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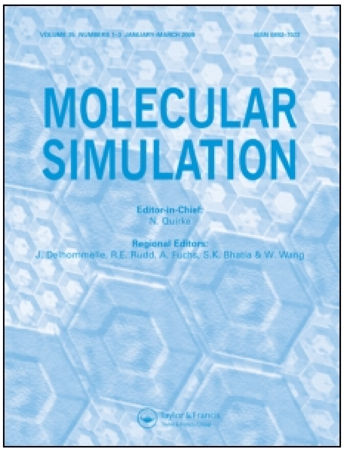

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Problems with transdermal drug delivery were directly associated with the skin barrier which is the lipid bilayer at the *stratum corneum*. Chemical penetration enhancers such as swollen micelles that formed from the solubilisation of the surfactants in the nano-emulsion system could provide an effective solution. However, the structural properties of swollen micelles from nano-emulsions of palm-oil esters, whose behaviour is related to colloidal systems, have not been studied in great detail. In this paper, we report on the use of molecular dynamics (MD) simulations to investigate the structural properties of swollen micelles of oleyl oleate (OE). Five series of 10 ns MD simulations were performed at different micelle compositions to determine the structural evolution of OE/Span20 (S20) swollen micelles. We also carried out four MD simulations on the structure of S20, OE/S20, Tween80 (T80) and OE/T80 micelles to study the effect of different surfactants and the addition of OE into the systems. The shapes of the swollen micelles were observed to vary by the difference in the micelle composition, the surfactants used and the addition of OE. The results were correlated with published theory, and consistent with experimental results on the phase behaviour of the nano-emulsion system.

Keywords: molecular dynamics; oleyl oleate; swollen micelle; nano-emulsions

1. Introduction

Solubilisation of surfactant micelles in the emulsion system gives many advantages as it produces swollen micelles that are more thermodynamically stable than the emulsion itself [1]. Swollen micelles are known for their potential application in pharmaceutical fields as a drug carrier for controlled release systems. These vehicles are reported to have a momentous potential to increase the penetration of amphiphilic, lipophilic and hydrophilic materials through the skin compared to conservative transporters [2]. The release mechanisms are dependent on physico-chemical properties of the components, internal structure of the swollen micelle and its interactions with the drug carried [3].

Nano-emulsions of palm-oil esters had shown promises to be employed as a chemical penetration enhancer for transdermal drug delivery systems [4]. The long hydrocarbon chain of these fatty esters is an advantage for producing oilier nano-emulsions. This highly hydrophobic system is a good carrier for hydrophobic drugs as it can hold the drugs until released by the drug release mechanism [5]. As with any other emulsion system, solubilisation of non-ionic surfactant micelles occurs in nano-emulsions of palm-oil esters. This process eventually involved the uptake of the oil droplet in the nano-emulsions by the non-ionic surfactants to form the palm-based swollen micelles [1].

1.1 *The system studied*

The ternary phase systems involved in this research are those of oleyl oleate (OE)/Span20 (S20)/H_2O and OE/Tween80 (T80)/H_2O. OE (Figure 1(a)) is a palm-oil ester that has been widely used in cosmetic, pharmaceutical and lubricant industries. OE is highly hydrophobic with two C_{18} hydrocarbon chains having a small polar ester group (head-group) area. The hydrophobicity of OE enables it to self-associate into colloidal systems such as micelles. OE can be synthesised by enzymatic reactions of oleic acid and oleyl alcohol [6]. Both surfactants (S20 and T80 in Figure 1(b) and (c), respectively) are non-ionic but differ by their hydrophile–lypophile balance (HLB) value. The phase behaviour of the OE/S20/H_2O nano-emulsion system had been reported elsewhere [7] while that of the OE/T80/H_2O system was determined experimentally.

