LETTER

Smart Nanofibers with a Photoresponsive Surface for Controlled Release

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ABSTRACT A novel photocontrolled "ON−OFF" release system for the α-cyclodextrin-5-fluorouracial (α-CD−5FU) prodrug, based on host−guest interaction on the photoresponsive and cross-linked nanofiber surface, was demonstrated. The nanofibers with a stimuli-responsive surface were electrospun from the block copolymer prepared via controlled radical polymerization, followed by surface modification via "Click Chemistry", and loading of the prodrug via host−guest interaction.

KEYWORDS: photoresponsive • controlled release • nanofibers • cyclodextrin prodrug • host−guest interaction

Controlled drug-delivery systems are able to improve therapeutic efficacy, reduce toxicity effects, and optimize clinical efficiency (1−3). Stimuli-responsive or "smart" materials, such as thermoresponsive (4, 5), pH-responsive (5, 6) and electrical-responsive polymers (7) and magnetic materials (8), as drug carriers have attracted much attention for controlled release under specific conditions (9−12). To date, drug carriers in the form of hydrogels (13, 14), nanofibers (15−17), particles (18−21) and micelles (22, 23) from these "smart" materials have been investigated. The photoresponsive delivery systems have been of special interest to scientists because of their unique advantage of quick response without the addition of any chemical stimulants, or the production of chemical waste, in the photoinduced release process (24). Recently, fine works on nanoparticles with photocontrolled "gates" (20, 25−27) for storage and release of organic molecules have been demonstrated.

An example of a photoresponsive host−guest pair involves cyclodextrins (CDs), a cyclic oligomer of (+)-D-glucopyranose and azobenzene (AB) molecules that can transform from the trans to cis configuration under photoirradiation (24, 28). Driven by hydrophobic and van der Waals interactions, *trans*-AB is well-recognized by α-cyclodextrin (α-CD). The host−guest interaction is hindered when AB transforms from the trans to cis configuration under UV irradiation. The photocontrolled host−guest interaction between AB and α-CD has been utilized in the fabrication of photoresponsive vesicles (29, 30), phototunable surfaces (31, 32) and photoresponsive gels (33−35). An active interface in gold electrodes for electrochemical and microgravimetric transduction of optical signals arises from host−guest interaction between surface-immobilized α-CD and a bipyridinium−AB diad (36). Recently, drug-immobilized CD, or the CD prodrug, has attracted a great deal of attention because of its ability to improve the physical and biopharmaceutical properties of drugs, including enhancing the stability and solubility of drugs, eliminating the side effects, and improving the transport of the drug through cellular membranes (37). Various CD prodrugs, such as synthetic drug−CD prodrug, peptide−CD prodrug, and DNA−CD prodrug, have been reported (38, 39). 5-Fluorouracil (5FU) has been in use against cancer for decades because it can be incorporated in DNA and RNA to inhibit DNA replication (40). The 5FU and α-CD conjugate (α-CD−5FU) has been synthesized and used as a prodrug for site-specific delivery of drugs to the colon (41).

In this work, by combination of the mechanisms of the host−guest interaction and drug conjugation with CD, a smart delivery system based on cross-linked nanofibers with surface-loaded CD prodrugs has been developed (Figure 1). The system exhibits rapid photoresponse and controlled release characteristics. Thus, this work reports the (i) preparation of cross-linked nanofibers with azido groups on the surface via electrospinning of the block copolymer of vinylbenzyl chloride (VBC) and glycidyl methacrylate (GMA) (PVBC-*b*-PGMA) prepared by consecutive reversible addition−fragmentation chain-transfer (RAFT) polymerization and subsequent reaction with sodium azide, (ii) introduction of photosensitive groups on the nanofiber surface by "Click Chemistry" with 4-propargyloxyazobenzene (PAB), (iii) synthesis of the α-CD−5FU prodrug, (iv) loading of the α-CD−5FU prodrug on the nanofiber surface via host−guest interaction, and (v) photocontrolled release of the α-CD−5FU prodrug from the nanofiber surface, as well as dissociation of 5FU

