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# Effective pH-responsive Hydrazine-Modified Silica for Doxorubicin Delivery

**Uyen Vy Vo[1,2,3], Tuong Vi Tran[1], Do Minh Thien Nguyen[1,4], Cuu Khoa Nguyen[1,2], Ngoc Tram Nguyen Thi[1,5] and Dai Hai Nguyen[1,2*]**

*[1]Institute of Applied Materials Science, Vietnam Academy of Science and Technology, 01 TL29, District 12, Ho Chi Minh City 700000, Vietnam.*
*[2]University of Science and Technology, Vietnam Academy of Science and Technology, Hanoi, Vietnam.*
*[3]Industrial University of Ho Chi Minh City, Ho Chi Minh City 700000, Vietnam.*
*[4]International University, Vietnam National University-HCMC (VNU-HCMC), HCMC 70000, Vietnam.*
*[5]Tra Vinh University, No. 126, Nguyen Thien Thanh, Ward 5, Tra Vinh City, Tra Vinh Province 940000, Vietnam.*

***Authors' contributions***

*This work was carried out in collaboration between all authors. Author UVV designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors TVT and DMTN managed the analyses of the study. Authors CKN and NTNT managed the literature searches. Author DHN managed the entire study. All authors read and approved the final manuscript.*

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## ABSTRACT

**Aims:** A type of pH-responsive porous nanosilica (PNS) for doxorubicin (DOX) delivery using Hydrazine was developed
**Study Design:** PNS was first prepared by a sol-gel method and then modified with Hydrazine via

**Corresponding author: E-mail: nguyendaihai@iams.vast.vn;*

3-glycidoxypropyltrimethoxysilane (GPTMS) as coupling agents, (PNS-GPTMS-Hydrazine) for loading of DOX (DOX/PNS-GPTMS-Hydrazine).
**Place and Duration of Study:** Department of Biomaterials & Bioengineering, Institute of Applied Materials Science, Vietnam Academy of Science and Technology, between February and June 2016.
**Methodology:** The obtained PNS-GPTMS-Hydrazine were characterized by Fourier transform infrared spectroscopy (FTIR), thermogravimetric analysis (TGA), and transmission electron microscopy (TEM). Moreover, DOX loading and release behavior of PNS-GPTMS-Hydrazine were also evaluated.
**Results:** The PNS-GPTMS-Hydrazine was successfully synthesized with spherical shape and diameter range of 45-75 nm, which was a little larger than that of PNS-GPTMS of 35-65 nm. In addition, DOX was effectively encapsulated into PNS-GPTMS-Hydrazine nanoparticles, which was approximately 61.6%, and was slowly released up to 96 h in phosphate buffer saline (PBS, pH 7.4). Especially, the modified PNS was found to be rapidly release DOX under acidic environment (PBS, pH 5.5), indicating the pH-responsive property.
**Conclusion:** These results demonstrated that PNS-GPTMS-Hydrazine can be used as an effective and pH-responsive nanocarriers for DOX delivery.

*Keywords: Porous nanosilica; hydrazine; 3-glycidoxypropyltrimethoxysilane; pH responsive; drug delivery system.*

## 1. INTRODUCTION

Discovered in 1969, doxorubicin (DOX), one of the most outstanding anticancer drugs, has been efficiently used to treat a variety of cancers. However, it has significant adverse effects, including short biological life time, dose-dependent side effects and cardiotoxicity caused by its nonspecific bio-distribution [1]. In order to overcome these limitations, the development of drug delivery systems (DDS) based on porous nanosilica (PNS) has received much more attention due to their promising properties such as high area and large pore volume, high chemical and thermal stability, and excellent biocompatibility and biodegradability [2,3]. Moreover, the guest molecules are efficiently entrapped and protected by silica matrix which are capable of preventing enzymatic degradation, induced by pH and temperature changes of the surrounding medium [4]. Despite the effectiveness of PNS on drug loading capacity, the loaded bioactive molecules would burst release and be poorly dispersible from the unmodified PNS, resulting in the loss of drug that actually reach cancer cells [5]. As a result, surface modification of PNS by polymer grafting has been widely studied, both the interfacial features of the modified nanoparticles can be engineered and the mechanical and thermal properties of the polymers can be improved at the same time. This preparation can precisely alter the release rate of drug molecules for controlled release system, instead of deciding when or where to release drug [6,7].

