Monte Carlo simulation of mixed nonionic Brij surfactants in water

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Abstract Nonionic surfactants such as the Brij® series are important in the preparation of transdermal drug nanodelivery products using nanoemulsions because of their low toxicity and low irritancy. Here, Monte Carlo (MC) simulation was used to examine the physical behavior of the model deterministic system by using sampling procedures. Metropolis MC simulations were run on three mixtures of two different nonionic surfactants, Brij92 and Brij96, with different compositions in aqueous solution. The system was simulated in the canonical ensemble with constant temperature, volume and number of molecules. Hence, the acceptance ratio for single atom moves of the mixed surfactants increased as the concentration of surfactants increased from 0.494 to 0.591. The lowest total energy for the mixed surfactant systems was −99,039 kcal mol^{-1} due to the interaction between all molecules in the system simulated. The physicochemical properties of models such as the radius of gyration and radial distribution function, were also determined. These observations indicate that the behavior and physicochemical of mixed surfactant and PKOEs nanoemulsion systems were described adequately during the simulation.

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Introduction

Surfactants show many practical applications, for example, in the management of soil water repellency [1], in the petroleum industry [2], food industry, and in cosmetics, pharmaceuticals, and agrochemicals [3]. They are usually classified into four main groups: anionic, nonionic, cationic, and amphoteric (or zwitterionic) molecules. An amphiphilic molecule contains both hydrophobic (the nonpolar tail) and hydrophilic (the polar head) moieties. Surfactants can aggregate in micelles and form liquid crystals in aqueous solution, depending on the temperature and total concentration, because of the lypophilicity of their hydrocarbon tails, which are segregated by water. Surfactant micellization is a relatively well-studied topic. Various surfactants have been investigated through experimental techniques such as light scattering, fluorescence quenching, calorimetry, potentiometry, etc., to determine the structure and micellization properties of the surfactants.

Various theoretical procedures have been developed to understand the physicochemical properties of the micelles from examining the molecular composition of the surfactants. The two main groups of computational simulation techniques are traditional molecular dynamics (MD) and Monte Carlo (MC) with several hybrid methods that combine features from both techniques, e.g., coarse-grained molecular dynamics (CG-MD). Traditional MD produces an atomistic description of molecular properties [4–6] but requires, for large systems, a lot of computational time to equilibrate the model system, and can be restricted to very small time scales. Therefore, the stochastic numerical methods such as MC can be a good alternative, as it investigates the behavior of deterministic systems based on sampling procedures. In this case, the

system configurations are selected randomly not following the Newton's equation of motions [7].

In general, the MC techniques applied were based mostly on lattice models in which a surfactant molecule was represented as a chain of chemical groups occupying certain grid sites on a 2D or 3D lattice. However, it was shown that surfactant self-assembly could be achieved by MC simulations even without having to resort any pre-assembled micellar structure or shape [8, 9]. Metropolis MC simulation in the canonical ensemble of 3D lattice model was used to study the aggregation of surfactants in binary mixtures of water and ionic surfactant. The simulations for each condition were started at athermal conditions and, after equilibrium was attained at each step, the interaction energy was increased in small steps until the desired interaction energy was reached. A systematic study on the effects of the various parameters on the micellization properties can also be performed due to the thermodynamic indication of the aggregates and disaggregates of the surfactant molecules at certain concentrations [10].

Extensive MC simulations of surfactants have been carried out in recent years. For example, a lattice model of a surfactant-solvent system was built by Rodriguez-Guadarrama and coworkers [11] to predict the thermodynamic properties of the self-association of nonionic surfactant molecules. Lattice models exhibit useful features of any characteristic properties and behaviors of self-associating systems, such as the temperature, and solvent quality, and had good agreement between theory and experiment [11]. The behavior of the model binary surfactant mixtures consisting of two similar surfactants was investigated by Poorgholami-Bejarpasi and colleagues [12] to analyze the head–head and tail–tail interactions among the mixed system while observing the distribution of aggregates. In this case, the authors calculated the activity coefficients of each surfactant species and compared with the regular solution theory, demonstrating that the large observed discrepancy is due to the nonrandom mixing of surfactants.