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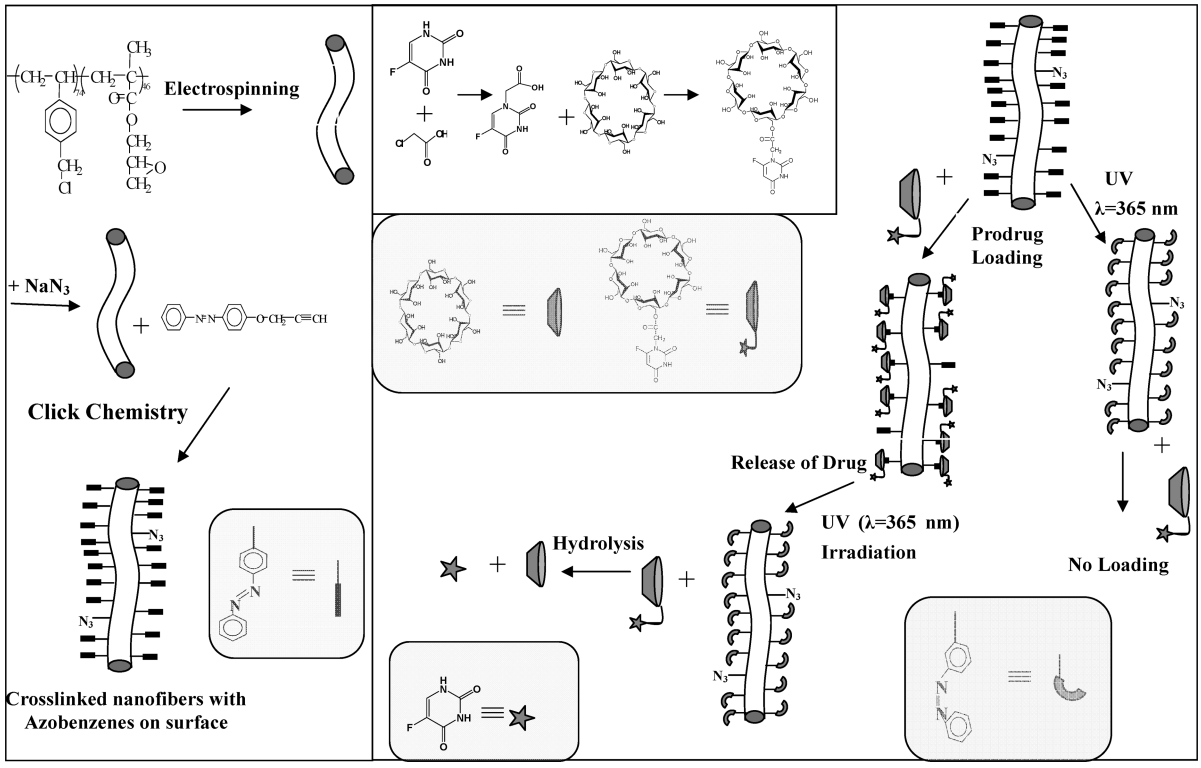

FIGURE 1. Schematic illustration of the preparation of the cross-linked nanofibers of PVBC-*b*-PGMA with AB groups on the surface ($CNF_{PVBC\text{-}b\text{-}PGMA}$−AB), the synthesis of the CD and 5FU prodrug (α-CD−5FU), and the photoresponsive loading and release of the α-CD−5FU prodrug on the $CNF_{PVBC\text{-}b\text{-}PGMA}$−AB surface by host−guest interaction.

from CD. The cross-linked nanofibers were used for controlled release because of their good environmental stability and large effective surface area for drug loading.

The synthesis procedures and chemical structure of the α-CD−5FU prodrug are shown in Figure 1. The successful preparation of the α-CD−5FU conjugate was confirmed by mass spectrometry and ^{1}H NMR spectroscopy (Figure S1 in the Supporting Information). Cross-linked nanofibers of PVBC-*b*-PGMA with azido groups on the surface ($CNF_{PVBC\text{-}b\text{-}PGMA}$−$N_3$) were prepared according to procedures developed earlier (41). The subsequent "click reaction" between $CNF_{PVBC\text{-}b\text{-}PGMA}$−$N_3$ and PAB allows the preparation of solvent-resistant nanofibers with photoresponsive AB groups on the surface ($CNF_{PVBC\text{-}b\text{-}PGMA}$−AB). Figure 2a shows the scanning electron microscopy (SEM) image of $CNF_{PVBC\text{-}b\text{-}PGMA}$−AB. The nanofibers are uniform in size with an average diameter of about 500 nm. The successful preparation of $CNF_{PVBC\text{-}b\text{-}PGMA}$−AB was confirmed by X-ray photoelectron spectroscopy (XPS; Figure 3a,b) and Fourier transform infrared (FTIR) spectroscopy (Figure S2 in the Supporting Information).