In recent years, stimuli-responsive PNS as programmable DDS have attracted rapidly growing interest and drug release from PNS can be triggered by using appropriate stimuli. 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) [8-12]. Among these different types of stimuli, pH stimulus has received special attention in the field of DDS because of the pH difference between tumor (pH 5-6.8) and normal tissue (pH 7.4) [5,13]. For instance, Li Yuan et al. developed doxorubicin (DOX)-loaded poly(acrylic acid) grafted PNS (PAA-PNS), DOX@PAA-PNS, as pH-responsive controlled drug systems for cancer therapy. The results indicated that the PAA-PNS are promising platforms to construct pH-responsive controlled nanocarriers for the treatment of cancer [14]. In addition, Ling Bai and co-workers synthesized pH-responsive cyclodextrin (CD)-capped PNS for DOX delivery. The CD-capped PNS showed pH-responsive release behavior and offer possibility for drug delivery uses [15]. Therefore, controlled delivery systems with pH-responsive ability have the potential to be used as safe and efficient nanocarriers to deliver drugs to specific sites within the body.

In this study, an efficient pH-responsive Hydrazine-modified PNS for DOX delivery has been achieved. In this modification, the attachment of DOX via hydrazone bond has been found to be an effective approach to improve the delivery of DOX due to the cleavage

of hydrozone linkage under the mild acidic environment to deliver DOX molecules that kill cancer cells [16]. Furthermore, the conjugation of Hydrazine and PNS were prepared using 3-glycidoxypropyltrimethoxysilane (GPTMS) as coupling agents, whose surface possesses functional epoxy groups. In detail, PNS was synthesized by the sol-gel process and the surface of these PNS was conjugated to GPTMS via Si-O-Si bridges (PNS-GPTMS), which was then modified with Hydrazine (PNS-GPTMS-Hydrazine) for DOX loading, DOX/PNS-GPTMS-Hydrazine. This study is expected to provide insights into the potential impacts of PNS-GPTMS-Hydrazine that can affect the efficacy of drug delivery.

## 2. MATERIALS AND METHODS

### 2.1 Materials

Tetraethyl orthosilicate (TEOS, 98%), aminopropyltrimethoxysilane (97%), dichloromethane ($CH_2Cl_2$, 99.8%), doxorubicin (DOX, 99%) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Cetyltrimethylammonium bromide (CTAB, 99%), hydrazine (98%), dichloromethane (≥99.8%), ammonia (99.99%), dimethyl sulfoxide (DMSO, ≥99.8%) were purchased from Merck (Darmstadt, Germany). They were all used without further purification.

### 2.2 Methods

#### 2.1.1 Preparation of PNS and PNS-GPTMS-hydrazine

Based on the literature with minor modification, PNS was synthesized by the sol-gel process in which 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 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, 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 [9].

The synthesis of PNS-GPTMS-Hydrazine was carried out in two main steps: (1) The PNS-GPTMS was prepared by stirring PNS (1 g) in toluene (30 mL) at room temperature under nitrogen environment for 30 min. Then, GPTMS was slowly added into the above solution with further stirring for 12 h under nitrogen condition. The suspension was dialyzed using a dialysis membrane (MWCO 12-14 kDa, Spectrum Laboratories, Inc., USA) against $deH_2O$ for 3 days to remove toluene. The $deH_2O$ was changed 5-6 times a day and the solution was then freeze-dried to obtain PNS-GPTMS. (2) The obtained PNS-GPTMS was dissolved in $deH_2O$, which was later added drop-wise into a hydrazine solution. This reaction was kept under constant stirring, at room temperature, and for 12 h. Thereafter, the solution was dialyzed against $deH_2O$ using dialysis membrane (MWCO 12-14 kDa) for 3 days, and finally lyophilized for obtaining PNS-GPTMS-Hydrazine.

#### 2.1.2 Preparation of DOX/PNS-GPTMS-hydrazine

DOX has been loaded into the PNS-GPTMS-Hydrazine by sonication method. DOX (18 mg) dissolved in DMSO (5 mL) and PNS-GPTMS-Hydrazine (0.2 g) dissolved in $deH_2O$ (5 mL) were added in the mixture, sonicated for 10 min, and stirred for overnight. The sample was purified by dialysis membrane (MWCO 3.5 kDa, Spectrum Laboratories, Inc., USA) against $deH_2O$ for 24 h to remove non-encapsulated drug and then lyophilized.

