respectively, whereas 0.7 nm⁻² was observed in the 30 mM mixture. As expected, the impact was more evident when the DTAB concentration was increased to 90 mM where more L81/DTAB micelles were formed, displaying a L81 micelle surface charge of 1.2 nm⁻² (Figure 12g).

In fact, at 90 mM DTAB, the mixture exhibited more micelles (Figure 12g), but the average diameter—roughly estimated by the maximum of the L81 PEO peak shown in orange in Figure 12h—was greater than that of the micelles.

**Figure 11.** (a) CG-MD simulation snapshot for the 3% w/v of L81 aqueous solution at 333 K. (b) Density profile of the obtained aggregate taking the CoM as reference. The color code is as follows; the PEO and PPO groups in the L81 are colored in orange and black, respectively, and water is in blue. The water molecules in the simulation snapshot (a) were removed for clarity.
(Figure 12e) obtained in the 30 mM DTAB mixture (Figure 12f). This reflects the different self-assembly mechanisms that dominate as the cationic surfactant concentration increases. By analyzing the CG-MD trajectories, the micelle formation can be explored at different self-assembly stages. Figure S1a–d shows the aggregation process at every 200 ns of simulation time for all DTAB concentrations. In the first 200 ns, the initial stages of self-assembly at the three lowest concentrations were dominated by the formation of L81 aggregates onto which DTAB molecules were adsorbed. In contrast, in the 90 mM mixture, the DTAB micelle formation competed with the formation of L81 aggregates, with some L81 monomers even adsorbing onto DTAB micelles. In fact, in the first 200 ns, the 90 mM system was the only one displaying isolated DTAB micelles. In the next stages of the simulation, the 5, 10, and 30 mM samples behaved similarly with L81 micelles dominating the aggregation and adsorbing DTAB moieties, especially noticeable in the 30 mM system since more DTAB units are available but not enough to form isolated DTAB micelles.

In summary, the MD simulations results for this system infer a relative gradual transition from Pluronic-rich to cationic surfactant-rich aggregation as the surfactant concentration is increased. Furthermore, at low ionic surfactant concentrations, the self-assembly process does not seem to be much affected by the presence of the ionic surfactant, with aggregates resembling those formed in the pure L81 solution.

L81/12-2-12/W Mixture. Four 12-2-12 concentrations (5, 10, 30, and 90 mM) were added to the 3% w/v L81 aqueous solution and simulated by CG-MD (runs 10, 11, 12, and 13 in Table S1). Figure 13a,c,e,g displays the last simulation snapshots for each system after 1000 ns. At 5 mM, the L81 quickly forms two micelles, the density profile of which is
Figure 14. CG-MD simulation snapshots, with the density profiles focused on the micelle surface, for the 3% w/v L81 aqueous solution with four DDAB concentrations; (a,b) 5, (c,d) 10, (e,f) 30, and (g,h) 90 mM. The color code is the same as that in Figure 11. Water and bromide counterions were removed in the simulation snapshots for clarity.

shown in Figure 13b, with adsorbed 12-2-12 molecules at the L81 micelle surface. For the 10 mM system, only one L81 micelle with adsorbed 12-2-12 was formed, as shown in Figure 13c. Thus, L81 still dominated the aggregation, and the 12-2-12 molecules seemed to cooperate in the L81 micelle formation. The increased charge density of the micelle surface from 0.3 nm$^{-2}$ in 5 mM to 0.7 nm$^{-2}$ in the 10 mM solution was not a barrier for micelle growth, and the hydrophobic strength of the double alkyl tail seemed to overcome any inter-micelle repulsions due to the increased density of charge. The micelle density profile is shown in Figure 13d, where all 12-2-12 head groups were arranged close to the L81 PEO groups at the micelle surface. Conversely, the 30 mM 12-2-12 mixture exhibited two micelles, as shown in Figure 13e, where the surfactant was more noticeable than at lower concentrations. At 30 mM, the charged 12-2-12 head groups seemed to overcome the double alkyl tail hydrophobic contribution in the self-assembly, exhibiting an increased micelle density of charge of 1.3 nm$^{-2}$. The 30 mM system yielded two micelles, like the 5 mM system, but the micelles were more voluminous, as can be noticed in the micelle density profile shown in Figure 13f. Furthermore, more 12-2-12 can be found out of the micelle surface, as can be seen if one compares the charged head groups (purple peak) in both the 5 and 30 mM profiles. Thus, between 10 and 30 mM 12-2-12 concentrations, we found a threshold in the L81 micelle formation, likely related with two competing forces: hydrophobic versus electrostatic interactions at the surface. Finally, Figure 13g shows the aggregates obtained in the 90 mM mixture with a clear dominance of 12-2-12, where the L81 moieties were adsorbed before having any chance to form separate micelles. The aggregate shown at the bottom right of Figure 13g is a folded micellar rod. The density profile is shown in Figure 13h, with the wider curves reflecting the fact that rod-like aggregates were formed.

