Preparation of Silica Nanoparticles based Multifunctional Therapeutic Systems via One-step Mussel Inspired Modification

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Abstract

Silica nanoparticles (SiO_2 NPs) have currently drawn great attention for various biomedical applications because of their outstanding physicochemical properties such as desirable biocompatibility, chemical inert and multifunctional potential. However, to achieve the optimal performance, surface modification of SiO_2 NPs with other components is generally required. In this work, we reported a facile one-step biomimetic strategy for surface modification of SiO_2 NPs with synthetic polymers. The hydrophilic polymers (poly(PEGMA-IA-DA)) were synthesized based on free radical polymerization of polyethylene glycol methyl ether methacrylate (PEGMA) and itaconic anhydride (IA). Then dopamine hydrochloride (DA) was reacted with the pendant IA of poly(PEGMA-IA-DA) by ring opening reaction. Taken advantage of the adhesion of DA, these synthetic polymers can effectively coat on SiO_2 NPs in aqueous solution at room temperature and without using any toxic agents. On the other hand, therapeutic agents such as cisplatin (DDP) can be loaded on SiO_2 -poly(PEGMA-IA-DA) with high efficiency and showed controlled release kinetics because a large number of carboxyl groups were generated during the ring opening reaction. The results showed that SiO_2 -poly(PEGMA-IA-DA) displayed high water dispersibility, low cytotoxicity and controllable drug loading and release behavior, making them promising for multifunctional biomedical applications.

Key words: Silica nanoparticles, PEGylation, mussel inspired chemistry, drug delivery, cancer therapy

1. Introduction

Nanostructured materials have been widely applied to electronics, medical and health, spaceflight, aviation and space exploration, environmental protection, energy conversion and storage and biotechnology, et al.[1-7] As a type of inorganic nonmetal materials, silica nanoparticles (SiO_2 NPs) have exhibited many excellent physicochemical properties and been extensively explored for a variety of applications.[8, 9] Especially, the unique attraction and application prospects are shown in biological and medical fields, including biological imaging, biological sensors and controlled drug release due to their chemical stability, nontoxicity, biological inert and optical transparent.[10-18] To achieve better performance, surface functionalization of SiO_2 NPs with different functional components (e.g. polymers, fluorescent dyes and targeting agents) is generally required.[19-21] Over the past few decades, great effort has been made and different strategies have been developed for fabrication of SiO_2 NPs based nanocomposites. Among them, the hydrolysis of silane derivatives to introduce functional groups on SiO_2 NPs is frequently adopted.[22-24] These functional groups can be further utilized for bioconjugation reaction or immobilization of polymerization initiators.[25, 26] For example, Zhou et al adopted a strategy that the poly((2-Dimethylamino)ethyl methacrylate) (PDMAEMA) was grafted from the surface of silica nanoparticles via atom transfer radical polymerization (ATRP) to form pH and temperature stimuli-responsive hybrid nanoparticles.[25] Zhong et al dramatically improve mechanical property of styrene-butadiene rubber composites by surface modification of silica with N-cyclohexyl-2-benzothiazole sulfonamide.[27] Wang et al developed a simple, efficient and cost-effective approach to improve mechanical properties of SiO_2 NPs, which poly(methyl methacrylate) were grafted onto SiO_2 NPs through combining noncovalent and covalent modification process.[28] Most of the above mentioned methods are based on the hydrolysis of silane derivatives, which can introduce functional groups on SiO_2 NPs for further conjugation or polymerization reaction. Only a few reports have demonstrated surface modification of SiO_2 NPs through synthetic copolymers directly.[29]

Dopamine (DA) has demonstrated to be one of the major components of mussel adhesive proteins. It can adhere to almost any materials to form multifunctional polymer coatings through simple dip-coating of objects in an aqueous solution of DA, which will form a thin coating on the material surfaces by self-polymerization of DA under weak alkaline aqueous solution.[30-42] Taken advantage

of the strong adhesion of polydopamine (PDA), a number of multifunctional nanocomposites have been fabricated, that have exhibited good performance for environmental protection, energy storage and conversion and fabrication of biomimetic hydrogels.[43-55] Most importantly, the fabrication of PDA based luminescent nanoprobe, drug delivery systems and tumor photothermal treatment have also demonstrated recently by some groups.[56-58] These results suggested that PDA could not only provide an useful and universal platform for surface modification, but also could improve the biocompatibility of nanomaterials and endow novel function such as imaging and photothermal treatment.[58-61] Therefore, we can expect that the modification of SiO₂ NPs can be used for multifunctional therapeutic systems through mussel inspired chemistry. However, to the best of our knowledge, only very limited literatures have reported surface modification of SiO₂ NPs through mussel inspired chemistry.[62-65] The fabrication of multifunctional SiO₂ NPs based nanotherapeutic systems has not been reported thus far.

In this contribution, we proposed a rapid and eco-friendly bioinspired method for surface modification of SiO₂ NPs. The detailed experimental procedure for synthesis of the poly(PEGMA-IA-DA) and fabrication of SiO₂-poly(PEGMA-IA-DA) have shown in **Scheme 1**. First, PEGMA and IA were copolymerized by free radical polymerization, and then DA was reacted with the anhydride of IA to form poly(PEGMA-IA-DA) based on ring opening reaction. Finally, the polymers poly(PEGMA-IA-DA) were facilely coated on SiO₂ NPs take advantage of the adhesion of DA to acquire the final products (SiO₂-poly(PEGMA-IA-DA)). Apart from PEGMA, a large number of carboxyl groups can be introduced on SiO₂ NPs, which can be utilized for high efficient loading the model tumor therapeutic agent cisplatin (DDP). DDP served as a hydrophobic drug, has been widely used in medical industry. However, the applications had a limited efficacy because of poor solubility and burst effect that have lowered its treatment outcome. In recent years, DDP was introduced into nanomaterials and served as an approach to ameliorate the poor water solubility, adjust DDP release behavior.[66, 67] The successful preparation of these multifunctional SiO₂ NPs based nanocomposites was confirmed by a number of characterization techniques. The DDP loading and release behavior, cell viability of SiO₂-poly(PEGMA-IA-DA) as well as therapeutic effects of SiO₂-poly(PEGMA-IA-DA)-DDP were also evaluated. Our results suggested that SiO₂ NPs can be facilely modified by these synthetic polymers through mussel inspired chemistry. And these

functionalized nanocomposites (SiO_2 -poly(PEGMA-IA-DA)) showed improved water dispersibility, good biocompatibility, high drug loading efficiency as well as controlled drug release behavior, making them promising for controlled drug delivery applications.

