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Supramolecular chemistry at interfaces: host-guest interactions for attaching PEG and 5-fluorouracil to the surface of porous nanosilica

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Abstract: Porous nanosilica (PNS) has been attracting much attention in fabrication of nanocarriers for a drug delivery system (DDS). However, the unmodified PNS-based carriers exhibited a significant initial burst release of drug, which may limit their potential clinical application. In this study, PNS was surface conjugated with cyclodextrin (CD) which was functionalized with adamantylamine-polyethylene glycol (APEG) for 5-fluorouracil (5-FU) delivery, in which case CD was used due to its ability to form a stable inclusion complex with 5-FU and APEG. The conjugated PNS (PNSC@APEG) was successfully prepared with spherical shape and diameter around 50 nm, determined by transmission electron microscopy (TEM). In addition, 5-FU was efficiently trapped in PNSC@APEG particles, which were around 63.4% ± 3.8% and was slowly released up to 3 days in phosphate buffer saline (PBS). Furthermore, the cell proliferation kit I (MTT) assay data showed that PNSC@APEG was a biocompatible nanocarrier. These results indicated that PNSC@APEG nanoparticles have a great potential as novel carriers for anticancer drug delivery.

Keywords: 5-fluorouracil; cancer therapy; drug delivery systems; porous nanosilica.

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1 Introduction

Porous nanosilica (PNS) has recently received great attention and has been identified as a promising candidate for a drug delivery system (DDS) due to its specific properties, high surface area and large pore volume, high chemical and thermal stability, and excellent biocompatibility and biodegradability [1–3]. Moreover, the guest molecules are effectively entrapped and protected by silica matrix which is capable of preventing enzymatic degradation, induced by pH and temperature changes of the surrounding medium [4]. Despite the effective impact of PNS on the drug loading capacity, the loading bioactive molecules would burst release and be poorly dispersible from the unmodified PNS. In order to overcome these challenges, surface modification of PNS by polymer grafting for DDS has captured the interest of the scientific community; both the interfacial features of the modified nanoparticles can be engineered and the mechanical and thermal properties of the polymers can be enhanced at the same time [5]. Polyethylene glycol (PEG), one of the most biocompatible materials, has been commonly used for surface modification of PNS because the molecular size of PEG can be sufficient to cap the mesoporous of the silica. Furthermore, the functionalization of PNS with PEG not only increases its blood residence time and improves the enhanced permeability and retention effect, but also delays the action of the reticuloendothelial system [6, 7]. For instance, Cui and co-workers [8] created a novel PEG surface-capped PNS (PNS-SS-mPEG) based nanocarrier for DDS, where disulfide-linked PEG chains were first developed for controlled molecular release. According to

the results obtained from the cell proliferation kit I (MTT) assay, PNS-SS-mPEG nanoparticles had no toxic effects in human MCF-7 breast cancer cells [8]. Additionally, Zhao et al. [9] reported a redox-responsive delivery based on 6-mercaptopurine (6-MP)-conjugated PNS via disulfide bonds and then being modified with mPEG to elongate the blood circulation time and expand the dispersibility of nanoparticles [10, 11]. The study introduced a new strategy to conjugate bioactive molecules and PEG to silica nanoparticles through disulfide bonds to obtain redox-responsive drug release [9]. These experiments indicated the potential functions of PEG, physiological stability and intracellular drug release ability to PNS for DDS.

Considering the effectiveness of the modification of PNS, cyclodextrin (CD) was also used in order to develop a better nanosilica delivery system for anticancer therapy. CD is a unique compound with lipophilic cavity and hydrophilic exterior surface, which can enhance the solubility of guest molecules [12]. Moreover, it is capable of forming host-guest inclusion complexes with many drugs, resulting in minimizing undesirable physiochemical properties of drugs. In such a host-guest system, the CD inclusion complex occurs through non-covalent interactions, such as hydrogen boding, van der Waals forces, and hydrophobic interaction, depending on the type of guest molecules. These interesting characteristics show the possibility of CD to improve the ability of PNS for DDS [13, 14]. However, either modification of CD on PNS to form a stable inclusion complex or of PNS with PEG to improve their dispersion and blood circulation time have just been studied independently.

