PNIPAM COATED BIOPOLYMER MULTILAYERS FOR TEMPERATURE-MEDIATED DRUG RELEASE

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Introduction

The layer-by-layer polymer assembly [1] is a powerful and versatile tool for fabrication of polymer-based coatings (multilayers) with tailor-made composition, permeability, hydration, and mechanical properties. Nowadays the multilayer films are extensively used to host and release bioactive molecules aiming at bio-applications such as drug delivery and tissue engineering. The multilayers serve as effective reservoirs for bioactive molecules (small drugs, nucleic acids, proteins, peptides, etc) [2-4], however, a control over the release rate without affecting the multilayers integrity and activity of the loaded biomolecules is still a challenge.

Here we focused on design of stimuli-sensitive biopolymer-based multilayers with temperature-mediated release. Soft composite films are designed by coating hyaluronic acid/poly-L-lysine (HA/PLL) multilayers with temperature responsive poly(N-isopropylacrylamide) (PNIPAM) microgels (MG) of 440 nm in diameter [5]. Drug loading/release performance is evaluated by molecular transport of fluorescently labeled PLL-FITC into the composite multilayers $(HA/PLL)_{24}$-MG as a function of temperature (below and above the volume phase transition temperature (VPTT) which is 32°C for PNIPAM. Atomic force microscopy (AFM) is used to analyze the structure of the composite $(HA/PLL)_{24}$ -MG films and understand the mechanism of temperature-mediated molecular transport.

Results and Discussion

Fig. 1a,b shows schematics of the PLL-FITC transport through the composite MG-coated multilayers (coating by spontaneous embedding into the multilayers). The MGs are flattened and immersed into the multilayers to maximize the number of contacts with the surrounding polyelectrolytes (HA and PLL). AFM micrographs proofed that the mechanism of volume phase transition on soft surfaces cannot be directly deduced from the processes taking place at solid substrates. Analysis of dimensions of the microgels on the soft multilayers allows to conclude about their positioning and changes of the morphology as a function of temperature [5]. The negatively charged microgels are spontaneously adsorbed on the multilayer surfaces with being flattened (Fig. 1) and immersed with their largest part. Full immersion into the multilayers and relaxing to spherical shape would be unfavourable because of the necessary rearrangement of the internal structure of the multilayer.

The MG coating serves as an efficient switchable barrier for the PLL transport into the multilayers. PLL diffusion into the film is significantly hindered at room temperature but is dramatically enhanced at 40 °C above the VPTT which is associated with microgel shrinkage (Fig. 1a-b). Fig. 1c shows the time evolution of the fluorescence recorded from the film (MG coated or not) after its contact with PLL-FITC solution. The processes of PLL interaction with the multilayers associated with changes of the fluorescent signal are depicted: replacement of buffer with PLL-FITC solution as indicated by the red arrow (I), desorption of excess of adsorbed PLL-FITC (II), and PLL-FITC diffusion into the multilayers (III) [5].

Conclusion

We demonstrated that PNIPAM microgels can form an effective temperature sensitive barrier for PLL molecular transport when adsorbed onto HA/PLL multilayers. Dramatic enhancement of PLL transport at temperature above the VPTT of PNIPAM is due to the shrinking of the microgels. The composite soft films assembled from multilayers and PNIPAM microgels may serve as attractive model of composite structures for soft matter studies. Temperature variation from room temperature to physiologically relevant one may significantly affect polymer diffusion into the multilayers [6] and should be considered as valuable stimulus for drug release opportunities using the multilayer-PNIPAM composites as drug reservoirs and release systems. The presented strategy offers new possibilities for the development of a novel generation of temperature-responsive materials for controlled drug release and the separation of drugs by their trap in the multilayers from outside medium.

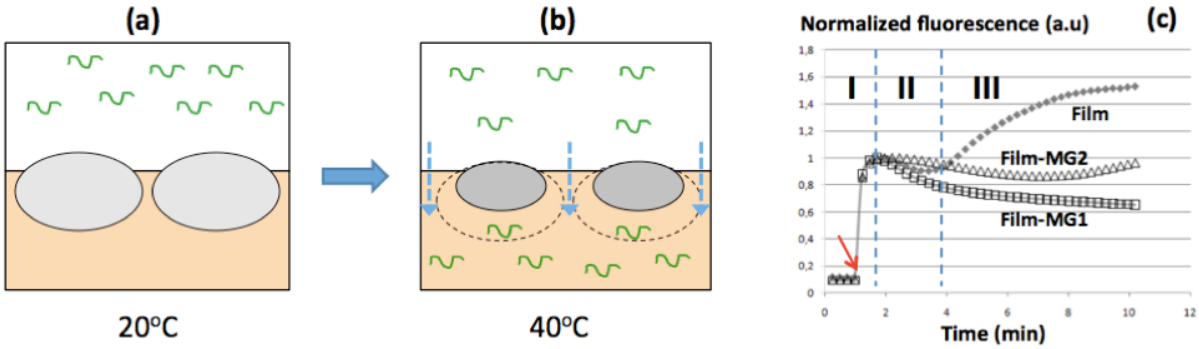

Fig. 1. Schematics (side view) of $(HA/PLL)_{24}$ multilayers coated with PNIPAM microgels (gray) in the presence of PLL-FITC (green) at 20 °C (a) and 40 °C (b). Temperature increase above the phase transition results in the collapse of the immobilized microgels followed by an increase of the free surface area between the microgels facilitating the PLL-FITC diffusion into the multilayers. (c) - normalized fluorescence detected from the multilayers (uncoated or coated with microgels) in contact with PLL-FITC (red arrow points on the initial contact time with PLL-FITC). Adopted from [5].

References

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