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Self-Assembly Behaviour of Amphiphile at Local Concentration: A Dissipative Particle Dynamics Simulation Study

SHAOGUI WU* and TINGTING DU

College of Chemistry and Materials Sciences, Sichuan Normal University, Chengdu 610068, P.R. China

*Corresponding author: Email: wsgchem@foxmail.com

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A dissipative particle dynamics simulation technique is used to elucidate the self-assembly behavior of amphiphilic molecules at local high concentration. The initial state is setup by coating an amphiphile solution with a layer of water, which prevents the formation of crossing periodic configuration. The influence of the concentration of the amphiphile solution is investigated. At low concentration, amphiphilic molecules aggregate into a lot of micelles and small vesicles. With the increase of amphiphile concentration, vesicles with simple and complex structures are formed. A new vesicle formation pathway, which is slightly different from the classic vesicle formation pathway, is observed in current simulation condition. Vesicle is formed by the union of many large micelles directly instead of by bilayer-vesicle transition. At high concentration, complex vesicles with multichamber structures are formed. These chambers are separated by bilayer membranes and filled with solvent particles. The volume of complex vesicle as well as its chamber number is increasing with the initial concentration. Present simulation results are in well agreement with experimental result.

Key Words: Complex vesicle, Dissipative particle dynamics, Self-assembly.

INTRODUCTION

Amphiphilic molecules such as lipids, surfactants and block copolymers self-assemble into a variety of structures in aqueous solution, *e.g.*, spherical or rod-like micelles, bilayer membranes and vesicles. In these structures, vesicle is a closed bilayer structure with a water chamber inside, which finds wide applications in drug delivery, gene therapy and artificial cells, *etc*. As a result, vesicles have attracted considerable interests both experimentally and theoretically, such as the formation mechanism of vesicle, vesicle fusion and fission process, *etc*. Since these processes occur on a length scale of tens of nanometers and a timescale of sub millisecond, it is not easy to investigate them by conventional experimental methods. To compensate the deficiencies of experimental approaches, computer simulation technologies have been employed to study these dynamics process. In previous simulation studies, vesicles are prepared from either a homogenous solution or a bilayer membrane. If starting from a homogenous solution, these amphiphilic molecules aggregate into a bilayer first, which then curls and encapsulates a certain amount of water to create a vesicle. Therefore bilayer is regarded as an essential intermediate during spontaneous vesicle formation. The bilayer intermediate is an important feature in the classic pathway of vesicle formation. In addition, amphiphile forms complex vesicles like onions, tube-walled vesicles and perforated vesicles in experiment and their formation mechanisms have been reported scarcely. In this paper, a dissipative particle dynamics simulation method is used to study the self-assembly behaviours of amphiphilic molecules under different concentrations. Dissipative particle dynamics is a mesoscopic simulation technique adopting coarse-grained models and soft potentials. So it can treat the simulation systems greater in length and time scales than those accessible for the classical molecular dynamics simulations. Because crossing periodic configurations form easily at high concentration, most of the previous simulation studies are focused on the self-assembly behaviours of amphiphile in dilute solutions. Nevertheless, dilute solutions are usually prepared from high concentration solutions in experiments and some amphiphilic block-copolymers can not even dissolve in water. Therefore, a preliminary investigation of the aggregation of amphiphilic molecules at high concentration is crucial to comprehensive understanding of the self-assembly behaviours of amphiphilic molecules. To prevent the formation of crossing periodic configuration under high concentration, a layer of water is coated around the amphiphilic molecule rich region. The dependences of the initial concentration of amphiphilic molecules on their self-assembly behaviours are investigated and simple or complex vesicles are obtained.

