MESOSCALE SIMULATION ON SELF-ASSEMBLING BEHAVIOR OF POLY(ETHYLENE OXIDE)-POLY (PROPYLENE OXIDE)-POLY (ETHYLENE OXIDE) TRIBLOCK COPOLYMER MICELLE

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Abstract

The aggregation and phase behavior of a Poly (ethylene oxide)-Poly (propylene oxide)-Poly (ethylene oxide), (PEO-PPO-PEO) triblock copolymer model was investigated by field-based mesoscale simulation (MesoDyn). The effects of the propylene oxide/ ethylene oxide (PPO/PEO) block ratio, copolymer concentrations, and adding a hydrophobic drug moleculeon the morphology of the polymer aggregation were studied. The results show that with increasing the polymer concentration, polymer aggregations of different types were obtained *i.e.* spherical micelle, disk-like micelle, worm-like micelle, and biphase. For a higher PPO/PEO block ratio, a lower critical micelle concentration *(cmc)* and larger micelle size were observed. Adding the hydrophobic drug *i.e.* haloperidol into the solution induced the spherical micelle to form more easily and the micelle sizeto become larger. Haloperidol was located at the interface between the PEO and PPO components.

Keyword: Triblock copolymer, polymer micelle, mesoscale simulation

Introduction

During recent years, there has been great interest inthe research and development of triblock copolymer micelles for drug delivery application. To understand the relationship between their structure and properties for this specific application there needs to be a deeper insight at the molecular level especially for the design of a block copolymer for drug encapsulation and control-released characteristics. Molecular modeling and simulation methods can be applied to meet this purpose for a better understanding of these phenomena, as well asfor the driving forces and mechanism behind this behavior.

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Simulation can also help to interpret and inspire experiments to provide a picture of the underlying microscopic processes at a single molecular resolution which frequently is not accessible experimentally.

Multiscale computer simulation that covers a broad range of size and time scale has been used in order to give sufficient information about the material systems (Kremer, 2003; Kotelyanskii and Theodorou, 2004; Fermeglia and Pricl, 2007). Many important phenomena of polymers usually involve a large distanceor time scale, for example microphase separation in copolymers cannot be studied by the method of fully atomistic simulation. On the other hand, mesoscale simulations such as the field-based technique *i.e.* mesoscopic dynamics (Mesodyn) (van Vlimmeren *et al.* 1999a) and the particle-based technique *i.e.* dissipative particle dynamics (Hoogerbrugge and Koelman, 1992), provide powerful approaches to predict the mesoscopic phenomena that cover the time and length scale up to almost a millisecond and millimeter, respectively, and the kinetic process of complex fuids and soft materials *i.e.* surfactants, emulsions, colloids, block copolymers, and polymer blends. The models form a bridge between fast molecular kinetics and the slow thermodynamic relaxation of macroscale properties. They treat the real polymer chains by grouping atoms together up to the persistence lengths of the polymer chains, which can be extended to length and time scales by several orders of magnitude as compared with all-atomistic simulations.

To model a specific chemical nature of the system in a mesoscopic simulation, there are 2 sets of parameters which have to be defined (van Vlimmeren *et al.*, 1999a; Lam and Goldbeck-Wood, 2003). The first parameter is the Gaussian chain architecture that depends on the degree of coarsening of the original system. The second parameter is the interaction between the different chemical components, which also captures the hydrophilicity and hydrophobicity of the components.

Mesodyn is based on the free energy of an inhomogeneous liquid which can be dissolved to obtain all thermodynamic functions. Phase transition can be investigated as a function of the density distribution (Yang *et al.*, 2008b). MesoDyn has been applied to study the longer length and time behaviorin the mesoscale regime (almost up to μm and μs) of complex fluid systems. It has gained wide respect in the literature and commercial circles with scientifically astute algorithms aimed at elucidating the important mesoscale structure and kinetics *i.e.* polymer, polymer blend, and copolymer in a pure and multicomponent system (Guo *et al.*, 2002; Lam and Goldbeck-Wood, 2003; Jawalkar and Aminabhavi, 2006).