Initially, the loading of the α-CD−5FU prodrug on the photosensitive $CNF_{PVBC\text{-}b\text{-}PGMA}$−AB was carried out by immersion of the nanofibers in a 1 mmol/L aqueous solution of α-CD−5FU for 12 h in the dark. The successful loading of the α-CD−5FU prodrug on the nanofiber surface was revealed by XPS analysis. Figure 3d shows the wide-scan spectrum of $CNF_{PVBC\text{-}b\text{-}PGMA}$−AB loaded with the α-CD-5FU prodrug. In comparison with pristine $CNF_{PVBC\text{-}b\text{-}PGMA}$−AB (Figure 3c), the appearance of the F 1s signal at the binding energy (BE) of about 688 eV suggests that the α-CD−5FU

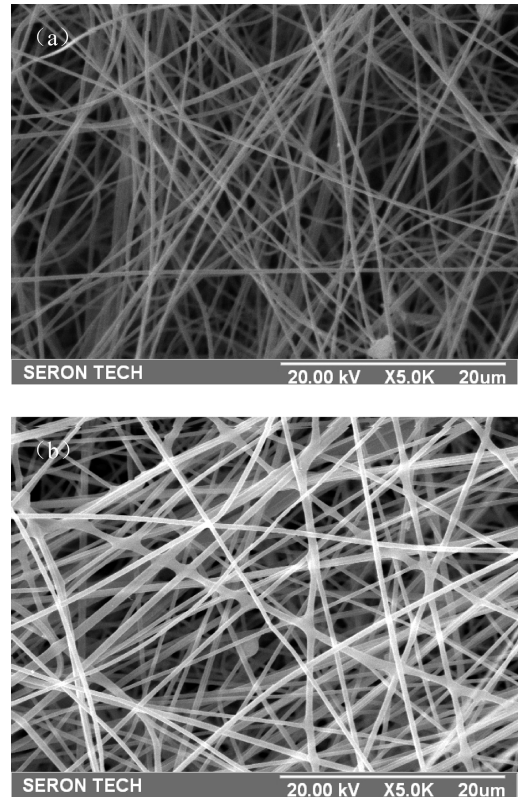

FIGURE 2. SEM images of the (a) as-synthesized $CNF_{PVBC\text{-}b\text{-}PGMA}$−AB (with 74 VBC repeat units and 46 GMA repeat units in the copolymer molecule) and (b) $CNF_{PVBC\text{-}b\text{-}PGMA}$−AB after loading and photocontrolled release of the α-CD−5FU prodrug.

prodrug has been successfully loaded on the nanofiber surface by the host−guest interaction between the *trans*-AB