The present study focused on model nonionic mixed surfactants of the Brij® series at different concentrations in order to determine the best composition to be used in a nanoemulsion mixture. These nonionic surfactants are important in transdermal drug nanodelivery products using nanoemulsions formulations because of their low toxicity and irritancy [13]. It has been shown that the hydrophilic-lipophilic balance (HLB) value of the surfactant, and the size and shape of both the alkyl chain and the polar group, influence the absorption ability of drug release into the body [13, 14]. Here, MC simulations were used to study the two specific nonionic surfactants, Brij92 and Brij96, with different compositions (10 %, 60 % and 80 %) in water. In this case, TIP3 was chosen to represent the water molecules in the simulation. According to Kincaid and colleagues [15] and also Hu and

colleagues [7], the present study explores a situation in which the model mixed surfactant molecule may at least result in an acceptance ratio rate of 30 % for a system with smooth energy, in contrast to the assumption of earlier practitioners, who found that 50 % was the best.

Figure 1 shows the molecular structure of both molecules. The structure of Brij92 contains ethylene oxide (EO) with a chain length of 2 and HLB value of 4.9, while Brij96 has a chain length of 10 and HLB value of 12.4. Their hydrophobic parts consist of oleyl portions. The Brij series could be very effective promoters of skin permeation, for example, in ibuprofen delivery [13], and could increase the penetration of the drug via both lipophilic and hydrophilic molecular mechanisms. Molecules in the Brij series interact with the polar head groups of lipids and modify the hydrogen bonding and ionic forces in addition to increasing the water content of proteins in the stratum corneum by hydrating lipid spheres [13, 14].

The paper is organized as follows. Firstly, in section 2, the Computational methods employed in the study were discussed. This includes the calculations on determination of excess chemical potential and also the prediction of the number of each molecule involved in the system at different compositions. This is followed in Results and discussion by an extensive discussion of the results, such as the energy obtained during the simulation, acceptance ratio, radial distribution function and other physicochemical properties. A brief summary and some concluding remarks follow in the Conclusions.

Computational methods

All Metropolis MC simulations and energy minimizations were performed using CHARMM software package version 35b5 [16]. The surfactant structures were changed into CHARMM-formatted files from the original Protein Data Bank files using the MMTSB tool set [17] and the molecules
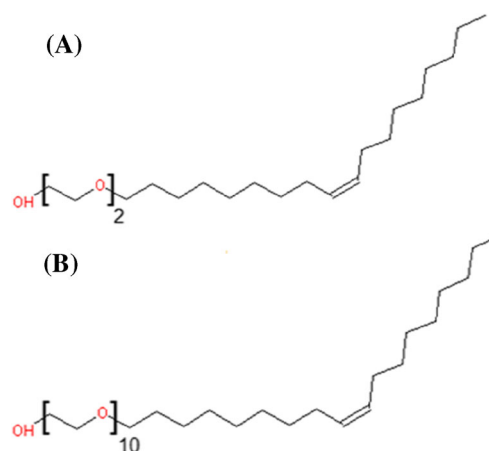
Fig. 1 The molecular structure of a Brij 92 and b Brij 96

were then optimized geometrically using winGAMESS [18] at the RHF/6-31G level of theory. Atomic charges were calculated using the restrained electrostatics potential (RESP) method [19] based on electrostatic potentials (ESP) calculated at the RHF/6-31G level using AMBER software packages [20]. The topological properties and parameters were then assigned based on CHARMM all-atom force field [21]. An aggregated system of Brij 92 and Brij 96 as well as the mixture of both surfactants was modeled on a three-dimensional (3D) cubic lattice with linear size L=8 nm.

The fractions of each surfactant were calculated based on our unpublished experimental data for specific regions of the phase diagram where micelles are present. The concentrations involved in this system were 20 %, 40 % and 80 %, with the point chosen being placed in the isotropic regions of the phase diagram. The number of molecules involved in this system was calculated using weight-to-weight ratio. The percentage ratio used for the specific surfactants in the system multiplied by box sizes and the density of the surfactants was divided by the molecular weight of the surfactants. The results obtained gave the number of moles, which was then multiplied by the Avogadro number to obtain the accurate number of molecules used in the model systems for each specific surfactant. The box sizes for each system involved were kept fixed in order to produce different micelle shapes for the different compositions of surfactants [22].

