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147

Design and decoration of heparin on porous nanosilica via reversible disulfide linkages for controlled drug release

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Abstract

Porous nanosilica (PNS) has been identified as a potential candidate for controlled drug delivery. However, unmodified PNS-based carriers exhibited an initial release of loaded bioactive agents, which may limit their potential clinical applications. In this study, the surface of PNS was functionalized with adamantylamine (ADA) via disulfide bonds (-S-S-), PNS-S-S-ADA, which was then modified with cyclodextrin (CD)-heparin (Hep) (CD-Hep), PNS-S-S-CDH, for redox triggered rhodamine B (RhB) delivery. The obtained samples were then characterized by proton nuclear magnetic resonance (^{1}H NMR), Fourier transform infrared (FTIR), and transmission electron microscope (TEM). These results showed that PNS-S-S-CDH was successfully formed with spherical shape and average diameter of 45.64 ± 2.33 nm. In addition, RhB was relatively encapsulated in the PNS-S-S-CDH (RhB@PNS-S-S-CDH) and slowly released up to 3 days. The release of RhB, in particular, was triggered due to the cleavage of -S-S- in the presence of dithiothreitol (DTT). It might be anticipated that the modified PNS can be used as redox-responsive drug delivery system in cancer therapy.

Key words: Porous nanosilica, cyclodextrin, heparin, rhodamine B, redox-responsive delivery system

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I. Introduction

Porous nanosilica (PNS), inorganic materials, have a honeycomb-like porous structure with hundreds of empty channels (mesopores) [1, 2]. Based on their unique structure, PNS are able to effectively encapsulate anticancer drug molecules in various sizes and shapes, transport these molecules into cancer cells, and kill them [2, 3]. Despite the effectiveness of PNS on the drug loading capacity, the loaded molecules would burst release and be poorly dispersible from the unmodified PNS, leading to the loss of drug that actually reach cancer cells. These disadvantages limit its possible clinical uses [1]. In recent years, stimuli-responsive PNS as programmable drug delivery systems have attracted rapidly growing interest and drug released from PNS can be triggered by using appropriate stimuli [4-6]. Enormous efforts have been devoted to formulate advanced PNS that are sensitive to either external stimuli (light, magnetic fields, and ultrasound) or internal stimuli (pH, temperature, and redox potential) [5, 6]. Among these different types of stimuli, the redox stimulus is one the most effective strategies because the concentration of reducing agent, such as glutathione (GSH) in abnormal cells (2-10 mM) is 100 to 1000-fold higher than that in normal healthy cells (1-2 μM). In order words, the difference in concentration of antioxidants could offer a significant opportunity for redox sensitive system to deliver chemotherapeutic agents at the targeted tumor sites [7, 8]. For instance, Lee and co-workers created a redox responsive system based PNS nanoparticles by using cyclodextrin (CD) as gatekeepers with GSH via disulfide bridges (-S-S- bonds). CD not only was used as an impactful stimulus-responsive gatekeeper but also was employed to increase the drug loading capacity. The results demonstrated the adequate intracellular release of doxorubicin (DOX) by PNS-S-S-DOX-CD-polyethylene glycol in human lung cell line A549 which was found at significantly high levels of GSH [9]. Therefore, the redox-responsive DOX-loaded PNS using CD could possibly be functioned as a promising candidate for cancer-targeted drug delivery system. On the other hand, heparin (Hep), a non-cytotoxic and bio-degradable molecule, has been widely used as an anticoagulant drug for conventional subcutaneous or intravenous injection [5-8]. Liang et al. reported the association of Hep with PNS via -S-S- bonds as nanocarriers for intracellular drug release triggered by GSH [2]. By coating with Hep agents, PNS was proved to be able to elicit various promising characteristics such as to prevent or at least delay the process of phagocytosis, to stop the formation of blood clots as a part of inflammation as well as to inhibit angiogenesis and metastasis. Additionally, this also has been shown to enhance the *in vitro* apoptosis and *in*

vivo suppression of tumor growth and expansion considering for the efficient DOX delivery [5, 6, 10]. These promising properties indicated that surface modification of PNS with Hep could be a promising approach for targeted drug delivery in the treatment of cancer.