Scheme 1. Schematic illustration for the preparation of PEGMA-IA-DA functionalized SiO_2 NPs by mussel inspired chemistry. The highly efficient loading of anticancer drug (DDP) onto the modified nanoparticles (SiO_2 -poly(PEGMA-IA-DA)) and controlled release of them from SiO_2 -poly(PEGMA-IA-DA)-DDP was also determined.

2 Experiment sections

2.1. Materials and characterization

All of the chemical reagents are analytically pure and without further purification. SiO_2 NPs were synthesized according to the stöber method.[9] In brief, 2.5 mL of TEOS was rapidly added into the mixture solution, which contained 27.5 mL ethanol, 22.5 mL H_2O , and 7.5 mL ammonium. Dopamine hydrochloride (DA, MW: 189.64 Da, >98%) were purchased from company of Sangon Biotech. Tris hydroxyl methyl aminomethan (Tris), poly (ethylene glycol) methyl ether methacrylate (PEGMA, 60 MW: 950 Da, 98%), itaconic anhydride (IA, MW: 112.19 Da, 96%), 2,2-Azodiisobutyronitrile (AIBN, MW: 164.21 Da, 98%) were supplied from Aladdin (Shanghai, China). Anhydrous ethyl acetate and methanol were offered by Heowns (Tianjin, China). Cisplatin (DDP, MW: 300.1 Da) was provided from Chengdu Huaxia chemical reagent co., LTD. ^1H nuclear magnetic resonance (^1H NMR) spectra were recorded on Bruker Avance-400 spectrometer with CDCl_3 as the solvent. The morphology, size and degree of uniformity were characterized by transmission

electron microscopy (TEM, Hitachi 7650B, Japan) Fourier transform infrared spectra (FT-IR) were obtained by using a Nicolet 380 spectrometer (Thermo Scientific Brand, America) and used to confirm the structure composition and chemical functional groups of modified SiO₂-poly(PEGMA-IA-DA). Thermal gravimetric analysis (TGA) and DTA data were obtained from TGA Q50 (TA instrument, USA). The X-ray photoelectron spectra (XPS) were performed on a VGESCALAB 220-IXL spectrometer (Thermo Fisher, USA) using an Al K α X-ray source (1486.6 eV). The energy scale was internally calibrated by referencing to the binding energy (Eb) of the C1s peak of a carbon contaminant at 284.6 eV.

2.2. Synthesis of poly (PEGMA-IA-DA)

The synthesis procedures of poly(PEGMA-IA-DA) copolymer were described as follow: 680 mg PEGMA, 120 mg IA and 33 mg AIBN were dissolved in 50 mL anhydrous ethyl acetate solution and stirring at 80 °C for 24 h, filling with dry N₂ and sealing. After 24 h, the DA dissolved in 10 mL methanol was injected into sealed system and maintain 2 h. The acquired crude products were purified by dialysis against deionized water for 2 days, and were soaked in ethyl alcohol for 2 h. The final polymers were dried in a vacuum oven at 40 °C for 24 h.

2.3 Preparation of SiO₂-poly(PEGMA-IA-DA) NPs

The SiO₂ NPs were modified with poly(PEGMA-IA-DA) by mussel-inspired chemistry. Briefly, 100 mg SiO₂ NPs were put into 100 mL of Tris buffer solution (pH = 8.5) and ultrasonic treatment for 10 min. Later, poly(PEGMA-IA-DA) was dissolved in Tris buffer solution (pH = 8.5) and injected into the SiO₂ NPs, and stirred at room temperature for 12 h, SiO₂-poly(PEGMA-IA-DA) nanocomposites were separated by centrifugation at 6000 rpm for 10 min. The modified SiO₂ NPs were washed and centrifuged repeatedly three times using deionized water and dried in vacuum drying oven at 40 °C for 12 h.

2.4 Drug loading capacity in SiO₂-poly(PEGMA-IA-DA)

Loading of DDP: Typically, 15 mg dry SiO₂-poly(PEGMA-IA-DA) nanoparticles and 5 mg DDP was dispersed in 100 mL of phosphate buffered saline (PBS) (pH = 7.4) under stirring at room temperature 48 h. After the mixture were centrifugated to collect the sediments of DDP-loaded SiO₂-poly(PEGMA-IA-DA) while centrifugal liquid was preserved with avoiding light, respectively.

The amount of DDP loaded on the SiO₂-poly(PEGMA-IA-DA) was monitored by an UV–visible spectrophotometer (TU-1810, China) at 710 nm (comparing with DDP calibration curve).[68]

The drug loading content (DLC) was calculated according the following equation.

$$\text{DLC}(\%, \text{DDP}) = \frac{M_a - M_b}{M} * 100\%$$

M_a is the initial weight of DDP (μg); M_b represents the weight of DDP in supernatant (μg) and M is the weight of drug loaded nanoparticles (μg)

2.5 Release of DDP from SiO₂-poly(PEGMA-IA-DA)-DDP complexes

The *in vitro* release of DDP from the drug-loaded vesicles was evaluated by the dialysis method. The DDP-loaded nanoparticles (10.0 mg) were dissolved in the release buffer and added to 3.5 kDa dialysis tubing. The DDP-loaded nanoparticles were dialyzed against the release buffer (50 mL) (pH = 7.4 and 5.5) at 37 °C with 0.1 mL aliquots withdrawn at time intervals and replaced with fresh buffer. Measured samples (0.1 mL) were added to 5 mL of pyrocatechol (OPD) (1.2 mg mL⁻¹) and 5 mL of hydrochloric acid (pH = 6.3) and heated at 100 °C for 10 min. The amount of DDP in the samples was also determined by measuring the UV–vis absorbance at 710 nm based on the DDP standard curve. The percentage of DDP released from the DDP loaded nanoparticles was expressed as a ratio of the amount of platinum in the released solution and that in the initial sample using the following equation:[69]

$$\% \text{DDP Released} = \frac{V(t) \times C}{Z}$$

Where V_(t) is the remaining volume in the releasing container at time t (mL); C is the concentration of cisplatin determined from UV–vis measurements at 710 nm (μg mL⁻¹); Z is the total amount of cisplatin at t = 0 present in the dialysis tubings (μg).