In this work, MesoDyn simulation is applied to study the aggregation and phase behavior of a Poly (ethylene oxide)-Poly (propylene oxide)-Poly (ethylene oxide), (PEO-PPO-PEO), triblock copolymer in aqueous solution. The main focus of this work is to investigate the effect of the PPO/PEO block ratio, copolymer concentrations, and adding a hydrophobic drug (haloperidol) molecule on the self-assembling behavior and drug encapsulation characteristics of this block copolymer micelle. Three PPO/PEO block ratios with the same overall chain length were selected as these cover the one that is commercially available. Our work in this reportcompared and extended the past simulation and experimental studiesof a PEO-PPO-PEO triblock copolymer micelle (Lam and Goldbeck-Wood, 2003; Lam *et al.*, 2004; Yang *et al.*, 2008b) to a different PPO/PEO block ratio which would be of benefit to the synthesis of newa PEO-PPO-PEO triblock copolymer with the appropriated PPO/PEO block ratio that can form the spherical micelle and encapsulate the drug molecule for control-released drug delivery application.

Model and Method

Mesoscopic Dynamics

The idea of the MesoDyn method is that the free energy, F, of an inhomogeneous

liquid is a function of the local density function, ρ, from which all thermodynamic functions can be derived (van Vlimmeren *et al*., 1999a. The model used in MesoDyn consists of beads of various types with interactions described by harmonic oscillator potentials for intra-molecular interactions and a mean field potential for all other interactions. The dynamic of the system is described by a set of functional Langevin equations, which are diffusion equations in the component densities and which take into account the noise in the system

On a coarse-grained time scale, $\rho_0(r)$ is defined as a collective concentration field for the type *i* beads at an instant of time and serves as a reference level. There is a certain distribution of bead positions, $\Psi(R_{11},\ldots,R_{\gamma s})$. The collective concentration of the bead *s* from all chains can be defined by the average of a microscopic density operator:

$$\rho_1\Psi(r) \equiv \sum_{\gamma=1}^{n}\sum_{s=1}^{N} \mathrm{Tr}\Psi\delta_s^k(\mathrm{r}-R_{\gamma s}) \quad (1)$$

where δ_s^k is the Kronecker function and $R_{\gamma s}$ is the position of bead *s* from chain γ. A set of distribution functions, Ψ, is defined with the constraint $\rho^0(r) = \rho_1\ [\Psi](r)$. All distributionslead to the same density, $\rho^0(r)$, to form an equivalent class Ω of distribution functions:

$$\Omega = \{\Psi(R_{11},\ldots,R_{nN}|\rho_1[\Psi](r) = \rho^0(r)\} \quad (2)$$

On the basis of this set of distribution functions, an intrinsic free energy function $F[\Psi]$ can be defined:

$$F[\Psi]= \mathrm{Tr}(\Psi H^{id} + \beta^{-1}\Psi\ln\Psi) + F^{nid}[\rho^0] \quad (3)$$

The first term is the average value of the Hamiltonian for internal Gaussian chain interactions. The second and third terms represent the Gibbs entropy of the distribution and the mean-field non-ideal contribution, respectively. The constraint minimization of the free energy function leads to an optimal distribution, which in turn, by the one-to-one relation between densities, distributions, and external potential, can be written as:

$$\beta F[\rho] = n\ln\Phi + \beta^{-1}\ln n! - \sum_1 \int U_1(r)\rho_1(r)dr + \beta F^{nid}[\rho] \quad (4)$$

Now the non-ideal free energy function is introduced,

$$F^{nid}[\rho] = \frac{1}{2}\iint \epsilon_{ii}(|r-r'|)\rho_i(r)\rho_i(r') + \epsilon_{ij}(|r-r'|)\rho_i(r)\rho_j(r') + \epsilon_{ji}(|r-r'|)\rho_j(r)\rho_i(r') + \epsilon_{jj}(|r-r'|)\rho_j(r)\rho_j(r') \quad (5)$$

where $\epsilon_{ij}(|r-r'|)$ is a mean-field energetic interaction between beads of type *i* at *r* and type *j* at *ŕ*. The mean-field intrinsic chemical potentials can easily be derived by functional differentiation of the free energy $\mu_i(r) = \delta F/\delta\rho_1\ (r)$.