Herein, we report a potential PNS based redox-responsive nanocarriers for controlling drug release in cancer treatment. Generally, the system was synthesized by following these steps: first, PNS was prepared and further immobilized with adamantylamine (ADA) via -S-S- bonds, PNS-S-S-ADA; then, the obtained PNS-S-S-ADA was modified with CD-Hep, PNS-S-S-CDH for rhodamine B (RhB) delivery (Fig. 1). Hence, the modified PNS would be efficient nanocarriers for targeted drug delivery *in vitro* based redox-responsive system.

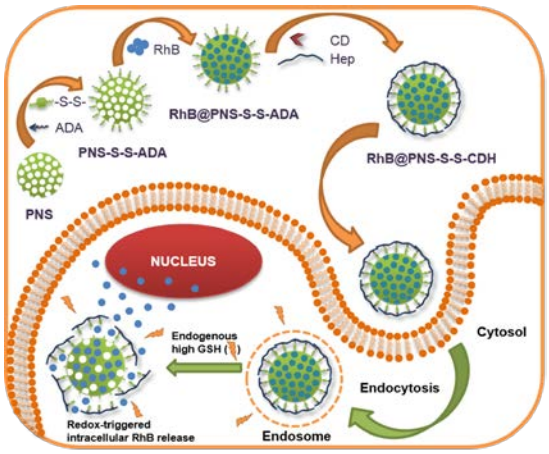

Fig. 1. Schematic illustration showing the formation and redox-sensitive intracellular delivery of PNS-S-S-CDH nanoparticles

II. Experiment

1. Materials

Tetraethyl orthosilicate 98% (TEOS), N,N-dimethyl formamide (DMF), dithiothreitol (DTT), ethylene-diamine (EDA), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), amantadine hydrochloride (ADA) were obtained from Sigma-Aldrich (St. Louis, MO, USA). N-cetyl-nnn-trimethylammonium bromide (CTAB), acetone nitrile (ACN) were purchased from Merck (Darmstadt, Germany). β-cyclodextrin (β-CD) was purchased from TCI Co. (Tokyo, Japan). 3,3' -dithiodipropionic acid 99% (DTDP) and 3-aminopropythiethoxysilane 99% (APS), heparin sodium (Hep) were purchased from Acros Organics (Geel, Belgium). All chemicals were used without further purification.

2. Methods

2.1 Preparation of PNS-S-S-ADA

Based on the literature with minor modification, the overall process of PNS-S-S-ADA synthesis can be described in four steps : (1) PNS was synthesized by the sol-gel process in which TEOS as silicon sources, CTAB as structure-directing agents, ethanol as a solvent, water as a reactant, and ammonia (NH_3) as catalyzed hydrolysis and condensation of TEOS. Briefly, deionized water (deH_2O, 64 mL), ethanol (11.25 mL, 0.2 mol), CTAB (2.6 g, 7.1 mmol), and 2.8% NH_3 solution (0.55 mL, 0.9 mmol) were

mixed at 60 ℃ with a stir-bar for 30 min. TEOS (8 mL, 35.8 mmol) were added drop-wise into the surfactant solution within 5 min under stirring and the stirring was continued for another 2 h, and then filtered. The filtrate was dialyzed using a dialysis membrane (MWCO 6-8 kDa, Spectrum Laboratories, Inc., USA) against deH_2O for 4 days at room temperature. The deH_2O was changed 5-6 times a day and the resulting solution was then lyophilized to obtain PNS; (2) the amino-functionalized PNS (PNS-NH_2) were prepared by stirring APS (1 mL, 5.7 mmol) and PNS (1 g) in toluene (30 mL) at room temperature under nitrogen environment for 24 h. The suspension was dialyzed using a dialysis membrane (MWCO 6-8 kDa) for 4 days against 2 M of acetic acid: ethanol (EtOH) (1:1 v/v, 250 mL). Acetic acid: ethanol solution was changed 5-6 times per day, and then the tube containing PNS was immersed into deH_2O to remove acetic acid/EtOH for 1 day. The deH_2O was changed 5-6 times a day and the solution was lyophilized to get PNS-NH_2; (3) the obtained PNS-NH_2 (1 g) and EDC (0.14 mL, 0.77 mmol) were dissolved in deH_2O (20 mL) under stirring for 10 min.