#### 2.1.3 Characterizations

For the purpose of investigating the presence of GPTMS and Hydrazine on the surface of PNS, Fourier transform infrared spectroscopy (FTIR) analysis (Nicolet Nexus 5700 FTIR, Thermo Electron Corporation, Waltham, MA, USA) of PNS, PNS-GPTMS, and PNS-GPTMS-Hydrazine was carried out with KBr pellets in 400-4000 $cm^{-1}$ range. The sizes and morphologies of PNS-GPTMS and PNS-GPTMS-Hydrazine were also confirmed by transmission electron microscopy (TEM, JEM-1400 TEM; JEOL, Tokyo, Japan). Moreover, thermal gravimetric analysis (TGA) was performed to investigate the thermal characteristics of PNS-GPTMS and PNS-GPTMS-Hydrazine

using TG Analyzer (Perkin Elmer Pryris 1, USA).

#### 2.1.4 DOX loading contents and *in vitro* DOX release

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:

DLE (%) = weight of drug in particles/ weight of drug feed initially × 100 (1)

DLC (%) = weight of drug in particles/ weight of particles and drug × 100 (2)

The *in vitro* DOX release experiments were performed in PBS buffer (0.01 M, pH 7.4) at 37 °C using dialysis method. First, suspension solution of DOX/PNS-GPTMS-Hydrazine in PBS (1 mL) was transferred to dialysis bags (MWCO 12-14 kDa), which were then immersed into the release 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 100 rpm. At specific time intervals, 14 mL of the release medium was collected and an equal volume of fresh media was added. The released amounts of DOX were determined using UV-Vis spectrophotometer. Particularly, to examine the pH-responsive property of DOX/PNS-GPTMS-Hydrazine, these experiments were repeated with pH 5.5 as described above.

#### 2.1.5 Statistical analysis

The data were expressed as mean ± SD. The statistical evaluation of the data was performed by analysis of variance (ANOVA) followed by Student's t-test with $p < 0.05$ considered statistically significant.

## 3. RESULTS AND DISCUSSION

The chemical structure of PNS-GPTMS-Hydrazine was determined by FTIR. As shown in Fig. 1a, the peaks at around 1083 $cm^{-1}$ and 870 $cm^{-1}$ were assigned to asymmetric stretching vibration of Si-O-Si bond and skeleton vibration involving C-O bond stretching of PNS, respectively. Moreover, the spectrum of PNS reveals vibrations bands at 3425 $cm^{-1}$, which was attributed to the OH group on the surface of PNS. These absorption groups in PNS still existed after surface coating with GPTMS and Hydrazine, indicating that both PNS-GPTMS and PNS-GPTMS-Hydrazine still keep the mesoporous structure of PNS. In the FTIR spectrum of PNS-GPTMS (Fig. 1b), the absorption peak at 917 $cm^{-1}$ was attributed to the epoxy group. Other peaks at 2417 $cm^{-1}$ and 2333 $cm^{-1}$ were found to correspond to C-H stretching vibration of PNS-GPTMS. These results demonstrated that GPTMS was conjugated on the surface of PNS. Moreover, the FTIR spectrum of PNS-GPTMS-Hydrazine also shows abroad peaks corresponding to the stretching of hydroxyl (-OH) and amine (-NH) groups at 3400-3500 $cm^{-1}$ and 2917 $cm^{-1}$ of Hydrazine monohydrate. Taken together it was clearly that PNS-GPTMS-Hydrazine was successfully synthesized.

The amount of GPTMS and Hydrazine on the surface of PNS nanoparticles was estimated by TGA (Fig. 2). The experimental temperature was ramped to 800°C with heating rate at 10°C/min. At a high temperature, an organic portion decomposes and vaporizes, leaving behind inorganic residues. As shown in the TGA curve of PNS-GPTMS, staring at about 145$^{o}$C, the slight weight loss of the sample was observed, which was assigned to the loss of physiorbed water, whereas in the range of 150°C-600°C it showed the most weight loss (approximately 11.94%) referring to the loss of GPTMS. These results confirmed the existence of GPTMS on the surface of PNS. Additionally, the weight loss profile of PNS-GPTMS-Hydrazine was significantly different. The weight loss of PNS-GPTMS-Hydrazine in the range of 150°C-600°C was shown around 13.31% corresponding to the loss of either GPTMS or Hydrazine, and was higher than the weight loss of PNS-GPTMS, around 1.373%. It is stated that Hydrazine was conjugated onto the PNS-GPTMS surface.