The aim of this study is to develop an effective therapeutic nanoparticle for a controlled delivery system. In detail, CD and adamantylamine conjugated PEG (APEG) were utilized to function PNS for the purpose of controlling 5-fluorouracil (5-FU) delivery (Figure 1). Medicinal drugs can be trapped in the hole of PNS and then it will be covered with biomaterials, therefore the medication can be slowly released. The obtained samples were characterized by proton nuclear magnetic resonance (^{1}H NMR), X-ray diffraction (XRD), Fourier transform infrared (FT-IR) spectroscopy, transmission electron microscopy (TEM), thermal gravimetric analysis (TGA), and MTT assay.

2 Materials and methods

2.1 Materials

Tetraethyl orthosilicate (TEOS, 98%), aminopropyltrimethoxysilane (97%), p-toluenesulfonyl chloride (TsCl), trimethylamine (Et_3N, 99.5%), dichloromethane (CH_2Cl_2, 99.8%), β-CD (CD, 97%), N,N-dimethyl formamide, 1-adamantylamine (A, 97%), 5-FU (99%), poly(ethylene glycol) methyl ether (mPEG, Mw 5000), and hydrochloric acid (36–38%) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Cetyltrimethylammonium bromide (CTAB, 99%) was purchased from Merck (Darmstadt, Germany). They were all used without further purification.

2.2 Methods

2.2.1 Preparation of PNS: Based on the literature with minor modification, PNS was synthesized by the sol-gel process with TEOS as silicon source, 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 (0.5 ml, 0.9 mmol) were mixed at 60°C under

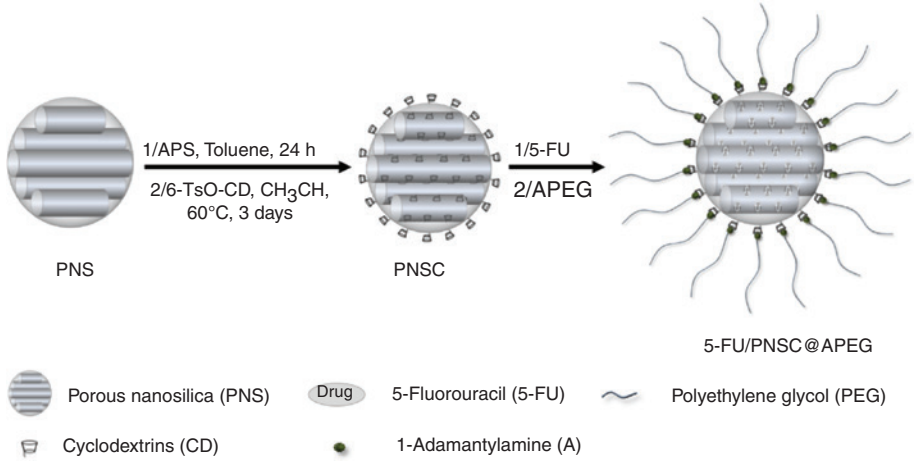

Figure 1: Schematic illustration of the fabrication of self-assembled 5-fluorouracil (5-FU)/adamantylamine-polyethylene glycol-functioned cyclodextrin-porous nanosilica (PNSC@APEG).

constant stirring. The mixture of TEOS (8 ml, 35.8 mmol) in 100 ml of deH_2O and ethanol (1:1 v/v) was added drop-wise to the surfactant solution within 5 min under stirring and the stirring was continued for another 2 h; then the solution was 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 five to six times a day and the resulting solution was then lyophilized to obtain PNS.

The amino-functionalized PNS (PNS-NH_2) were prepared by stirring aminopropyltrimethoxysilane (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, Spectrum Laboratories, Inc., Rancho Dominguez, CA, USA) against deH_2O for 4 days. The deH_2O was changed five to six times a day and the solution was then freeze-dried to obtain PNS-NH_2 [15–18].

2.2.2 Preparation of APEG: The synthesis of APEG was carried out in two steps: (1) tosyl PEG was prepared by mPEG (5 g, 1 mmol) and TsCl (0.382 g, 2 mmol) in the presence of Et_3N and CH_2Cl_2. The solution was then dialyzed against deH_2O (MWCO 3.5 kDa, Spectrum Laboratories, Inc., USA) for 3 days, and finally lyophilized; (2) tosyl PEG and A were fabricated using acetonitrile solution under controlled conditions of temperature and nitrogen environment. Initially, tosyl PEG (1 g, 0.2 mmol) and A (0.045 g, 0.3 mmol) were dissolved into 200 ml of acetonitrile, and the mixture was heated at 75°C under nitrogen atmosphere for 3 days. Thereafter, the solution was allowed to cool down to room temperature, dialyzed against deH_2O using a dialysis membrane (MWCO 3.5 kDa, Spectrum Laboratories, Inc., Rancho Dominguez, CA, USA) for 3 days, and finally lyophilized for future synthesis.