Then, DTDP (0.16 g, 0.77 mmol) in DMF (20 mL) were added into the mixture and the reaction was maintained for 24 h. After that, the sample was purified by a dialysis membrane (MWCO 6-8 kDa) against deH_2O at room temperature for 4 days. The reaction was stirred at room temperature for 24 h, and then filtered. The sample was then dialyzed at room temperature for 4 days. The deH_2O was changed 5-6 times per day and the solution was lyophilized to obtain PNS-S-S-COOH; (4) PNS-S-S-COOH (1 g) and ADA (0.12 g, 0.77 mmol) in deH_2O (40 mL) were mixed under stirring condition, followed by the addition of EDC (0.11 mL, 0.64 mmol). The reaction was stirred at room temperature for 24 h, and then filtered. The sample was then dialyzed at room temperature for 4 days. The deH_2O was changed 5-6 times per day and the solution was lyophilized to obtain PNS-S-S-ADA [11, 12].

2.2 Preparation of CD-Hep

CD-NH_2 was synthesized as described previously [13, 14]. CD-NH_2 was conjugated into Hep by using EDC chemistry. Initially, Hep (0.2 g) and EDC (35 μL, 0.2 mmol) were dissolved in deH_2O (10 mL) under stirring for 10 min. After that, the solution of CD-NH_2 (0.26 g in 10 mL of deH_2O) was added into the mixture and the reaction was maintained for 24 h. The solution was filtered and dialyzed by a dialysis membrane (MWCO 6-8 kDa) against deH_2O at room temperature for 4 days. The deH_2O was changed 5-6 times per day and the solution was then lyophilized for obtaining CD-Hep.

2.3 Synthesis of PNS-S-S-CDH

PNS-S-S-CDH was prepared by a simple method described below. First, 0.23 g of CD-

Hep was dissolved into 20 mL of deH_2O, followed by adding of 0.06 g of PNS−S−S−ADA. Next, the mixture was sonicated, vigorously stirred at room temperature and dialyzed using a dialysis membrane (MWCO 12−14 kDa, Spectrum Laboratories, Inc., USA). Lastly, the resulting solution was lyophilized to obtain PNS−S−S−CDH [14].

2.4 Characterization

Morphologies and sizes of PNS and PNS−S−S−CDH were imaged by transmission electron microscopy (TEM) using JEM−1400 (300 kV; JEOL, Tokyo, Japan) at an accelerating voltage of 300 kV. The samples for TEM observations were prepared by placing a drop of solution in deH_2O (1 mg/mL) onto a carbon−copper grid (300−mesh, Ted Pella, Inc., USA) and air−drying for 10 min. ^{1}H NMR spectra were obtained on a Mercury 400 MHz (Varian Co., Palo Alto, CA, USA) diffractometer equipped with Cu/Kα radiation at a scanning rate of 4°/min (λ = 0.15405 nm, 40 kV, 40 mA). Fourier transform infrared (FTIR) spectra were recorded on a Bruker Equinox 55 FTIR (Bruker Optics, Billeria, MA, USA) spectrometer.

2.5 Drug loading contents and *in vitro* drug release

RhB was loaded into the PNS−S−S−ADA (RhB@PNS−S−S−ADA) and PNS−S−S−CDH (RhB@PNS−S−S−CDH) by sonication method. Typically, 10 mg of both samples were independently added into 2 mL of RhB solution. Then, the two solution were sonicated for 10 min, stirred for 24 h under dark condition and centrifuged for obtaining the resulting products [14].

