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Understanding the interactions between porphyrin-containing photosensitizers and polymer-coated nanoparticles in model biological environments

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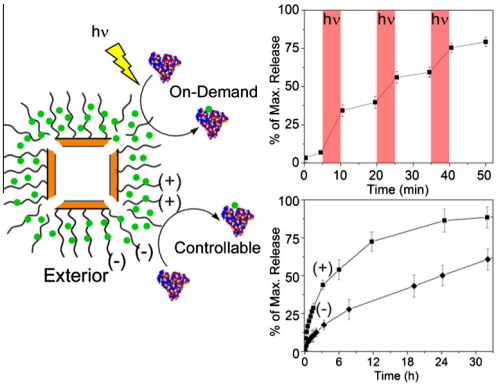
GRAPHICAL ABSTRACT



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ABSTRACT

Non-covalent incorporation of hydrophobic drugs into polymeric systems is a commonly-used strategy for drug delivery because non-covalent interactions minimize modification of the drug molecules whose efficacy is retained upon release. The behaviors of the drug–polymer delivery system in the biological environments it encounters will affect the efficacy of treatment. In this report, we have investigated the interaction between a hydrophobic drug and its encapsulating polymer in model biological environments using a photosensitizer encapsulated in a polymer-coated nanoparticle system. The photosensitizer, 3-(1′-hexyloxyethyl)-3-devinylpyropheophorbide-a (HPPH), was non-covalently incorporated to the poly(ethylene glycol) (PEG) layer coated on Au nanocages (AuNCs) to yield AuNC–HPPH complexes. The non-covalent binding was characterized by Scatchard analysis, fluorescence lifetime, and Raman experiments. The dissociation constant between PEG and HPPH was found to be ~35 μM with a maximum loading of ~2.5×10^5 HPPHs/AuNC. The release was studied in serum-mimetic environment and in vesicles that model human cell membranes. The rate of protein-mediated drug release decreased when using a negatively-charged or cross-linked terminus of the surface-modified PEG. Furthermore, the photothermal effect of AuNCs can initiate burst release, and thus allow control of the release kinetics, demonstrating on-demand drug release. This study provides insights regarding the actions and release kinetics of non-covalent drug delivery systems in biological environments.

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1. Introduction

Controlled release systems for drug delivery using nanocarriers have been developed and studied for more than three decades [1]. Au nanostructures have been used as drug delivery vehicles in chemotherapy because of their biocompatibility, facile surface modification, and robust optical properties [2–8]. While drug molecules can be covalently immobilized on the nanoparticles' surface [2,8–10], non-covalent interactions are particularly appealing because they minimize modification of the drug molecules, whose efficacy is then largely retained upon release. Several strategies have been developed to non-covalently tether molecules through electrostatic and hydrophobic interactions to polymer-coated nanoparticles, which include wrapping into layer-by-layer assembled polyelectrolytes [11], entrapping in a polymer monolayer [12–14], encapsulating into a phospholipid bilayer [15], and absorbing into a hydrogel [16]. Among these methods, poly(ethylene glycol) (PEG) coated nanoparticles are advantageous because PEG, used widely in the pharmaceutical industry, is generally non-toxic and possesses antifouling properties well-suited for increasing circulation half-life and minimizing immunological clearance [17]. The graft density of PEG was found to significantly affect the biological fate of the particles [18]. Hydrophobic phthalocyanine photosensitizers [19–21] or anti-cancer drugs [22,23] have been delivered within the surface PEG layer or inside the hydrophobic pocket for photodynamic therapy or chemotherapy. We recently applied a similar system to deliver a hydrophobic porphyrin-derivative (3-(1′-hexyloxyethyl)-3-devinylpyropheophorbide-a, HPPH, structure shown in Fig. 1A) for image-guided photodynamic therapy with enhanced efficacy [14].