The functional Langevin equations for the diffusive dynamics of the density fields are:

$$\frac{\partial\rho_i}{\partial t} = Mv_i\nabla\rho_i\rho_j\nabla\left[\mu_i-\mu_j\right] + \eta \quad (6)$$

$$\frac{\partial\rho_j}{\partial t} = Mv_j\nabla\rho_i\rho_j\nabla\left[\mu_j-\mu_i\right] + \eta \quad (7)$$

The distribution of the Gaussian noise satisfies the fluctuation dissipation theorem:

$$\langle\eta(r,t)\rangle = 0 \quad (8)$$

$$\langle\eta(r,t)\rangle\langle\eta(r',t')\rangle = -\frac{2Mv_j}{\beta}\delta(t-t')\nabla_r \times \delta(r-r')\rho_i\rho_j\nabla_{r'} \quad (9)$$

where *M* is a bead mobility parameter. The kinetic coefficient $Mv\rho_i\rho_j$ models a local exchange mechanism. The Langevin equations are constructed for an incompressible system with dynamic constraint:

$$(\rho_i(r,t) + \rho_j(r,t) = \frac{1}{v_j} \quad (10)$$

where v_j is the average bead volume.

Generally, to map the representative polymer chains onto the coarse-grained chains, the bead number (N_{meso})can be estimated,

(Mu *et al*., 2011), by:

$$N_{meso} = \frac{N_{mon}}{C_{\infty}} \quad (11)$$

where N_{monis} the number of repeating units in the polymer chainand C_{∞} is the characteristic ratio of a chain of infinite length that can be determined from an experiment, for example the intrinsic viscosity of a dilute polymer solution.

The interaction between the beads connection ($v^{-1}\ \varepsilon_{ij}$) can be obtained as:

$$v^{-1}\varepsilon_{ij} = \chi_{ij}RT \quad (12)$$

where the parameter X_{ij} is the interaction between *A* and *B* at different temperatures. This parameter can also be obtained from an experimentbased on the thermodynamic properties of the polymer mixture. *R* is the molar gas constant, 8.314 J/molK, and *T* is the temperature.

All the parameters used in our simulation have already been validated in the previous reported studies of PEO-PPO-PEO micelle in aqueous solution (Lam and Goldbeck-Wood, 2003; Lam *et al*., 2004; Yang *et a*l., 2008b).

Simulation Systems

MesoDyn was used to investigate the aggregation behavior of a Poly(ethylene oxide)-Poly(propylene oxide)-Poly(ethylene oxide), (PEO-PPO-PEO) triblock copolymer. The effect of the PPO/PEO block ratio on the critical micelle concentration *(cmc)* and micelle formation kineticswere studied. Forthe MesoDyn simulation, 2 sets of parameters must be defined to specify the chemical nature of the system: one is the chain topology in terms of the repeating segments, and the other is the interaction energy between different components as shown by equations 11 and 12, respectively. For the first parameter set, MesoDyn uses a Gaussian chain "springs and beads" description, where each bead in the Gaussian chain is a statistical unit, representing a number of "real" monomers and different types of beads correspond to diverse components. All the ABA sequencesof the Gaussian chain topology (A = PEO unit and B = PPO unit) are illustrated in Table 1. The relationship between the real atomic molecule and the Gaussian chain model was first approximated by van Vlimmeren and coworkers (van Vlimmeren *et al*., 1999b) and which corresponded to the number of the monomer unit/bead ratio of 4.3 for the PEO and 3.3 for the PPO. A water molecule and the haloperidol drug were approximated with a single bead as W and H, respectively. The interaction energy ($v^{-1}\varepsilon_{ij}$) between various types of beads was presented in Table 2

Table 1. Designated Gaussian chain for A-B-A triblock copolymers

Real copolymer chain	Gaussian chain	A/B block ratio
(1) $PEO_{34}PPO_{26}PEO_{34}$	$A_8B_8A_8$	2.00
(2) $PEO_{26}PPO_{40}PEO_{26}$	$A_6B_{12}A_6$	1.00
(3) $PEO_{17}PPO_{53}PEO_{17}$	$A_4B_{16}A_4$	0.50

Table 2. Interaction parameters for polymer species, water, and haloperidol drug molecule

	A	B	W	H
A	-	7.30	3.34	5.13
B	7.30	-	4.07	2.79
W	3.34	4.07	-	12.09
H	5.13	2.79	12.09	-

(Lam *et al.*, 2004). The bond length was 1.154 nm. All bead diffusion coefficients were 1.0×10^{-7} cm^2/s. A box size $32 \times 32 \times 32$ with periodic boundary conditions was used. The total simulation time was 20000 time steps.