The drug loading efficiency (DLE) and drug loading content (DLC) were quantified using a UV−Vis spectrophotometer (NIR−V670, JASCO, Japan) and presented by equation (1) and (2), respectively:

$$\text{DLE}\ (\%) = \frac{\text{weight of drug in particles}}{\text{weight of drug feed initially}} \times 100 \quad (1)$$

$$\text{DLC}\ (\%) = \frac{\text{weight of drug in particles}}{\text{weight of particles and drug}} \times 100 \quad (2)$$

The *in vitro* RhB release experiments were performed in PBS buffer (0.01 M, pH 7.4) at 37 °C using dialysis method. First, suspension solution of RhB@PNS−S−S−ADA and RhB@PNS−S−S−CDH in PBS (1 mL) were transferred to dialysis bags (MWCO 6−8 kDa), which were then immersed into the medium (14 mL) in vials at 37 °C. The vials were placed in an orbital shaker bath, which was maintained at 37 °C and shaken horizontally. At specific time intervals, 14 mL of the release medium was collected and an equal volume of fresh medium was added. The release amounts of RhB were determined using UV−Vis spectrophotometer. To examine the ability of redox−agent to trigger the release of RhB, the release of RhB from PNS−S−S−CDH in PBS containing 5 mM DTT was carried out.

III. Results and Discussion

1. Characterization

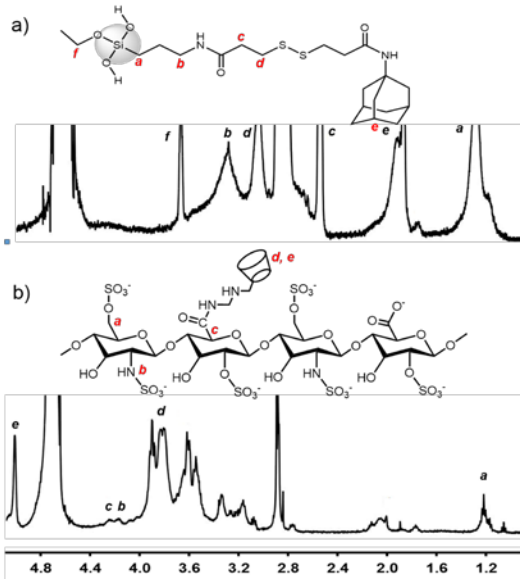

Fig. 2. ^{1}H NMR (D_2O) spectra of (a) PNS-S-S-ADA, (b) CD-Hep

^{1}H NMR spectra of (a) PNS-S-S-ADA and (b) CD-Hep are shown in Fig. 2. As shown in Fig. 2a, protons at 0.71 ppm (peak a), 3.35 ppm (peak b), 2.56 ppm (peak c), 2.92 ppm (peak d), 1.83-2.03 ppm (peak e), and 3.75 ppm (peak f) were assigned to CH_2-Si, CH_2-NH, CH_2-CO, CH_2-S-S, H of ADA, and CH_2-OSi groups, respectively. The presence of all these signals demonstrated the successful preparation of PNS-SS-ADA. Besides, Fig. 2b shows the ^{1}H NMR of CD-Hep in which the resonance signals appear at 1.9 (s, CH-CH_2), 4.19 (s, NH-SO_3), 4.25 (s, CH-COO), 5.1 (s, CH-OH) and 3.7-3.9 (m, C-O), 3.6-3.7 (m, CH-CH), indicating the successful synthesis of CD-Hep.