2. Molecular dynamics simulations

2.1 *Self-assembly of swollen micelles*

The assembly of molecules into an aggregate is not entropically encouraging and occurs only when it is energetically favoured. However, isotropic molecules such as dissolved hydrocarbons in water can associate into large droplets which, above the solubility limit, grow into a separate phase [8]. This association is due to the strong

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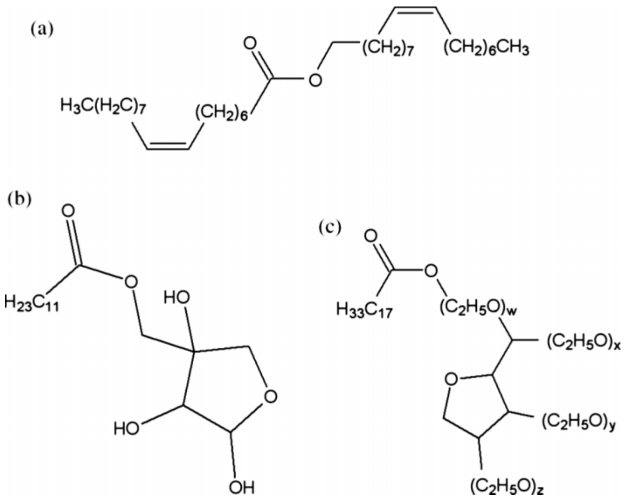

Figure 1. Molecular structures of (a) OE, (b) S20 and (c) T80.

hydrophobic attraction between hydrocarbon molecules in water. The self-assembly of the swollen micelles is primarily driven by the hydrophobic effect supplied by the polar and non-polar groups of the associated molecules. However, the formation of swollen micelles is dependent on the presence of water in large quantities relative to the oil and surfactants. Theoretically, in the studied swollen micelles, the surfactant molecules hold the role of minimising the energetically unfavourable interactions of their hydrophobic tails and OE molecules with water [9]. Based on the structural and physico-chemical properties of OE, we predicted that its addition will increase the non-polar region in the core of the aggregate that formed. Thus, the shape and size of the aggregate formed, which are intimately related and sensitive to the composition, temperature and solution conditions, will be effected. The relationship between the head-group area and chain length to the shape of the resulting aggregate has been previously reported [8] (Supplementary Material, Part I).

This will lead to the estimation that the resulting structure from the solubilisation of surfactants will vary in terms of shape such as spherical, cylindrical or cubical micelle, lamellar and even inverted structures [10]. The formation of a spherical micelle is, however, most favourable due to its lowest surface area and size for a given volume. In the case of swollen micelles, it is not straightforward to find such a parameter that allows their shape to be predicted. This is because the factors of each surfactant and co-surfactant molecule can only be calculated by assuming ideal mixing.

There are internal forces acting on the micellar system which should be taken into consideration such as bond, angle and dihedral, as well as external forces such as attractive and repulsive forces between molecules in an aggregate and between aggregates and solvent. The movements of the molecules in the interior micelle structure are largely determined by the interactions between OE and the non-ionic surfactant molecules due to non-covalent, electrostatic forces including the van der Waals interactions between aggregates in the nano-emulsion droplet. The outer surface of the micelle interactions involved the steric attraction between the non-ionic surfactants with the surrounding water molecules [11]. The force f, which influences the system behaviour, can be proposed as:

$$f_{\mathrm{OE(bond)}} \quad \text{and} \quad f_{\mathrm{surf(bond)}},$$

$$f_{\mathrm{OE(angle)}} \quad \text{and} \quad f_{\mathrm{surf(angle)}},$$

$$f_{\mathrm{OE(dihedral)}} \quad \text{and} \quad f_{\mathrm{surf(dihedral)}},$$

$$f_{\mathrm{OE(att)}} - f_{\mathrm{OE(att)}}, f_{\mathrm{OE(att)}} - f_{\mathrm{surf(att)}} \quad \text{and} \quad f_{\mathrm{surf(att)}} - f_{\mathrm{surf(att)}},$$

$$f_{\mathrm{OE(rep)}} - f_{\mathrm{OE(rep)}}, f_{\mathrm{OE(rep)}} - f_{\mathrm{surf(rep)}} \quad \text{and} \quad f_{\mathrm{surf(rep)}} - f_{\mathrm{surf(rep)}},$$

where the bond, angle and dihedral are internal forces while the external forces consist of electrostatic and van der Waals repulsive (rep) and attractive (att) forces. These external forces are responsible for the self-assembly phenomena of such system. Each of these forces can be described in more detail using the functional form of the potential energy functions [12] (Supplementary Materials, Part II).

