Controlled-Release System of Small Molecules Triggered by the Photothermal Effect of Polypyrrole

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In this paper, a novel synthesis of polyethylene glycol (PEG)-modified polypyrrole (PPy) nanomaterials is demonstrated by combining reversible addition-fragmentation chain transfer polymerization and oxidative polymerization. Dye molecules with a heat-labile linker are used as a model drug and covalently anchored onto the PEGlated PPy nanomaterials via “click chemistry.” The strong absorption of such PPy nanomaterials in the near-infrared region endows the system excellent photothermal effect, which can be used not only as efficient photothermal agents for photothermal therapy but also good controllers of a drug-release system by retro D–A reaction.

1. Introduction

Controlled-release systems based on light irradiation,[1–5] pH,[6–9] temperature,[10–13] enzymatic hydrolysis,[14–17] as well as redox reaction,[18–20] have gained significant attention in recent years for their wide applications in medical treatments such as for drug delivery to specific sites. Among these various strategies, the photolysis represents a unique approach due to the possibility of remote control and temporal release of loaded molecules from the carrier systems. Great efforts have been made in the photolysis delivery systems using high-energy ultraviolet (UV) or visible light irradiation.[21,22] However, the unavoidable cellular damage and reduced tissue penetration would hamper their potential use in medical field.

As compared, longer-wavelength near-infrared (NIR) light is more suitable for biomedical applications due to its capability of deeper penetration into tissue and minimal damage to living cells.[23] Recently, controlled-release of molecules on the basis of photothermal effect produced by NIR irradiation provides an alternative way for drug delivery and targeted therapy.[24,25] Because of the high photothermal transition efficiency and flexibility in morphology design, gold nanomaterials have been the most explored photothermal reagents.[26–29] Meanwhile, there are a few reports exploiting photothermal effect to trigger dissociation of small molecules on the gold nanomaterials.[30–32] For example, Branda and co-workers[33] and Takuroet and co-workers[34] described a photothermal release system based on the retro Diels–Alder reaction, which was induced by the photothermal effect of gold nanomaterials under NIR irradiation. However, these gold nanomaterials usually have a big size which is adverse to body clearance efficiency.

Recently, polypyrrole (PPy) nanoparticles as a new type of NIR photothermal reagent have received great attention in biomedical application due to their outstanding stability, controllable size, and good biocompatibility.[35–37] For example, Dai and co-workers[38] and Liu and co-workers[39] have successfully used them as NIR absorbing agents for photothermal therapy both in vitro and in vivo. Especially, Ramanaviciene et al. reported that PPy nanoparticles with low concentration have very low long-term cytotoxicity.[40] Although PPy nanoparticles can produce a significant NIR photothermal effect for effective...
cancer therapy using NIR irradiation, the use of PPy conductive polymers for photothermal controlled-release has, to the best of our knowledge, not yet been reported. Herein, we demonstrated for the first time that polyethylene glycol (PEG) and pyrene-oxabicycloheptene-alkyne (POA) modified PPy (PEG-POA PPy) nanomaterials can be used not only as efficient photothermal agents for photothermal therapy but also as a controller of a drug-release system by the retro D–A reaction under NIR irradiation (Figure 1, for details see the Supporting Information).

2. Experimental Section
All experiment details were described in the Supporting Information.

3. Results and Discussion

3.1. Synthesis of Dye Molecules POA
A novel Diels–Alder cycloadduct POA comprising an alkynyl group and a heat-labile linker (oxabicycloheptenegroup) was first synthesized (Scheme S1, characterization in Figures S1–S6, Supporting Information). The alkynyl group is responsible to anchor the pyrene dye onto the PPy nanomaterials via “click chemistry,” whereas the oxabicycloheptene segment provides the programming of photothermal release due to its readily undergoing predictable bond breaking when the temperature is raised to 60–70 °C.

