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Research paper

Interaction of PCL based self-assembled nano-polymeric micelles with model lipid bilayers using coarse-grained molecular dynamics simulations

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HIGHLIGHTS

- Interaction of self-assembled PCL based polymeric micelles with bilayers is investigated.
- Potential of mean force for micelle internalization is computed using umbrella sampling.
- Distinct changes in the micelle morphology is observed during internalization.

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ABSTRACT

Poly-ε-caprolactone (PCL) has been widely used in nanoparticle based drug delivery devices, owing to its hydrophobicity and biodegradability. In this study, we investigated the interaction of single block copolymer chains of PCL and Methoxy-polyethylene glycol (MePEG), as well as the self-assembled nano-polymeric micelles of these copolymers, with a model dioleoylphosphatidylcholine (DOPC) lipid bilayer using coarse-grained molecular dynamics simulations in conjunction with umbrella sampling. Our studies showed that the hydrophilic-to-hydrophobic ratio of the micelle plays a crucial role in the interaction with the bilayer. Significant changes in the micelle morphology akin to the 'snorkeling effect' was also observed.

1. Introduction

PCL, a hydrophobic and biodegradable polyester has been used for several applications such as medical devices and nanoparticle based drug-delivery devices [1]. Typically, for drug-delivery applications, ligand functionalized or amphiphilic block copolymer based nano-carriers, based on polyethylene glycol (PEG), where PCL forms the hydrophobic component, have found considerable success [2–4]. This has led to many computational studies on the PEG-PCL system, mainly focusing on the self-assembly, morphology and drug-loading characteristics of the micelles formed by these diblock copolymers [5–8]. Further, with considerable advances in computational power over the last decade, several studies have focused on the interaction and translocation of regular and functionalized nanoparticles with model lipid bilayers [9,10], developing a detailed understanding on the effect of surface chemistry [11,12], shape and size [12–15], and charge [16] on the internalization process. Further, the translocation and interaction of fullerenes [17], dendrimers [18] and polymers such as pluronics [19,20] have all been investigated, while with polymeric micelles, the focus has still largely remained on the conformation, morphology and self-assembly process.

In this study, we investigated the interaction of Methoxy-polyethylene glycol MePEG-b-PCL linear diblock copolymers, and the self-assembled micelles that they form, with a model DOPC lipid layer, for differing hydrophilic-to-hydrophobic (MePEG-to-PCL) ratios. Our objectives are to identify the morphological changes and compute the free energy landscape associated with the internalization of these polymeric micelles, with different hydrophilic-to-hydrophobic ratios, into a bilayer. Specifically, we considered the largely hydrophilic $MePEG_{17}$-b-PCL_3 and largely hydrophobic $MePEG_5$-b-PCL_9 copolymers and their corresponding self-assembled micelles. Using a combination of coarse-grained molecular dynamics simulations and enhanced sampling methods, we computed the potential of mean force characterizing the free energy barriers for internalization and identified the changes in the morphology of the micelle and the structural and mechanical properties of the bilayer. This paper begins with a brief overview of the computational methods, followed by the results and discussion, before closing with a brief conclusion.

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2. Computational methods

We performed unbiased and biased (umbrella sampling) molecular dynamics simulations to study the internalization of polymer micelles into a bilayer. All molecular dynamics (MD) simulations were performed using the Gromacs software package [21,22]. We used the standard MARTINI coarse-grained force field [23,24] to model the interactions of all the molecules, with a time step of 20 fs, and a short-range cut-off of 1.2 nm for both the dispersion and electrostatic interactions. The representation of the copolymers are based on our previous work, which accurately captured the conformation and the self-assembly of MePEG-b-PCL copolymers [8]. A brief description of the self-assembly of the nanopolymeric micelles is provided in the Supporting information. The lipid bilayer was setup using *'insane'* [25], the computational lipidomics tool. The initial structures were first optimized to a suitable starting configuration using the steepest descents method. We considered a 30 nm × 30 nm (10 nm × 10 nm for the biased simulations) symmetric DOPC bilayer, centered in a periodic simulation cell with 17 nm along the bilayer normal (30 nm for the biased simulations). All simulations were performed in the NPT ensemble, with the temperature controlled (300 K or 310 K) using a velocity-rescale thermostat [26], and pressure coupled semi-isotropically using the Berendsen barostat [27] to 1 bar. For the unbiased simulations, preferential starting configurations in close proximity to the bilayer were considered, to force interaction, with typical simulation times of 3 μs. For the biased simulations, we performed umbrella sampling [28] to obtain the free energy barriers for the internalization process, by restraining the center of mass of the copolymers and micelles along the normal to the center of mass of the bilayer using a harmonic potential with a force constant of 1000 kJ/mol nm^2. Sampling was performed on windows spaced 0.1 nm apart along this reaction coordinate, with typical simulation times of 350–500 ns on each window. The potential of mean force was calculated using the weighted histogram analysis method [29,30], as implemented in the g_wham [31] tool in Gromacs. For the umbrella sampling involving the hydrophobic MePEG$_5$-b-PCL$_9$ micelle, we also applied stiff harmonic restraints between select adjacent groups to mimic cross-links preventing micelle rupture during internalization [32,33]. All reported membrane properties such as area per lipid, lateral diffusion constant, average order parameter, and area compressibility modulus were computed based on previous studies [17].