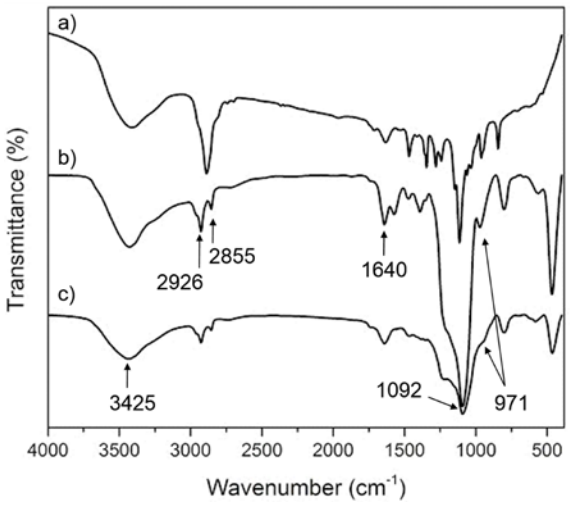

Fig. 3. FTIR spectra of (a) CD-Hep, (b) PNS-S-S-ADA, (c) PNS-S-S-CDH

The chemical structure of CD-Hep, PNS-S-S-ADA and PNS-S-S-CDH were determined by FTIR. As shown in Fig. 3, the peak around 1092 cm^{-1} and 971 cm^{-1} were assigned to asymmetric stretching vibration of Si-O-Si bond and skeleton vibrations involving C-O bond stretching of PNS, respectively [15]. The peak intensity at 3425 cm^{-1} was assigned to the OH group on the surface of PNS. These absorption groups in PNS still existed after surface modification with polymers, indicating that either PNS-S-S-ADA (Fig. 3b) or PNS-S-S-CDH (Fig. 3c) would keep the mesoporous structure of PNS even after the modification. As seen in Fig. 3b, the characteristic absorption bands at 1723 cm^{-1} were attributed to the absorption of carboxyl groups. The sharp band at 2926 cm^{-1} and the minor sharp band at 2855 cm^{-1} were assigned to CH_2 antisymmetric and CH_2 symmetric stretching of ADA, respectively, suggesting the formation of PNS-S-S-ADA. The peaks at 1640 cm^{-1} and 1572 cm^{-1} were found to correspond to C=O

stretching vibration of amide groups (amide I) and N–H bending vibration band of amide groups (amide II), respectively. The appearance of amide I and amide II peaks indicated the existence of DTDP and ADA on the surface of PNS. In Fig. 3a and c, the bands at 1174 cm^{-1} was assigned to C–O stretch in β–CD. [16]. The intensity of the peaks at 1280 cm^{-1} of SO_2, 1147 cm^{-1} of S=O stretching, 1445–1479 cm^{-1} of CH_3 stretching band, 1370–1380 cm^{-1} of CH_2 stretching band of Hep were obtained. These results demonstrated that CD–Hep was prepared and was modified onto the surface of PNS–S–S–ADA [17].

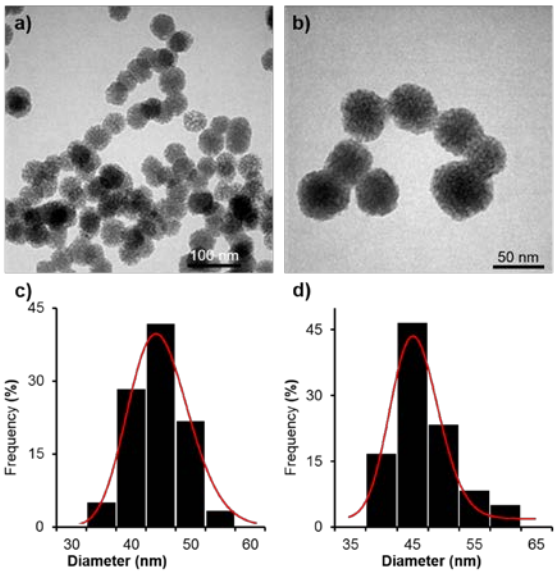

Fig. 4. TEM images and particle size distributions of (a, c) prepared PNS and (b, d) PNS–S–S–CDH, respectively

TEM images and particle size distributions of (a, c) PNS and (b, d) PNS–S–S–CDH are shown in Fig. 4, respectively. The average sizes of PNS was found to be 44.53 ± 0.89 nm. However, by complexation with –S–S–CDH, the size of PNS–S–S–CDH was slightly increased to 45.64 ± 2.33 nm. In biomedical application, PNS should be used as drug delivery systems for the purpose of delivering therapeutic agents to targeted cancer cells. Particle size in particular plays a crucial role in pharmacokinetics of nanoparticles by affecting the clearance and particle bio–distribution [10, 18–20]. The efficiency of the cellular uptake decreases when increasing the particle size. It is stated that particles (diameter < 100 nm) are mostly removed by renal clearance, while particles (diameter> 200 nm) become accumulated in the spleen or taken up rapidly by cells of the mononuclear phagocyte system (MPS). Besides, the particle size distribution within the size range of 10–100 nm is able to penetrate through extremely small capillaries and to be non–selective uptake by MPS for prolonging circulation times, resulting in the high–efficiency targeting of drug. Moreover, the small size of PNS–S–S–CDH would be responsible for the enhanced permeability and retention (EPR) effect results in higher particles concentration in tumor tissue. For instance, the particles range from 50 to 200 nm and > 500 nm are easily taken up in a clathrin–mediated endocytosis and raft–dependent pathway, respectively, whereas the small particle (40–50 nm) diffuse freely on the cell surface. Therefore, PNS–S–S–CDH with spherical form and the size of around 50 nm

might serve as nanocarriers with long-term circulation in the bloodstream and cellular uptake into cancer cells via endocytosis.