2.2.3 Preparation of CD-TsCl and CD conjugated PNS: Mono-6-deoxy-6-(p-tolylsulfonyl)-CD (6-TsO-CD) was prepared as in a previous report. CD (15 g, 13.225 mmol) was suspended in 125 ml of deH_2O, followed by dropping 5 ml of NaOH solution (1.643 g, 41.063 mmol) and 7.5 ml of acetonitrile with TsCl (2.520 g, 13.225 mmol). After being cooled in an ice-water bath for 2 h, the precipitate was removed by suction filtration and the filtrate was stored in a refrigerator at 4°C overnight and dried in vacuum before using.

The conjugation of CD on PNS (PNSC) was carried out according to the following procedure. 6-TsO-CD (0.25 g) was dissolved into 50 ml of N,N-dimethyl formamide, followed by addition of PNS-NH_2. The solution was stirred at 60°C under nitrogen condition for 3 days, evaporated, precipitated in acetone, and dried in vacuum.

2.2.4 Preparation of 5-FU/PNSC@APEG: 5-FU was loaded into the PNSC by the sonication method. First, 5-FU (10 mg) and PNSC (20 mg) were dissolved in 1 ml of deH_2O and sonicated for 10 min. Next, APEG (100 mg, 25 μmol) was added into the mixture and sonicated for 10 min. The product was purified by dialysis membrane against deH_2O (MWCO 50 kDa, Spectrum Laboratories, Inc., Rancho Dominguez, CA, USA) and then lyophilized.

2.2.5 Characterization: ^1H NMR spectra were obtained on a Mercury 400 MHz (Varian Co., Palo Alto, CA, USA) spectrometer. XRD was performed using a Rigaku DMAX 2200PC (Rigaku Americas Co., Woodlands, TX, USA) diffractometer equipped with Cu/Kα radiation at a scanning rate of 4°/min (λ = 0.15405 nm, 40 kV, 40 mA). FT-IR spectra were recorded on a Bruker Equinox 55 FT-IR (Bruker Optics, Billerica, MA, USA) spectrometer. Morphology and size of particles were imaged by 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. TGA was carried out using a TG analyzer (Pyris 1 TGA Perkin Elmer, MA, USA).

2.2.6 5-FU loading contents and *in vitro* 5-FU release: The drug loading efficiency (DLE) and drug loading content (DLC) were quantified by high performance liquid chromatography (HPLC, HP 50 Quaternary Pump) and presented by Eqs. (1) and (2), respectively:

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

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

The *in vitro* 5-FU release experiments were performed in phosphate buffer saline (PBS) (0.01 M, pH 7.4) at 37°C using the dialysis method. First, 1 ml of 5-FU/PNSC@APEG suspended in PBS (5-FU content, 0.3 mg/ml) was transferred to a dialysis bag (MWCO 12–14 kDa, Spectrum Laboratories, Inc., Rancho Dominguez, CA, USA) and then immersed it into 14 ml of the release medium in vials at 37°C. The vials were then placed in an orbital shaker bath, which was maintained at 37°C and shaken horizontally at 100 rpm. At specific time intervals, 14 ml of the release medium was collected and an equal volume of fresh medium was added. After lyophilization of the collected medium, the released amounts of 5-FU were determined HPLC [19, 20].

2.2.7 MTT viability test: The MTT assay was used to determine cytotoxicity of 5-FU loaded PNSC@APEG on mouse NIH3T3 cells. These cells were seeded in a 96-well plate at a density of 1×10^4 cells/well in 130 μl of Dulbecco's Modified Eagle's medium supplemented with 10% FBS and 1% penicillin-streptomycin, and cultured for 1 day at 37°C. Then, the medium was removed and the cells were incubated with samples. The cells were incubated for 48 h, followed by removal of medium, and washing twice with PBS. MTT solution (25 μl) and culture medium (130 μl) were added into each well and the cells were cultured for 3 h. DMSO (130 μl) was added into each well to dissolve the precipitate. The cells cultured with medium only were used as a control and assigned to 100% survival. The absorbance was measured at 570 nm using a multi-plate reader (SpectraMax M2e, Molecular Devices Co., USA) [20–23].