3.2. Synthesis of PEGlated Pyrrole-Containing Bottlebrush Copolymers
PEGlated pyrrole-containing bottlebrush copolymers were successfully synthesized by “graft-from” approach with the help of reversible addition-fragmentation chain transfer (RAFT) polymerization. The structure of the target bottlebrush copolymer precursor is shown in Scheme S2 of the Supporting Information. First, a well-defined poly(glycidyl methacrylate) (PGM) backbone was prepared by RAFT polymerization with narrow molecular weight distribution ($M_w/M_n < 1.1$). The pendant epoxide groups of PGM were then hydrolyzed to produce diols (Figure S7, Supporting Information),[42] which served as initiators for S-1-dodecyl-S′-[α,α′-dimethyl-α′′-acetacitic acid] trithiocarbonate RAFT modification. According to the previously
reported method,[42] an average of 63% of hydroxy units were successfully converted to RAFT groups (Figure S8, Supporting Information). Then, 4-vinylbenzyl chloride (VBC) and 4-(pyrrolylmethyl)styrene (PMS) were randomly grafted onto the PGM backbone by RAFT to form bottlebrush copolymers.[43,44] In $^1$H NMR spectrum of poly(GM-g-PMS/VBC) (Figure 59A, Supporting Information), the signal at 4.9 and 4.5 ppm corresponds to the pendant methylene groups of PMS and VBC, respectively. In order to improve the water-solubility and biocompatibility, a poly(ethylene glycol)methyl ether methacrylate (PEGMA) shell layer was introduced into the bottlebrush architecture to produce a core–shell structural precursor. A new peak at 3.4 ppm in the $^1$H NMR spectrum (Figure S9B, Supporting Information) was assigned to the pendant methyl groups of PEGMA. Finally, the PEGlated pyrrole-containing bottlebrush copolymers were composed of the poly(PMS/VBC) core block with an average of 5 PMS and 6 VBC units and a PEGMA shell block with an average of 43 units, confirmed by $^1$H NMR spectroscopy analysis. Gel permeation chromatography (GPC) traces of the bottlebrush copolymer precursor exhibited monomodal molecular weight distribution (Figure S10, Supporting Information), which indicated efficient reinitiation and the formation of well-defined copolymers. Poly(GM-g-PMS/VBC-PEGMA) bottlebrush copolymers, despite much higher molecular weight, elute slightly quicker and have a relatively wider polydispersity ($\text{PDI} = 1.28$) than the poly(GM-g-PMS/VBC) precursors. This behavior may be attributed to the interaction of PEGMA with the GPC column.

### 3.3. Synthesis of PEG-POA PPy Nanoparticles Decorated with Thermal-Cleavable Dye Molecules

In this work, the core benzyl chlorides in poly(GM-g-PMS/VBC-PEGMA) bottlebrush copolymers were further converted to azide by treatment with sodium azide (Figure 1). The success of this reaction was confirmed by IR spectroscopy, where peaks emerged at 2100 cm$^{-1}$ corresponding to the azide group (Figure S11B, Supporting Information). Then, we utilized CuAAC to couple sodium propynesulfonate and dye...
molecules (POA) into the core section. The introduction of sodium propynesulfonate will not only improve the water-solubility of the precursor but also act as a self-doping group for conjugated PPy. The reaction was monitored by the disappearance of azide peak at 2100 cm$^{-1}$ (Figure S11C, Supporting Information). Moreover, the UV–vis-NIR spectrum also showed the characteristic absorption peaks of pyrene dye at 331 and 344 nm after “click reaction” (Figure 2Ab), which further confirmed that POA was successfully anchored into the poly(GM-g-PMS/VBC-PEGMA) bottlebrush precursor. According to the nitrogen contents (2.18%) in elemental analysis (Table S1, Supporting Information), the number of dye POA and sodium propynesulfonate attached to each side chain was calculated to be 3 and 3, respectively. So, the loading capacity of POA in such pyrrole-containing bottlebrush copolymers was calculated to be 9 wt%. Finally, the synthesized core–shell PEG-POA pyrrole bottlebrush copolymers were transformed into the PEG-POA PPy nanoparticles by treating with free pyrrole monomer, HCl, and (NH$_4$)$_2$S$_2$O$_8$. Free pyrrole molecules can be performed as crosslinkers and oxidatively copolymerized with the pendant pyrrole groups of PMS/VBC to form a crosslinked PPy core layer (Figure 1). To confirm the presence of a conjugated PPy, UV–vis-NIR spectrum of PEG-POA PPy nanoparticles was obtained and showed a distinct band at 450 nm and a broad band centered at 950 nm (Figure 2Ac), which are characteristic transitions of a doped PPy containing a bipolaron and an antibipolaron bands within the band gap.$^{[45]}$ These results indicate that the conjugated PPy core can be obtained through copolymerization of free pyrrole and pendant pyrrole groups in the bottlebrush copolymer. In addition, two adsorption peaks of pyrene dye at 331 and 344 nm were also observed (Figure 2Ac), which evidenced that POA molecules still remained in the resulting PEG-POA PPy nanoparticles after the oxidative copolymerization. The morphology of the PEG-POA pyrrole bottlebrush copolymers was changed to nanoparticles due to the formation of the crosslinked PPy core layer, which was further characterized by transmission electron microscopy (TEM). As shown in Figure 3, clearly distinguishable nanoparticles with diameter of 50 ± 5 nm were observed. However, the average size of PEG-POA PPy nanoparticles measured by DLS experiment reached approximately to 105 nm (Figure S12, Supporting Information), which is larger than the diameter of PPy nanoparticles (50 nm) observed in TEM (Figure 3). This difference is due to that the PEGMA corona with poor contrast cannot be observed in TEM.