SIMULATION METHOD

Dissipative particle dynamics formulation: Dissipative particle dynamics simulation is a valid technique to study the hydrodynamic behaviour of complex fluids, originally developed by Hoogerbrugge and Koelman[1,2]. Particle's position r and velocity v are governed by Newtonian second law of motion. Particles interact with each other *via* conservative force F^C, dissipative force F^D and random force F^R, which are truncated by the cutoff radius r_c.

$$f_i = \sum_{i \neq j} (F_{ij}^C + F_{ij}^D + F_{ij}^R)$$

These forces take the forms as follows:

$$F_{ij}^C = a_{ij}(1 - r_{ij}/r_0)\hat{r}_{ij},\ F_{ij}^D = -\gamma(1 - r_{ij}/r_0)^2(\hat{r}_{ij} \cdot v_{ij})\hat{r}_{ij}$$

$$F_{ij}^F = \sqrt{2\gamma k_B T}(1 - r_{ij}/r_0)\xi_{ij}\hat{r}_{ij}$$

where, a_{ij} is a maximum repulsion force between particles i and j. r_{ij} is the distance between particles i and j. γ is friction parameter, set at:

$$\gamma = 4.5\sqrt{m_0 k_B T r_0^2}$$

and $v_{ij} = v_i - v_j$ is the relative velocity between particles i and j. ξ_{ij} is a Gaussian-distributed random element. Dissipative and random forces serve as thermostat that ensures the evolution of system towards a Boltzmann-distributed equilibrium state. An amphiphile chain is modeled by tying particles together using Hookean springs with harmonic force F^S,

$$F^S = -k_2(|r_{i,i+1}| - l_0)$$

where, i, i+1 represent adjacent beads in amphiphile chain. The unstretched bond length l_0 is chosen at 0.7 r_0 and spring constant k_2 is set at100 kBT/r_0^2.

Dissipative particle dynamics models: For simplicity, our simulation system contains just water and lipid-like amphiphilic molecules. They are constructed by three types of beads: water (W), tail (T) and head (H) beads. A CG water bead (W) represents three or four water molecules. A coarse-grained model for amphiphile molecules $H_3(T_5)_2$ used in our previous studies has been adopt here. It is composed of one head moiety and two tails. The head moiety consists of three hydrophilic particles (H) and each tail is composed of five hydrophobic particles (T). No bending potentials are applied to the coarse-grained model, meaning that the molecular chain is flexible. Therefore, the self-assembly of amphiphilic molecules can be reproduced in relatively small time and space scales.

All physical quantities in this paper are presented in reduced units. The units for mass, length, time, energy are m_0, r_0, t_0, k_BT respectively. For simplicity, it is assumed that all particles have the same mass m_0 and size r_0. All the simulations are carried out in the NVT ensemble with temperature $k_BT = 1$. The time evolution of the system is calculated using a modified version of the velocity-Verlet algorithm at $\lambda = 0.65$ with time steps of $\Delta t = 0.05$. The parameters are set at $a_{ij} = 25\ k_BT$ for the hydrophilic interaction (head-water) and 75 k_BT for the hydrophobic interaction (tail-water and head-tail). The repulsion parameters between particles of the same type (head-head, tail-tail and water-water) are set at $a_{ii} = 25\ k_BT$.

To circumvent the influence of periodic boundary condition, a preferable way is to simulate a large system, so no periodic structures can be formed. However, this solution is too computationally expensive. An alternative method is to construct initial configuration by coating a water-layer outside the solution of amphiphilic molecules, thus the probability that amphiphile aggregate merges with its periodic image can be reduced. The starting structure in current study is prepared in this way: First, a cubic box (side length $l_0 = 48.4\ r_0$) is filled with amphiphile solution in a certain concentration. Then the system is dispersed sufficiently to create a homogenous solution. After that, the box is extended to 1.5 times of its original size. Water particles are added to the newly increased space. After the water filling, the final side length of simulation box is up to 72.1 r_0 and the total particle number is 1124864 for all systems. Due to the coating water layer around the initial amphiphile solution, the probability that the formed structure fuses with its periodic image is reduced. Thus our simulations can be carried out at any concentrations, which only represent a local rich region in a heterogeneous amphiphile solution as mentioned above. The initial concentrations are 10, 20, 30, 50, 70 and 100 % for each system. After the water coating, the final concentrations are decreased to 3.04, 6.1, 9.1, 15.2, 21.3 and 30.5 % for each system respectively. In all systems, the time evolution of the dissipative particle dynamics particles is calculated until no further morphology transition is observed.