3 Results and discussion

The 6-TsO-CD and APEG were characterized by ^1H NMR spectroscopy (Figure 2). The ^1H NMR spectrum of 6-TsO-CD (Figure 2A) has peaks at 7.74 (Ar), 5.7–5.6 (CH-OH), 4.8–4.7 (CH-O), 4.5–4.4 (CH_2-O), 3.6–3.4 and 3.6–3.2 (CHO, overlaps with HOD), and 2.4 (3H). The presence of all

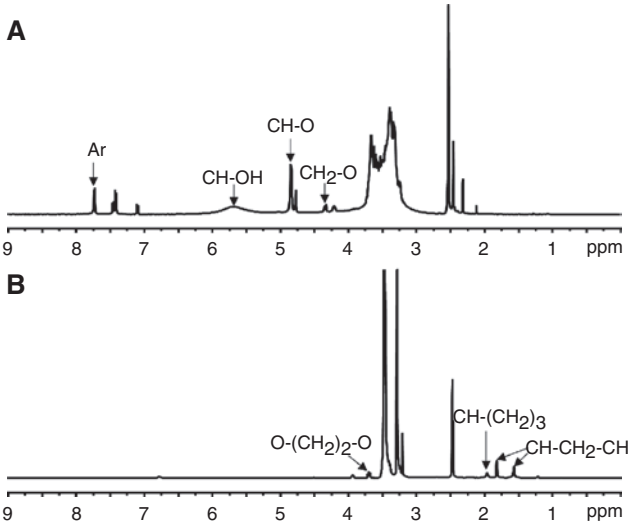

Figure 2: ^{1}H Nuclear magnetic resonance (NMR) (DMSO-d6, δ in ppm) spectra of (A) mono-6-deoxy-6-(p-tolylsulfonyl)-CD (6-TsO-CD) and (B) adamantylamine-polyethylene glycol (APEG).

the resonance signals indicates that 6-TsO-CD were successfully prepared. Besides, Figure 2B shows the ^{1}H NMR of APEG in which the resonance signals appear at 3.67 (O-[CH_2]$_2$-O), 1.91 (CH-[CH_2]$_3$), 1.75 (CH-CH_2-CH), and 1.50 (CH-CH_2-CH). These results demonstrate that A was conjugated to mPEG.

The XRD diagrams of PNS and PNSC are shown in Figure 3A. A strong road peak located at 22° (2θ) confirms the amorphous nature of silica particles. There are no significant differences in the diffraction peak positions of PNS and PNSC, indicating a stable structure of PNSC after conjugation with CD. Furthermore, the pore size distributions obtained from the adsorption branch of the isotherm for the two samples are quite similar, around 4 nm (Figure 3Bi) and around 3.3 nm (Figure 3Bii). These results show that PNSC were synthesized without instability.

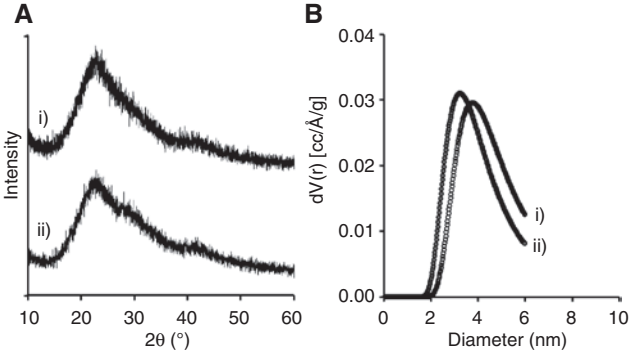

Figure 3: (A) X-ray diffraction (XRD) spectra and (B) pore size distributions of porous nanosilica (PNS) (i) and PNSC (ii).