Results and Discussion

The Effect of Polymer Concentration on Phase Morphology

The Gaussian chain models of the ampliphilic triblock PEO-PPO-PEO copolymer (A and B beads for the PEO and PPO parts, respectively) with the same total length but different A/B block ratio ($A_4B_{16}A_4$, $A_6B_{12}A_6$ and $A_8B_8A_8$) in aqueous solution were studied. The isosurface of 3-dimensional density fields of the B block for each of the chain topologies on its concentration are shown in Figure 1. Because it is more convenient to justify the micelle or other types of phase formation by looking at the hydrophobic (PPO) part that can self-assembly in the core of the micelle rather than the hydrophilic (PEO) part which forms the corona, only the PPO portion was shown in the Figures. The density field suggests the dependence of the polymer morphology on its concentration. The phase diagram of $A_4B_{16}A_4$ and $A_6B_{12}A_6$ has a qualitatively similar pattern. The morphologies of $A_4B_{16}A_4$ and $A_6B_{12}A_6$ were transformed as: disordered phase (Dis) → spherical micelle (M) → disk-like micelle (D) or worm-like micelle (Wm) → bi-phase (BP) region with an increase ofthe copolymer concentration. The change of the micelle phase for $A_6B_{12}A_6$ was in good agreement with a previous study (Yang *et al.*, 2008a). In contrast, $A_8B_8A_8$ cannot form the spherical micelle. Instead, the morphologies were transformed as: a disordered phase (Dis) → disk-like micelle (D) → worm-like micelle (Wm). That means only the appropriated A/B block ratio (< 1.00) can induce the formation of the spherical micelle. As shown in the Figure 1, the concentrations at which spherical micelles

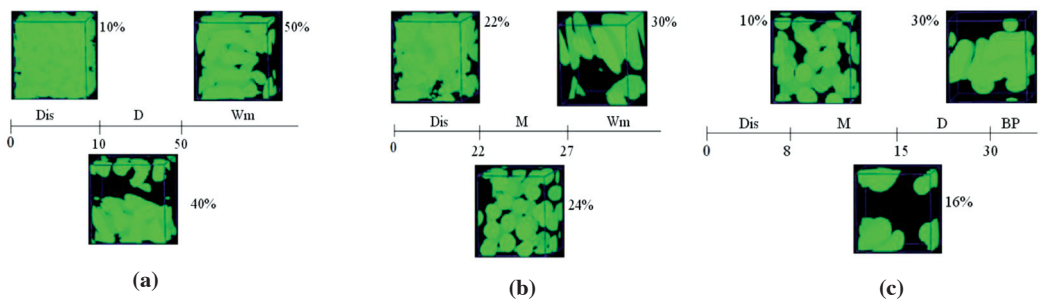

Figure 1. Phase morphology in aqueous solution at 298 K for (a) $A_8B_8A_8$, (b) $A_6B_{12}A_6$, and (c) $A_4B_{16}A_4$. Dis (disordered phase), M (micelle), D (disk-like micelle), Wm (worm-like micelle), and BP (bi-phase)

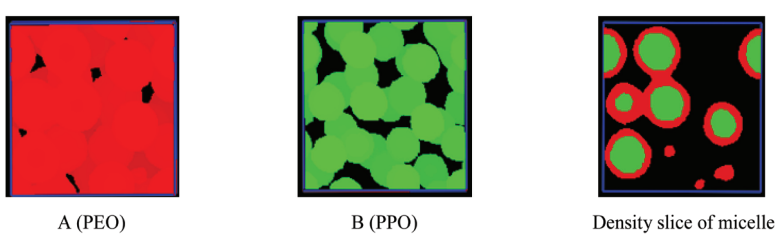

Figure 2. The isosurface of A and B species and the density slices for 12%v of A4B16A4 in aqueous solution at 298 K.

are stable are 8–15 vol% and 23-27 vol % for $A_4B_{16}A_4$ and $A_6B_{12}A_6$, respectively. For a smaller A/B ratio, the spherical micelle was formedmore easily at a lower concentration.

To understand the detailed structure of each spherical micelle, 12 vol% of $A_4B_{16}A_4$ was chosen to show the structures of spherical micelles through the density fields of different beads that represent each different species. First, the best density slices of A, B, and W along the reference axis of a cubic grid were created. Then, 3 slices of each bead in the same spherical micelle were divided, as shown in Figure 2. The structure of the spherical micelle presented by the hydrophillic A part forms the corona of the micelle, whereas the hydrophobic B part forms the micelle core. Some water molecules still remained in the micelle core in agreement with Yang *et al.*, 2008a. This isbecausethe spherical micelle is composed of a loose core of the hydrophobic part, as usually found in typical experimental results of a PEO-PPO-PEO triblock copolymer (Batrakova and Kabanov, 2008; Kabanov *et al.*, 2002).