To understand the complex micelle formation scenario displayed in Figure 13 with the conflicting impact of the hydrophobic and charge contributions of 12-2-12 in the L81 self-assembly, the initial stages of micelle formation were analyzed. The simulation snapshots at every 200 ns of simulation time for 5, 10, 30, and 90 mM 12-2-12 concentrations are shown in Figure S2. In the initial stage of aggregation of the 5 mM system (Figure S2a), L81 clearly dominated the aggregation where the 12-2-12 monomers were adsorbed onto L81 aggregates. Then, in the first 200 ns, the L81 initial small aggregates grew to form four micelles, which were relatively stable until 600 ns with the formation of two micelles that were stable during the next 400 ns. It is likely that these two micelles will fuse to form a single aggregate at equilibrium, given sufficient simulation time. Conversely, in the initial stages of the 10 mM system (Figure S2b), some 12-2-12 small aggregates were formed and coexisted with the L81 aggregates. However, after 200 ns, three L81 micelles with all 12-2-12 adsorbed were stable until 600 ns, finalizing with micelle fusion into a single aggregate in the next 400 ns. By comparing the dynamics of the micelle distribution along the 1000 ns of simulation for the 5 and 10 mM systems, the micelle fusion processes proceeded faster in the more concentrated system if one compares the micelle distributions between 200 and 600 ns displayed in Figure S2a,b. For the 30 mM solution, Figure S2c shows a similar scenario when compared with the 10 mM system, but the formation of 12-2-12 micelles in the initial stages was more evident. Over 1000 ns, the 30 mM system displayed more micelles when compared with that in the 10 mM solution, suggesting that inter-micelle repulsions—due to increased micelle surface charge density—began to play an important role in the aggregation process. At 90 mM, the initial stage was dominated by the formation of 12-2-12 micelles, as clearly illustrated in Figure S2d, where only a few L81 moieties were able to form some small aggregates with no more than two or three monomers each. After 200 ns, the system already formed micellar rods with adsorbed L81 as expected in a pure 12-2-12 aqueous solution (Figure 2d), and these remained stable along the next 800 ns.

Hence, the MD results for this solution also show a clear transition from Pluronic-rich aggregates to cationic surfactant-rich aggregates, as observed in the solution with DTAB. However, the 12-2-12 surfactant seems to exert a stronger effect at low concentrations, leading to the formation of smaller aggregates than in the pure L81 solution, or at least to a significant slow-down of the dynamics of micelle fusion.
Furthermore, the 12-2-12 surfactant seems to promote the formation of rod-like, or at least elongated structures at high surfactant concentrations. Given the limited time and length scales of the simulations, it is not completely clear if these represent true equilibrium structures or transient structures that would evolve, say, toward larger vesicles, as seems to be implied by the analysis of SANS data.

**L81/DDAB/W Mixture.** Four simulations (runs 14, 15, 16, and 17 in Table S1) were carried for the 3% w/v L81 aqueous solutions with four DDAB concentrations (5, 10, 30, and 90 mM). The CG-MD simulation snapshots after 1000 ns are shown in Figure 14a, c, e, g. At 5 mM, the L81 quickly formed two micelles with adsorbed DDAB (Figure 14a), as was also observed in the 5 mM 12-2-12 system (Figure 14a), but different from that in the 5 mM DTAB system (Figure 12a) where a single micelle was formed after 1000 ns. Thus, even at a low DDAB surfactant concentration, the charge density of the surfactant head groups seems to impact the L81 aggregation. The micelle density profile displayed in Figure 14b shows a similar surfactant arrangement around the micelle surface to that in the 12-2-12 and DTAB solutions, where the cationic head groups (purple) were placed close to the L81 PEO groups (orange). At 30 mM, L81 still dominates the aggregation, exhibiting an L81 micelle with adsorbed DDAB, as was found in the 12-2-12 and DTAB 10 mM mixtures shown in Figures 14c and 12c, respectively. However, the density profile shown in Figure 14d highlights the fact that the DDAB charged head groups were arranged further inside the L81 micelle surface delimited by the PEO groups colored in orange. This suggests that the double alkyl tail facilitates the arrangement (more hydrophobic) of DDAB in the L81 micelle core, in contrast to the lower hydrophobic strength of DTAB, while the lower charge density of the DDAB head group facilitates this task when compared with the case of 12-2-12. DDAB increased the hydrophobicity, and a lower head group charge density character became more pronounced at 30 mM. Figure 14e shows the obtained micelle, which Basically consists of DDABs with adsorbed L81 moieties, as was observed in the DTAB system (Figure 12c) but different from the case of 12-2-12 (Figure 13e), where two micelles were obtained. This reflects the fact that the head group charge density played the main role in the aggregation process in the 12-2-12 system, as pointed out previously. In DDAB, the lower charge density of the head group facilitates this task when compared with the case of 12-2-12. The micelle density profile of DDAB 30 mM is shown in Figure 14f where the wider curves point toward a prolate-shaped micelle with the DDAB alkyl tails well inside the core. In fact, the peaks observed at ~0 (micelle CoM) mean that the prolate-shaped aggregate is a proto-vesicle since bromides (red) and DDAB head groups (purple) are found at the CoM (red and purple maximum peaks at ~0). When the DDAB concentration is increased to 90 mM, the ion surfactant clearly dominates the aggregation, displaying a large rod-like aggregate basically formed by DDABs with adsorbed L81, as shown in Figure 14g. At this high concentration, DDAB behaves more like the 12-2-12 surfactant since a similar aggregate was found (Figure 13g). Nevertheless, the density profile shown in Figure 14h clearly describes a rod-like vesicle since not only bromides and DDAB head groups—red and purple, respectively—but also water and L81 PEO groups—blue and orange, respectively—are found in the CoM.