2.2 Simulation methodology

The effect of the micelle composition in the OE/S20/H_2O system was investigated based on a ternary phase diagram of the mixture [6], in which the concentration (in w/w percentage) of OE and S20 was taken from different spots according to the micelle composition (OE/S20) in the system. The system was prepared by packing the molecules together in random positions using Packmol software [13]. The arrangement of the molecules was then solvated with water molecules in a cubic simulation box. All molecular dynamics (MD) simulations were performed using GROMACS v3.3 software with OPLS-AA force field applied for the OE and S20 molecules (Supplementary Material; Tables S1–S3) and the SPC water model for the solvent molecules [14–16].

Five series of MD simulations were performed, which comprised 10, 20, 30, 40 and 50% of the micelle composition in the system in order to determine the effect of the OE/S20 composition on the structure of the swollen micelles. The number of molecules (Table 1) was limited within a 125 nm^3 simulation box based on the ratio of OE to S20 volume in the ternary phase diagram and in

Table 1. Number of OE and S20 molecules according to the micelle composition in the system.

OE/S20 (%)	N_{OE}	N_{S20}	N_{H_2O}
10	3	15	3021
20	5	30	2546
30	8	45	2252
40	10	60	1874
50	13	75	1646

accordance with the molecular weight of each molecule. The system was energetically minimised using both steepest-descents and conjugate-gradients algorithms. Equilibration simulation was performed to stabilise the system in constant *NPT* ensemble before continuing with production simulation in constant *NVT* ensemble up to 10 ns in a cubic simulation box.

All simulations were performed with a step size of 1 fs. The electrostatic interactions were cut off at 0.9 nm using the particle-mesh Ewald algorithm, and the van der Waals interactions were also cut off at 0.9 nm. The temperature was coupled to an external bath using the Berendsen thermostat at 300 K with τ_T equal to 0.1 for each type of molecules and the pressure coupled with the same method at 1.0 bar with τ_P of 1.0 [17]. Periodic boundary condition was applied to all directions of the system with constraint applied to all bonds using the LINCS algorithm [18].

The same simulation conditions were applied to four systems comprising S20, OE/S20, T80 and OE/T80 swollen micelles. The purpose was to differentiate the effect of the HLB value of non-ionic surfactants used and the effect of the OE addition to the structural properties of the swollen micelles. The radius of gyration R_g and the eccentricity e of the structure formed from the simulations were calculated.

3. Results and discussion

Different shapes of the OE/S20 system were predicted as the micelle composition increased. From the graphical snapshots of each of the simulations, the structure at 20% (Figure 2(a)) and 30% (Figure 2(b)) of the micelle composition exhibited a micellar system. The snapshot picture at 30% clearly showed an infinite cylindrical micelle structure with a radius of ± 3.54 nm. An abrupt change in the surface tension analysis (Figure 3) showed that the micelle formation occurs between 10 and 20% of the micelle composition, which is in agreement with the experimental results, located in the isotropic region in the ternary phase diagram [6]. This was further explained by the fact that when surfactant solubilisation occurs, a thermodynamically stable isotropic solution will be produced, and it is closely associated with the phase behaviour of amphiphilic material that is used to enhance the stability [1].

At 40% of the micelle composition (Figure 2(c)), the snapshot picture after 10 ns of the MD simulation showed a formation of separated arrangements of OE and S20 molecules, which were closely related to a cubical or hexagonal micellar system. At 50% of the micelle composition (Figure 2(d)), a lamellar-like structure formed after 10 ns of the simulation displaying three layers of arrangements of molecules with OE located at the centre of the system with an estimated *d*-spacing of ± 2.24 nm. The molecules were observed as highly disordered in