TEM images and size distributions of PNS-GPTMS and PNS-GPTMS-Hydrazine are shown in Fig. 3. Development of DDS with suitable size plays an important role in the field of biomedical applications by affecting the clearance and bio-distribution of particles. Several early studies have reported that the cellular uptake efficiency of nanoparticles decreases when increasing the particle size. Nanoparticles in the range of 100-200 nm have the highest potential to extend circulation time because they are large enough to avoid selective uptake in the liver, but small enough to avoid mechanical filtration by the

spleen. Besides, small size (10-100 nm) permits nanoparticles passively target tumor cells through the enhanced permeability and retention (EPR) effect, enhancing intracellular accumulation and localization of nanoparticles in tumor area [17]. As shown in Fig. 3, PNS-GPTMS and PNS-GPTMS-Hydrazine were spherical in shape with diameter range of 35-60 nm and 45-70 nm, respectively. The particle size of PNS-GPTMS and PNS-GPTMS-Hydrazine were not significantly different and their distributions were quite narrow. In comparison with mean diameter of approximately 150 nm of PAA-PNS and 100 nm of CD-capped PNS, their particle size were relatively smaller [14,16]. Consequently, the modified PNS might serve as nanocarriers with long-term blood circulation.

DLE is a crucial factor in drug-loaded nanocarriers and directly affects the therapeutic effect of the system. In this study, the DLE and DLC of PNS-GPTMS-Hydrazine were found to be 61.6% and 9.98%, respectively. In comparison with other studies, Ling Huang et al. developed a multifunctional nanocarrier based on hollow mesoporous silica nanoparticles (HMSNs) for targeted cancer therapy. In which case, DOX was first loaded into HMSNs and then blocked with cytochrome C conjugated lactobionic acid (CytC-LA) via disulfide bonds and pH-disassociation boronate ester bonds (HMSNs-S-S-CPA-CytC-LA@DOX). The results showed that the drug loading degree and DLE of HMSNs-S-S-CPA-CytC-LA@DOX were around 14.73 wt% and 62.8% [18]. In other previous study by Thu Thao Nguyen Thi et al., the surface of PNS was conjugated with adamantylamine (A) via disulfide bonds (PNS-SS-A) which was functionalized with CD-heparin-polyethylene glycol (CD-HPEG), PNS-SS-A@CD-HPEG, for redox triggered DOX delivery. The resulting nanoparticles had DLE and DLC of 56.2 ± 2.5% and 10.5 ± 2.8%, respectively [9]. These results implied that PNS-GPTMS-Hydrazine with the high DLE have the potential to be delivered more efficiently to tumor tissues.

As shown in Fig. 4, the release profile of DOX from PNS-GPTMS-Hydrazine was investigated in PBS at 37°C under different conditions of pH. In the condition of pH 7.4, the PNS-GPTMS-Hydrazine showed a long term stable drug release profile up to 96 h. The cumulative release amount of DOX in first 2 h was around 11% as compared with 43% of loaded DOX at pH 5.5. After 24 h, only 21% of loaded DOX at pH 7.4 was released as compared with approximately 67% at pH 5.5. Additionally, the total release amount of DOX at pH 7.4 was 27.7% after 96 h, whereas approximately 74% of DOX was released at pH 5.5. In order words, the in vitro release rate of DOX at pH 5.5 was significantly faster than pH 7.4. The release behavior of two kinds of pH conditions were consistent with other research studies [16,19]. The release of DOX could be explained by the cleavage of hydrazone bonds under acidic condition, and therefore the functionalization of Hydrazine on the surface of PNS via GPTMS might undergo pH-sensitive dissociation and accelerate the DOX release rate in the tumor sites.