The surface area and pore volume of PNS and PNS-S-S-CDH nanoparticles were measured by N_2 adsorption-desorption method. There was a significant difference in nitrogen and structure parameters between PNS and PNS-S-S-CDH. The prepared samples showed a typical IV feature, and PNS had a high specific surface area (S_{BET}, and 561 m^2/g) and pore volume (V_p, 0.24 cm^3/g). After modification with CD-Hep, however, the S_{BET} (708.027 m^2/g) and V_p (0.336 cm^3/g) of PNS-S-S-CDH were reduced to 505.708 m^2/g and 0.242 cm^3/g, respectively. The S_{BET} and V_p values of the modified PNS were smaller than these of PNS which could be explained that some of the pores were blocked by CD-Hep. These results confirmed that PNS was successful modified with CD-Hep.

2. Loading and *in vitro* release of RhB

DLE plays an important role in the formation of drug delivery system and directly affects the therapeutic effect of the system. The drug-loading amounts were determined by UV-vis spectroscopy and the results demonstrated that DLE of PNS and PNS-S-S-CDH were 11.89 ± 1.71% and 18.96 ± 0.37%, respectively.

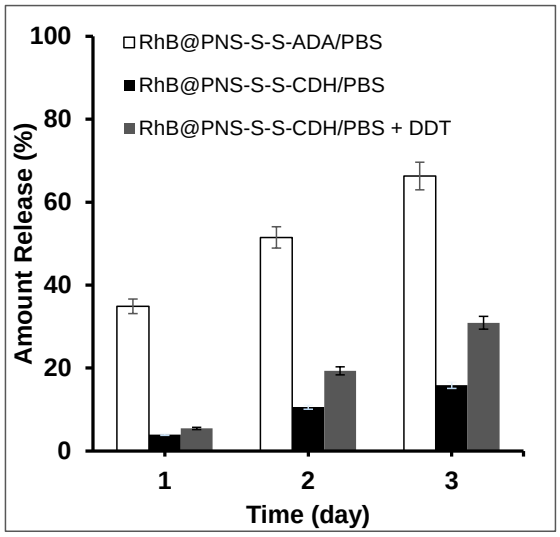

Fig. 5. Release profiles of PNS-S-S-ADA in pH 7.4 PBS buffer and PNS-S-S-CDH in pH 7.4 PBS buffer with and without DTT

The cumulative release amount of RhB from PNS-S-S-ADA over 3 days was around 67%, compared with 32% and 18% from PNS-S-S-CDH in the absence of DTT and in the presence of DTT, respectively. The released amount of RhB from PNS-S-S-CDH was significantly smaller than from PNS-S-S-ADA, indicating the potential application of PNS-S-S-CDH for sustained drug release, and was increased in the presence of DTT. This means that the disulfide links were exceedingly sensitive to DTT, which may result in its enhanced efficacy in the intracellular delivery. These results showed that PNS-S-S-CDH might undergo redox-sensitive dissociation and accelerate the RhB-release rate in the intracellular region, but not in extracellular environments.

IV. Conclusion

A surface modification of PNS with CD-Hep as a redox-responsive controlled release system have been prepared successfully. The modified PNS was spherical in shape with a diameter of approximately 50 nm, which would be suitable for the development of drug delivery system. The resulting nanoparticles had DLE of 18.96 ± 0.37%. More importantly, the release profile of the modified PNS nanoparticles showed sustained release of RhB and redox potential-sensitively in the presence of DTT. Our results suggest that the modified PNS nanoparticles have potential as a redox-responsive RhB delivery system for cancer therapy.

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