RESULTS AND DISCUSSION

Firstly, we studied the vesicle formation at the initial concentration of C = 20 %. According to the "standard" vesicle formation pathway, amphiphilic molecules self-assemble into small micelles firstly and then merge into a bilayer in further. Finally, the bilayer curves and closes up to form a vesicle. Water is encapsulated inside simultaneously[3,4]. In this study, we observed a vesicle formation which is slightly differently from the "standard" vesicle formation pathway. Our study is started from homogenous amphiphile solution coated with a layer of water, which represents a small amphiphile-rich region in a large bulk solution. Initially these dispersed amphiphilic molecules aggregate rapidly into many small micelles and further merge into large ones (Fig. 1A). At $t = 100t_0$, the simulation system can be described as a class of associated bilayers (Fig. 1B). This process is the same as the "standard" pathway. However, these bilayers are still not large enough to curl. Due to very close distances between them, these bilayers merge with each other, giving rising to a semi-vesicle. As shown in Fig. 1C, the semi-vesicle is a very coarse one with some water pores and some part evolved incompletely. This process is similar to the reunion of fragments into a whole. There were plenty of water particles among these bilayers. During the merging process, water particles are encapsulated spontaneously inside the vesicle. Water pores are sealed at last and the further evolution contributes to a perfect vesicle (Fig. 1D). Additionally several small unmerged micelles are drifting outside. It is obvious that this vesicle formation pathway is

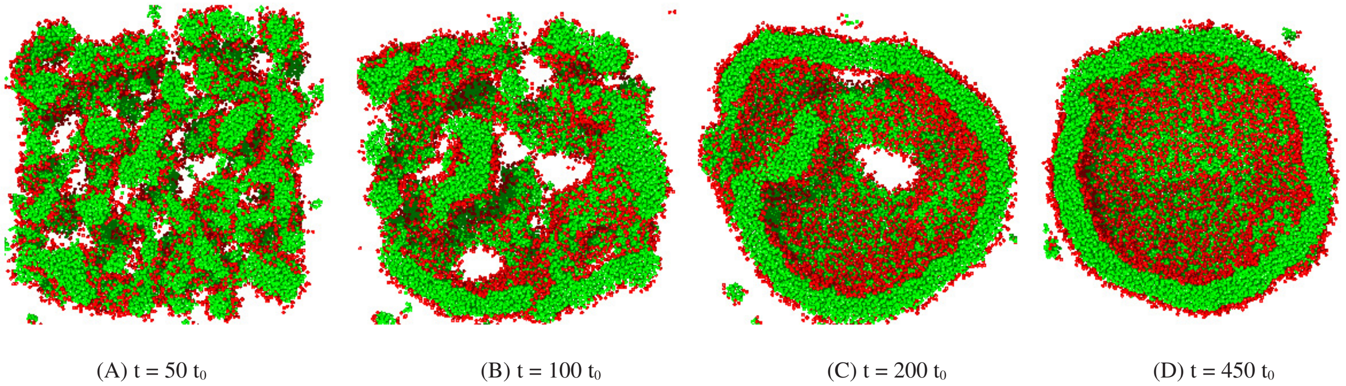
(A) t = 50 t_0 (B) t = 100 t_0 (C) t = 200 t_0 (D) t = 450 t_0

Fig. 1. An alternative pathway of vesicle formation. H and T particles are displayed in red and green. S particles are not plotted. Images correspond to transverse sections through the simulation box. Illustrated are (A) micelles, (B) a series of connected micelles, (C) semi-vesicle with water pores and (D) final vesicle