### 3.4. Photothermal Release of Dye Molecules from PEG-POA PPy Nanoparticles

The photothermal effect of PEG-POA PPy nanoparticles was investigated by monitoring the temperature of an aqueous suspension of PPy nanoparticles (48 μg mL$^{-1}$) under NIR laser irradiation (808 nm, 2 W cm$^{-2}$). As shown in Figure 2B, the temperature of PPy nanoparticles solution increased to 70–80 °C within 30 min. However, under the same irradiation condition, in contrast, the solution temperature of pure water and the PEG-POA pyrrole-containing bottlebrush precursor in the absence of NIR-absorbing PPy layer only increased to 35–40 °C, which indicated that the synthesized PEG-POA PPy nanoparticles have an excellent photothermal conversion effect and can act as efficient photothermal agents.

To demonstrate the controlled-release of target molecules from the PEG-POA PPy nanoparticles system, an...
aqueous solution of PEG-POA PPy nanoparticles was irradiated under a pulsed laser light (808 nm, 2 W cm\(^{-2}\)) for various time from 5 to 60 min. Since the dye molecules released by the retro D–A reaction are water-insoluble, the released dye at different irradiation time was extracted with DCM from the aqueous solution and then detected by UV–vis-NIR spectra (Figures 4 and 2D). The amount of released dye increased when irradiation time prolonged (Figure 2C), and can be calculated by the equation which was obtained from the standard curve (Figure S13, Supporting Information). The total release rate of dye can rise up to 89% when the irradiation time reaches to 60 min. The disappearance of adsorption peaks of pyrene dye at 331 and 344 nm in the UV–vis-NIR spectrum of PEG-POA PPy nanoparticles also further confirmed the above release behavior (Figure 2Ad). However, in the case of the PEG-POA pyrrole-containing bottlebrush copolymers, no release of pyrene dye was detected under the same irradiation condition, which is ascribed to their low photothermal transition ability in the absence of conjugated PPy core layer. This is consistent with the result of their photothermal experiment (Figure 2B). Thus, the presence of conjugated PPy core layer in the PEG-POA PPy nanoparticles is essential for producing photothermal effect for controlled-release of dye molecules through the retro D–A reaction.

4. Conclusions

In summary, we prepared a novel class of PEG-POA PPy nanomaterials as a new controlled-release system that can covalently append hydrophobic guest molecules and release them in response to a NIR light trigger. This was achieved by incorporating thermal-sensitive functionalities at the core layer of core–shell bottlebrush copolymer. The controlled-release of the guest molecules was triggered by the retro D–A reaction induced through the photothermal effect of conjugated PPy under NIR irradiation. This research paves a way for the exploration of efficient controlled-release systems responsive to NIR light stimuli. Moreover, the resultant PEG-modified PPy nanoparticles may be suitable as efficient photothermal agents for photothermal therapy in the future.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements: This work was supported by National Natural Science Foundation of China (Grant Nos. 51273066, 21574042, and 21204022), Shanghai Pujiang Program (Grant No. 13PJ1402300), Research Fund for the Doctoral Program of Higher Education of China (20120076120005), and the Fundamental Research Funds for the Central Universities.

Received: August 31, 2015; Revised: October 5, 2015; Published online: November 2, 2015; DOI: 10.1002/marc.201500523

Keywords: controlled-release; NIR light; photothermal effect; PPy nanoparticles; retro D–A reaction