2.6 Cell viability of SiO₂-poly(PEGMA-IA-DA) NPs

Cell viability of SiO₂-poly (PEGMA-IA-DA) NPs on A549 cells was determined by WST assay according to our previous report.[70-72] Briefly, cells were seeded in 96-well microplates at a density of 5 × 10⁴ cells mL⁻¹ in 160 μL of respective media containing 10% FBS. After 24 h of cell attachment, the cells were incubated with 10, 20, 40, 80, 120 μg mL⁻¹ SiO₂-poly(PEGMA-IA-DA) NPs for 12 and

24 h. Then nanoparticles were removed and cells were washed with PBS for three times. 10 μL of CCK-8 dye and 100 μL of DMEM cell culture media was added to each well and incubated for 2 h at 37 $^{\circ}\text{C}$. Plates were then analyzed with a microplate reader (VictorIII, Perkin-Elmer). Measurements of dye absorbance were carried out at 450 nm, with the reference wavelength at 620 nm. The values were proportional to the number of live cells. The percent reduction of WST was compared to controls (cells not exposed to nanoparticles), which represented 100% WST reduction. Three replicate wells were used for each control and test concentrations per microplate, and the experiment was repeated three times. Cell survival was expressed as absorbance relative to that of untreated controls. Results are presented as mean $\pm$ standard deviation (SD)

2.7 Cellular effects of SiO_2 -poly(PEGMA-IA-DA)-DDP

The cellular effects of SiO_2 -poly(PEGMA-IA-DA)-DDP complexes were determined using the WST assay as described above. Briefly, cells were seeded in 96-well microplates at a density of 5×10^4 cells mL^{-1} in 160 μL of respective media containing 10% FBS. After 24 h of cell attachment, the cells were incubated with 10, 20, 40, 80, 120 $\mu\text{g mL}^{-1}$ of SiO_2 -poly(PEGMA-IA-DA)-DDP complexes (the concentration of SiO_2 -poly(PEGMA-IA-DA)-DDP complexes) for 24 h. Then nanoparticles were removed and cells were washed with PBS for three times. 10 μL of CCK-8 dye and 100 μL of DMEM cell culture media were added into each well and incubated for 2 h at 37 $^{\circ}\text{C}$. Plates were then analyzed with a microplate reader (VictorIII, Perkin-Elmer). Measurements of dye absorbance were carried out at 450 nm, with the reference wavelength at 620 nm. The values were proportional to the number of live cells. The percent reduction of WST was compared to controls (cells not exposed to nanoparticles), which represented 100% WST reduction. Three replicate wells were used for each control and test concentrations per microplate, and the experiment was repeated three times. Cell survival was expressed as absorbance relative to that of untreated controls. Results are presented as mean $\pm$ standard deviation (SD).

3. Results and discussion

The synthesis of poly(PEGMA-IA-DA) copolymers was implemented as shown in **Scheme 1**. The structure of poly(PEGMA-IA-DA) copolymers was determined by ^1H NMR and showed in **Fig. 1**. First, the feature peaks of PEGMA existed at about 3.62-2.53 ppm. The characteristic information of phenyl

group located at 7.03-6.32 ppm. As a consequence, the detailed description belong to poly(PEGMA-IA-DA) could be summarized as follows: $\delta = 3.62$ ppm (NH-CH₂), $\delta = 3.28$ ppm (-O-CH₂), $\delta = 7.03$ -6.32 ppm (C₆H₅-), $\delta = 4.05$ ppm (-COO-CH₂), $\delta = 2.69$ ppm (Ph-CH₂), $\delta = 1.70$ ppm (-CH₂-CH₂-), $\delta = 1.21$ ppm (-CH₃). All the above results suggested the successful synthesis of poly(PEGMA-IA-DA).

Fig. 1 ¹H NMR spectrum of poly(PEGMA-IA-DA). The chemical structure of aromatic ring of DA and the alkyl group of PEGMA was evidenced by ¹H NMR spectrum.

In addition, the size and morphology of SiO₂ NPs and SiO₂-poly(PEGMA-IA-DA) were characterized by TEM (**Fig. 2**). First, the feature of primordial SiO₂ NPs showed spherical morphology with relatively uniform size ranged from 50 to 200 nm. However, after modifying SiO₂ NPs with poly(PEGMA-IA-DA), the morphology structure of SiO₂ NPs bring into correspondence with the original morphology (**Fig. 2B**). From **Fig. 2B**, we can easily observe that some polymer films coated on the SiO₂ NPs. The successful formation of SiO₂ NPs indicated that poly(PEGMA-IA-DA) can be successfully functionalized with SiO₂ NPs by mussel inspired chemistry.

Fig. 2 Representative TEM images of (A) SiO₂ NPs, (B) SiO₂-poly(PEGMA-IA-DA) dispersed in ethyl alcohol, scale bar = 100 nm (the inset of enlarged images) and 500 nm, respectively.

The third point is that functional groups of SiO₂ NPs and SiO₂-poly(PEGMA-IA-DA) inter-polymers were further confirmed by FT-IR spectra. The characteristic peaks of SiO₂ NPs are located at 1064.7 and 850.9 cm⁻¹, which have been displayed two strong Si-O-Si and Si-C stretching vibration bands, respectively. Nonetheless, after embellishing SiO₂ NPs with polymers of poly(PEGMA-IA-DA), a broadband appeared in the near of 3489.2 cm⁻¹, which should be thought as N-H or O-H stretching vibration. Meanwhile, strong bending vibration of -C=O at about 1740 cm⁻¹ was observed in the samples of SiO₂-poly(PEGMA-IA-DA). The results of FT-IR spectra further confirmed successful formation of SiO₂-poly(PEGMA-IA-DA).

Fig. 3 FT-IR spectra of SiO₂ NPs and SiO₂-poly(PEGMA-IA-DA) nanocomposites. Apart from the signals about the Si-O bond, many other peaks corresponding to the N-H, C=O were observed in the sample of SiO₂-poly(PEGMA-IA-DA).