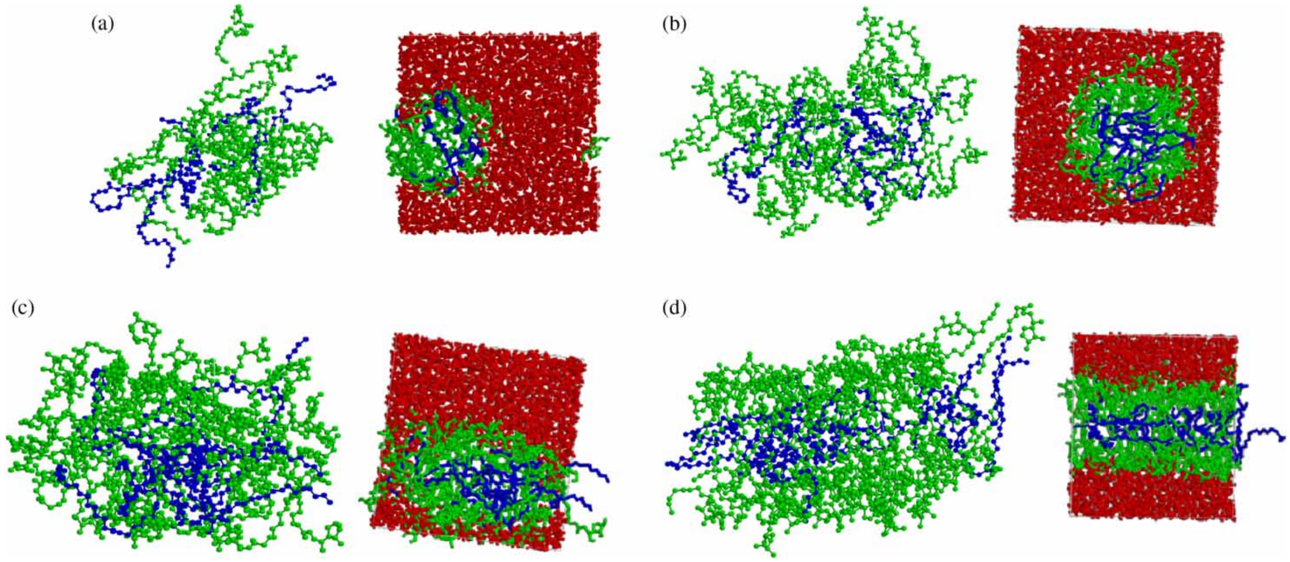

Figure 2. Snapshot pictures of the OE/S20/H_2O system at (a) 20%, (b) 30%, infinite cylindrical structure, (c) 40%, cubical form and (d) 50%, lamellar arrangement of micelle compositions at 10 ns. OE, blue; S20, green; water, red (colour online).

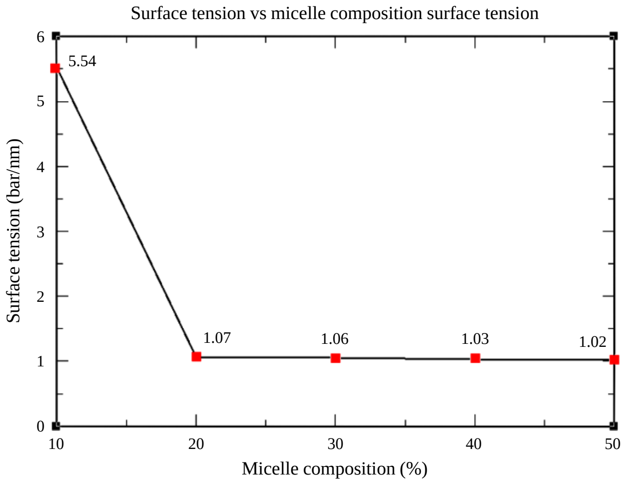

Figure 3. Surface tension plot of the OE/S20/H_2O system against the micelle composition.

terms of the head and tails of the oil and surfactants. However, these results were in agreement with Davis' [19] reports about structural properties based on the ternary phase diagram for the emulsion system.

Simulations on different non-ionic surfactants revealed the effect of different HLB values, which are closely related to the size of the polar and non-polar groups of the non-ionic surfactants used [20]. Four micelle systems were investigated, comprising S20, OE/S20, T80 and OE/T80. Although, from the previous results, the infinite cylindrical micelle was found at 20–30% of the micelle composition, the percentage of the micelle composition for this study was reduced to 15%. By considering the reported theories [8] and the surface tension analysis, at this micelle composition region, there is a strong possibility that a spherical micelle structure can be produced.

