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ORIGINAL PAPER

Investigation of ibuprofen loading in PEG–PLGA–PEG micelles by coarse-grained DPD simulations

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Abstract

Investigation of drug encapsulation behavior is important to design efficient drug delivery materials. With this aim, we strive to perform coarse-grained simulations to study the drug encapsulation behavior of a particular micelle-forming co-polymer composed of hydrophilic PEG and hydrophobic PLGA units. The study is performed at the mesoscopic scale to overcome the time scale problem associated with the micelle formation at the atomistic scale. The structure and drug loading properties are studied at different polymer concentrations and drug loading. The resulting micellar structures that are obtained via dissipative particle dynamics simulations are observed to encapsulate the drug with high efficiency values. Moreover, the DPD simulations performed in this work reveal physical insight on the interactions and molecular structure as well as the temporal evolution of the encapsulation process. Our work can be considered as an attempt to computationally characterize the drug encapsulation behavior and structure of a prospective drug delivery system.

Introduction

Targeted drug delivery is one of the most advancing areas of nano-materials research [1–4]. Designing polymeric materials with the ability to encapsulate drugs has become one of the principal motives to increase systemic exposure, limit the chemical degradation of the drug, and decrease the adverse effects such as cytotoxicity, which therefore, lead to the enhanced permeability and retention (EPR) effect [5, 6] and stability [7]. The EPR effect is required to stimulate the accumulation of the drug at the target tissue. This can be achieved via passive and active targeting [8–10].

One way to encapsulate a hydrophobic drug is to use a particular block co-polymeric system with an amphiphilic character in the form of spherical micelles. Within these micelles, the hydrophobic drug can be carried within the hydrophobic core, while the hydrophilic part interacts with the aqueous environment. The designed block co-polymeric drug carrier system is expected to carry its load to the target zone and release it upon stimuli from the environment. Therefore, systems that are susceptible to the physical or chemical changes in the environment can be used to construct the co-polymer system of interest. At this point, poly(lactic-co-glycolic acid) (PLGA) can be used as the sub-unit due to its non-toxic, biodegradable, and thermo-sensitive properties [11]. Most commonly, poly(ethylene glycol) (PEG) acts as the hydrophilic part and PLGA as the hydrophobic part of the block co-polymer [12].

One of the major issues in designing drug delivery micelles is to optimize the chemical properties of the micelles, such as molar ratio of the hydrophilic/hydrophobic groups, molecular weight of the chains, and micelle size. The latter is especially important and affected from the concentration in which the micelle is prepared. Therefore, efforts to optimize the conditions for maximizing the drug loading capacity is of utmost importance in designing new drug carrier nano-structures [13–16].

At this step, molecular simulation studies comprise a great deal of efforts to study the micelle-forming polymers with the motivation to help designing new drug carrier nano-structures. Moreover, the key parameters influencing the micelle-forming conditions can be studied at the molecular level. In addition, the molecular-level information obtained

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by the simulations would lead to a significant physical insight on the system of interest, along with guiding the experimental studies. One of the widely employed simulation techniques to achieve to that purpose is referred as coarse-grained simulations, where the atoms of particular chemical sub-units are combined together to form larger super-atoms referred as *beads* [17]. Within the coarse-grained methods, for over two decades, dissipative particle dynamics (DPD) simulation method [18, 19] has emerged as a simulation technique to model fluids and polymeric materials recently, with a significant emphasis on the drug delivery systems [20–23]. In this work, we aim to study the encapsulation behavior of a particular PEG–PLGA–PEG system, which is known to exhibit micelle structures [24] by using the DPD method.

Our study presented herein consists of our efforts to model and simulate the block co-polymer system encapsulating a particular drug molecule, namely ibuprofen. Ibuprofen is a suitable model drug for hydrophobic drugs in general. We choose to study different block co-polymers at different drug loadings in the system to comment on the effect of the changing concentration on the structure and drug encapsulation behavior. Moreover, we study the time evolution of the encapsulation process to investigate the encapsulation dynamics.

