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Sepideh Khoee, Ali Hashemi, Sajjad Molavipordanjani

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Synthesis and Characterization of IUdR Loaded PEG/PCL/PEG Polymersome in Mixed DCM/DMF Solvent: Experimental and Molecular Dynamics Insights into the Role of Solvent Composition and Star Architecture in Drug Dispersion and Diffusion

Sepideh Khoee *[a], Ali Hashemi ‡[b], Sajjad Molavipordanjani ‡[a]

Abstract: Combined experimental and simulation investigations have provided molecular level insights into 5-iodo-2'-deoxyuridine (IUdR) loading behavior for the novel PEG/PCL/PEG polymersome-like carriers in mixed dichloromethane/N,N-dimethylformamide (DCM/DMF) solvent. As with the experiments, a novel approach was applied for layer by layer tailoring of polyethylene glycol (PEG) and polycaprolactone (PCL) as PEG/PCL/PEG copolymer on the surface of magnetite nanoparticles (MNPs) by click chemistry. Experimental results indicated that IUdR, as an anti-cancer drug, could be encapsulated up to 80% EE in this nanocarrier and could be in-vitro released up to 90% during 120 hrs. Computational studies, on the other hand, provide molecular level insights into the optimal performance of the carrier in terms of drug “Dispersion” and “Diffusion” patterns in equimolar DCM/DMF solvent. Molecular dynamics simulations of the system in four distinct solvation scenarios including pure DCM, mixed DCM/DMF, pure DMF and water, have proven that while hydrophobic solvents give rise to better “dispersion” of drugs, hydrophilic solvents lead for drug molecules to penetrate into the carrier and improve “diffusion” properties. Optimal conditions for drug encapsulation, as also confirmed through experiments, was observed for mixed DCM/DMF solvent in terms of proper diffusion and well dispersion. While drug “aggregates” were observed in DCM, poorly stable drug molecules with lowered penetrations were observed in pure DMF. Proper release properties with IUdR molecules staying on the surface of the carrier was also observed in water. The interesting role of the star-linear architecture was further scrutinized through distinctions made through analysis of interactions between IUdR molecules with “inner” and “outer” PEG sections.

[a] Sepideh Khoee*, Sajjad Molavipordanjani
Polymer Laboratory, School of Chemistry,
College of Science,
University of Tehran,
P.O. Box 14155-6455,
Tehran, Iran;
Email: Khoee@khayam.ut.ac.ir
[b] Ali Hashemi
Pharmaceutical Engineering Laboratory,
School of Chemical Engineering,
College of Engineering,
University of Tehran, P.O. Box 11155-4563,
Tehran, Iran
Author Contributions
‡ Ali Hashemi and Sajjad Molavipordanjani have contributed equally to this work.
Supporting information for this article is given via a link at the end of the document.

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1. Introduction

MNPs have recently attracted vast interest because of their widespread application and simple methods for production and functionalization. Applications of MNPs in human medical areas include: magnetic resonance imaging contrast agents (Felton et al., 2014) magnetic induction hyperthermia (MIH) (Dong and Zink, 2014; Yu et al., 2014) as well as targeted (Sanchez et al., 2014) and specific drug (Shakerizadeh et al., 2015) and genes delivery systems (Wang et al., 2014) for cancer therapy. Besides the biomedical fields, MNPs can be used as ferrofluids, data storage and catalysis (Abu-Reziq et al., 2006; Sahoo et al., 2005; Wu et al., 2014).

Naked MNPs tend to aggregate into bigger particles which are more stable than the single nanocrystals. Surface modification then becomes necessary to prevent self-aggregation not only for MNPs but for most of nanoparticles (Bohara et al., 2016; Shaikh et al., 2016). Stabilization with hydrophilic or lipophilic coating allows preparation of MNP dispersions in a liquid medium and to keep them stable without aggregation for long time. The coating can further introduce specific functional groups such as azide groups to the surface of MNPs for click chemistry (Chen et al., 2016; Richards et al., 2017). Click reactions are applicable to many substrates by using copper (I)-catalyzed 1,3-dipolar Huisgen cycloaddition between alkynes and organic azides. The Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC) reaction provides a facile way for quantitative introduction of various polymeric shell and functional groups onto the MNPs surface and is related to their unique properties as mentioned (Shi et al., 2016; Thirumurugan et al., 2013).

Nucleoside analogs have proven to have essential applications in the treatment of cancer and viral infections (De Clercq, 2009). One of the remarkable nucleosides analogs used in medicine, IUdR, is an anticancer drug and thymidine analog. IUdR has been used in combination with radiation in the treatment of malignant glioma and advanced head and neck cancers (Epstein et al., 1998; Rousseau et al., 2009). Photo-activated Auger electron therapy of IUdR could preferentially target cancer cells via a binary therapy: (1) as a radiosensitizer and (2) as a