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Photo- and thermo-responsive multicompartment hydrogels for synergistic delivery of gemcitabine and doxorubicin

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ABSTRACT

Hydrogels have found promising applications in drug delivery due to their biocompatibility, high drug loading capability, and tunable release profiles. However, hydrogel-based carriers are primarily employed for delivering hydrophilic payloads while hydrophobic drugs cannot be efficiently delivered due to the lack of hydrophobic domains within conventional hydrogel matrices. Herein, we report that thermo- and photo-responsive hydrogels could be constructed from amphiphilic triblock copolymers, poly(*N*-isopropylacrylamide)-*b*-poly(4-acryloylmorpholine)-*b*-poly(2-((((2-nitrobenzyl)oxy)carbonyl) amino)ethyl methacrylate) (PNIPAM-*b*-PNAM-*b*-PNBOC), and the resulting hydrogels could be further engineered a new carrier for both hydrophilic gemcitabine (GCT) and hydrophobic doxorubicin (DOX). PNIPAM-*b*-PNAM-*b*-PNBOC triblock copolymers were first self-assembled into micelles with hydrophobic photosensitive PNBOC cores, hydrophilic PNAM inner shells, and thermoresponsive PNIPAM coronas below the lower critical solution temperature (LCST), while hydrogels of physically cross-linked micellar nanoparticles were achieved at elevated polymer concentrations and high temperatures above the critical gelation temperature (CGT). Rheological experiments revealed that the CGT was highly dependent on polymer compositions and concentrations, that is, a longer hydrophobic PNBOC block or a higher polymer concentration led to a decreased CGT. However, the CGT prior to UV irradiation (CGT_0) could be drastically elevated after UV irradiation (CGT_{UV}) as a result of UV irradiation-induced concurrently cross-linking and hydrophobic-to-hydrophilic transition within PNBOC cores. As such, gel-to-sol transition could be accomplished by either temperature decrease or exposure to UV irradiation at a fixed temperature lower than the CGT_{UV}. Note that both GCT and DOX could be simultaneously encapsulated into the hydrogels due to the coexistence of extramicellar aqueous phase and hydrophobic micellar cores. Intriguingly, the subsequent co-release of GCT and DOX could be regulated by taking advantage of either temperature or UV irradiation-mediated gel-to-sol transitions.

1. Introduction

The development of novel drug carriers on the basis of stimuli-responsive polymers is of considerable interest. These smart drug vehicles can, at least in part, conquer the drawbacks of small molecule counterparts such as systemic toxicity, insufficient circulation time, and lack of long-term stability [1–6]. Previously, supramolecular aggregates with diverse self-assembled morphologies have been engineered as smart nanovehicles for site-specific delivery of therapeutic agents, exhibiting improved therapeutic efficiency [7–15]. Further, recent studies have suggested that combinatorial therapy that integrates several different therapeutic agents into one system is of superior efficiency in treating formidable diseases [16,17]. For instance, chemotherapeutical drugs, hydrophilic gemcitabine (GCT) and hydrophobic doxorubicin (DOX), show synergistic anticancer efficacy due to their non-overlapping toxicities. However, it is difficult to incorporate two categories of therapeutic drugs with distinct water-solubility into one nanocontainer since conventional nanovectors (e.g., micelles and nanorods) only possess hydrophobic domains that can solely be employed for delivery of hydrophobic payloads. Of these, polymersomes also referred to as vesicles, are distinguished by the coexistence of both aqueous interiors and hydrophobic bilayer membranes that can simultaneously encapsulate both hydrophilic and water-immiscible drugs [6,18–20]. Nevertheless, conventional polymersomes suffer from poor permeability of bilayer membranes, rendering the release of encapsulated payloads uncontrollable, although the development of stimuli-responsive polymersomes has remarkably alleviated this cumbersome issue [21–23].

