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Nanogels as a Chemically Controllable Platform for Targeted Drug Delivery

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Extended Abstract

The vascular administration of targeted nanocarriers (NCs) enables precise delivery of drugs to diseased or inflamed endothelial cells. The primary therapeutic goal we are pursuing is to optimize endothelial delivery of antioxidant and anti-inflammatory agents for alleviation of acute pulmonary inflammation and oxidative stress through multiscale modeling with validating experimentation. In particular, we consider deformable gel-based nanocarriers, for which we have developed a Brownian dynamics framework incorporating hydrodynamic interactions to model cross-linked lysozyme-core/dextran-shell nanogels exposed to hydrodynamic shear forces. This work is motivated by our recent development of dextran-lysozyme nanogels (Coll Ferrer et al., 2013a, 2013b) and their recent application in targeted anti-inflammatory drug delivery to pulmonary endothelium in an endotoxin-induced murine experimental model of pulmonary inflammation (Coll Ferrer et al., 2014) which we will describe. Our theoretical as well as numerical investigations of deformable NCs are first addressed under physiologically relevant flow conditions (Sarkar et al., 2015) Specifically, we model the deformable lysozyme-core/dextran-shell crosslinked polymer based NC with internal nanostructure and subject it to external hydrodynamic shear. In this approach we have introduced a coarse-grained model for the NC and have adopted a Brownian dynamics framework, which incorporates hydrodynamic interactions, in order to describe the static and dynamic properties of the NC. In order to represent the fluidity of the polymer network in the dextran brush-like corona, we coarsegrain the structure of the NC based on the hypothesis that Brownian motion, polymer melt reptations, and crosslinking density dominate their structure and dynamics. In our model, we specify a crosslinking density and employ the simulated annealing protocol to mimic the experimental synthesis steps in order to obtain the appropriate internal structure of the core–shell polymer. We then compute the equilibrium as well as steady shear rheological properties as functions of the Peclet and the crosslinking density, in the presence of hydrodynamic interactions. We find that with increasing crosslinking, the stiffness of the nanocarrier increases, the radius of gyration decreases, and consequently the self-diffusivity increases. The nanocarrier under shear deforms and orients along the direction of the applied shear and we find that the orientation and deformation under shear are dependent on the shear rate and the crosslinking density. We compare various dynamic properties of the NC as a function of the shear force, such as orientation, deformation, intrinsic stresses. etc., with previously reported computational and experimental results of other model systems. The computational approach described here serves as a powerful tool for the rational design of NCs by taking both the physiological as well as the hydrodynamic environments into consideration. Development of such models, coupled with experimental evaluation of crosslinking effects on nanogel mechanical behaviors, drug loading and drug delivery, is essential in order to gain useful insights that may be translated into the optimal design of NCs for diagnostic as well as targeted drug delivery applications.

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