The Effect of the EO/ PO Block Length Ratio

To investigate the effect of the A/B (EO/PO) block length ratio on the morphology change and micelle formation kinetics, the aggregated morphology of $A_6B_{12}A_6$ (A/B = 1.00) and $A_4B_{16}A_4$ (A/B = 0.50) were compared, as shown in Figure 1. Next, the order parameter was employed to determine the phase separation behavior for the process of the micelle formation.The order parameter in Mesodyn is defined as the volume average of the difference between the local density squared and the overall density squared:

$$P_1 = \frac{1}{V}\int_V [\eta_I^2(r) - \eta_I^2]dr \qquad (13)$$

where η_I is a dimensionless density (volume fraction) for species I. Order parameters with large values indicate a strong phase segregation. Conversely, very small values indicate a mixed system. Also from Figure 1, the spherical micelles start to grow at different concentrations. The size of the $A_4B_{16}A_4$ micelle is slightly larger than that of $A_6B_{12}A_6$. The kinetics of the spherical micelle formation for $A_6B_{12}A_6$ and $A_4B_{16}A_4$ were compared in Figure 3. Because of the smaller hydrophobic content, $A_6B_{12}A_6$ had more difficulty in forming spherical micelles than $A_4B_{16}A_4$, as seen by a slower rate ofthe order parameter evolution to reach an equilibrium point. However, at a rough approximation, it seems

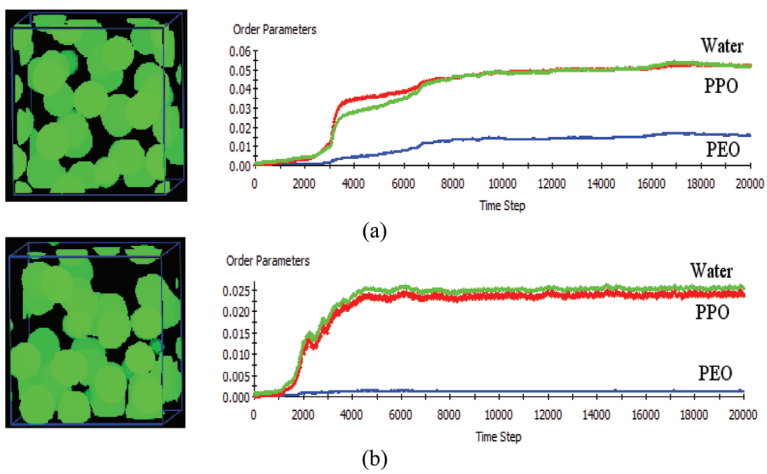

Figure 3. The isosurface of B part and the order parameter plot simulation time step in aqueous solution at 298 K for (a) 24% v. of $A_6B_{12}A_6$ and (b) 12% v. of $A_4B_{16}A_4$.

that the micelle size for each copolymer system is relatively the same. The micelle of the $A_4B_{16}A_4$ system has a higher number of aggregated particles than those of the $A_6B_{12}A_6$ system. To gain more insight about phase separation kinetics, the order parameters for each component of the $A_6B_{12}A_6$ system with a simulation time were carefully analyzed and are shown in Figure 4. There are 4 states for micelle growth as suggested by the change in the order parameter. The first state only takes about 0.1 microseconds (or 1000 time steps), in which the order parameter is slightly changed from the beginning. The phase is still disordered and homogeneous. Then, the order parameter was largely increased resulting from the transition from a disorderedstate to almost spherical micelles and then they rearranged themselves to form spherical micelles in the second and third state, respectively. After that, the order parameter was changed slowly to overcome their initial morphology to reach the equilibrium at the final state (Guo *et al.*, 2002; Yang *et al.*, 2008b). Phase transition of the second and the third states is very fast, especially at a higher concentration. The micelle formation rate at a higher concentration needs less time for phase separation.

To validate our simulation results with the experiment, an aggregation behavior of the $PEO_{17}PPO_{60}PEO_{17}$ (P103) copolymer wascompared with our results (Yang *et al.*, 2008b). P103 can be mapped to a Gaussian chain model as A4B18A4 (A/B = 0.44). P103 has an experimental value of *cmc* = 4 vol%, while the simulated *cmc* of $A_4B_{16}A_4$ (A/B = 0.50) in this study gives 8 vol%. Since *cmc* values can be varied depending on the experimental methods, the predicted *cmc* from this simulation is in the satisfactory range. In addition, our simulation results also give a similar morphology change with an increasing concentration as: disordered (Dis) → spherical micelle (S) → disk-like micelle (D) → bi-phase (BP) which is in good agreement with other experiment findings (Alexandridis *et al.*, 1995).