Covalent binding of PEG to the surface of PNS was confirmed by Fourier transform infrared spectroscopy (FT-IR). The spectrum of PNS reveals vibration bands at 1160–1050 cm^{-1} (Si-OR), 1084 cm^{-1} and 806 cm^{-1} (Si-O-Si), and 950 cm^{-1} (Si-OH) (Figure 4i). After modification, the increased intensities of two new peaks at around 2880–2960 cm^{-1} and 1450–1490 cm^{-1} show the stretching and bending vibration of C-H bonds in PEG, and 1607 cm^{-1} NH-bend, respectively (Figure 4ii), and therefore PEG was conjugated to PNS.

TEM and size distributions of unmodified PNS and modified PNS (PNSC@APEG) are shown in Figure 5. Development of DDS with suitable size plays a crucial role in the field of biomedical applications by affecting the clearance and bio-distribution of particles. 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 (> 200 nm) become accumulated in the spleen or are taken up quickly by cells of the mononuclear phagocyte system. 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 the mononuclear phagocyte system for prolonging circulation times, resulting in the high-efficiency targeting of drug. Moreover, the small size of PNSC@APEG would be responsible for the enhanced permeability and retention effect results in higher particles concentration in tumor tissue. For example, the particles range from 50 nm to 200 nm and > 500 nm are easily taken up in a clathrin-mediated endocytosis and raft-dependent pathway, respectively, whereas the small particles (40–50 nm in diameter) diffuse freely on the cell surface. Importantly, the surface area of PNSC@APEG has been increased after modification, which tends to effectively absorb therapeutic agents for targeted drug

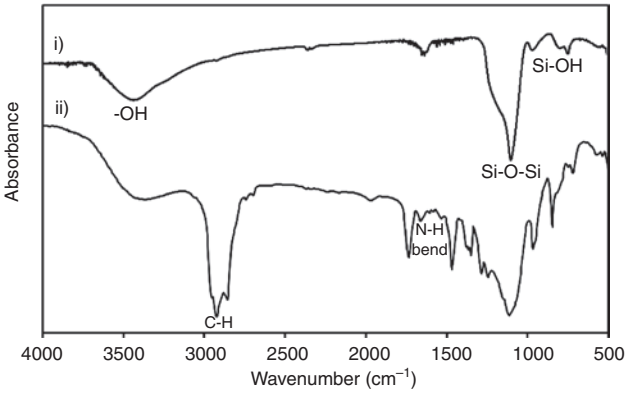

Figure 4: Fourier transform infrared (FT-IR) spectra of porous nanosilica (PNS) (i) and adamantylamine-polyethylene glycol-functioned cyclodextrin-porous nanosilica (PNSC@APEG) (ii).

