Intermolecular Interaction of Tween 80, Water and Butanol in Micelles Formation via Molecular Dynamics Simulation

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Abstract. Micelles entrapment approach is one of the methods to synthesize silica nanoparticles as carriers for drug delivery system. This method is useful in enhancing drug solubility, extend the circulation of blood half-life and possesses lower toxicity. The shape and size of the silica nanoparticles could be excellently controlled by manipulating the parameters such as the concentration of surfactants and composition during the synthesis process. In this study, water and butanol have been used as solvent and co-solvent, while Tween 80 has been used as the surfactant. The structural properties of the micellar system from binary (water and Tween 80) and ternary (water, Tween 80 and butanol) were reported in terms of radial distribution function (RDF) and radius of gyration (Rg). The molecular dynamics simulations were performed using Material Studio by applying COMPASS Force Field in the Forcite Module. The simulation box was created by using Amorphous Cell Module. Initially, the simulation for both system was executed under a constant number of moles, volume and energy (NVE) ensemble for 200 ps and followed by a constant number of moles, pressure and temperature (NPT) ensemble for 2000 ps. From RDF analysis, both systems have the same distance of 0.97Å, but different value of g(r) intensity, 12 and 6.35 respectively. Meanwhile, the Rg result shows a higher value in ternary systems compared to the binary system. These findings revealed that the presence of butanol would weaken the intermolecular interaction of hydrogen bond and increase the size of the micelle and consequently will affect the size of nanoparticles.

1.0 Introduction
The drugs delivery has restricted because of the mechanical and chemical instability in biological systems [1]. Current studies revealed that the physicochemical properties such as shape, size and surface charge show a vital roles in influencing the behaviour of the particles in the biological environment [1,2]. These properties will affect circulation time, particle stability, therapeutic ability and cellular uptake [3]. Size of particles has been considered as one of the significant properties in the synthesis of silica nanoparticles for drug delivery applications. The range of size between 50 nm to 200 nm is preferred to achieve stability in the bloodstream [4]. Besides, smaller particles could diffuse in the blood capillary walls, whereas macrophages trap the bigger particles and accumulated in the spleen and liver [5]. Moreover, the spherical shape and small sizes of silica nanoparticles make them easier for the injection in the human body [6]. Among many synthesis methods, the micelles entrapment experimental model has been used as a reference in this study. Micelles entrapment technique is a combination of microemulsion and sol-gel process to synthesize homogenous particle size in a colloidal form so that the drug could be directly encapsulated inside silica [7]. The size and shape of silica nanoparticles could
be excellently controlled by manipulating the parameters such as the concentration of surfactants and composition during the synthesis process [8].

Nonionic surfactant systems can produce various phases such as micellar, hexagonal and lamellar depending on the experimental parameters such as temperature, hydrophobic and hydrophilic chains length and concentration of the solvent. In aqueous solution and above the critical micelle concentration (CMC), the surfactants molecules assemble in regular micelles [9]. Self-assembled surfactant templates such as microemulsion and micelle have been extensively used to control particle morphology in silica nanoparticles synthesis [10,11]. Other than that, water-alcohol-surfactant systems are regularly used as a medium in the studies of chemical equilibria and reaction rates. Addition of alcohols to aqueous solutions of surfactants affects the hydrophobic interactions on the micellar structure [12]. For these reasons, it is essential to investigate the effect of alcohol on the CMC of the surfactants in micelles formation as it will affect the silica nanoparticles structural properties.

Recently, the attention for most of the researcher is solely on the experimental part. Nevertheless, there is a limitation of current studies, which is the inability to elucidate the interaction of the molecule in micelles formation at the molecular level. Therefore, to examine the interactions between the variables, a method with atomic resolution is needed. Molecular modelling simulation can provide detailed information on the presence and type of interactions over a short time scale, although it cannot give a complete picture of what is observed microscopically. The system under investigation can be designed to reflect a detailed configuration of interest down to the atomic level and the phenomena observed during the simulations can indicate possible leading causes of the macroscopic observables. Thus, the primary focus of this research is to understand the intermolecular interaction in micelles formation via molecular dynamics.

2.0 Materials Methodologies

2.1. Computational Approach

In this study, the simulations were performed in Accerys Materials Studio (MS), version 5.5. The calculations of interaction energy, geometry optimizations, and dynamics simulation were executed by using condensed-phase optimized molecular potentials for atomistic simulation studies (COMPASS) force field. The geometry optimization and energy minimization were carried out by using Smart minimizer. The simulation box with the periodic boundary for the arbitrary configuration of the binary system (water and Tween 80) and ternary system (water, Tween 80 and butanol) were constructed using the Amorphous cell module.