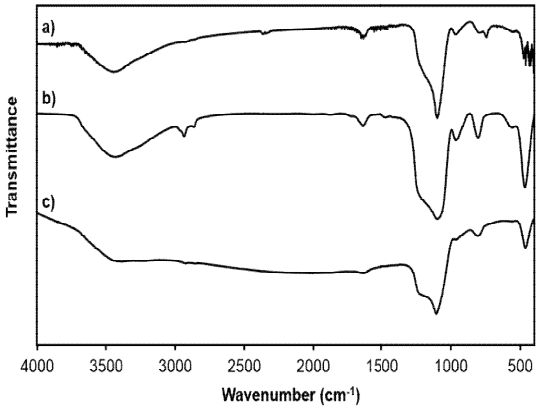


**Fig. 1. FTIR spectra of (a) PNS, (b) PNS-GPTMS and (c) PNS-GPTMS-Hydrazine**

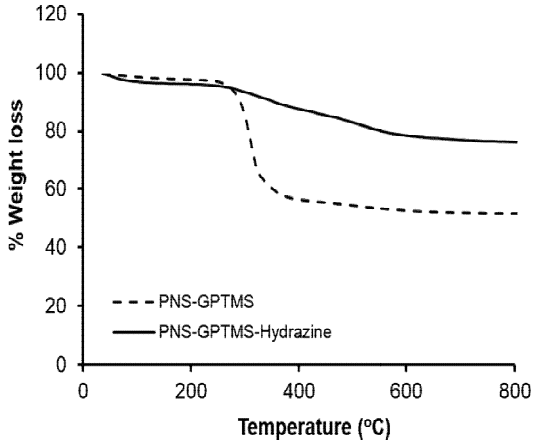


**Fig. 2. TGA curves of PNS-GPTMS and PNS-GPTMS-Hydrazine**

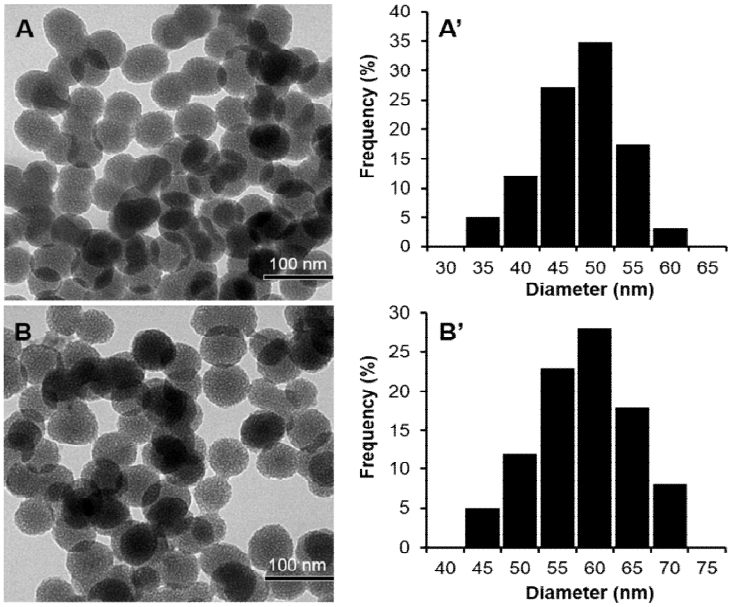


**Fig. 3. TEM images and particle size distributions of PNS-GPTMS (A, A') and PNS-GPTMS-Hydrazine (B, B'), respectively**

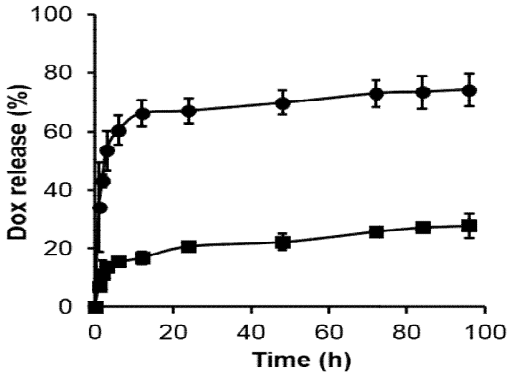


**Fig. 4. *In vitro* release profiles of PNS-GPTMS-Hydrazine in PBS at pH 7.4 (square) and pH 5.5 (circle)**

## 4. CONCLUSION

A surface modification on PNS with Hydrazine as a pH-responsive controlled release system have been successfully developed. The modified PNS was spherical in shape with range diameter of 45-75 nm, which would be suitable for the development of DDS. Besides, the modified PNS had DLE of 61.1% and DLC of 9.98% and their release profile showed sustained release of DOX in PBS at pH 7.4, compared with quickly release DOX under acidic condition (pH 5.5). As a result, the PNS-GPTMS-Hydrazine have a potential application as an effective pH-responsive DOX delivery system in the treatment of cancer.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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