Chemical Engineering Science 71 (2012) 400–408

Contents lists available at SciVerse ScienceDirect

Chemical Engineering Science

journal homepage: www.elsevier.com/locate/ces

Dissipative particle dynamics simulation of poly(ethylene oxide)–poly(ethyl ethylene) block copolymer properties for enhancement of cell membrane rupture under stress

Michael D. Tomasini [a], M. Silvina Tomassone [b,*]

[a] Department of Biomedical Engineering, Rutgers, The State University of New Jersey, Piscataway, New Jersey, USA
[b] Department of Chemical and Biochemical Engineering, Rutgers, The State University of New Jersey, Piscataway, New Jersey, 98 Brett Rd.,C-234 Engineering, Piscataway, NJ 08854, USA

ARTICLE INFO

Article history:
Received 12 July 2011
Received in revised form
11 October 2011
Accepted 27 October 2011
Available online 15 November 2011

Keywords:
Membranes
Bilayers
Polymers
Nanostructure
Simulation
Dissipative particle dynamics

ABSTRACT

Magnetic Fluid Hyperthermia (MFH) is an encouraging cancer treatment involving superparamagnetic nanoparticles coated with bio-active molecules. When placed in an oscillating magnetic field, the particles release heat into the tumor environment. The generally accepted mechanism of cell death is through hyperthermia, but it is plausible that destruction of the cell through mechanical means could also play a significant role. In this study, we examine mechanical disruption of a model cell membrane in the presence of a representative magnetic nanoparticle coating, the copolymer poly(ethylene oxide)–poly(ethyl ethylene) (PEO–PEE). Our goal is to determine the effect of polymer properties on the mechanical rupture of a cell membrane under stress. Using dissipative particle dynamics, we create an interacting system of dipalmitoylphosphatidylcholine lipids, PEO–PEE polymers, and water and apply an incremental tension until bilayer rupture occurs. Our findings show that the optimal structure of the block copolymers to enhance rupture is relatively short polymers with a hydrophobic–hydrophilic–hydrophobic block structure containing a high hydrophilic content. Additionally, we compare the energy necessary to rupture a cell membrane with the magnetostatic energy of magnetic nanoparticles in MFH and our results indicate that nanoparticle sizes of the order of those currently used in standard MFH treatment produce enough energy for mechanical rupture, thus suggesting that mechanical means may be exploited in MFH to enhance the destruction of tumor cells.

1. Introduction

Magnetic fluid hyperthermia (MFH) is a cancer treatment in which magnetic nanoparticles (MNPs) are delivered to a tumor and a high frequency, oscillating magnetic field is externally applied. In response to the applied field MNPs dissipate heat and cause a localized temperature increase in the tumor mass (Jordan et al., 1999; Jordan et al., 2001; Gupta and Gupta, 2005; Pankhurst et al., 2009). Increased intratumoral temperatures can influence the stability of tumor cell membranes, alter the function of membrane proteins, and impair DNA and RNA synthesis resulting in cell injury or death. Hyperthermic conditions also increase the sensitivity of cells to radiation and chemotherapy, making MFH ideal for combination therapy (Hildebrandt et al., 2002, Kumar and Mohammad, in press). Currently, the major hurdle associated with MFH is obtaining an adequate distribution of heat confined solely to the tumor mass. Studies have shown that substantial peripheral heating can occur resulting in excessive patient pain and damage to surrounding healthy tissue (Johannsen et al., 2007, Salloum et al., 2008). As a result, there is interest in reducing the intensity and frequency of the applied magnetic field while still maintaining efficacy in tumor suppression. One possible method to satisfy this restraint is to enhance tumor cell destruction by mechanical means. When MNPs dissipate energy, they do so through either Néel relaxation (relaxation of the magnetic dipole within the crystal lattice) or Brownian relaxation (physical rotation of the particle to align with the field). In MFH hyperthermia is widely accepted as the dominant mechanism leading to cell death; however it is conceivable that Brownian relaxation of MNPs associated with a cell membrane could generate forces sufficient to cause membrane rupture, especially for larger nanoparticles with magnetic dipoles that are locked into the nanoparticle crystal structure. Studies exist in the literature indicating a macroscopic rise in temperature may not be the only mechanism involved in tumor cell destruction. In a study conducted by Halbreich et al. (2002) MNPs in an

* Corresponding author. Tel.: 732 445 2972; fax: 732 445 2581.
E-mail address: silvina@soemail.rutgers.edu (M. Silvina Tomassone).