The lattice was then fully occupied by one of the two species of surfactants and water molecules. The system was made to evolve in time by applying insertion/deletion moves, single chain displacements, and cluster displacements [23]. The chain insertions and deletions were performed using a configuration-bias method that allows chain growth only into unoccupied spaces as described in previous studies based on non-ionic surfactant models [6]. In the single chain and counterion displacement move, a chain is selected randomly and displaced in a random direction. The chain of the surfactant molecule was chosen randomly for a specific move. As a result, a random number was obtained to determine whether a chain underwent a local move or a reptation.

The initial configuration of the system was chosen randomly (as a high temperature system) and the total energy of this configuration, E, was calculated. The new configuration was obtained by the random movement of a chosen molecule. The trial configuration was accepted based on the standard Metropolis algorithm [24]. The Metropolis probability, P is given by:

$$P = \min\left\{1, \exp\left(-\frac{\Delta E}{k_B T}\right)\right\} \tag{1}$$

Where ΔE is the difference between the energies of the trial and the old configurations, k_B is the Boltzmann constant and T

is the absolute temperature. The procedure was continued until equilibrium was attained. The optimum number of MC steps generally depends on the temperature and the concentration of the surfactant molecules. For our simulation, the optimum number was selected as 5×10^6 MC steps with a 1,000 step size at a temperature T=300 K. The simulations were repeated three times per samples for every condition in order to validate the results obtained.

Results and discussion

Total energy

Monte Carlo simulation simply imposes random motions on the system and determines whether the altered structure is energetically feasible at the temperature simulated. The systems were samples based on conformation space without realistic dynamic trajectory for which the time-dependent quantities cannot be provided. The use of interaction energy to investigate the micellization process has shown very promising results [25]. To describe a surfactant mixture, the governing interaction energies must include the interspecies interactions by treating the head unit for one surfactant species as equally hydrophilic or hydrophobic to the head unit of the other species. The total energy of all simulated mixed models was calculated after 5 million MC steps with a step size of 1,000. The total energy was defined by the summation of potential energy and kinetic energy. The molecules in the model system were selected randomly, then displaced in a random direction within the periodic box. The reptation move was used to move the chain, and the chain end to be the lead end for reptation was chosen randomly. The probability for the moves was calculated according to the standard Metropolis algorithm given by Eq. 1. The moves were accepted with the probability based on the Metropolis prescription where the potential energy changes caused by moving these particles from their old location to the new location were computed [16].

The energy changed between −39,529 and −99,039 kcal mol^{-1} as shown in Fig. 2. The average total energy against MC steps during the simulation for each model is summarized in Table 1. The exponential term in Eq. 1 is greater than 1, which causes negative energy values where the move is accepted with the probability of 1. The average total energy for mixture A, consisting of six molecules of Brij 92 and five molecules of Brij 96, was −39,529 kcal mol^{-1}. On the other hand, for mixture B with 40 % of surfactants, the energy was −57,899 kcal mol^{-1}; and the last system (System C), containing an 80 % mixture of Brij 92 and Brij 96, had an energy value of −99,039 kcal mol^{-1}, which was the lowest energy produced. Interaction between the molecules requires a high energy gesture to stabilize the mixed surfactant system in

Fig. 2 Total energy for three mixed systems at 300 K in 5 million Monte Carlo (MC) steps with 1,000 differences in step size. System A = 20 %, System B = 40 %, System C = 80 %
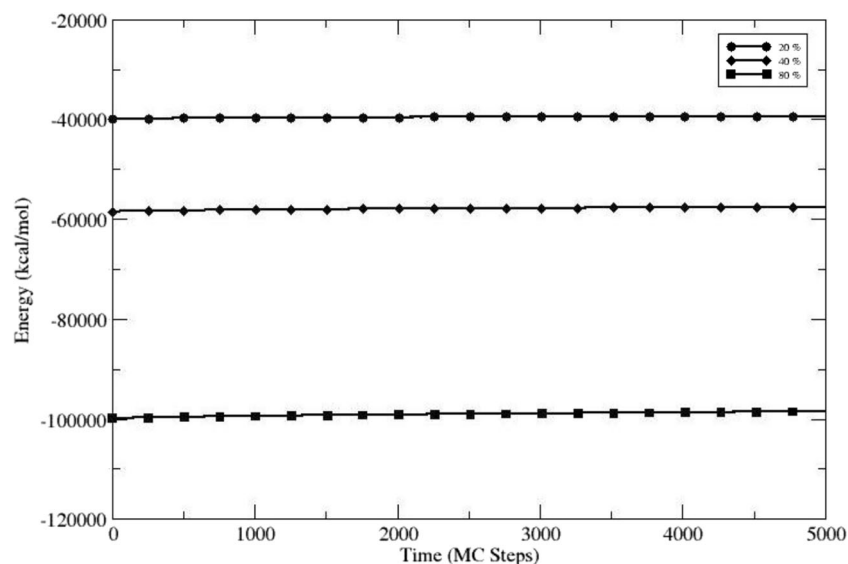
order to form a micelle. Hence, the lowest energy input needed is during the mixed surfactants simulations that produce a micelle easily. Thus, as the number of surfactant molecules increased, the average energy per mole of the system also increased, with surfactants being assigned repulsive values between the head–tail and tail–solvent units of the molecules.