Materials and system details

Materials

The block co-polymer system is composed of poly(ethylene glycol) and poly(lactic-co-glycolic acid). The block co-polymer has a molecular weight of 3560 g/gmol resulting in the number of repeating units and coarse-graining as presented in Fig. 1. Water is used as solvent in the simulations, where a single water molecule represents one water bead W. All molecules are capped with required number of hydrogen atoms to form proper molecules in the formation of beads. The physical properties of coarse-grained beads are given in Supplementary Information.

System details

The details of the DPD method and simulation details are extensively discussed in the Supplementary Information. The simulation boxes are constructed for simulation of different polymer and drug weight percent values. Three weight percent values are set for the polymer in the system: 5%, 10%, and 15%. For each polymer weight percent, drug molecules are added to the system corresponding to different drug weight percent values: 0.1%, 1%, and 2%. The drug loading values in the systems are set in line with the experimental conditions [25, 26]. As noted in Eq. S2, the DPD interaction parameters are computed as a function of the molar fraction of individual bead types. Therefore, for each simulated system, a different set of DPD interaction parameters are computed. The equilibrium structure is mainly dictated by the excess repulsion and hydrogen bond strength values of beads rather than the absolute values of the DPD interactions. As an example, we report in Table S2 of the Supplementary Information the DPD parameters for the 5% polymer and 0.1% drug, and 15% polymer and 0.1% drug systems.

Results and discussion

Structure of ibuprofen-loaded micelles

We initially demonstrate the simulation snapshots of the drug-loaded systems in Fig. S1 in the Supplementary Information. It is immediately noticed that the hydrophilic part

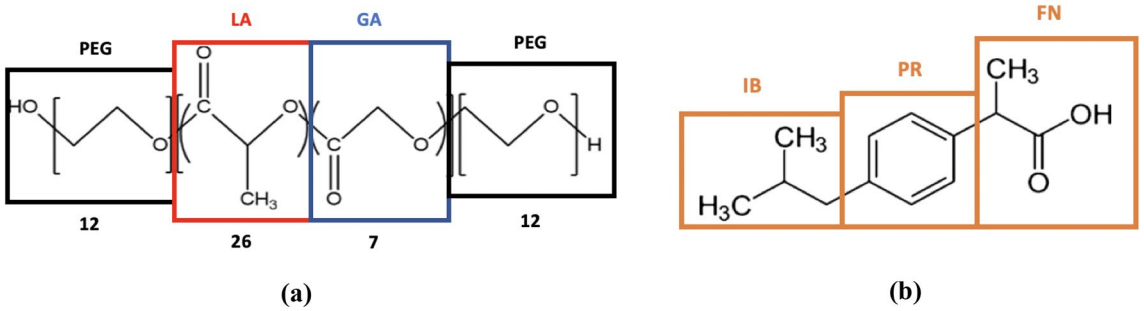

Fig. 1 Chemical structures and coarse-grained bead definitions of **a** PEG–PLGA–PEG and **b** ibuprofen. The numbers indicate the number of repeating units

of the block co-polymer PEG, constructing the corona part of the micelles, interacts with the solvent water beads due to the hydrogen bond attraction incorporated in the parameterization. In contrast, the hydrophobic parts prefer to stay away from water and form the core of the micelles. Ibuprofen molecule, which has a hydrophobic nature, is observed to be mainly accumulated near the core region of the micelles. However, the slight hydrophilicity of the FN bead of ibuprofen leads to a preferential attraction to water resulting in dragging of ibuprofen towards core/corona interface. This is why the drug is mainly observed on the surface of the hydrophobic core.