0009-2509/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ces.2011.10.061

oscillating magnetic field were used to damage mouse liver cells *in vivo*. Cell damage was found to occur in the absence of any observable temperature increase yielding the possibility that other mechanisms besides hyperthermia were at play. Nappini et al. (2011) recently studied cobalt ferrite nanoparticles coated with oleic acid contained in phosphatidylcholine (PC) liposomes. When subjected to an alternating magnetic field, the magnetoliposomes caused a temperature increase to 40 °C and enhanced instability of the surrounding PC bilayer. When compared to magnetoliposomes that were thermally heated to 40 °C without the application of a magnetic field, the instability effect was lost leading the authors to conclude that temperature only weakly influences PC bilayer stability. It is our hypothesis that rotations and oscillations of the MNPs associated with a cell membrane enhance the formation of pores in the lipid bilayer leading to instabilities and possibly cell death.

In previous work, we examined the energy necessary to rupture a lipid bilayer under longitudinal tension and shear stress (Tomasini et al., 2010). In the present work, we focus on the influence of molecules used to coat MNPs and their interaction with a lipid bilayer under stress. The particles used in MFH can be made of a variety of materials but are most frequently composed of iron oxide. The particles are generally coated with a bio-active molecule to improve bioavailability, reduce toxicity, prevent agglomeration, target specific cells, etc (Zhou et al., 2006; Shamim et al., 2007; Zhang and Mista, 2007). Typically the coating molecules are polymers such as dextran (Hilger et al., 2004; Barrera et al., 2009) and poly(ethylene glycol) (PEG) (Barrera et al., 2008), which act to increase the circulation time of the MNPs in the system and provide for favorable particle-cell interactions. For our studies, we have selected a model block copolymer poly(ethylene oxide)–poly(ethyl ethylene) (PEO–PEE) of varying length, structure, and concentration and explored its interaction with a lipid bilayer under stress.

The stability of lipid bilayers to applied stresses has been examined both by molecular dynamics (MD) (Tieleman et al., 2002; Leontiadou et al., 2004) and mesoscale simulation techniques (Groot and Rabone, 2001). In our previous work (Tomasini et al., 2010) we determined a lipid bilayer could withstand approximately 90 mN/m prior to rupture, which could then be compared to the energy of an MNP rotating in a magnetic field. This analysis yielded an MNP with an 80 nm magnetic core sufficient to induce rupture. This prior study focused solely on the core of the MNP and did not include any interaction between the molecules coating the MNP surface. Groot and Rabone (2001) focused on the rupture of bilayers under stress but they do not study the effect of polymers. There exist studies on the interaction between lipid bilayers and long-chain polymers (Srinivas and Klein, 2004) and polymer-grafted lipids (Thakkar and Ayappa, 2010a, 2010b) but none of that work focuses on the response to an externally applied stress. To the best of our knowledge, a systematic study on the effect of polymer properties on a bilayer under stress has not been performed.