The TGA curves of SiO₂ NPs and SiO₂-poly(PEGMA-IA-DA) were displayed in **Fig. 4**. On the one hand, the weight loss percentages of primordial SiO₂ NPs were 5.7% when the temperature was increased upto 600 °C, indicating that excellent thermal stability of SiO₂ NPs. On the other hand, after modified with poly(PEGMA-IA-DA), the weight loss of SiO₂-poly(PEGMA-IA-DA) was rapidly increased to 18.5% under the identical experimental conditions, symbolizing that poly(PEGMA-IA-DA) copolymers were breezily adhered to the surface of SiO₂ NPs by mussel inspired chemistry. And the net weight loss percentage of poly(PEGMA-IA-DA) on SiO₂ NPs is about 12.8%. In addition, the data of differential Thermal Analysis (DTA) can be used to assist analysis. First of all, we can observe a gradual peak was appeared around 200 °C from **Fig. 4B**. Secondly, moving from left to right across the results presented in **Fig. 4C**, we see a decent boost in performance that can be attributed to the poly(PEGMA-IA-DA) grafted onto SiO₂ NPs. Therefore the TGA and DTA data powerfully proved that poly (PEGMA-IA-DA) copolymers were successfully coated on the SiO₂ NPs through mussel inspired chemistry.

Fig. 4 TGA (A) and DTA curves (B and C) of SiO₂ NPs and SiO₂-poly(PEGMA-IA-DA).

The chemical constituents of SiO₂ NPs and SiO₂-poly(PEGMA-IA-DA) were further characterized by XPS spectra in detail. We detected several elements including silicon (Si), oxygen (O) carbon (C) and nitrogen (N) existed in bare SiO₂ NPs. As indicated by **Fig. 5A**, we could see that C, Si and O were detected in the sample of primitive SiO₂ NPs. Surprisingly, we found that C was also existed in the raw SiO₂ NPs. The element C is likely derived from the partially hydrolyzed TEOS. The existence of C was also found in the mesoporous silica nanoparticles.[63] Nevertheless, the signal of N1s was appeared in

the samples of SiO₂-poly(PEGMA-IA-DA), suggesting that SiO₂ NPs were modified with poly(PEGMA-IA-DA) prosperously. The detailed information of Si2p, O1s, C1s and N1s XPS spectra were characterized in **Fig. 5B-E**. First, we have observed the binding energy peak of Si is situated in 103.17 eV, which was considered to Si lie in SiO₂ NPs by **Fig. 5B**. Second, with regard to O1s spectra (**Fig. 5C**), the detailed information of O1s signals consist in 528.0-540.0 eV in the sample of SiO₂-poly(PEGMA-IA-DA) copolymers are much less than that of primordial SiO₂ NPs. In addition, we can clearly see that the shoulder peaks of C1s moved to the high binding energy between 286.65-286.88 eV (**Fig. 5D**). The C1s peaks of SiO₂ NPs can be considered to tetraethyl orthosilicate (TEOS). But more importantly, the peak of SiO₂-poly(PEGMA-IA-DA) of C1s at high binding energy is much powerful as compared with bare SiO₂ NPs, indicating that SiO₂ NPs can be modified with poly(PEGMA-IA-DA) through mussel inspired chemistry. There is no doubt that the enhanced peaks can be attributed to the C-O and C=O bonds of poly(PEGMA-IA-DA). No surprisingly, the forceful peaks can be attributed to the C-O and C=O bonds of poly(PEGMA-IA-DA). In **Fig. 5E**, the distinct N1s signal peak consist in 396.2-405.2 eV, which consisted in the sample of SiO₂-poly(PEGMA-IA-DA). So poly(PEGMA-IA-DA) copolymers were successfully grafted to SiO₂ NPs take advantage of the adhesion of DA.

Fig. 5 (A) the representative XPS spectra of SiO₂, and SiO₂-poly (PEGMA-IA-DA); (B) Si2p; (C) O1s; (D) C1s; (E) N1s.

The percentages of elements in bare SiO₂ NPs and modified SiO₂ NPs were calculated based on the XPS spectra. As displayed in **Table 1**, three elements of Si, C and O were found in primordial SiO₂ NPs, and percentage compositions of their percentages are 16.83%, 18.14% and 65.03%, respectively. After surface grafting with poly(PEGMA-IA-DA), the quality percentage of the Si, C, N and O were changed to 14.24%, 33.87%, 4.29% and 47.6%, respectively. The introduction of element N should be from the DA, indicating that poly(PEGMA-IA-DA) was coated SiO₂ NPs through mussel inspired chemistry. These results further demonstrated that these copolymer of poly(PEGMA-IA-DA) can be used for surface modification of SiO₂ NPs through combination of mussel inspired chemistry and free radical polymerization.

Table 1 Element contents (%) of SiO₂ NPs based on XPS analysis

Sample	Si	C	N	O
SiO ₂ NPs	16.83	18.14	0	65.03
SiO ₂ -poly(PEGMA-IA-DA)	14.24	33.87	4.29	47.6

It is well known that PEG is a hydrophilic polymer, which can not only significantly enhance the dispersibility of modified materials, but could also influence the interaction between PEGylated nanomaterials and proteins.[73] PEGylation can therefore reduce the accumulation of nanomaterials in reticuloendothelial system, prolong the blood circulation time of PEGylated nanomaterials.[74] The successful PEGylation of SiO₂ NPs through mussel inspired chemistry was also evidenced by the difference water dispersibility of bare and modified SiO₂ NPs. As shown in **Fig. S1**, the primordial SiO₂ NPs were quickly precipitated about 5 min. However, SiO₂-poly(PEGMA-IA-DA) nanoparticles are still well dispersed in water and PBS after 24 h. These results really show that the SiO₂ NPs were successfully embellished with poly(PEGMA-IA-DA) through mussel inspired chemistry. Apart from PEG and DA, other functional group such as –COOH was also introduced onto SiO₂ NPs because a large number of carboxyl groups were generated during the ring-opening reaction between DA and anhydride group. It has been widely demonstrated that the –COOH can be used for carrying anticancer drug DDP through formation of metal complexes between the –COOH and DDP. And DDP can be further controlled release from these complexes under different pH environment. Therefore, the potential application of PEGylated SiO₂ NPs for drug delivery was subsequently evaluated. We