To comment more on the structure, we plot the radial distribution functions (RDF) $g(r)$ computed as $g(r) = \langle \Delta N_{ij}(r \to r + \Delta r) \rangle V / 4\pi r^2 \Delta r N_i N_j$. The numerator is the product of the ensemble averaged number of j bead around i bead within a shell from r to $r + \Delta r$ and the volume V, and the denominator is proportional to the product of the total number of beads N_i and N_j in a particular shell. The RDF is computed between the beads that form the polymer micelle and drug molecules to quantify the local structure and interactions and plotted in Fig. 2. The RDF is a widely used parameter to quantify the structural differences at the molecular scale. The RDF can be compared with experimental X-ray diffraction profile by taking the Fourier transform of the XRD intensity data. Therefore, yielding information that could be beneficial for experimental pharmaceutical development scientists.

The local structure as revealed by the RDFs in Fig. 2a between the polymer beads and drug beads are qualitatively quite similar such that the RDFs indicate attraction due to the highly concentrated first neighboring beads, which is followed by a slowly decaying RDF profile. Nevertheless, the RDF lines exhibit some quantitative differences. That is, as the polymer concentration and drug amount are increased, the first peak values are decreased. The profiles with the highest first peaks are noticed to decay much faster compared to the RDFs with lower first peaks. This means that if a particular polymer system interacts more with the drug at shorter distances, they interact less at longer distances. The interactions of polymer and the solvent water beads in Fig. 2b indicate that the polymer interacts much less with water compared to the drug. This is expected due to the micellar morphology of the co-polymers, where water beads only interact with the hydrophilic beads. Overall, the difference in the polymer–water RDFs can be considered as minor and all systems exhibit similar structures.

Drug encapsulation properties

As noticed from the simulation snapshots, a high concentration of drug beads near the core of the micelle is noticed. In order to quantify the encapsulation, we compute the drug EE values of the simulated systems as plotted in Fig. 3.

Overall, PEG–PLGA–PEG micelles have significantly high EE values, having the minimum value for the system with 5% polymer and 0.1% drug, and the maximum value for the 15% polymer and 0.1% drug. The EE values are about 65% to 89% for the minimum and maximum EE values, respectively. A proper comparison to the experimental data is difficult, since, to the best of our knowledge, similar block co-polymer systems with similar concentrations are unavailable in literature. Nevertheless, high encapsulation efficiency values for PEG/PLGA micelles are encountered for different drugs in experiments as well [27, 28]. It is immediately noted that there is an increasing trend for 0.1% and 2% ibuprofen concentrations as the polymer weight percent is increased. For the 1% ibuprofen system, the values are almost the same within the error bars. If the RDFs of 5% polymer system in Fig. 2 is considered, the RDF profile of the 1% drug system has a higher first peak and a long-decaying tail indicating strong interactions of polymer with the drug compared to 0.1% and 2% drug systems. Therefore, higher EE value of the 5% polymer and 1% drug system can be attributed to the presence of dominant short-range and long-range interactions of the polymer and the drug compared to the other systems.

The drug encapsulation is a dynamic process. To comment on the structural change associated with the drug encapsulation, we plot the temporal evolution of the drug encapsulation and the formation of the micelles in Fig. 4 for the system with the highest EE value, that is 15% co-polymer and 0.1% drug system.

The profile in Fig. 4 can be interpreted such that the drug encapsulation takes place in two phases: an initial fast rate followed by a slow rate of drug encapsulation. In our simulations, the drug molecules are initially positioned inside the simulation box randomly. As the simulation runs, the micelles form and the drug molecules are encapsulated simultaneously. As seen in Fig. 4, there is a fast formation of the micelles. Therefore, the main reason for the rapid increase in the EE value rate (until about 70%) is that the drug molecules are encapsulated in the process of micelle formation. Later, after the micelles are formed the remaining drug molecules in the solvent slowly diffuse inside the