In comparison with polymersomes, hydrogels are three-dimensional, cross-linked networks, which have been widely used for drug delivery application because of their excellent biocompatibility, high drug loading efficiency, and programmable release profiles [24–34]. Although hydrogels could be fabricated through either covalent or noncovalent bonds,

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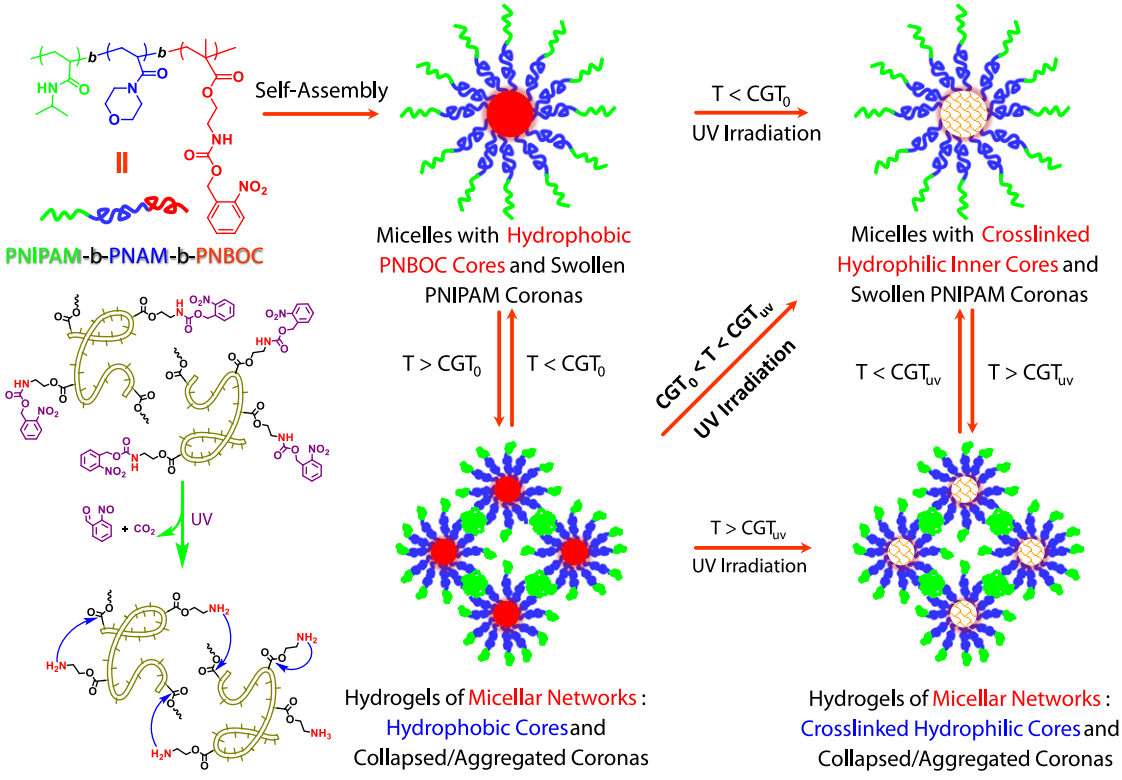
hydrogels are generally composed of hydrophilic polymers that can only be used for loading hydrophilic payloads [34–42], preventing them from delivering hydrophobic therapeutic drugs. To resolve this issue, multicompartment hydrogels were fabricated in a stepwise manner from amphiphilic triblock copolymers [43–49], which formed micellar nanoparticles and then subsequently underwent gelation process as a result of 'cross-linking' of micellar nanoparticles. Consequently, hydrogels comprising both hydrophilic and hydrophobic domains could be achieved [43]. Notably, the fabrication of hydrogels \with multi-domains was of promising potential in delivering multiple encapsulants. For example, the Duvall group explored the drug delivery application of thermo- and reactive oxygen species (ROS)-responsive hydrogels from poly(propylenesulfide)-*b*-(*N*,*N*-dimethylacrylamide)-*b*-(*N*-isopropylacrylamide) (PPS-*b*-PDMA-*b*-PNIPAM) amphiphilic triblock copolymers, revealing that the release of hydrophobic model drug, Nile red (NR), could be regulated by ROS [50]. This study clearly demonstrated that water-immiscible payloads could be incorporated into hydrogel matrices consisting of hydrophobic domains originating from preformed micellar cores. However, the co-delivery of both hydrophobic and hydrophobic payloads in this hydrogel system was not assessed. Given that hydrogels have been proved to be potent in delivering hydrophilic drugs, we surmised that both hydrophilic and hydrophobic drugs could be incorporated into multicompartment hydrogel-based carriers with built-in hydrophobic domains [51]. Moreover, hydrogel-based carriers with multi-domains should exhibit unique advantages in terms of scale-up products, increased drug loading contents, and extended release durations as compared to vesicle-based nanovehicles [24–28].