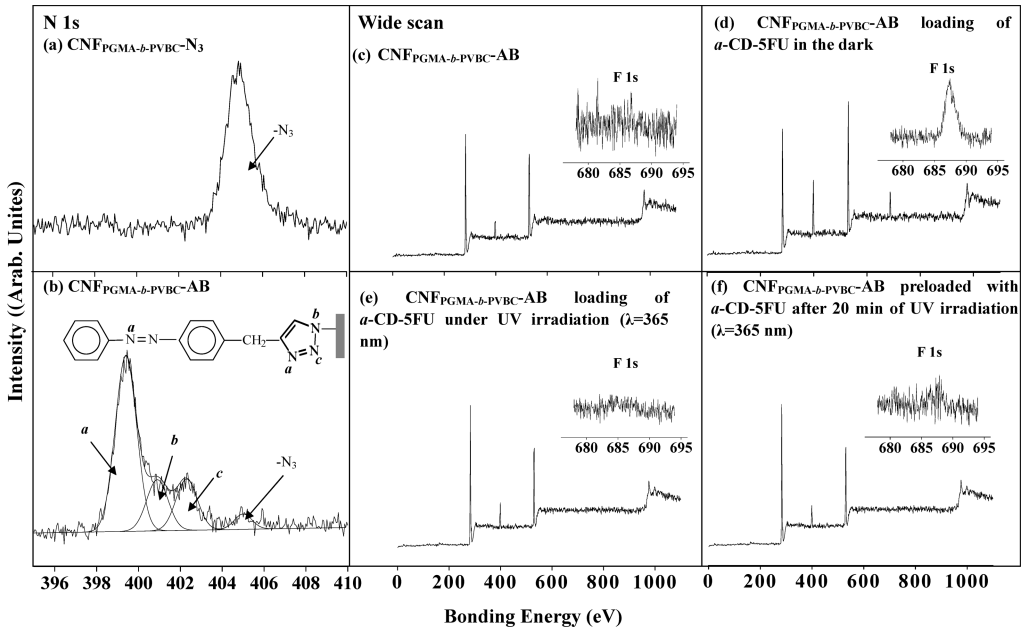

FIGURE 3. XPS N 1s core-level spectra of (a) CNF$_{PVBC-b-PGMA}$−N$_3$ and (b) CNF$_{PVBC-b-PGMA}$−AB, XPS wide-scan spectra of (c) CNF$_{PVBC-b-PGMA}$−AB and (d) CNF$_{PVBC-b-PGMA}$−AB after loading of the α-CD−5FU prodrug in the dark for 12 h, (e) CNF$_{PVBC-b-PGMA}$−AB after loading of the α-CD−5FU prodrug under UV irradiation ($\lambda = 365$ nm) for 12 h, and (f) α-CD−5FU-loaded CNF$_{PVBC-b-PGMA}$−AB after release of the prodrug by 20 min of UV irradiation ($\lambda = 365$ nm).

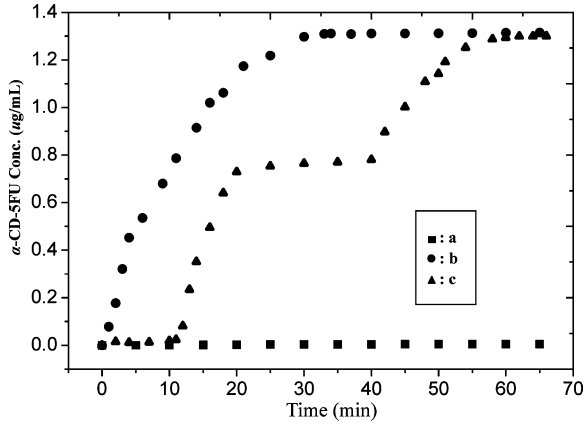

FIGURE 4. Time release profile of the α-CD−5FU prodrug in 20 mL of water from 10 mg of CNF$_{PVBC-b-PGMA}$−AB with surface-loaded α-CD−5FU. Curve a is the release profile in the dark. Curve b is the release profile upon continuous exposure to 365 nm UV irradiation. Curve c is the release profile upon intermittent exposure to 365 nm UV irradiation in the time intervals of 10−20 and 40−70 min.

group and the α-CD−5FU prodrug. The photoresponsive property of the CNF$_{PVBC-b-PGMA}$−AB surface was also studied by loading the α-CD−5FU prodrug under UV irradiation at a wavelength of 365 nm. No F 1s signal is discernible at a BE of 688 eV in Figure 3e, suggesting that the host−guest interaction cannot occur when the AB has been transformed to the cis configuration by UV irradiation.