A detailed analysis of the aggregation processes at different stages is shown in Figure S3. At 5 and 10 mM (Figure S3a, b), L81 governed the aggregation with the formation of early micelles, where the DDAB monomers were adsorbed completely in the first 200 ns before any chance to form surfactant micelles. Then, the L81 micelle growth proceeded by fusion processes, similarly in both systems, with the micellization being slightly slower in the 5 mM system, in which two micelles remained in solution but only one remained in the 10 mM system. At 30 mM, there was a clear competition between the L81 and DDAB micelle formation, as can be seen in the first snapshot of Figure S3c. In the first stage, the L81/DDAB and DDAB/L81 micelles coexisted, quickly forming L81/DDAB hybrid micelles after 200 ns. Above 400 ns, all micelles were unified in one rod-like vesicle, as shown by the density profile in Figure 14f, which was stable for the next 600 ns. When the DDAB concentration was increased to 90 mM, DDAB clearly dominated the micelle formation in the initial stage, as can be seen in Figure S3d. However, L81 still formed some small aggregates, but they were completely adsorbed by the DDAB micelles in the first 200 ns. Then, a quick micelle fusion yielded a rod-like vesicle that remained stable for the next 600 ns.

Thus, the main conclusion that can be extracted from the CG-MD simulations is that the hydrophobicity of the alkyl tails and the density of charge of the head groups had a significant impact on the L81 aggregation. The dilute aqueous solution of the studied surfactants displayed spherical micelles, rod-like micelles, and vesicles for DTAB, 12-2-12, and DDAB, respectively, as in the experiments. This diverse behavior, related to the hydrophobic versus head group charge density balance, was translated in different structures, depending on the surfactant concentration; from L81/DDAB (5–10 mM) or DTAB/L81 (30–90 mM) micelles to L81/DDAB (5–10 mM) spherical micelles, 12-2-12/L81 (30–90 mM) rod-like structures, L81/DDAB (5–10 mM) spherical micelles, or DDAB/L81 (30–90 mM) vesicles. Thus, above the 10 mM surfactant concentration, in all studied systems, the surfactant overcome the L81 aggregation dominance, but slight differences were also found at lower concentrations. A brief visual analysis of the simulation snapshots displayed in Figures S1–S3 reveals that DTAB yielded smaller micelles than the 12-2-12 solutions, and the micelle size distribution of DDAB was in between them. The double alkyl tail and double head group charge displayed by 12-2-12 produced bigger aggregates overall, whereas the double alkyl tail/single charge head group promoted the formation of vesicles with aggregates slightly smaller than those found in the 12-2-12 solutions. Finally, the single alkyl tail/single head group charge of DTAB yielded spherical micelles over all concentrations with a decreased micellar distribution size as soon as the ionic surfactant concentration is increased, in agreement with CP measurements of Pluronic aqueous solutions with ionic liquids.37