3. Results and discussion

3.1. Unbiased simulations

We considered the interaction of micelles formed by the spontaneous self-assembly of 30 MePEG-b-PCL copolymers. Two nano-polymeric micelles corresponding to disparate hydrophobicities, but the same total number of MARTINI coarse-grained units; MePEG$_{17}$-b-PCL$_3$ and MePEG$_5$-b-PCL$_9$ were studied. We found that the largely hydrophilic MePEG$_{17}$-b-PCL$_3$ micelle did not interact with the bilayer through the entire course of the simulation (not shown here), despite its preferential starting configuration in very close proximity to the bilayer. This is expected, considering the significant hydrophilic nature of the micelle, driving its preference to remain in solution over internalization into the bilayer. On the other hand, the hydrophobic MePEG$_5$-b-PCL$_9$ micelle interacted with the bilayer, resulting in its internalization during the course of the simulation, showing a distinct change in morphology from a spherical core-shell to a 'Janus' configuration (See Supporting information) in which the hydrophilic and hydrophobic groups are oriented away from each other into opposite ends. Further, we computed the structural, dynamic and mechanical properties of the bilayer before and after the internalization of the micelle at both 300 K and 310 K, which is shown in Table 1. While it is likely that micelle size would also have an effect on these properties, we have considered the internalization of only the hydrophobic MePEG$_5$-b-PCL$_9$ micelle composed of 30 copolymers, in this study.

It can be seen that the structural parameters, specifically the area per lipid and average order parameter showed no change, indicating that the bilayer was not damaged due to the internalization of the micelle. However, the lateral diffusion constant showed a decrease, reflecting the constrained diffusion of the lipids in the leaflets as a result of the interacting micelle. The area compressibility modulus also showed a decrease upon the internalization of the micelle, reflecting the softening of the membrane as observed in previous studies involving fullerene translocation [17]. It should be noted that no mechanical rupture or irreversible damage to the bilayer was observed. This was also verified by analyzing the change in the thickness landscape of the bilayer before and after internalization (See Supporting information), which showed only local perturbation, and a retention of the average thickness of the bilayer and area per lipid.

3.2. Biased simulations

To determine the free energy barriers for the internalization process, we performed umbrella sampling as detailed above. First, we considered the interaction of the individual polymer chains to delineate the effect of the hydrophobicity on the internalization. The homopolymers MePEG and PCL (N = 10), as well as the linear diblock copolymers MePEG$_{17}$-b-PCL$_3$ and MePEG$_5$-b-PCL$_9$ were modelled, whose potential of mean force for the internalization into the hydrophobic bilayer core is shown in Fig. 1. The bilayer head-group region ends at ~3.0 nm, partitioning into the aqueous solution.

It can be seen that the hydrophobicity plays a vital role in the free energy barrier for passive internalization into the bilayer. The hydrophilic MePEG homopolymer shows a significant free energy barrier for partitioning into the bilayer, indicating its preference to stay in solution owing to the favorable interactions between MePEG and water. On the other hand, the hydrophobic PCL homopolymer clearly prefers to stay in the bilayer, with a free energy minimum just below the head group region, showing its favorable interaction with the hydrophobic bilayer core. Interesting trends are also observed with the copolymers, with the degree of hydrophobicity again dictating the free energy profile. For the largely hydrophilic MePEG$_{17}$-b-PCL$_3$, a free energy minimum around the bilayer head group region (approximately 3.0 nm) can be seen, owing to the unfavorable interactions with the bilayer core due to the hydrophilic MePEG, as well as the hydrophobic PCL causing unfavorable interactions with the water outside the bilayer. On the other hand, increasing the hydrophobic content of the polymer results in a largely favorable interaction with the bilayer core, with the MePEG$_5$-b-PCL$_9$ copolymer showing a large free energy barrier to partition into solution, similar to the PCL homopolymer. This was also visualized by observing the conformation of the copolymer chains during their internalization, as shown in Fig. 2. It can be seen that in both cases, the copolymer takes up a conformation that maximizes favorable interactions, by exposing the hydrophilic MePEG to the water outside the bilayer, with the hydrophobic PCL interacting favorably with the bilayer core.

We then performed a similar set of calculations on the self-assembled micelles (30 copolymer chains) formed from the two sets of copolymers to understand their interaction with the bilayer membrane. As discussed in Section 2, cross-links mimicked using stiff harmonic restraints were applied only to the MePEG$_5$-b-PCL$_9$ micelle, since it was not possible to apply the same on the MePEG$_{17}$-b-PCL$_3$ micelle, without modifying its core-shell shape. The potential of mean force for the internalization of the two micelles is shown in Fig. 3.

It can be seen that with increasing hydrophilic content due to the longer MePEG chains, the MePEG$_{17}$-b-PCL$_3$ micelle has a very large free energy barrier to be overcome to facilitate passive internalization into the bilayer. This is consistent with the unbiased simulations where even with the preferential starting configuration close to the bilayer, the micelle never interacted with the bilayer, preferring to stay in solution. This is a result of the extremely favorable interactions between water