In this work, we systematically investigate the binding affinity and the release kinetics of HPPH from PEG-coated Au nanocages (AuNCs) to further elucidate the behavior of the drug–polymer delivery system. The induced-dipole/induced-dipole interactions between the pheophorbide and the PEG backbone serve as the driving force to load molecules into the PEG layer [24]. HPPH is stably integrated within the PEG coating of AuNC–HPPH in saline solution. The release itself is mediated by either serum proteins (specifically albumin in our model) or cell membranes (modelled here with vesicles). The serum proteins unloaded the drug over several hours and the release of entrapped molecules can be endogenously controlled by the charge and functionality of the PEG terminus. Additionally, the release rate can be exogenously controlled by utilizing the photothermal (PT) effect of Au nanostructures which allows external and temporal control of the drug release by non-invasive near-infrared light [25–27,11,28]. By manipulating these variables, we are able to demonstrate on-demand unloading of the drug with minimal premature loss and were able to suggest the relative affinity of the drug for soluble proteins versus cell membranes.

2. Methods

2.1. Incorporation of HPPH to AuNC–PEG to form AuNC–HPPH complexes

HPPH (7 mg, 11 μmol) was dissolved in 2.5 mL DMSO at a concentration of 4.5 mM as stock solution. This stock solution (0.25 mL) was diluted in 4 mL of phosphate buffered saline (PBS) via dropwise addition in an ice bath to a concentration of ~183 μM. The diluted HPPH solution was flushed with Ar for 5 min and allowed to mix for 5 additional min. The AuNC–PEG suspension (3 nM, 2 mL) was added dropwise to the HPPH solution. The reaction was allowed to stir overnight under the protection

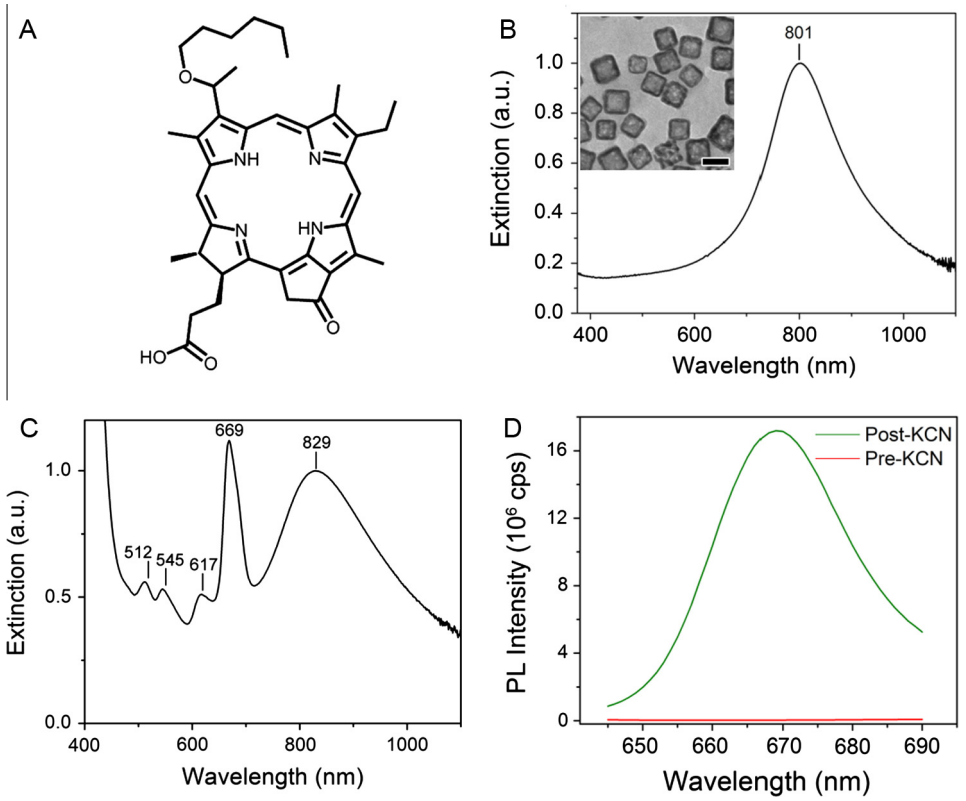

Fig. 1. (A) Structure of HPPH. Normalized UV–vis–NIR spectra of AuNC (B) before and (C) after loading with HPPH. Inset shows TEM image of AuNCs with a 50 nm scale bar. (D) Fluorescence spectra of HPPH-loaded AuNCs, before (green) and after (red) KCN digestion of AuNCs. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)