The energy of all hydrophilic–hydrophobic interactions depended on the energy parameters employed, where the complexity of the models varied from only one energy parameter to several energy parameters. We observed that the surfactant head–head interaction could safely be neglected when modelling the process of micellization of non-ionic surfactants [10]. The large discrepancies observed for the systems with head–head repulsions could be attributed to the disregarding of the correlation effect on interactions among surfactant molecules and the nonrandom mixing effect in the theory [12]. To describe a surfactant mixture, the governing interaction energies must include interspecies interactions. This can be accomplished by treating the head unit for one surfactant species as equally hydrophilic (or hydrophobic) as the head unit of the other species. Therefore, the results suggest that surfactant molecules and water were mixed well in all simulated models. An effective hydrophilic interaction between the head and water molecules was obtained by ignoring the interaction between head–water, in contrast to tail–water

repulsions. This was done to stabilize the interaction energies between the two different surfactant molecules and water.

Acceptance ratio

Acceptance ratio is the percentage of the move that has been accepted or rejected in each simulation based on the moves proposed [7]. Thus, the ratio can be controlled by the number of surfactant molecules to be moved and the step size. In our case, the use of a macromolecular system will result in a lower ratio, which can be much smaller than 30 % of the time after equilibrium is achieved [26]. In our study, the acceptance ratio was applied with and without calculating the forces to bias the displacements, with appropriate modification of the acceptance criterion depending strongly on the choice of move chosen for the system involved. However, the composition of the model system was also important in calculation of the percentage [16].

Table 2 reports a summary of the number of molecules, the compositions, and the acceptance ratio after 5 million MC steps for our simulated models. The acceptance ratios for the surfactant mixture were incorporated with single atom moves, individual rotation of surfactant bonds, concerted rotation of the main chain with the flexible surfactants bonds and automatic optimization. The acceptance ratios for single atom

Table 1 Summary of percentage of surfactants, number of molecules of each surfactant, and total energy after 5 million Monte Carlo (MC) steps for all simulated models

Model prepared	Percentage of surfactants (%)	N_{B92}	N_{B96}	Total energy (kcal mol^{-1})
A	20	6	5	−39,529±15
B	40	12	10	−57,899±15
C	80	31	26	−99,039±14

Table 2 A summary of the number of molecules, compositions, and acceptance ratio after 5 million MC steps for all simulated models

System (Brij92+Brij96: water)	A	B	C
Number of molecules	11:17227	22:16888	57:15860
Composition (w%)	20:80	40:60	80:20
Single atom moves	0.494	0.551	0.592
Individual rotational of the surfactants bond	0.352	0.389	0.357
Automatic optimization	0.455	0.464	0.443
Concerted rotation of the main chain with flexible surfactants bonds	0.449	0.459	0.450

moves in the mixture of Brij 92 and Brij 96 were increased as the composition of the mixture increased. The acceptance ratio values were 0.494, 0.551, and 0.592 for 20 %, 40 %, and 80 % of surfactants in aqueous solutions. However, system B showed the highest values of all the systems tested for individual rotation of surfactants bonds, automatic optimization and concerted rotation of the main chain with flexible surfactants bonds, followed by system A and system C, which had the lowest values.

Automatic optimization will happen only if the acceptance ratio method probability (ARMP) > 0 and the dynamically optimized MC factor (DOMCf) > 0 [7]. The lowest value for this part was 0.443 (system C), whereas for system A had a value of 0.455, and the value for system B, consisting of 40 % of surfactant mixture, was highest at 0.464. The acceptance ratio of individual rotational for the surfactant bond for a system with 40 % (B) of surfactants achieved the highest values of 0.389, whereas, system A (20 %) and C (80 %) reached values of 0.352 and 0.357, respectively. The moves involve movement of the bonds of each atom in the surfactant molecules. For the concerted rotation of the main chain with flexible surfactant, each additional pair of selections defines non-rotatable bonds, where non-rotatable bonds are not allowed as the third or fifth bonds. Systems A and C were 0.449 and 0.450, respectively, where system B had the highest value of this ratio, 0.459. Here, we can conclude that system B had the best acceptance ratio of the three systems tested.

