Dissipative Particle Dynamics Simulation on Paclitaxel Loaded PEO–PPO–PEO Block Copolymer Micelles

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Self-assembly behavior of the polymer drug loading micelle PEO–PPO–PEO was studied using dissipative particle dynamics (DPD) simulation method with various simulation steps. The distributions of drugs in polymer carriers were also investigated with different drug feed ratios. Polymer carriers distributed on the surface of the spherical micelle, and drugs were almost encapsulated in the inner of the micelle. Our simulation work demonstrates that the DPD simulation is effective to study the drug loaded systems and can give useful guidance on the design and preparation of new drug carriers with tailored properties.

Keywords: DPD, Polymer, PEO–PPO–PEO, Micelles.

Dissipative particle dynamics (DPD) simulation was introduced to study the PEO–PPO–PEO drug-loaded polymeric micelles. DPD is a mesoscale simulation method introduced by Hoogerbrugge and Koelman in 1992,12,13 which is used to simulate a wide range of complex fluid systems such as polymeric micelles,14,15 surface surfactants,16,17 and drug delivery systems.18–21 In this method, one bead represents a group of atoms or a volume of fluid. The force between each pair of beads comprises of a conservative force $F^C_{ij}$, a dissipative force $F^D_{ij}$ and a random force $F^R_{ij}$. Each force is pairwise additive:22

$$f_i = \sum_{i\neq j} \left( F^C_{ij} + F^D_{ij} + F^R_{ij} \right)$$  \hspace{1cm} (1)

Groot and Warren22,23 proposed the relationship between the repulsive parameter $a_{ii}$ and the Flory–Huggins parameters ($\chi_{ij}$). The repulsion parameter $a_{ii}$ is calculated according to:

$$a_{ii} = 75k_B T / \rho$$  \hspace{1cm} (2)

where $a_{ii}$ is the repulsion parameter between same types of particles, $k_B$ is the Boltzmann constant and $T$ is the system temperature. $\rho = 3$ is the particle density in this simulation, and $k_B T = 1$ has been used. The repulsion parameter $a_{ii} = 25$. The repulsion parameters ($a_{ij}$) between different types of particles are linearly related with the Flory–Huggins parameters ($\chi_{ij}$) with the following equation:

$$a_{ij} = a_{ii} + 3.27 \chi_{ij}$$  \hspace{1cm} (3)
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where the $X_{ij}$ parameter between pairs of particles can be obtained from Eq. (4),

$$X_{ij} = (\delta_i - \delta_j) V_{ref}/kT$$

Figure 1. Molecular structures and coarse grained models of PEO–PPO–PEO, paclitaxel, and water.

Figure 2. Aggregate morphologies of drug delivery system with increasing simulation steps. (a) 100, (b) 500, (c) 1,000, (d) 5,000, (e) 10,000, (f) 20,000, (g) 30,000, (h) 50,000, (i) 100,000. Red beads: paclitaxel, green beads: PEO–PPO–PEO.

where $k$ is the Boltzman constant, $T$ is the temperature, $\delta_i$ and $\delta_j$ are the solubility parameters of a pair of interacting beads, $V_{ref}$ is the average molar volumes of a pair of beads, which could be calculated using Discover and Amorphous Cell modules in Materials Studio 5.0 software with the COMPASS force field at 298 K and under atmospheric pressure.

The anti-tumor drug paclitaxel was selected as the drug model, and PEO–PPO–PEO as the nano carrier to load paclitaxel. The molecular structure and coarse-grained models of the polymer and drug are shown in Figure 1. PEO–PPO–PEO is composed of hydrophilic PEO units and hydrophobic PPO units. Paclitaxel is divided into three types of beads (D1, D2 and D3) in Figure 1. Water molecule is treated as an individual bead. In the drug delivery system, 5% PEO–PPO–PEO loading 1%, 3%, 5% paclitaxel was calculated, while the remaining part was water. The simulation system contained polymer carrier, drug, and water in a cubic cell of size $20 \times 20 \times 20\bar{r}$ with 24,000 beads. To obtain the steady results, 100,000 DPD steps have been adopted with a time step of 0.05 ns. All the simulations were carried out using DPD module in the Materials Studio 5.0 software program (Accelrys Software Inc., San Diego, CA, USA).
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Figure 3. Aggregate morphologies of drug loading system at different contents of drug. (a) 1%, (b) 3%, (c) 5%, and section views (d) 1%, (e) 3%, (f) 5%. Red beads: paclitaxel, green beads: PEO–PPO–PEO.

Figure 2 illustrates the aggregate morphologies of the drug loading micelle with increasing simulation steps. The system comprises of 5% PEO–PPO–PEO, 5% paclitaxel and 90% water, red beads represent drugs and green beads represent polymer carriers. To observe the aggregation morphologies clearly, the water beads were not displayed. Shown in Figure 2(a), all components were randomly distributed in aqueous solution at the beginning (100 simulation steps). At the step of 500, 1000, polymer and drug molecules began to aggregate and form small micelles of different sizes (Figs. 2(b), (c)). With the simulation steps increased to 10,000, these small micelles collided and fused, gradually forming larger aggregates (Figs. 2(d), (e)). Hydrophilic PEO spread around the surface, while hydrophobic PPO distributed inside the core. The drug paclitaxel in water gradually diffused into the core. Finally only one big spherical micelle was formed at 30,000 steps (Fig. 2(g)), red drugs were almost wrapped in the inner of the micelle core, and the morphology did not change visibly with the simulation steps further increased to 100,000, indicating that this system reached a dynamic equilibrium and a stable spherical micelle was observed.

The micelles at different drug contents were also investigated using DPD simulation method. The simulation snapshots after 100,000 time steps are shown in Figure 3. The polymer content was set as 5%, when the molar fraction of drug increased from 1% to 5%, red drugs were almost entrapped in the inner of spherical micelle, while green polymers well distributed on the surface of the micelle. With the increase of drug content, more drugs distributed inside the micelle (Figs. 3(a)–(c)). In order to observe the drug distribution in polymeric micelle more directly, their section views were displayed in Figures 3(d)–(f). We can see clearly from the drug loading micelles that the drug carrier PEO–PPO–PEO coated around the core formed by the drug paclitaxel, producing a core–shell spherical structure. The PEO blocks increased the hydrophilicity of the polymer carrier, allowing it a protective layer between the core and water. The PPO chains resulted in a strong hydrophobic block aggregating tightly and forming a hydrophobic core to entrap hydrophobic drugs. The hydrophobic drug paclitaxel dispersed into the PPO core, due to the hydrophobic effect. With the increase of drug content, more and more drug molecules were distributed into the matrix, and the micelle became larger. 5% paclitaxel system entrapped much more drugs into micelle than 1% and 3% paclitaxel system. Therefore, even if when the molar fraction of paclitaxel increases, polymer carrier can well wrap them inside the micelle.

In conclusion, the DPD simulation provides deeper insights for the preparation of drug-loaded polymeric micelles. Desired properties of drug carrier can be obtained from correlating and optimizing its microstructure and feed ratio. New drug carrier material can be better understood and designed.

References and Notes

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Received: 23 July 2012. Accepted: 9 October 2012.