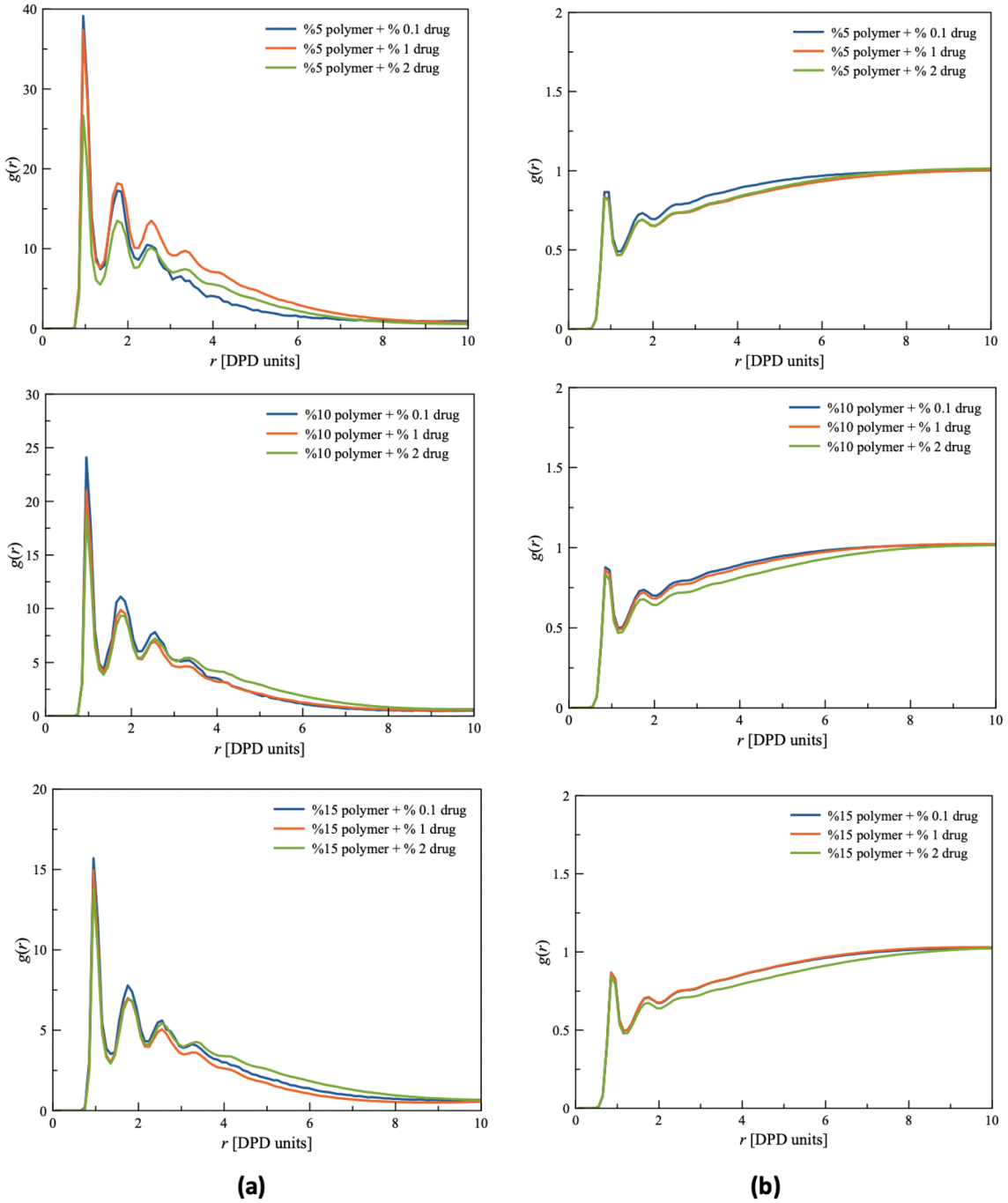

Fig. 2 RDF graphics are plotted between **a** PEG–PLGA–PEG and ibuprofen, and **b** PEG–PLGA–PEG and water