demonstrated that DDP was easily loaded in SiO₂-poly(PEGMA-IA-DA) NPs with high DLC (26.36%) simultaneously because the chloride ligands in DDP may be substituted with carboxyl ligands in PBS medium.[75] As the control experiments, we also prepared the samples of SiO₂-poly(PEGMA-IA-DA) merely loading DDP. Accounting for the varying pH and redox potential between the extracellular and intracellular environment of tumor cells, the drug release experiment was designed and conducted by subjecting to different buffer solutions with pH values of 7.4 and 5.5. As shown in **Fig. 6**, the amount of released DDP is only 18% at pH 7.4 over a period time of 48 h. However, DDP released from the carriers at pH 5.5 was about 61.7 wt% after 48 h. All the DDP release curves approached nearly flattening after 48 h. Apparently, the release of DDP is an andante course of events, which could produce subsequent killing for the remaining cells survived from first-round attack to solve the problem of tumor cell tolerance.

Fig. 6 pH-responsive drug release profiles from the drug-loaded SiO₂-poly(PEGMA-IA-DA). It can be seen that the DDP release from SiO₂-poly(PEGMA-IA-DA)-DDP complexes is much fast in acid PBS (pH = 5.5).

The biocompatibility of SiO₂-poly(PEGMA-IA-DA) NPs was evaluated using CCK-8 assay. A549 Cells were incubated with 10-120 $\mu\text{g mL}^{-1}$ of SiO₂-poly(PEGMA-IA-DA) NPs for 12 and 24 h. Results showed that no significant cell viability decrease was observed after SiO₂-poly(PEGMA-IA-DA) NPs

incubated with A549 cells for 12 and 24 h. The cell viability is still greater than 90% even the concentration of SiO₂-poly(PEGMA-IA-DA) NPs is as high as 120 µg mL⁻¹. Based on the cell viability results, half maximal inhibitory concentration (IC₅₀) values of SiO₂-poly(PEGMA-IA-DA) NPs toward A549 cells were calculated. We demonstrated that the IC₅₀ values at 12 and 24 h are 211.1 and 185.0 µg mL⁻¹, respectively. The excellent biocompatibility of SiO₂-poly(PEGMA-IA-DA) NPs can be expected due to the bioinert of SiO₂ NPs and the nontoxic of polymers. The biocompatibility evaluation results indicated that the SiO₂-poly(PEGMA-IA-DA) NPs are promising for biomedical applications. The cellular effects of SiO₂-poly(PEGMA-IA-DA)-DDP complexes to A549 cells were also examined using CCK-8 assay. Dose-dependent cytotoxicity of SiO₂-poly(PEGMA-IA-DA)-DDP complexes toward A549 cells can be observed (**Fig. 7**). When the concentrations of SiO₂-poly(PEGMA-IA-DA) NPs are 20 and 80 µg mL⁻¹, the cell viability values are 63.66% and 20.9%, respectively. These results clearly demonstrated that the SiO₂-poly(PEGMA-IA-DA) NPs can effectively delivery of DDP into cells and potential for cancer treatment. Although great effort has been developed for surface modification of SiO₂ NPs over the past few decades, most of them are relied on the introduction of functional groups on the surface of SiO₂ NPs through the hydrolysis of silane derivates. And then surface modification of SiO₂ NPs based on these functional groups through covalent conjugation reaction or immobilization of polymerization initiators for surface initiated polymerization. These procedures are relative complex and time consuming. In this work, we reported a rather facile biomimic strategy for surface modification of SiO₂ NPs relied on the strong and universal adhesion of DA toward various materials in a “one-step” procedure. We just need mixing DA pendent polymers with SiO₂ NPs at room temperature under weak alkaline aqueous solution for a short term. The reaction is rather simple, benign and effective. More importantly, other functional components such as anhydride and –COOH can also be introduced on the surface of SiO₂ NPs, which therefore can be useful for further conjugation reaction and for high efficient loading anticancer drug (DDP).

Fig. 7 The cell viability of SiO₂-poly(PEGMA-IA-DA)-DDP toward A549 cells. The concentrations of SiO₂-poly(PEGMA-IA-DA) NPs are ranged from 10-120 $\mu\text{g mL}^{-1}$.

4. Conclusions

In summary, a novel one-step biomimic strategy was developed for surface modification of SiO₂ NPs through directly adhesion of DA-contained copolymers (poly(PEGMA-IA-DA)) with bare SiO₂ NPs. The modification procedure is rather simple, efficient and can occur under rather mild conditions (e. g. room temperature, aqueous solution, air atmosphere, short reaction time and without using metal catalysts). On the other hand, many functional components such as PEG, drug carrying group (COOH) and photothermal agents (PDA) can be integrated onto SiO₂ NPs. The obtained PEGylated SiO₂ NPs exhibited enhanced water dispersibility and high drug loading efficiency. Cell viability examination results confirmed that SiO₂-poly(PEGMA-IA-DA) NPs possess excellent biocompatibility toward A549 cells, and can effectively transport DDP into cells for cancer therapy. Combination the advantages of biomimetic strategy and excellent properties of SiO₂-poly(PEGMA-IA-DA), various multifunctional nanotherapeutic systems can thus be fabricated through the similar strategy. Some other work along this line was conducted in our lab. And the obtained SiO₂-poly(PEGMA-IA-DA) NPs are also possible for cancer photothermal treatment due to the high photothermal conversion efficiency of PDA. Therefore, we could conclude that the biomimic strategy developed in this work should be an important and useful route for fabrication of multifunctional therapeutic systems in the future.