2.2. Creation of a simulation box of the binary and ternary system.

The molecular structures of the water (solvent), Tween 80 (surfactant) and butanol (co-solvent) molecules, as illustrated in figure 1, were sketched using embedded tools available in the MS. The molecules were subjected to energy minimization and geometry optimization procedures. A periodic amorphous cell model containing all molecules was built with specific lattice dimensions, depending on the size and number of the molecules present in the cell. Table 1 shows the simulation data, and cell volume corresponds to the number of molecules in the system. The temperature was set at 298 K. Ewald summation method was selected for van der Waals and electrostatic interactions. The Ewald summation is an efficient technique to sum all the interactions between a molecule and all its periodic images. This approach emphasizes the continuum nature of a polar fluid and need a priori estimation of the relative permittivity [13].
2.3. Molecular Dynamics
Forcite Module was used to equilibrate and minimize the energy of simulation boxes. In a dynamic system, the cell pressure was fixed at 1 atm (1 x 10^{-4} GPa) at 298 K. The simulation started with equilibration of the system under a constant number of moles, volume and energy (NVE) ensemble for 200 ps. After equilibration, the systems were applied with a constant number of moles, pressure and temperature (NPT) ensemble for a total simulation time of 2000 ps with 1 fs stepsize. In order to maintain the system at the required temperature, Nose [14] and Berendsen et al. [15] assumption methods were used.

2.4. Structural Properties Analysis
The output from the molecular modelling simulation was determined by the radius of gyration (R_g) and radial distribution function (RDF) analysis. R_g was used to determine the compactness of the micelle in

| System  | Number of Molecules | Weight (%) | Density (g/cm³) | Cell volume: A × B × C [Å³] |
|---------|---------------------|------------|-----------------|-------------------------------|
| **Binary** |                     |            |                 |                               |
| Water  | 200                 | 78.4       | 1.0015          | 30.3 x 30.3 x 30.3            |
| Tween 80 | 10                  | 21.6       |                 |                               |
| **Ternary** |                   |            |                 |                               |
| Water  | 200                 | 17.7       | 0.9961          | 32.4 x 32.4 x 32.4            |
| Tween 80 | 10                  | 64.2       |                 |                               |
| Butanol | 50                  | 18.2       |                 |                               |

**Figure 1.** Molecules after geometry optimization (a) water, (b) butanol and (c) Tween 80

**Table 1.** Data for Simulation
RDF, as shown in the following equations by $g_x(r)$, defines the probability of finding a particle at a distance of $r$ from another reference particle:

$$g_{xy}(r) = \frac{<N_{xy}(r,r+dr)>}{\rho_y \pi r^2 dr}$$

(1)

### 3.0 Results

#### 3.1 Radial Distribution Function Analysis

Figure 2 and 3 show the intermolecular interaction in binary and ternary system, measured as RDF. The first hydrogen bond interaction recorded for both systems are at 0.97Å, with different $g(r)$ value of 12 and 6.35 respectively. Both systems have the same distance of 0.97Å, and these show the hydrogen bond exists for both systems because the distance is less than 3.25Å. The shorter radius demonstrated by the results indicates that the hydrogen bonds formed are stronger than the first peak shown at higher radius distance [16]. However, the binary system shows higher value in $g(r)$ intensity, reflecting the closest and preferential localization of surfactant molecules together. The addition of butanol in the ternary system reduced the $g(r)$ intensity, which means the localization of molecules were expanded, leads to the larger size of the micellar system. This phenomenon also showed that the presence of the alcohol in water decreases the surface tension of water, so the surfactants tend to form micelles in lower concentrations.

![Figure 2. RDF for the binary system](image-url)
3.2 Radius of Gyration Analysis

Rg analysis was performed to determine the compactness and structural size of the systems. Rg for both systems is shown in figure 4. The result shows higher Rg value in ternary systems. These results may suggest that in the ternary system, the addition of butanol made the molecules shift away from each other, which reflect the increase of the size of the micelles. In both systems, the models exhibited a consistent fluctuation in the Rg until the simulation is finished. Rg results proposed the formation of a stable and large aggregate for both simulated systems [17].
4.0 Conclusion
In this study, molecular dynamics simulations have been performed for the binary and ternary system. From the RDF analysis, the first hydrogen bond interaction recorded for both systems are at 0.97Å, with different g(r) intensity value of 12 and 6.35, respectively. The addition of butanol in the ternary system reduced the g(r) intensity, which means the localization of molecules were lengthened, leads to the higher size of micelles. Meanwhile, the Rg result shows a higher value in ternary systems showed the increase of the size of the micelles. In summary, the presence of butanol will weaken the intermolecular interaction of hydrogen bond and increase the size of the micelle and consequently will affect the size of nanoparticles.

5.0 References
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