The Effect of Adding Drug Molecule

The micelle structures of 12 vol% $A_4B_{16}A_4$ in the absence and presence of 2 vol% haloperidol were compared, as shown in Figure 5. The isosurface of each species in the spherical micelle reveals that the size of the micelle for the system with the addition of the drug becomes larger, but that there is a lesser number of micelle particles. The drug molecules were located at the interface between the A and B parts of the micelle. To gain more insight about the micelle formation rate and the kinetics of the phase transition, the order parameters for each component with their simulation times were analyzed, as shown in Figure 6. There are 3 major states for micelle growth when the drug molecule is added into the polymer solution, as suggested by the change in the

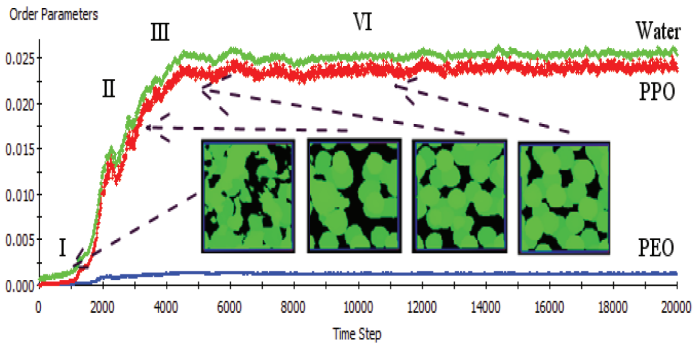

Figure 4. The order parameter versus the simulation time for 12% v of $A_4B_{16}A_4$ in water

order parameter. The first state also takes about 0.1 microseconds (or 1000 time steps), the phase solution was still disordered and homogeneous in which the order parameter was unchanged from the beginning. Then, the order parameter was largely increased as a resultof the phase transition from the disordered phase to spherical micelles in the second state. After that, the system was slowly changed. The order parameter in the last state was slowly changed toreach the equilibrium compared with the micelle without drug addition. A difference in the number of the micelle formation state between these 2 systems suggests that it is harder for the micelle to form and reach the equilibration state when the drug isalso dissolvedin the solution. Moreover, the solution needs a longer time to transform the disordered phase to the spherical micelle at equilibrium. Phase separation of the system with adding the drug molecule, as illustrated by the magnitude order parameters, was also stronger.

Conclusions

The effects of the PEO/PPO block ratio and copolymer concentration on the morphology of a designed triblock copolymer at a fixed total number of units were studied bythe MesoDyn simulation. The results suggested that the PEO/PPO block ratio has significant effects on the phase aggregation, *cmc*, and the formation rate of the micelle. The cmc

Figure 5. The morphology for 12%v of $A_4B_{16}A_4$ in aqueous solution at 298 K. (a) without and (b) with adding 2% v. of drug molecule

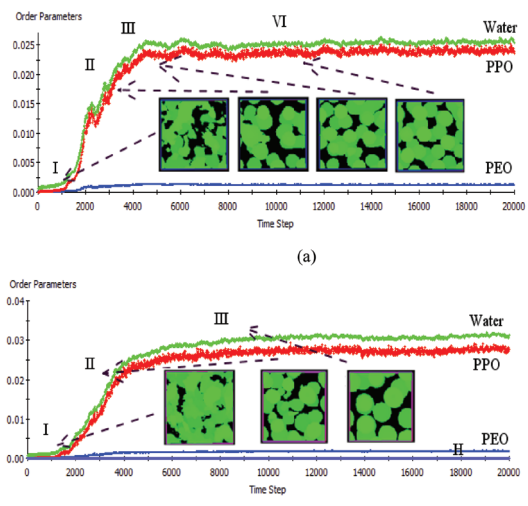

Figure 6. Time evolution of order parameter for 12%v of $A_4B_{16}A_4$ in aqueous solution at 298 K. (a) without and (b) with 2% v. of drug

was increased with increasing the PEO/PPO block ratio and only the appropriated ratio can induce a spherical micelle formation. A tiblock copolymer with a longer PPO block can forma micelle more easily and the micelle size becomes bigger. The presence of a hydrophobic drug molecule (haloperidol) causeda micelle to form more easily and with a larger micelle size. The drug molecules were located at the interface between the EO and PO parts.

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