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Application of DPD in the design of polymeric nano-micelles as drug carriers

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ABSTRACT

Developing new drug carrier systems are of a great importance in the treatment approach for a wide range of diseases. The simulation techniques can be valuable for decreasing the time and cost of developing novel drug carriers. Among the simulation methods there are a vast number of studies using dissipative particle dynamics (DPD) method for the prediction of different aspects of polymeric nano-micelles for encapsulating drugs. Here, we reviewed the results of the studies employing DPD for the simulation of drug loading and release in different polymeric micelles carriers. In some cases the simulation results were compared with the experimental results by the authors that were demonstrated the reliability of the DPD predictions.

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1. Introduction

Drug carriers are widely used for encapsulation, controlled release and delivery of various pharmaceutical ingredients. For example in developing anti-cancer therapeutics there is a trend in designing the drug carriers that have pH-sensitive [1–3] or thermosensitive [4–7] release properties. Drug carriers include nanoparticles, liposomes, non-micelle-forming polymeric carriers and polymeric micelles. Compared with other drug carriers, polymeric micelles are self-assembled and have the advantages of very small size (10–100 nm), which is important for passive drug delivery to the solid tumors. This is called enhanced permeability and retention (EPR) effect [8–10]. Formed polymeric micelles composed of an inner core and an outer shell and they have a spherical or a cylindrical shape. For the purpose of drug loading, most polymeric micelle studies have considered the polymeric micelles with spherical shape. The most commonly used hydrophilic segment of micelles for drug delivery is poly(ethylene glycol) (PEG), with a molecular weight of 2–15 kDa. PEG is water-soluble, neutrally charged and forms a hydrophilic corona on the surface of micelles, thus showing a stealth property during blood circulation by minimizing the non-specific interaction with blood components. Polyesters such as poly(lactic acid) (PLA) were used as the hydrophobic domain [9,11,12].

Molecular dynamic simulation can be used for simulation of the behavior of drug and carrier molecules in solution. The main

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drawback of this approach is that the method is computationally expensive for large systems and long times. One of the main mesoscale modeling methods is DPD. The methods have some shared feature and application but DPD is preferred for dilute systems [13–15]. The mesoscale methods especially DPD became more popular in recent years as its results showed good agreements (at least qualitatively) with retrospective and prospective experimental results in several studies [16–20].

In summary, in the DPD method introduced by Hoogerbrugge and Koelman [21,22] a set of soft interacting particles is used to simulate a fluid system. Each bead represents several atoms, repeating units or a volume of fluids. Their dynamics evolution is governed by Newton's second law, as given in Eq. (1):

$$\frac{d\boldsymbol{r}_i}{dt} = \boldsymbol{v}_i, m_i \frac{dv_i}{dt} = \boldsymbol{f}_i \tag{1}$$

where $\boldsymbol{r}_i$, v_i and $\boldsymbol{f}_i$ are the position vector, velocity and total force on the particle i, respectively. All the bead masses m_i are assumed to be the same and can be set equal to unity for simplicity. Thus, the masses of all beads can be set to 1 DPD unit [23].

The force between each pair of beads comprises of a conservative force $\boldsymbol{F}_{ij}{}^{C}$, a dissipative force $\boldsymbol{F}_{ij}{}^{D}$ and a random force $\boldsymbol{F}_{ij}{}^{R}$ [24]:

$$\boldsymbol{f}_i = \sum_{i \neq j} \left(\boldsymbol{F}_{ij}^{C} + \boldsymbol{F}_{ij}^{D} + \boldsymbol{F}_{ij}^{R} \right) \tag{2}$$

where the sum runs over all particles within a certain cutoff radius, r_c, whose value can be set to 1 unit of length in simulations. $\boldsymbol{F}_{ij}{}^{C}$ is given by:

$$F_{ij}^{C} = \begin{cases} a_{ij}\left(1 - r_{ij}\right)\hat{\mathbf{r}}_{ij} & r_{ij} < 1 \\ 0 & r_{ij} \geq 1 \end{cases} \tag{3}$$

Where a_{ij} is the maximum repulsion between bead i and j, $\mathbf{r}_{ij} = \mathbf{r}_i - \mathbf{r}_j$, $r_{ij} = |\boldsymbol{r}_{ij}|$ and $\hat{\mathbf{r}}_{ij} = \boldsymbol{r}_{ij}/|\boldsymbol{r}_{ij}|$. $\boldsymbol{F}_{ij}{}^{D}$ and $\boldsymbol{F}_{ij}{}^{R}$ are given by the following expressions:

$$\boldsymbol{F}_{ij}^{D} = \begin{cases} \sigma\omega^{R}\left(r_{ij}\right)\theta_{ij}\hat{\mathrm{r}}_{ij} & r_{ij} < 1 \\ 0 & r_{ij} \geq 1 \end{cases} \tag{4}$$