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References

- [1] S.A. Ansari, Q. Husain, Potential applications of enzymes immobilized on/in nano materials: A review, *Biotechnol Adv* 30 (2012) 512-523.
- [2] X. Lai, J.E. Halpert, D. Wang, Recent advances in micro-/nano-structured hollow spheres for energy applications: from simple to complex systems, *Energy Environ Sci* 5 (2012) 5604-5618.
- [3] K. Ariga, H. Ito, J.P. Hill, H. Tsukube, Molecular recognition: from solution science to nano/materials technology, *Chem Soc Rev* 41 (2012) 5800-5835.
- [4] R. Weissleder, Molecular imaging in cancer, *Science* 312 (2006) 1168-1171.
- [5] N.Ž. Knežević, E. Ruiz-Hernández, W.E. Hennink, M. Vallet-Regí, Magnetic mesoporous silica-based core/shell nanoparticles for biomedical applications, *RSC Adv.* 3 (2013) 9584-9593.
- [6] Y. Liu, K. Ai, L. Lu, Polydopamine and its Derivative Materials: Synthesis and Promising Applications in Energy, Environmental, and Biomedical fields, *Chem. Rev.* (2014) DOI: 10.1021/cr400407a.
- [7] H. Li, L.-L. Tan, P. Jia, Q.-L. Li, Y.-L. Sun, J. Zhang, Y.-Q. Ning, J. Yu, Y.-W. Yang, Near-infrared light-responsive supramolecular nanovalve based on mesoporous silica-coated gold nanorods, *Chem. Sci.* 5 (2014) 2804-2808.
- [8] X. Zhang, X. Zhang, S. Wang, M. Liu, Y. Zhang, L. Tao, Y. Wei, Facile Incorporation of Aggregation-induced Emission Materials into Mesoporous Silica Nanoparticles for Intracellular Imaging and Cancer Therapy, *ACS Appl. Mater. Interf.* 5 (2013) 1943-1947.
- [9] X. Zhang, X. Zhang, B. Yang, L. Liu, J. Hui, M. Liu, Y. Chen, Y. Wei, Aggregation-induced Emission Dyes Based Luminescent Silica Nanoparticles: Facile Preparation, Biocompatibility Evaluation and Cell Imaging Applications, *RSC Adv.* 4 (2014) 10060-10066.
- [10] F. Hussain, M. Hojjati, M. Okamoto, R.E. Gorga, Review article: polymer-matrix nanocomposites, processing, manufacturing, and application: an overview, *J Compos Mater* 40 (2006) 1511-1575.
- [11] M. De, P.S. Ghosh, V.M. Rotello, Applications of nanoparticles in biology, *Adv Mater* 20 (2008) 4225-4241.
- [12] F. Tang, F. He, H. Cheng, L. Li, Self-assembly of conjugated polymer-Ag@ SiO₂ hybrid fluorescent nanoparticles for application to cellular imaging, *Langmuir* 26 (2010) 11774-11778.
- [13] N. O'Farrell, A. Houlton, B.R. Horrocks, Silicon nanoparticles: applications in cell biology and medicine, *Int J Nanomed* 1 (2006) 451.
- [14] Q.A. Pankhurst, J. Connolly, S. Jones, J. Dobson, Applications of magnetic nanoparticles in biomedicine, *J Phys D: Appl Phys* 36 (2003) R167.
- [15] C. Ma, C. Li, N. He, F. Wang, N. Ma, L. Zhang, Z. Lu, Z. Ali, Z. Xi, X. Li, Preparation and characterization of monodisperse core-shell Fe₃O₄@ SiO₂ microspheres and its application

for magnetic separation of nucleic acids from E. coli BL21, *J Biomed Nanotechnol* 8 (2012) 1000-1005.

[16] S.T. Wang, M.Y. Wang, X. Su, B.-F. Yuan, Y.-Q. Feng, Facile preparation of SiO₂/TiO₂ composite monolithic capillary column and its application in enrichment of phosphopeptides, *Anal Chem* 84 (2012) 7763-7770.

[17] T. Yu, A. Malugin, H. Ghandehari, Impact of silica nanoparticle design on cellular toxicity and hemolytic activity, *ACS nano* 5 (2011) 5717-5728.

[18] L. Tang, J. Cheng, Nonporous silica nanoparticles for nanomedicine application, *Nano Today* 8 (2013) 290-312.

[19] I. Gill, Bio-doped nanocomposite polymers: sol-gel bioencapsulates, *Chem Mater* 13 (2001) 3404-3421.

[20] Q. Huo, J. Liu, L.Q. Wang, Y. Jiang, T.N. Lambert, E. Fang, A new class of silica cross-linked micellar core-shell nanoparticles, *J Am ical Soc* 128 (2006) 6447-6453.

[21] F. Muhammad, M. Guo, W. Qi, F. Sun, A. Wang, Y. Guo, G. Zhu, pH-Triggered controlled drug release from mesoporous silica nanoparticles via intracellular dissolution of ZnO nanolids, *J. Am. Chem. Soc* 133 (2011) 8778-8781.

[22] Y. Kotsuchibashi, M. Ebara, T. Aoyagi, R. Narain, Fabrication of doubly responsive polymer functionalized silica nanoparticles via a simple thiol-ene click chemistry, *Polym. Chem.* 3 (2012) 2545-2550.

[23] T. Borase, M. Iacono, S.I. Ali, P.D. Thornton, A. Heise, Polypeptide core-shell silica nanoparticles with high grafting density by N-carboxyanhydride (NCA) ring opening polymerization as responsive materials and for bioconjugation, *Polym. Chem.* 3 (2012) 1267-1275.

[24] Y. Liu, X. Wang, W. Song, G. Wang, Synthesis and characterization of silica nanoparticles functionalized with multiple TEMPO groups and investigation on their oxidation activity, *Polym. Chem.* 6 (2015) 7514-7523.

[25] L. Zhou, W. Yuan, J. Yuan, X. Hong, Preparation of double-responsive SiO₂-g-PDMAEMA nanoparticles via ATRP, *Mater Lett* 62 (2008) 1372-1375.

[26] H. Lin, G. Zhu, J. Xing, B. Gao, S. Qiu, Polymer-Mesoporous Silica Materials Templated with an Oppositely Charged Surfactant/Polymer System for Drug Delivery, *Langmuir* 25 (2009) 10159-10164.

[27] B. Zhong, Z. Jia, Y. Luo, D. Jia, Surface modification of silica with N-cyclohexyl-2-benzothiazole sulfenamide for styrene-butadiene rubber composites with dramatically improved mechanical property, *Mater Lett* 145 (2015) 41-43.

