RSC Advances

PAPER

Cite this: *RSC Adv.*, 2018, **8**, 27988

Formation of nanopores in DiynePC–DPPC complex lipid bilayers triggered by on-demand photo-polymerization†

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Received 8th June 2018
Accepted 20th July 2018

DOI: 10.1039/c8ra04908d

rsc.li/rsc-advances

Vesicles have unique characteristics that enable the release of drugs as well as encapsulation while maintaining biocompatibility. A photo-polymerizable liposome composed of 1,2-bis(10,12-tricosadiynoyl)-*sn-glycero*-3-phosphocholine (23:2 DiynePC) has been investigated as vehicles for triggered delivery of drugs to cells. In this study, we confirmed for the first time that supported lipid bilayers (SLBs) prepared with a 1,2-dipalmitoyl-*sn-glycero*-3-phosphocholine (DPPC)/DiynePC mixture generated pores *ca.* 100–300 nm in size on the membrane after UV polymerization. This direct observation was done by analyzing the SLBs formed with the DPPC/DiynePC mixture by employing atomic force microscopy (AFM) in a liquid environment. However, photo-polymerization did not occur in the 1,2-dioleoyl-*sn-glycero*-3-phosphocholine (DOPC)/DiynePC mixed bilayer and pores were not formed. A theoretical study was performed to explore the phase behavior of the lipid mixtures. A coarse-grained model of DiynePC was developed that is comparable with the Martini force field; the parameters were validated against atomistic simulations. Transition from fluidic to gel phase was observed only when DiynePC was mixed with DPPC, whereas the DOPC mixture remained fluidic over the entire domain. This implies a correlation between the formation of DiynePC-rich gel phase domains and the generation of pores after polymerization. The size of the pores were found to be controlled by the amount of polymerizable lipid which results in higher release rate of encapsulated calcein from the vesicles with larger pores.

Introduction

Encapsulation of drugs in liposomes is utilized for targeted delivery of biologically active compounds and controlled release at the site of action using unique properties including biocompatibility, low toxicity, and non-activation of the immune system.[1,2] For biomedical applications, encapsulated drug release should be controlled for the desired rates and quantity. To achieve these goals, temperature changes, mechanical disruption and light stimulation have been applied to trigger the release and to control the release rate.[3] Photo-activation is an attractive option for triggering release because it provides a broad range of adjustable parameters, such as wavelength, duration, and intensity which can be optimized to suit application needs.[4] Suitable light treatment can modulate phospholipid molecules, which undergo photo-polymerization,[5] photo-sensitization by membrane anchored hydrophobic moieties,[6,7] photo-isomerization[8] and photo-oxidation.[9] Thereby, photo-triggered liposome systems have been extensively studied.[10–13] 1,2-bis(10,12-tricosadiynoyl)-*sn-glycero*-3-phosphocholine (DiynePC), one of the photo-polymerizable synthetic phospholipids, has been studied as an artificial membrane component along with its unique colored feature due to the conjugated nature of the cross-linked diacetylene groups.[14,15] Benefits of using polymerizable lipid in vesicle systems have been focused in order to improve physical stability.[11,16,17] The concept of polymerizable lipids as photo-triggered drug carriers has only recently been used for drug delivery applications.[18,19] These studies have shown that DiynePC could become a good candidate for drug release owing to the fact that the vesicles containing DiynePC are biocompatible and can release the drug on demand. However, the generation of membrane pores by photopolymerization has purely been a hypothesis without evidence. Hence, in this study, we attempt to discover empirical evidence of the appearance of the pores generated upon photo-polymerization of the lipid membrane containing DiynePC, for the first time. The bilayers of 1,2-dipalmitoyl-*sn-glycero*-3-phosphocholine (DPPC) and 1,2-dioleoyl-*sn-glycero*-3-phosphocholine (DOPC) mixed with DiynePC were analyzed utilizing atomic force microscopy (AFM) in liquid

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c8ra04908d

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