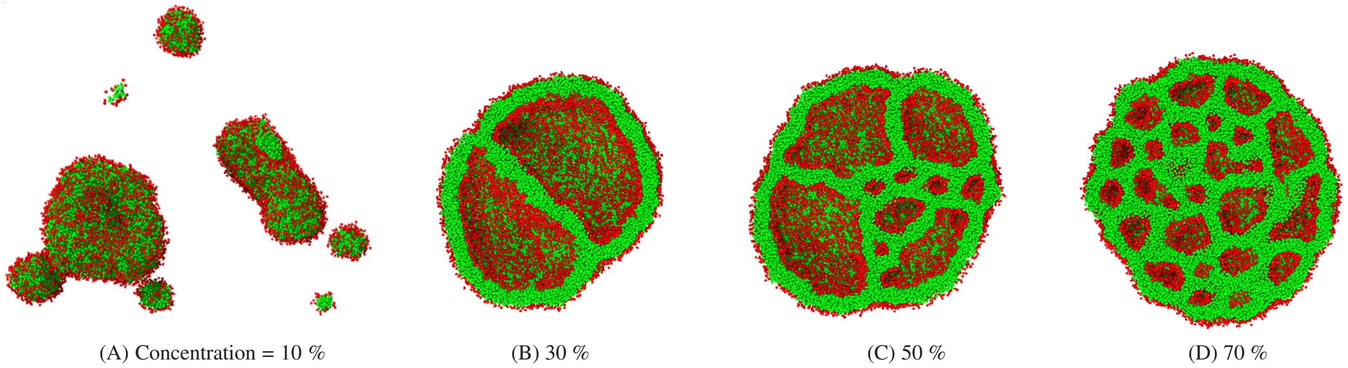
(A) Concentration = 10 % (B) 30 % (C) 50 % (D) 70 %

Fig. 2. Obtained morphologies at different initial concentrations

slightly different from the "standard" pathway. During the vesicle formation, amphiphilic molecules need not to aggregate into a single large bilayer before transforming into a vesicle. Instead, these formed small bilayers fuse with each other and unit into a semi-vesicle directly. It suggests that the large bilayer may not be an essential intermediate for vesicle formation and its bending process has not been observed in this study. Our simulation result is in fully agreement with Marrink *et al.*[5] atomistic simulation work.

Then, we investigated the influence of initial concentration of amphiphilic molecules on final morphology. At the initial concentration of 10 %, many small aggregates are formed. Due to the relatively lower concentration, amphiphilic molecules collide with each other to form many micelles as well, which merge further to create larger ones and some small vesicles (Fig. 2A). Prolonging the simulation time may facilitate the fusing of these micelles or small vesicles. However, due to plenty of water among them, it is hard for these micelles and small vesicles to fuse into large vesicles further. The largest aggregate observed is consisting of 300 amphiphilic molecules at the t = 10000 t_0.

At higher concentration (> 20 %), vesicles with simple or complex structures are formed and their volumes are increased with the increase of initial concentrations. As shown in Fig. 2 (B-D), the formed morphologies are some porous structures in fact. These morphologies are similar to unilamellar vesicle, except their inner spaces are divided into several chambers by the diaphragms (bilayers). These chambers are different in size and filled with water. The chamber number is increasing with amphiphile's concentration. There are 2, 6 and 16 chambers inside these vesicles, corresponding to the simulations with the initial concentrations of 30, 50 and 70 % respectively. These structures are expected to evolve into multilamellar vesicles. However, no significant configuration transitions are observed even the simulation time is prolonged to t = 100000 t_0. As shown in Fig. 2B, at the concentration = 30 %, a complex vesicle is form with two chambers separated by a diaphragm. This structure is similar to two fusing vesicles trapped in a "hemi-fusion diaphragm" state[6]. Two chambers contain 5835 and 3818 W particles respectively. To degrade this diaphragm, an energy barrier needs to be overcome. As a result, the system remains trapped in the state of multichamber structure for the entire simulated period (100000 t_0). For systems with concentrations = 50 % and 70 %, complex vesicles with more water chambers are formed. These chambers also have not fused into a single large one at last, as shown in Fig. 2C and 2D.