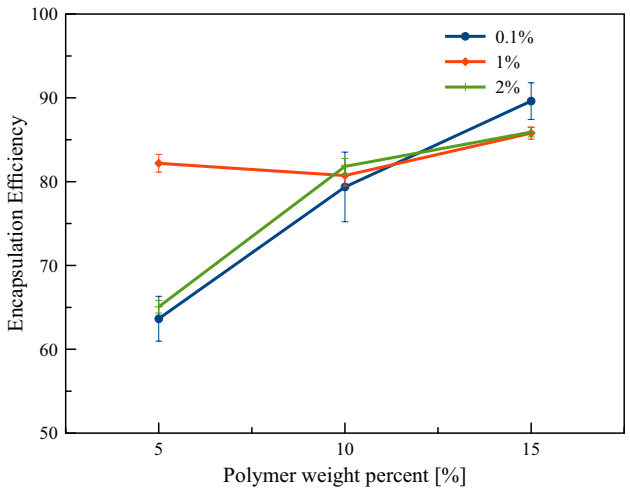

Fig. 3 Encapsulation efficiency values of the simulated systems. Error bars show the standard error of the mean

micelles due to the hydrophobic interactions between the core of the micelle and the drug, which is evident from the increase in the EE profile after 1000 DPD time. Overall, the drug encapsulation dynamics are obtained as similar to the drug loading process of liposomes and can be represented by the passive drug loading model [29].

Conclusions

Polymeric micelles are widely employed materials to encapsulate drugs with the purpose of targeted drug delivery. Therefore, designing micelles with the ability to encapsulate drugs with high encapsulation efficiencies is of utmost importance to pave the way to personalized medicine. In this work, we strive to perform computer simulations to quantify the drug encapsulation efficiencies of a particular block co-polymer system at different polymer concentrations and drug loading values. Moreover, we study the local structure and interactions between the polymeric micelles, drug, and solvent water as well. Our simulations show that the PEG/PLGA micelles can have high encapsulation efficiency values of about 90%, which is in line with experiments. The temporal evolution of the drug loading and its relation to the structure yield that the encapsulation process can be defined by two phases: an initial high encapsulation rate followed by a slow-rate diffusive encapsulation. Although, we model and simulate the encapsulation behavior and study the molecular structure of a particular material, the stimuli responsive drug release and the associated dynamics can be considered as future directions that this work would evolve.

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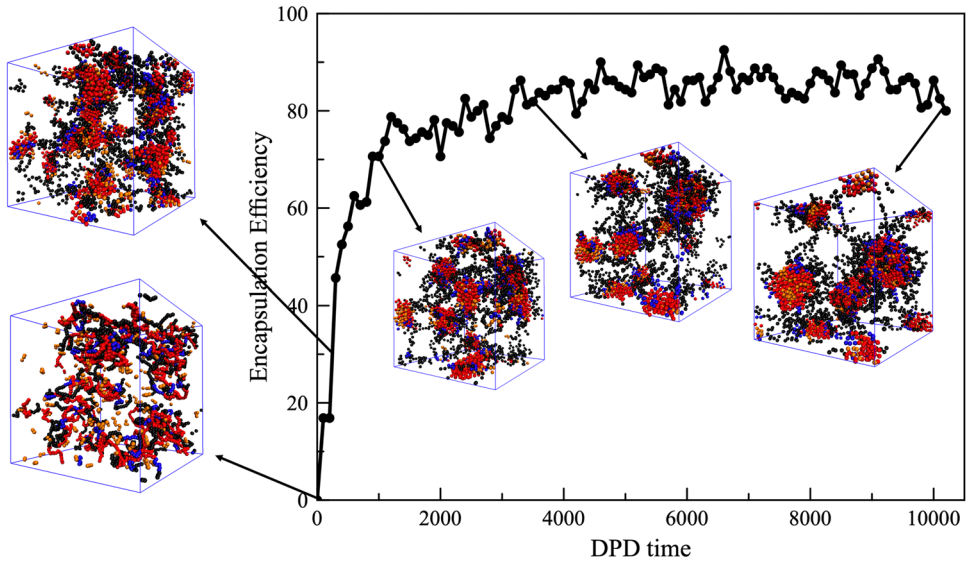

Fig. 4 Time evolution of the encapsulation efficiency and corresponding snapshots of the simulation box

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare no conflict of interest.

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