MNPs along with their surface coatings can be on the order of tens of nanometers in size. To study their interaction with lipid bilayers, we thus need a computational method that allows for large system sizes and long time scales. Dissipative Particle Dynamics (DPD) is a mesoscale simulation technique in which several heavy atoms are lumped together to form a single DPD bead. Beads interact with each other through soft potentials allowing for much larger time steps that traditional MD. DPD has been successfully used to study structural properties of lipid bilayers (Groot and Rabone, 2001; Kranenburg et al., 2004; Gao et al., 2007) as well as polymer phase separation and polymersome formation (Groot and Madden, 1998; Ortiz et al., 2005). Yang and Ma (2010) used DPD to study the influence of size and shape of MNPs on penetration through a lipid bilayer. The nature of the DPD technique thus allows computational feasibility for the system sizes and times scales necessary to probe bilayer-polymer interaction under stress. In this study we aim to model the interaction of a polymer-coated MNP exerting a force on a cell membrane resulting from an applied magnetic field. We approximate this by exploring the interaction of a specific polymer with a lipid bilayer under tension. We measure the surface tension and area extension at which bilayer rupture occurs and calculate the resulting energy needed to rupture the bilayer-polymer composite system.

The paper is organized as follows: the next section describes the simulation technique, the system to be simulated, and the methodology used. In Section 3 we present the results of bilayer rupture in the presence of polymer and discuss the results in Section 4. Section 5 is devoted to the conclusions.

2. Materials and methods

2.1. The dissipative particle dynamics (DPD) simulation technique

DPD is a simulation technique introduced by Hoogerbrugge and Koelman (1992) and later refined by Español and Warren (1995) that allows for the large length and time scales associated with our system. It is a coarse-grained (CG) technique in which atoms are grouped together into beads of equal diameter. Generally three to four heavy atoms comprise one bead, representative of a specific fluid volume. The particles interact through soft potentials permitting significantly greater time steps than traditional MD simulation. The potential function in DPD consists of bonded interactions (bond stretching and angle bending) between linked atoms of the same molecule and non-bonded interactions between all beads of the system meant to mimic electrostatic and dispersion forces. The non-bonded interaction force between particles is taken as a sum of three terms, a conservative force (F_C), a random force (F_R), and a dissipative force (F_D):

$$\vec{F} = \vec{F}^{C}_{ij} + \vec{F}^{R}_{ij} + \vec{F}^{D}_{ij} \tag{1}$$

The conservative force has the form shown in Eq. 2 where $r_{ij}=\|r_{ij}\|$, is the distance between beads i and j and R_c is the maximum distance between beads for which the non-bonded interactions are calculated. The conservative force is a repulsive force scaled by the mutual repulsive parameter a_{ij}, which determines the maximum repulsion at $r_{ij}=0$. It has been shown that a_{ij} is related to the Flory–Huggins parameter χ through the relation $\chi=(0.231\pm0.001)\Delta a_{ij}$ for the case in which $\rho=3$ heavy atoms per bead (Groot and Rabone, 2001), where $\Delta a_{ij}=a_{ij}-a_{ii}$ is the excess i–j repulsion over the i–i repulsion.

$$\begin{aligned} \vec{F}^{C}_{ij} &= a_{ij}\frac{r_{ij}-R_C}{R_C}\frac{\vec{r}_{ij}}{r_{ij}} \quad \text{if} \quad r_{ij} < R_C \\ \vec{F}^{C}_{ij} &= 0 \qquad\qquad\qquad \text{if} \quad r_{ij} \geq R_C \end{aligned} \tag{2}$$

The random is defined as $\vec{F}^{R}_{ij} = \sigma\omega^{R}\theta_{ij}(t)\hat{r}_{ij}$ where θ_{ij} is a random variable with Gaussian statistics, ω^R is a weighting function, and σ is the strength of the random force for which, following Groot and Warren (1997) we chose $\sigma=3$ to achieve proper temperature control. The dissipative force is a drag force that is related to the relative velocities (v_{ij}) between two beads: $\vec{F}^{D}_{ij} = -\gamma\omega^{D}(\vec{r}_{ij}\vec{v}_{ij})\hat{r}_{ij}$, where ω^D is a weighting function and γ is the magnitude of the drag coefficient. Español and Warren (1995) showed that the dissipative force and the random force are related through the fluctuation-dissipation theorem, which states that $\sigma^2=2\gamma k_B T$ and $\omega^D=[\omega^R]^2$. This has been shown to result in a