To characterize the structure evolution for each system, the time dependence of the number of water chambers for each multichamber vesicle is monitored. For larger simulation systems (S2-S5), the bilayer divides the inner space of the vesicle into a lot of small chambers. Each chamber is filled with a lot of water particles, which can be regarded as a water cluster. Therefore, the number of water clusters is the chamber number for each vesicle. To determine whether a water particle belongs to a water cluster, an option is to consider the distance of this water particle to any of the water particles that is already in the cluster. If particle i is already in the cluster, particle j will be included if the distance between them rij satisfies the relation rij < rd, where rd is the chosen threshold separation. Here, rd is set as 1.2, which is larger than r cut to ensure a long enough distance to distinguish two clusters. The analyzing result of the cluster properties is shown in Fig. 3. At the initial stage, because amphiphilic molecules are dispersed homogenously in the solution and all water particles link up into a continuous phase. On the other hand, there is no aggregate existing at the initial stage, so the number of water chamber (Nw) is zero for all systems. For comparison, the Nw for the S1 system is also displayed, in which the amphiphilic molecules self assembly into a unilamellar vesicle eventually. There is only one cavity in the resulting vesicle, corresponding to one water cluster. For other systems, Nw is not a constant but changing with the time. For example, in the S2 system, the coarse structure is already formed at the time t = 500 t_0, which owns two chambers containing 5835 and 3818 water particles respectively (Nw = 2). Then Nw increases to 3 at the time t = 1000 t_0 and 4 and 5 at t = 1500 t_0 and 2000 t_0 respectively. After that Nw decreases to 3 again at t = 2500 t_0. During the whole simulation time, Nw is kept fluctuating. On the other hand, the sizes of the two largest chambers remain almost unchanged, which contain -5800 and -3800 water particles respectively. The other water chambers formed are very small, containing less than 100 water particles. The smallest chamber observed contains only 2 water particles. These small water chambers are formed by a part of water particles escaping from the two largest chambers at one instant of time. They are stable less than 500 t_0 before fusing into one of the two largest water chambers. Additionally, there is no sign that the two large water chambers will merge into a whole. Based on the analysis above, we conclude that these multichamber vesicles are in a homeostasis.

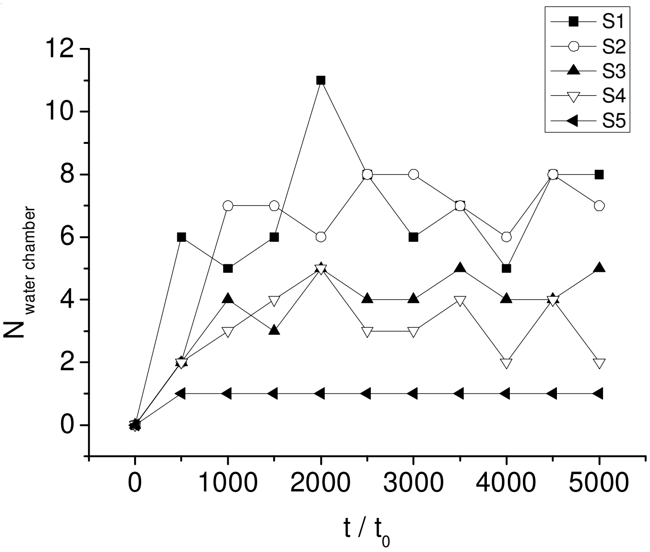

Fig. 3. Time evolution of water chamber number for each simulation system

Fig. 4A presents a complex vesicle formed at the initial concentration of 70 %. Locally high concentration of amphiphilic molecules facilitates the formation of this structure. This complex vesicle is a not artificial configuration created by simulations. Fig. 4B shows a polymeric vesicle from actual experiment, which is prepared using polybutadiene-block-poly-(ethylene oxide) (PB-b-PEO) block copolymer[7]. The cross section shows that this structure is a multichamber vesicle with highly folded internal bilayers. The inner space is divided into a lot of small chambers by these bilayers and each chamber is filled with solvent.