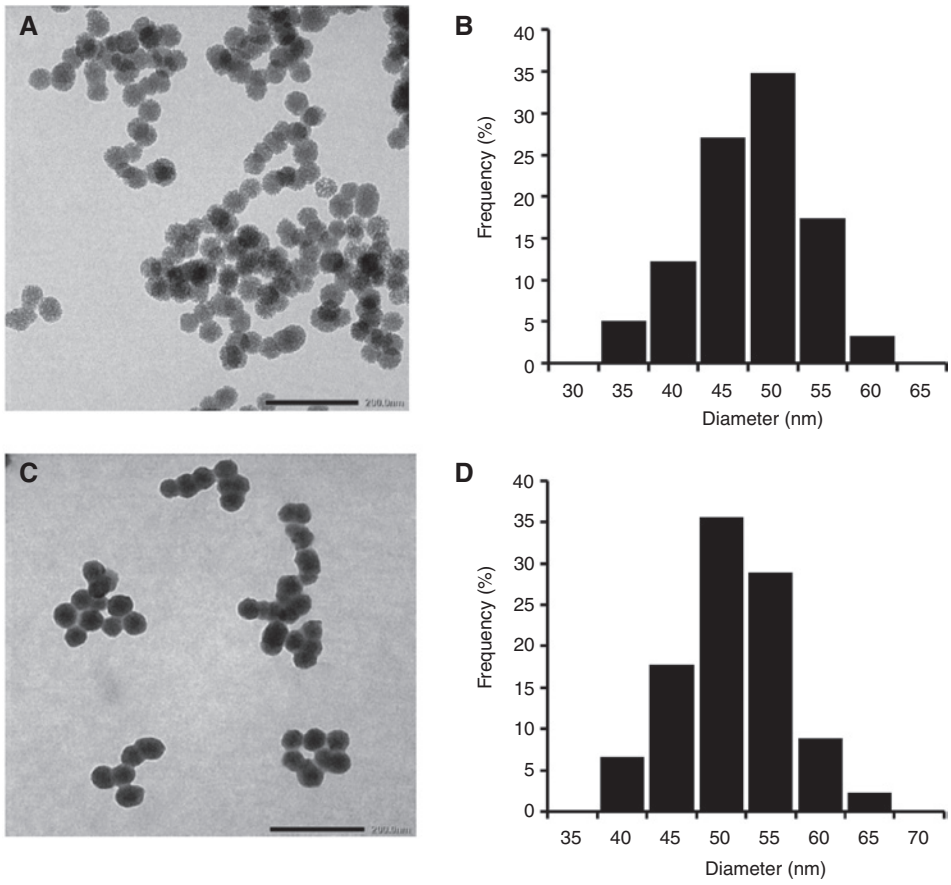

Figure 5: (A, C) Transmission electron microscopy (TEM) micrographs and (B, D) size distributions of porous nanosilica (PNS) (A, B) and adamantylamine-polyethylene glycol-functioned cyclodextrin-porous nanosilica (PNSC@APEG) (C, D).

delivery. Therefore, PNSC@APEG with spherical form and size of nearly 50 nm might serve as nanocarriers with long-term circulation in the bloodstream.

The amount of anchored PEG chains in PNS was estimated by TGA, with the temperature increased up to 800°C (Figure 6). At high temperature, the organic portion of modified PNS totally decomposes and vaporizes, leaving behind inorganic residues. The loss in weight of PNS, PNSC, and PNSC@APEG in the range of 100–200°C is due to the loss of physisorbed water. Starting at about 300°C, the slight weight loss of PNSC is shown around 4.81% corresponding to the loss of CD, whereas the PNSC@APEG sample shows the most weight loss (about 13.5%) corresponding to the loss of both organic compounds (CD) and polyether compounds (anchored PEG chains). These results indicate the existence of PEG conjugated to silica particles, PNSC@APEG.

Drug loading efficacy plays an important role in the formation of DDS and directly affects the therapeutic effect of the system. The drug-loading amounts of PNSC@APEG were determined by HPLC and the results showed that DLC and DLE were 63.4±3.8% and 11.2±2.3%, respectively. *In vitro* release profile of 5-FU from PNSC@APEG was performed in order to evaluate the stability and release behavior of particles (Figure 7A). As shown

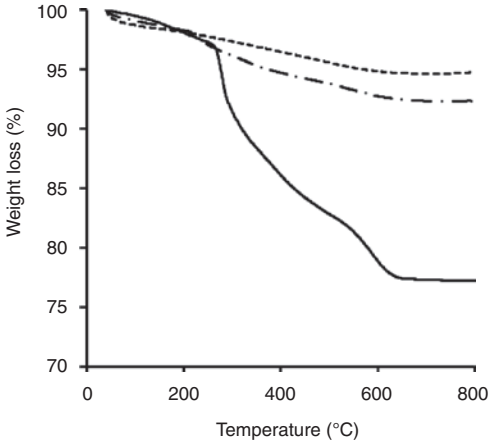

Figure 6: Thermal gravimetric analyses (TGA) curves of porous nanosilica (PNS) (square dot line), PNSC (long dast dot line), and adamantylamine-polyethylene glycol-functioned cyclodextrin-porous nanosilica (PNSC@APEG) (solid line).