Photocontrolled release of the α-CD−5FU prodrug from the CNF$_{PVBC-b-PGMA}$−AB surface was conducted by immerssion of 10 mg of the α-CD−5FU-loaded nanofibers in 20 mL of water, followed by UV irradiation at a wavelength of 365 nm. Figure 4 shows the release profiles of α-CD−5FU from the CNF$_{PVBC-b-PGMA}$−AB surface as a function of the UV irradiation time. In the dark, there was almost no release of α-CD−5FU from the α-CD−5FU prodrug-loaded CNF$_{PVBC-b-PGMA}$−AB after 1 h of immersion in water (curve a in Figure 4), suggesting that dissociation of the host−guest interaction between α-CD−5FU and CNF$_{PVBC-b-PGMA}$−AB did not occur in the absence of UV irradiation and AB isomerization. When exposed to UV irradiation, α-CD−5FU was released quickly into the solution, as the AB transformed from the trans to cis configuration. An α-CD−5FU solution concentration of 0.5 μg/mL was reached after 5 min of UV irradiation (curve b in Figure 4). The release of the α-CD−5FU prodrug from the nanofiber surface was also revealed by XPS. Figure 3f shows the XPS F 1s core-level spectrum of the α-CD−5FU prodrug-loaded CNF$_{PVBC-b-PGMA}$−AB after 20 min of UV irradiation in water at a wavelength of 365 nm. The nearly complete disappearance of the F 1s signal at a BE of 688 eV is consistent with the release of the α-CD−5FU prodrug from the CNF$_{PVBC-b-PGMA}$−AB surface. Thus, the maximum loading of α-CD−5FU on CNF$_{PVBC-b-PGMA}$−AB can be estimated from the XPS results and release profile under UV irradiation. For CNF$_{PVBC-b-PGMA}$−AB with an average diameter of about 500 nm used in this work, an α-CD−5FU loading of 2.6 mg/g of nanofibers can be achieved. The isomerization of AB on the CNF$_{PVBC-b-PGMA}$−AB surface was also characterized by UV−visible absorption spectroscopy (Figure S3 in the Supporting Information). The UV−visible absorption results indicate isomerization yields of 34% and 92%, respectively, after 5 and 15 min of UV irradiation. Thus, the UV−visible absorption results are consistent with the XPS results.

The quick response and controllable release of the α-CD−5FU prodrug in this delivery system are revealed by the multistep "ON−OFF" release profile under UV irradiation (curve c in Figure 4). The release profile shows that there is no release of α-CD−5FU from the nanofiber surface during the initial period (10 min) in the dark. The concentration of α-CD−5FU in solution increases gradually in the next 10 min

upon UV exposure. The concentration of α-CD−5FU ceases to increase upon removal of the UV irradiation at $t = 20$ min. The concentration of α-CD−5FU remains almost constant in the next 20 min, in the absence of UV irradiation. When UV irradiation is resumed at $t = 40$ min, the concentration of α-CD−5FU in solution increases again. Figure 2b shows the SEM image of $CNF_{PVBC\text{-}b\text{-}PGMA}$−AB after the photoresponsive release of α-CD−5FU. The nanostructure of $CNF_{PVBC\text{-}b\text{-}PGMA}$−AB is well-preserved after surface loading and release of the α-CD−5FU prodrug. The stability of the nanofibers can be attributed to their chemically cross-linked structure. $CNF_{PVBC\text{-}b\text{-}PGMA}$−AB can be used for loading and release of the α-CD−5FU prodrug repeatedly. Moreover, the dissociation of 5FU from α-CD−5FU can be realized at pH above 8 (43, 44). High-performance liquid chromatography results show that, in a medium of pH 8.1, about 66% of α-CD−5FU dissociates into 5FU and α-CD in 60 min.

In summary, we have demonstrated a novel photoresponsive controlled release system, in which the α-CD−5FU prodrugs are loaded on the photoresponsive and cross-linked nanofiber surface via host−guest interaction. Differing from the other controlled release systems, in which the drug is loaded inside the carrier and is susceptible to release delays in response to external stimuli, the present system provides a photocontrolled fast "ON−OFF" release characteristic. With the availability of a wide variety of CD prodrugs, stimuli-responsive nanofiber systems with loaded CD prodrugs are expected to provide unique opportunities for the effective and controlled "ON−OFF" release of therapeutic agents.

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Supporting Information Available: ^{1}H NMR spectrum of α-CD−5FU, FTIR spectra of nanofibers, UV−visible adsorption spectra of nanofibers, and experimental details on the synthesis of the α-CD−5FU prodrug, the preparation of nanofibers, and the controlled release. This material is available free of charge via the Internet at http://pubs.acs.org.

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