[28] X. Wang, P. Wang, Y. Jiang, Q. Su, J. Zheng, Facile surface modification of silica nanoparticles with a combination of noncovalent and covalent methods for composites application, *Compos Sci Technol* 104 (2014) 1-8.

[29] B. Yu, D.A. Wang, Q. Ye, F. Zhou, W. Liu, Robust polydopamine nano/microcapsules and their loading and release behavior, *Chem. Commun.* (2009) 6789-6791.

[30] J. Jiang, L. Zhu, L. Zhu, B. Zhu, Y. Xu, Surface characteristics of a self-polymerized dopamine coating deposited on hydrophobic polymer films, *Langmuir* 27 (2011) 14180-14187.

- [31] H.W. Kim, B.D. McCloskey, T.H. Choi, C. Lee, M.-J. Kim, B.D. Freeman, H.B. Park, Oxygen concentration control of dopamine-induced high uniformity surface coating chemistry, *ACS Appl Mater Inter* 5 (2013) 233-238.
- [32] W.O. Yah, H. Xu, H. Soejima, W. Ma, Y. Lvov, A. Takahara, Biomimetic dopamine derivative for selective polymer modification of halloysite nanotube lumen, *J Am Chem Soc* 134 (2012) 12134-12137.
- [33] L. Zhang, J. Wu, Y. Wang, Y. Long, N. Zhao, J. Xu, Combination of bioinspiration: a general route to superhydrophobic particles, *J erican Chem Soc* 134 (2012) 9879-9881.
- [34] F. Bernsmann, V. Ball, F. Addiego, A. Ponche, M. Michel, J.J.d.A. Gracio, V. Toniazzo, D. Ruch, Dopamine– melanin film deposition depends on the used oxidant and buffer solution, *Langmuir* 27 (2011) 2819-2825.
- [35] Y. Cao, X. Zhang, L. Tao, K. Li, Z. Xue, L. Feng, Y. Wei, Mussel-inspired chemistry and michael addition reaction for efficient oil/water separation, *ACS Appl Mater Inter* 5 (2013) 4438-4442.
- [36] C. Hu, Y. Liu, Y. Yang, J. Cui, Z. Huang, Y. Wang, L. Yang, H. Wang, Y. Xiao, J. Rong, One-step preparation of nitrogen-doped graphene quantum dots from oxidized debris of graphene oxide, *J. Mater. Chem. B* 1 (2013) 39-42.
- [37] Q. Wan, M. Liu, J. Tian, F. Deng, G. Zeng, Z. Li, K. Wang, Q. Zhang, X. Zhang, Y. Wei, Surface modification of carbon nanotubes by combination of mussel inspired chemistry and SET-LRP, *Polym. Chem.* 6 (2015) 1786-1792.
- [38] Y. Shi, M. Liu, K. Wang, F. Deng, Q. Wan, Q. Huang, L. Fu, X. Zhang, Y. Wei, Bioinspired preparation of thermo-responsive graphene oxide nanocomposites in an aqueous solution, *Polym. Chem.* 6 (2015) 5876-5883.
- [39] S.M. Kang, S. Park, D. Kim, S.Y. Park, R.S. Ruoff, H. Lee, Simultaneous Reduction and Surface Functionalization of Graphene Oxide by Mussel-Inspired Chemistry, *Adv. Funct. Mater.* 21 (2011) 108-112.
- [40] Q. Wan, M. Liu, J. Tian, F. Deng, Y. Dai, K. Wang, Z. Li, Q. Zhang, X. Zhang, Y. Wei, Toward the development of versatile functionalized carbon nanotubes, *RSC Adv.* 5 (2015) 38316-38323.
- [41] X. Zhang, J. Ji, X. Zhang, B. Yang, M. Liu, W. Liu, L. Tao, Y. Chen, Y. Wei, Mussel Inspired Modification of Carbon Nanotubes Using RAFT Derived Stimuli-responsive Polymers, *RSC Adv.* 3 (2013) 21817-21823.
- [42] X. Zhang, M. Liu, Y. Zhang, B. Yang, Y. Ji, L. Feng, L. Tao, S. Li, Y. Wei, Combining Mussel-inspired Chemistry and the Michael Addition Reaction to Disperse Carbon Nanotubes, *RSC Adv.* 2 (2012) 12153-12155.
- [43] C. Wang, W. Zhu, Y. Lan, M. Zhang, T. Tian, H. Wang, G. Li, Facile Fabrication of Reactive Plasmonic Substrates for Fluorescence Enhancement via Mussel-Inspired Chemistry, *J Phys Chem C* 118 (2014) 10754-10763.
- [44] Y. Xie, C. He, L. Liu, L. Mao, K. Wang, Q. Huang, M. Liu, Q. Wan, F. Deng, H. Huang, Carbon nanotube based polymer nanocomposites: biomimic preparation and organic dye adsorption applications, *RSC Adv.* 5 (2015) 82503-82512.
- [45] Y. Xie, Q. Huang, M. Liu, K. Wang, Q. Wan, F. Deng, L. Lu, X. Zhang, Y. Wei, Mussel inspired functionalization of carbon nanotubes for heavy metal ion removal, *RSC Adv.* 5 (2015) 68430-68438.