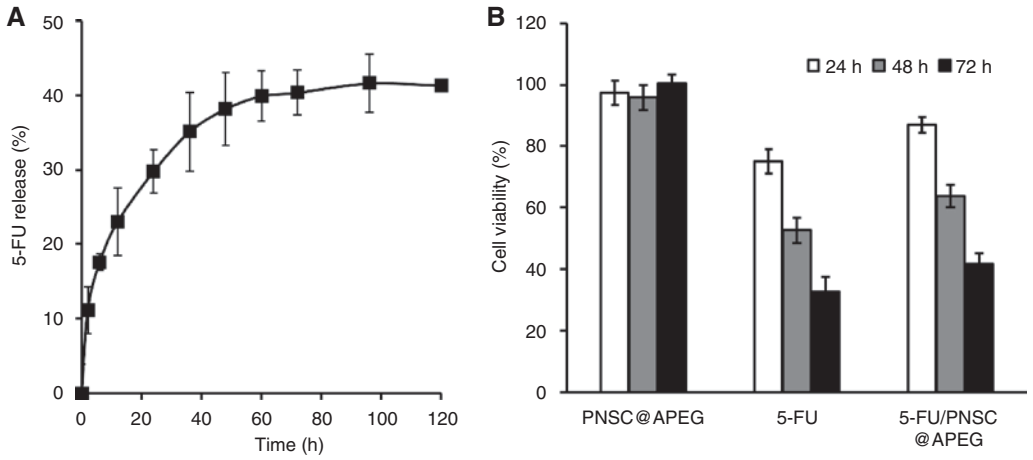

Figure 7: (A) *In vitro* release profiles of 5-fluorouracil (5-FU) from adamantylamine-polyethylene glycol-functioned cyclodextrin-porous nanosilica (PNSC@APEG) (■). (B) Toxicity profiles of samples against NIH3T3 cells by the MTT assay. Experiments were performed three times and the results are expressed as mean ± S.E. of triplicates of one representative experiment. The cells were incubated with PNSC@APEG (100 μg/ml), 5-FU (1 μg/ml), and 5-FU/PNSC@APEG at concentration of 1 μg/ml equivalents 5-FU.

in Figure 7A, more than 25% of loaded 5-FU was released for 20 h. The release behavior of 5-FU could be explained by the release of hydrophilic drug loosely bound on the surface of PNSC@APEG. After that period of time, the accumulative release rate increased up to over 40% for 80 h. In aqueous medium, the pores and hydrophilic PEG chains on the surface of PNSC@APEG are diffused through by water uptake, and therefore loosely bound drug would be delivered. Furthermore, the amount of 5-FU from PNSC@APEG from 80 h to 120 h stayed nearly the same at around 1.5%. These results suggest that PNSC@APEG nanoparticles may be possible for controlling the release rate of anticancer drugs.

Biocompatibility of a material is an important factor for its success in biomedical applications. Figure 7B shows the cytotoxicity of PNSC@APEG (100 μg/ml), 5-FU (1 μg/ml), and 5-FU/PNSC@APEG (1 μg/ml) against NIH3T3 cell lines. The results illustrate that the conjugated PNS showed no obvious cytotoxicity towards NIH3T3 cells. Almost 100% of cells were still viable at 100 μg/ml of PNSC@APEG for 3 days, indicating biocompatibility of it. In contrast, the majority of NIH3T3 cells were all killed when they were treated with 5-FU at a concentration of 1 μg/ml for 3 days. The biocompatibility of PNS and toxicity of 5-FU were consistent with previous research. It is expected that 5-FU encapsulated in PNS would reduce its toxicity. As we can see in Figure 7B, around 50% was viable at 1 μg/ml of 5-FU/PNSC@APEG. Free 5-FU was highly effective in *in vitro* experiments due to its aqueous solubility and membrane permeability. It should be noted that PNSC@APEG showed no toxicity against the cells. Therefore, the PNSC@APEG could be safely used as a drug delivery vehicle for *in vivo* applications.

4 Conclusions

In this study, spherical PNSC@APEG nanoparticles were successfully prepared with average diameter of around 50 nm. The modified PNS was capable of loading 5-FU up to 63.4 ± 3.8% and 5-FU in 5-FU/PNSC@APEG nanoparticles was slowly released. More importantly, it was clear that PNSC@APEG could reduce the toxicity of 5-FU. All these results suggest the promising application of 5-FU/PNSC@APEG nanoparticles for developing a novel DDS.

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Thi Hiep Nguyen has a PhD in Medical Science, and 10 years of experience in tissue engineering and regenerative medicine. Her research focuses on the regeneration of skin and bone, and her work has covered a full range from fabricating biomaterials to *in vitro* and *in vivo* studies. Hiep defended her PhD thesis at Soonchunhyang University in 2012 and moved to work at International University (IU), Vietnam National University, Ho Chi Minh City (VNU-HCM) until now. She currently has a senior lecturer position at IU, leads the tissue engineering and regenerative group and manages her own laboratory. Hiep is running two projects which are funded by Vietnam National University and Office of Naval Research Global. She has published 20 articles in international journals and seven articles in domestic journals. Hiep has joined more than 40 conferences so far.

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