**CONCLUSIONS**

The present study focuses on the phase behavior and micellization conduct of L81 in the presence of cationic surfactants (DTAB, 12-2-12, and DDAB) investigated from different techniques. The difference in the interactions of these ionic surfactants with Pluronics L81 stems from the dissimilarities in the size/structure and hydration of the head groups. This influences the clouding behavior of L81. That is,
the CP of L81 gets influenced (delayed) dramatically in the presence of the cationic surfactants, which is attributed to the hydrogen bond interactions between the cation of the ionic surfactant and PEO units of L81 and the induced hydrophobic interactions between the alkyl chain of the cationic surfactant and the hydrophobic chain of L81. The DLS results showed that the micelle size decreases as the electrostatic repulsion between PEO groups of L81 is increased due to the permeation of the cationic surfactant and forms small scale aggregates. The presence of the cationic surfactant within the micelles results in enhanced polarity with the significantly altered CP, micelle size, and aggregation number. Furthermore, the structure of the head groups of surfactants and the hydrophobic character of Pluronics affect the structure of the final micellar aggregates. This has been probed from SANS analysis where the composition dependence of the mixed aggregates is depicted quantitatively to derive the micellar shape parameters. Such a trend is attributed to the incorporation of the cationic surfactant correlated with the appearance of positive charge adsorbed at the surface of L81 micelles, which induced micellar transitions. That is, at a low concentration (≤3 mM), the cationic surfactant stimulated the formation of smaller Pluronics-rich mixed micelles in a higher number, while at its high concentrations (50 mM) it formed cationic surfactant-rich mixed micelles. Experimental findings explaining the effect of cationic surfactants on the behavior of Pluronics in an aqueous solution were further corroborated employing MD simulations, and the approach was able to reproduce the micelle distribution experimentally obtained as well as the micelle shapes. Overall, the study here reported offered a fresh insight into the aggregation behavior of hydrophobic Pluronics L81 in the presence of cationic surfactants to form mixed micellar systems, which may turn out to be fairly useful in many applications involving micellar media.

■ ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.langmuir.2c03176.

The modeling of the SANS data described in detail following the eqs S1 to S18; details of the CG-MD simulations carried out in this work; CG-MD simulation snapshots at different stages for the 3% w/v L-81 aqueous solution mixed with (a) 5, (b) 10, (c) 30, and (d) 90 mM concentration of DTAB, 12-2-12, and DDAB (PDF)

■ AUTHOR INFORMATION

Corresponding Author
Ketan Kuperkar — Department of Chemistry, Sardar Vallabhbhai National Institute of Technology (SVNIT), Surat, Gujarat 395 007, India; orcid.org/0000-0001-8039-9012; Email: ketankuperkar@gmail.com

Authors
Divya Patel — Department of Chemistry, Sardar Vallabhbhai National Institute of Technology (SVNIT), Surat, Gujarat 395 007, India
Germán Pérez-Sánchez — CICECO—Aveiro Institute of Materials, Department of Chemistry, University of Aveiro, Aveiro 3810-1933, Portugal

Miguel Jorge — Department of Chemical and Process Engineering, University of Strathclyde, Glasgow G1 1XJ, U.K.; orcid.org/0000-0003-3009-4725
Debes Ray — Solid State Physics Division, Bhabha Atomic Research Centre (BARC), Mumbai, Maharashtra 400 085, India; Biomacromolecular Systems and Processes, Institute of Biological Information Processing, Forschungszentrum Julich, Julich 52428, Germany; orcid.org/0000-0001-5564-2973
Vinod K. Aswal — Solid State Physics Division, Bhabha Atomic Research Centre (BARC), Mumbai, Maharashtra 400 085, India
João A. P. Coutinho — CICECO—Aveiro Institute of Materials, Department of Chemistry, University of Aveiro, Aveiro 3810-1933, Portugal; orcid.org/0000-0002-3841-743X
Pratap Bahadur — Department of Chemistry, Veer Narmad South Gujarat University (VNSGU), Surat, Gujarat 395 007, India

Complete contact information is available at: https://pubs.acs.org/doi/10.1021/acs.langmuir.2c03176

Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge the Sardar Vallabhbhai National Institute of Technology (SVNIT), Gujarat, India, for providing the instrumentation facilities. The computational part of this work was funded by CICECO-Aveiro Institute of Materials under the projects UIDB/50011/2020, UIDP/50011/2020, and LA/P/0006/2020 and financed by national funds through the FCT/MEC (PIDDAC). G.P.-S. acknowledges national funds (OE), through FCT—Fundação para a Ciência e a Tecnologia, LP5 in the scope of the framework contract foreseen in the numbers 4, 5, and 6 of the articles 23, of the Decree-Law 57/2016, of August 29th, changed by Law 57/2017, of July 19th.

■ REFERENCES


(47) Sangwai, V.; Suresh Kumar, R. Coarse-grained molecular dynamics simulations of the sphere to rod transition in surfactant micelles. *Langmuir* 2011, 27, 6628−6638.