$$\boldsymbol{F}_{ij}^{R} = \begin{cases} -\gamma\omega^{D}\left(r_{ij}\right)\left(\hat{\mathrm{r}}_{\boldsymbol{ij}}.\boldsymbol{v}_{ij}\right)\hat{\mathrm{r}}_{ij} & r_{ij} < 1 \\ 0 & r_{ij} \geq 1 \end{cases} \tag{5}$$

where θ_{ij} is a randomly fluctuating variable between 0 and 1, γ is the viscosity coefficient, σ is the noise strength, $v_{ij} = v_i - v_j$ is the relative velocity of particles i and j. The terms ω^{D} and ω^{R} are r-dependent weight functions vanishing for $r > r_c$. One of the two weight functions can be chosen arbitrarily, therefore fixing the other weight function [24]. The relations of the parameters are:

$$\omega^{D}\left(r_{ij}\right) = \left[\omega^{R}\left(r_{ij}\right)\right]^2 \tag{6}$$

$$\sigma^2 = 2\gamma k_B T \tag{7}$$

where T is the absolute temperature and k_B is the Boltzmann's constant. In addition, a spring force $\boldsymbol{F}_i{}^{S}$ acts between particles which are connected in molecules [24]. The spring force is:

$$\boldsymbol{F}_i^{S} = \sum_j C\boldsymbol{r}_{ij} \tag{8}$$

where C is the spring constant, and the sum runs over all particles to which particle i is connected.To calculate the conservation force, Groot and Warren [25] proposed a relationship between the repulsive parameter a_{ii} and the Flory–Huggins parameters (χ_{ij}). The repulsion parameter can be calculated as:

$$a_{\mathrm{ii}} = \frac{75k_BT}{p} \tag{9}$$

Where a_{ii} is the repulsion parameter between same types of particles. The compressibility of pure fluid can be set as $\rho = 3$ (close to that of water), and the value of $k_BT = 1$ (as Hoogerbrugge and Koelman did [22]) can be used in the simulations. The values of the repulsion parameters between different types of particles (a_{ij}) are linearly related to the Flory–Huggins parameters (χ_{ij}) according to the equation:

$$a_{ij} = a_{ii} + 3.5x_{ij} \tag{10}$$

where the χ_{ij} parameter between pairs of particles can be obtained from Eq. (11).:

$$x_{ij} = \frac{\left(\delta_i - \delta_j\right)^2 V_{ref}}{k_BT} \tag{11}$$

where δ_i and δ_j are the solubility parameters of a pair of interacting beads, V_{ref} is the average molar volumes of a pair of beads. The solubility parameter can be calculated by atomistic Molecular Dynamic simulations or experiments.

Introducing this relationship between the simple function form of a_{ij} in DPD and the Flory–Huggins parameter theory led to the broad application of DPD in the study of mesoscale structures. In this review, we discussed the studies that employed DPD mainly for investigation on drug/carrier self-assembly, drug loading, drug release and pH sensitive drug carriers.

2. Self-assembly of the carriers and their drug loading capacity

There are a lot of studies in which the ability of DPD simulation to successfully predict qualitative and semi-quantitative of self-assembly behavior of drug carriers as well as drug or nanoparticles loading was demonstrated [26–29]. DPD showed that systems with low concentration of homopolymer poly(propylene oxide) (PPO) and short chain diblock copolymer poly(ethyl ethylene)-block-poly(ethylene oxide) (PEE-b-PEO) formed core–shell–corona structured micelle after mixing, while by using long chain PEE-b-PEO, micelles had a two compartmental spherical structure [20]. The estimated size for the micelle and suggested morphology were consistent with the experimental results. The structure of a self-assembled micelle from amphiphilic four-arm star triblock poly(ε-caprolactone)-*b*-poly(2-(diethylamino) ethyl methacrylate)-*b*-poly(poly-(ethylene glycol) methyl ether methacrylate) (4AS-PCL-*b*-PDEAE-MA-*b*-PPEGMA) was approved by DPD. They were micro-spherical micelles with stable core–shell structure [17]. The PCL was located in the core whereas PDEAEMA and poly(ethylene glycol) PEG were in the interlayer and shell, respectively. The simulation showed that doxorubicin can be loaded into the core and interlayer of the micelles with a good loading efficiency and a maximum loading. The ability of G5-PEG polyester dendrimers for the loading of doxorubicin was also evaluated by DPD model and was compared to experimental results [19]. The core consisted of the hydrophobic G5 dendritic blocks and the shell was originated from the hydrophilic PEG blocks. Doxorubicin was loaded (loaded drug content = 16.7%) with loading efficiency of 100% in the core which was in agreement with those obtained from the experiments (15.2% and 99%, respectively). The loading efficiency and its mechanism of a hydrophobic anticancer drug, camptothecin, in a pH-sensitive amphiphilic copolymer, composed of hydrophobic poly(β-amino ester) (PAE) and hydrophilic methyl ether-capped PEG was investigated [30]. It was suggested