The results observed may have been due to the higher probability of overlap between the molecules to be accepted between the molecules already present in the simulation cell. Our results may also suggest that the acceptance rates are ideal for these model surfactants and that surfactant molecules were moved around the lattice sites. In principle, a sampling scheme may be optimal for one quantity, but not for another. For instance, consider the choice of the parameter that determines the size of the trial move. If it is very small, the change in potential energy is probably small and most moves will be accepted and vice versa. The optimum acceptance ratio is one that leads to the most efficient sampling of configuration space. Metropolis MC works best if the acceptance of trial moves by each surfactant atom is accepted by the laws of ARMP and DOMCf. Metropolis MC can be implemented easily for mixtures and inhomogeneous systems, such as fluids near interfaces [27].

Radial distribution function

The radial distribution function, g(r), gives the probability of finding a particle at a distance r from another particle. In general, for a micellized system, the radial distribution function displays a local maximum at the micellar contact radius and a global minimum occurs at the distance of closest approach. The contact values can be slightly greater than 1 and then decrease somewhat with increasing aggregation number. The local minimum can be moved slightly away from the micellar surface as the aggregation number increases. The magnitude of the fluctuations indicates that a fixed number of ions would provide a poor approximation to an open system obeying the statistics of the grand canonical ensemble [28].

Figure 3 shows the behavior of the radial distribution function for the mixed surfactants at a fixed density. For the 1st and 3rd system model, the system became stable rapidly at the beginning of the simulation, which might be due to the value of the aggregation number. As the composition of the
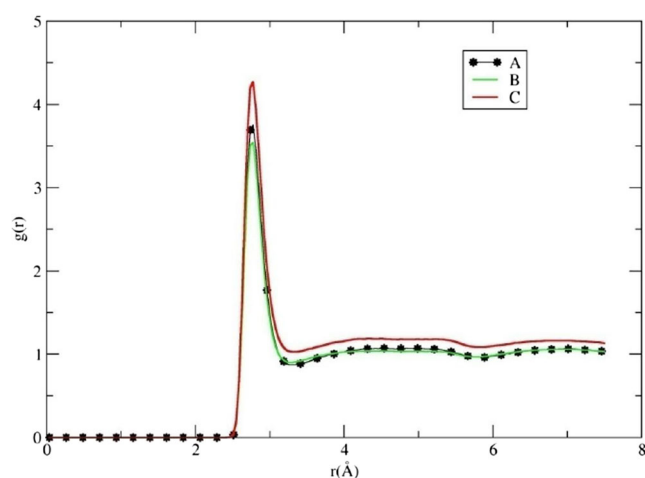
Fig. 3 Radial distribution functions, g(r), for three mixed systems. *Black* System A, *green* System B, *red* System C

mixture approaches the equimolar point, the peaks of the radial distribution function become less pronounced, although there was still more clustering at the same state conditions [29]. As the aggregation number increased, the local concentration also increased and the maximum came closer to the micellar surface. Because of the effect of increasing the surfactant tail length, the surfactant molecules used the adsorbed micellar layer. In addition, the micellar layer around the micelle became more prominent, and the micelle polar parts became more depleted in the neighborhood of the micelle [30].

Radius of gyration

The radius of gyration is the average distance between an atom and its centre-of-mass at a given timestep. It is also used to describe how much atoms move around during a dynamic simulation. The resulting average R_g value can be used to describe the size and compactness of the involved system [31]. Table 3 shows the radius of gyration for a MC simulation with three different compositions of surfactant molecules after 5 million MC steps. The radius of gyration of the systems increased as the surfactant content increased, giving values of 16.8, 17.7 and 20.7, respectively, for model systems A, B and C. This result can be explained by the radius of surfactants needed to form the micelle. Thus, it can be concluded that the surfactant tail density has a wider distribution than the surfactant head density.