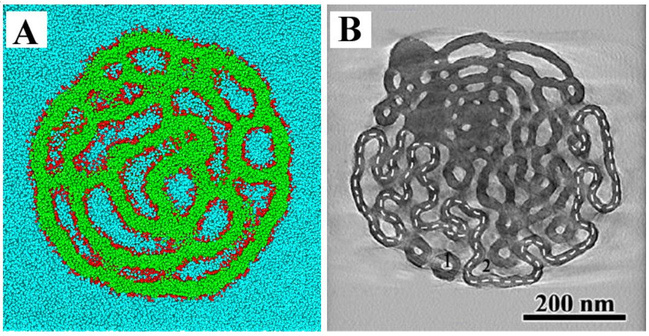

Fig. 4. Comparison between morphologies obtained in simulation (A) and in experiment (B)

At last, we investigated an extreme case of a nanodroplet of pure amphiphile in water. After a simulation time of t = 10000 t_0, the obtained morphology is a spherical nanosphere coated with hydrophilic beads on the surface (Fig. 5A). This morphology is favourable for minimizing the hydrophobic interaction between water and amphiphilic molecules. From the sectional view, it is found that its inner structure is neither a hollow cavity nor an onion structure, but a solid nanosphere with many red domains. The red domains are clusters consisting of hydrophilic H particles, surrounded by T particles. This structure is similar to the "Plum Pudding Model". These red domains are different in shape, round, cylindrical and other irregular shapes, homogonously distributed in the nanosphere. A careful observation shows these red domains are aligned in concentric rings, similar to a shooting target, which maybe formed driven by energy minimization. Additionally, a small number of water particles are found in these red domains. They are encapsulated at the initial stage of the morphology evolution.

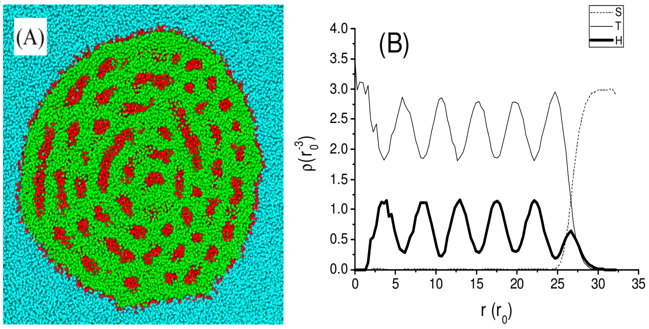

Fig. 5. Morphology of a nanodroplet of pure amphiphilic molecules in water. (A) Cross section of the obtained aggregate. (B) Density distribution along radial direction

Particle density curves are plotted to characterize the nanosphere's structure (Fig. 5B). The dashed, thin and thick lines denote the number densities for S, T and H particles respectively. T peaks and H peaks are arranged regularly and alternately present as undulate. H peaks denote the gathering areas of H particles in space. There are six obvious H peaks for the nanosphere, suggesting that the H domains are aligned in concentric rings. It should be noted that the normal density value of the whole system is set at $\rho \approx 3r_0^{-3}$ while the value of T peak density is about $\rho_T \approx 2.75r_0^{-3}$ and the density value of H trough is $\rho_H \approx 0.25r_0^{-3}$, which is caused by the asphericity of the nanosphere. S curve almost closes to the value $\rho_S \approx 0r_0^{-3}$ except at $r \approx 2.5r_0$ and $r \approx 7r_0$, confirming that small amounts of S particles exist in the nanosphere. These S particles are distributed in H domains.

Conclusion

In this paper, the self-assembly behaviour of amphiphile in a water-wall wrapped circumstance is investigated using a dissipative particle dynamics simulation method. The effect of concentration on the self-assembly behaviour of amphiphilic molecules is discussed. At low concentration, micelles and small vesicles are formed, which are dispersed anywhere. It is difficult for them to fuse further into a large aggregate. At higher concentration, amphiphilic molecules aggregate into vesicles with simple or complex structure. The observed pathway for unilamellar vesicle formation is slightly different from that described by literature recordation. As the increasing of initial concentration, complex vesicles are formed, which own multichamber structure. These chambers are separated by the bilayer membranes and filled with water particles. The chamber number is increasing with the initial concentration. The complex vesicle with multichamber structure is in well agreement with the real experimental result. Additionally the morphology evolution of a nanodroplet of pure amphiphilic molecules in water has been investigated and special configuration has been observed. It is expected this simulation study may shed light on the general principles of the self-assembly behaviour of amphiphilic molecules.

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