To verify our hypothesis, herein, photo- and thermo-responsive amphiphilic triblock copolymers, poly(*N*-isopropylacrylamide)-*b*-poly(4-acryloylmorpholine)-*b*-poly(2-((((2-nitrobenzyl)oxy)carbonyl)amino) ethyl methacrylate) (PNIPAM-*b*-PNAM-*b*-PNBOC), were synthesized via consecutive RAFT polymerizations. Photoresponsive PNBOC block can not only serve as the hydrophobic building block to facilitate the formation of PNBOC-cored micelles but also provide an additional opportunity to tune the phase transition temperatures of resulting triblock copolymers by UV irradiation [52–56]. The as-synthesized triblock copolymer self-assembled into three-layered micellar nanoparticles with photoresponsive PNBOC cores and hydrophilic PNAM inner shells and thermoresponsive PNIPAM coronas when the temperature was lower than the lower critical solution temperature (LCST) at a relatively low concentration (e.g., 2.5 g/L). Upon elevating the polymer concentrations to higher than 10.0 wt%, opaque sol solutions were formed at ambient temperature and the sol solutions experienced gelation subjected to a temperature rise to higher than the critical gelation temperature (CGT_0) of triblock copolymers (Scheme 1). Notably, NBOC moieties can produce primary amine groups under UV irradiation from decaged carbamate linkages, which further implemented aminolysis reactions and thus cross-linked nanoassemblies and concurrently rendered the cross-linked micellar cores hydrophilic, [23] thereby elevating the CGT (defined as CGT_{UV}) of irradiated triblock copolymers. As such, at an intermediate temperature ($CGT_0 < T < CGT_{UV}$), a gel-to-sol transition was observed, whereas the irradiated sol solutions could be further transformed to hydrogels upon a further temperature increase ($T > CGT_{UV}$). Moreover, the dual-responsive hydrogels could be engineered as a new drug carrier and the synergistic release of GCT and DOX drugs could be triggered by UV irradiation- and temperature-induced gel-to-sol transitions. This work demonstrated, for the first time, that the co-delivery of chemotherapeutic drugs with synergistic efficacy but distinct water-solubility could be achieved, exhibiting promising application in site-specific drug delivery and selective release of drugs for efficient therapy.



Scheme 1. Schematics of the construction of temperature- and UV-responsive micelles and supramolecular hydrogels (i.e., micellar networks) with tunable critical sol-to-gel transition temperatures from PNIPAM-*b*-PNAM-*b*-PNBOC triblock copolymers. As-synthesized amphiphilic triblock copolymers self-assemble into three-layered micellar nanoparticles with PNBOC cores, PNAM inner shells, and swollen PNIPAM coronas at temperatures below the LCST of thermoresponsive PNIPAM block. At elevated temperature and high concentrations, physical hydrogels of micellar networks form due to temperature-induced collapse and aggregation of PNIPAM coronas. Under UV irradiation, initially hydrophobic PNBOC cores within self-assembled micelles and physical hydrogels undergo amidation-induced cross-linking and hydrophobic-to-hydrophilic transition, leading to the elevation of critical gelation temperatures (CGTs) from CGT_0 (before UV irradiation) to CGT_{UV} (after UV irradiation). This process is also accompanied by temperature-regulated co-release of hydrophobic drugs initially encapsulated in micellar cores and hydrophilic drugs loaded within extramicellar aqueous phase of hydrogel networks.