Eccentricity values were calculated for the micelle structure to analyse the shape by monitoring the moment of inertia of the molecules during the simulation. The eccentricity *e* can be calculated from the following equation [21]:

$$e = 1 - \frac{I_{\min}}{I_{\text{avg}}}, \qquad (1)$$

where $I_{\min}$ is the moment of inertia along either the x-, y- or z-axis with the smallest value and I_{avg} is the average of the moment of inertia of each axis. The structure evaluated with eccentricity will have a zero value if it is a perfect sphere. From the results (Table 2), we considered that all four structures were spherical. Comparing the average *e* values, OE/T80 showed the highest tendency to form a spherical micelle, although the difference between the four systems investigated was not significant. It was observed that the addition of OE into the system did not give the essential effect on the shape of the structure at 15% of the lipid composition.

Table 2. Eccentricity values of four different micellar systems.

Structure	Eccentricity, *e*
S20	0.124
OE/S20	0.100
T80	0.116
OE/T80	0.098

Note: The zero value indicates a perfect spherical micelle.

The micelle size of the resulting structures was observed using the R_g analysis. Figure 4 displayed a consistent R_g values during 2.5 ns of MD simulations of the four different systems. In the case of OE/S20, a small polar group of S20 meant that the hydrophobic attraction was much stronger than the hydrophilic attraction, thus the allowed OE molecules that were added to pull the surfactant closer resulted in the shrinkage of the swollen micelle [22]. Therefore, we could see that the size of the OE/S20 swollen micelle was ±0.045 nm^3 smaller than the S20 micelle. This led us to the assumption that not all swollen micelles resulting from the solubilisation of surfactants are bigger in size compared to the surfactant micelles. However, a different phenomenon was observed in the T80 and OE/T80 systems. The difference in the HLB value of T80 (15±1.0) and S20 (8.6±1.0) [23] is considerably large. Therefore, in the OE/T80 system, the hydrophilic attraction between the polar groups of T80 and water molecules was dominant compared to the hydrophobic interaction. Thus, the structure of the OE/T80 swollen micelle was expanded as much as ±0.091 nm^3 compared to the T80 micelle.

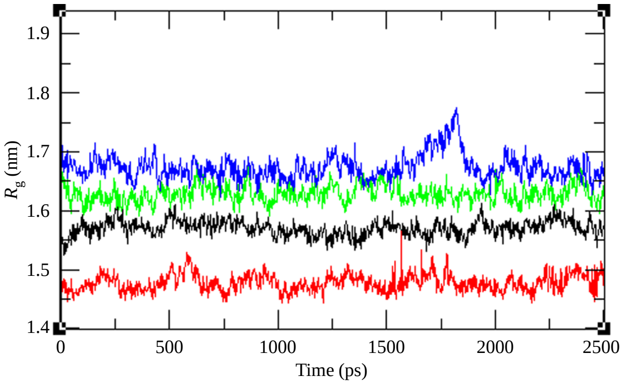

Figure 4. Radius of gyration (R_g) for S20 (blue), T80 (red), OE/S20 (green) and OE/T80 (black) swollen micelles as a function of time (colour online).

4. Conclusion

The MD simulation method was able to investigate the structural properties of swollen micelles in the OE nano-emulsion system that resulted from the solubilisation of surfactants. The results showed that OE swollen micelles behave similar to other micellar systems through the structural analysis and are in relation to previously reported properties for such system. The composition of lipid (oil and surfactant) molecules in the formulation of the nano-emulsions was determined to be significant in contributing to the shape of the swollen micelles that formed. The inclusion of OE molecules did give the effects on the structural properties of the swollen micelles. However, the changes were related to the type of the surfactant that involved in terms of the hydrophobic and hydrophilic forces. There are still many more that have yet to be discovered about these palm-based nano-emulsion colloidal systems such as the self-assembly characteristics, the thermodynamics properties and so on. These studies can be carried out using computational approach such as MD due to its capability to characterise these nano-emulsion systems.

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