As the number of hydrophobic tail groups increases, the ratio of the radius of gyration of the surfactant located at the interface to the radius of gyration of the total surfactant increases. Roughly speaking, as more solvophobic groups are incorporated into the tail block of the surfactant, the surfactant molecule becomes relatively more stretched at the interface. In addition, the length and radius of gyration of the tail groups are relatively longer than the head groups at the interface. Therefore, when more surfactants pack at the interface, there are no intersurfactant interactions driving configuration change [32]. As the number of molecules in the system increases, the possibility of intermolecular aggregation becomes favorable, since it entails the possibility of maintaining the energy gain by contacts between endgroups while offering an entropy increase due to the possibilities of the chains to wander towards neighboring molecules [33].

Solvent accessible surface area

The solvent accessible solvent area (SASA) is the surface area of a biomolecule that is accessible to a solvent. SASA depends on the area of the surface constructed by the center of a probe rolling over a molecule in which the atoms are in a spherical shape with various radii. The SASA is the boundary of the atoms that have their radii increased by the probe radius—typically 1.6 Å in the CHARMM program. The analytical function can simply be extracted for the SASA of every solute atom in CHARMM. Therefore, SASA obtained can be used to calculate the SASA analytically, as well as the potential energy of polar hydrogen, two atomic solvation parameters, and it also involves relative solvent shielding effects for the charges. SASA has shown great performance for solving the computational problems arising from the analytical calculation of surface areas that depend on interatomic distances [16].

The accessible term is described as the atom, or group of atoms brought together into a van der Waal's contact by a specific size of a solvent molecule. From the values recorded (Table 4), system C had the highest accessible solvent area of 18,428.3 Å^2 followed by system B with a value of 11,152.1 Å^2, whereas the lowest value was shown by the first system with a SASA value of 8,704.4 Å^2. Therefore, system C shows the highest SASA value, which means that more solvent were attached here. Even though system A exhibits a smaller amount of surfactants, the results for this particular composition are also acceptable because of the existence of van der Waals forces between the solute and solvent. Hence, the shielding effect does not depend on the environment, and it will be more accurate where the maximum number of the atoms is closer to, or located on, the surface. The accessibility of the configurational space to the solute can be reduced by the effect of the solvent, where in explicit solvent simulation the dissociation between the solute configurational entropy and solvent entropy is not genuine [34].
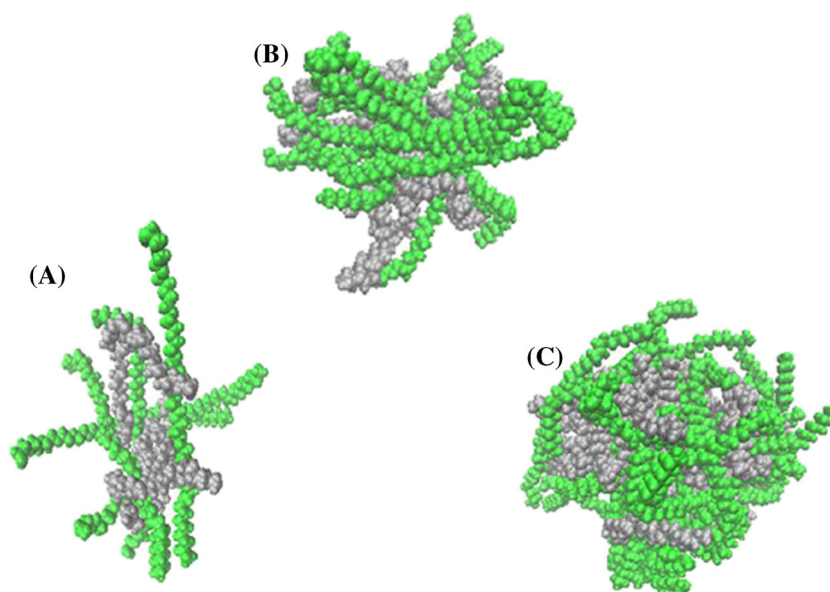
Shape of the micelle

Self-assembly of nonionic surfactants was simulated in the presence of water at a constant temperature of 300 K in various compositions as shown in Table 1. The total number of MC steps was 5 million. In general, the micelles are polydisperse and have a distribution of aggregation numbers. Hence, it is convenient to represent the size of a micelle by either number-average aggregation number or weight-average

Table 3 The radius of gyration (R_g) for three selected models after 5 million MC steps

System	R_g
A	16.83897
B	17.70100
C	20.68348

Table 4 The solvent accessible surface area (SASA) for three selected models after 5 million MC steps

System	SASA (Å^2)
A	8,704.4
B	11,152.1
C	18,428.3

Fig. 4 Snapshot of the mixed system after 5 million MC Steps. *Grey* Brij 92, *green* Brij 96

aggregation number [35]. However, multiple surfactants are often deliberately mixed to improve the performance characteristics of surfactant formulations. The shape of mixed micelles and the thermodynamic nature of the transition (geometry of surfactants and temperature) vary with the characteristics of the system [36]. The roles of surfactants are diverse because the shapes and phase behavior of surfactants vary depending on factors such as their molecular structure and concentration. The shape accepted by the micelle is important in determining its suitability in any reaction. The mobility of the hydrocarbon chains gives indications of how species inside micelles diffuse through the interior [37].

As the content of mixed surfactants increased, the shape of the system changed to be more spherical in shape. The aggregation and disaggregation of molecules were observed throughout the simulation. The results showed that the shape of the aggregated structures can be affected by the composition ratio (see Fig. 4). The shape of aggregate surfactants can be determined by calculating the principal moments of inertia with respect to its center of mass: I_1, I_2, and I_3. The average shape of such an aggregate was characterized by averaging the ratio of the largest and the medium moment of inertia (I_1/I_2) and of the medium and smallest components (I_2/I_3). Here, the shape of micelles was examined using the ratio of the principal moments of inertia I_1/I_2 and I_2/I_3, with the condition that $I_1 \leq I_2 \leq I_3$. These ratios describe the shape of micelles in the following manner: for spherical micelles, $I_1 \approx I_2 \approx I_3$ and thus $I_1/I_2 \approx I_2/I_3 \approx 1$; for disk-like micelles $I_1 \approx I_2 \leq I_3$ and so $I_1/I_2 \approx 1$ and $I_2/I_3 \approx 0$ [38].

From Table 5 above, the principal moment of inertia for all simulated models differed slightly between the *x*-axis, *y*-axis and *z*-axis. The principal moment of inertia of each system was calculated using the average ratio between *x*-axis, *y*-axis and *y*-axis, *z*-axis. The results shown are the average ratio for

all systems, $I_1/I_2 \approx I_2/I_3 \approx 1$. Thus, the shape of all simulated models resulted in spherical micelles that became bigger as the percentage concentration of surfactants increased. Hence, it can be concluded that the micelles mix indiscriminately, and that the micelle size and shape also depend on the concentration ratio of the two species [37]. Figure 4 shows that model system C produces a bigger micelle compared to the other two model systems due to the 80 % surfactant content at a ratio of 0.3 and 0.45 of Brij 92 and Brij 96, respectively. Furthermore, this model system was situated in the homogeneous phase of the binary phase diagram while systems A and B were placed in the isotropic region of the phase diagram (unpublished data).

Conclusions

Metropolis MC simulations were carried out for three different percentages of mixtures of nonionic Brij92 and Brij96 molecules in aqueous solution. From these three systems, we concluded that MC simulation can be used successfully in the mixed surfactant model system in order to determine the

Table 5 Principal moment of inertia, and averaged over 5 million MC steps of simulation

Model	Moments of inertia (Å)			Average moment of inertia		
	x-axis (I_1)	*y*-axis (I_2)	*z*-axis (I_3)	I_1/I_2	I_2/I_3	$I_1/I_2 : I_2/I_3$
A	0.2641	0.2693	0.2940	0.981	0.916	1 : 1
B	0.5620	0.5680	0.5917	0.989	0.960	1 : 1
C	0.1115	0.1132	0.1310	0.984	0.865	1 : 1

physical properties of the models, and also to choose the most reliable system to be used as a surfactant mixture. The surfactants were mixed well throughout the simulation and produced reliable values for acceptance ratio, energy, and spherical shape micelles. The optimal mixture will be mixed with palm kernel oil esters to form nanoemulsions for future use. The nonionic Brij molecules are usually used in nanoemulsion formulations that can then be used as a potential drug carriers for transdermal drug nanodelivery systems. The properties estimated here using MC techniques provide a more detailed insight into the self-assembly of these classes of surfactants.

Supporting data For further details on Metropolis Monte Carlo simulation analysis of the single surfactants and the mixture of single surfactant you may refer to the supporting data available.

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