- [46] X. Zhang, Q. Huang, M. Liu, J. Tian, G. Zeng, Z. Li, K. Wang, Q. Zhang, Q. Wan, F. Deng, Preparation of amine functionalized carbon nanotubes via a bioinspired strategy and their application in Cu^{2+} removal, *Appl. Surf. Sci.* 343 (2015) 19-27.
- [47] M.-H. Ryou, Y.M. Lee, J.-K. Park, J.W. Choi, Mussel-Inspired Polydopamine-Treated Polyethylene Separators for High-Power Li-Ion Batteries, *Adv. Mater.* 23 (2011) 3066-3070.
- [48] H. Lee, J. Rho, P.B. Messersmith, Facile conjugation of biomolecules onto surfaces via mussel adhesive protein inspired coatings, *Adv. Mater.* 21 (2009) 431-434.
- [49] K. Ai, Y. Liu, C. Ruan, L. Lu, G.M. Lu, Sp^2 C-Dominant N-Doped Carbon Sub-Micrometer Spheres with a Tunable Size: A Versatile Platform for Highly Efficient Oxygen-Reduction Catalysts, *Adv. Mater.* 25 (2013) 998-1003.
- [50] J. Ryu, S.H. Ku, H. Lee, C.B. Park, Mussel-Inspired Polydopamine Coating as a Universal Route to Hydroxyapatite Crystallization, *Adv. Funct. Mater.* 20 (2010) 2132-2139.
- [51] Y. Cao, X. Zhang, L. Tao, K. Li, Z. Xue, L. Feng, Y. Wei, Mussel-inspired Chemistry and Michael addition Reaction for Efficient Oil/water Separation, *ACS Appl. Mater. Interf.* 5 (2013) 4438-4442.
- [52] L. Xu, N. Liu, Y. Cao, F. Lu, Y. Chen, X. Zhang, L. Feng, Y. Wei, Mercury Ion Responsive Wettability and Oil Water Separation, *ACS Appl. Mater. Interf.* 6 (2014) 13324-13329.
- [53] C. Cheng, S. Li, J. Zhao, X. Li, Z. Liu, L. Ma, X. Zhang, S. Sun, C. Zhao, Biomimetic assembly of polydopamine-layer on graphene: Mechanisms, versatile 2D and 3D architectures and pollutant disposal, *Chem. Eng. J.* 228 (2013) 468-481.
- [54] J. Fu, Z. Chen, M. Wang, S. Liu, J. Zhang, J. Zhang, R. Han, Q. Xu, Adsorption of methylene blue by a high-efficiency adsorbent (polydopamine microspheres): kinetics, isotherm, thermodynamics and mechanism analysis, *Chem. Eng. J.* 259 (2015) 53-61.
- [55] H. Wu, J. Kong, X. Yao, C. Zhao, Y. Dong, X. Lu, Polydopamine-assisted attachment of β -cyclodextrin on porous electrospun fibers for water purification under highly basic condition, *Chem. Eng. J.* 270 (2015) 101-109.
- [56] M. Liu, J. Ji, X. Zhang, X. Zhang, B. Yang, F. Deng, Z. Li, K. Wang, Y. Yang, Y. Wei, Self-polymerization of dopamine and polyethyleneimine: novel fluorescent organic nanoprobes for biological imaging applications, *J. Mater. Chem. B* 3 (2015) 3476-3482.
- [57] X. Zhang, S. Wang, L. Xu, Y. Ji, L. Feng, L. Tao, S. Li, Y. Wei, Biocompatible Polydopamine Fluorescent Organic Nanoparticles: Facile Preparation and Cell Imaging, *Nanoscale* 4 (2012) 5581-5584.
- [58] Y. Liu, K. Ai, J. Liu, M. Deng, Y. He, L. Lu, Dopamine-Melanin Colloidal Nanospheres: An Efficient Near-Infrared Photothermal Therapeutic Agent for In Vivo Cancer Therapy, *Adv. Mater.* 25 (2013) 1353-1359.
- [59] Q. Wan, J. Tian, M. Liu, G. Zeng, Z. Li, K. Wang, Q. Zhang, F. Deng, X. Zhang, Y. Wei, Mussel inspired preparation of highly dispersible and biocompatible carbon nanotubes, *RSC Adv.* 5 (2015) 25329-25336.
- [60] S. Hong, K.Y. Kim, H.J. Wook, S.Y. Park, K.D. Lee, D.Y. Lee, H. Lee, Attenuation of the in vivo toxicity of biomaterials by polydopamine surface modification, *Nanomedicine* 6 (2011) 793-801.
- [61] X. Zhang, G. Zeng, J. Tian, Q. Wan, Q. Huang, K. Wang, Q. Zhang, M. Liu, F. Deng, Y. Wei, PEGylation of carbon nanotubes via mussel inspired chemistry: Preparation, characterization and biocompatibility evaluation, *Appl. Surf. Sci.* 351 (2015) 425-432.

- [62] M.-H. Ryou, J. Kim, I. Lee, S. Kim, Y.K. Jeong, S. Hong, J.H. Ryu, T.-S. Kim, J.-K. Park, H. Lee, Mussel-Inspired Adhesive Binders for High-Performance Silicon Nanoparticle Anodes in Lithium-ion Batteries, *Adv. Mater.* 25 (2013) 1571-1576.
- [63] Q. Zheng, T. Lin, H. Wu, L. Guo, P. Ye, Y. Hao, Q. Guo, J. Jiang, F. Fu, G. Chen, Mussel-inspired polydopamine coated mesoporous silica nanoparticles as pH-sensitive nanocarriers for controlled release, *Int. J. Pharmaceut.* 463 (2014) 22-26.
- [64] C. Wang, A. Braendle, M. Menyo, C. Pester, E. Perl, I. Arias, C. Hawker, D. Klinger, Catechol-based layer-by-layer assembly of composite coatings: a versatile platform to hierarchical nano-materials, *Soft Matter* 11 (2015) 6173-6178.
- [65] S. Le-Masurier, G. Gody, S. Perrier, A. Granville, One-pot polymer brush synthesis via simultaneous isocyanate coupling chemistry and Grafting from RAFT polymerization, *Polym. Chem.* 5 (2014) 2816-2823.
- [66] I.W. Hamley, PEG-peptide conjugates, *Biomacromolecules* 15 (2014) 1543-1559.
- [67] X. Wan, G. Zhang, S. Liu, pH-Disintegrable Polyelectrolyte Multilayer-Coated Mesoporous Silica Nanoparticles Exhibiting Triggered Co-Release of Cisplatin and Model Drug Molecules, *Macromol. Rapid Commun.* 32 (2011) 1082-1089.
- [68] Q. Wan, L. Mao, M. Liu, K. Wang, G. Zeng, D. Xu, H. Huang, X. Zhang, Y. Wei, Towards development of a versatile and efficient strategy for fabrication of GO based polymer nanocomposites, *Polym. Chem.* 6 (2015) 7211-7218.
- [69] S.J. Shirbin, K. Ladewig, Q. Fu, M. Klimak, X. Zhang, W. Duan, G.G. Qiao, Cisplatin-induced formation of biocompatible and biodegradable polypeptide-based vesicles for targeted anticancer drug delivery, *Biomacromolecules* 16 (2015) 2463-2474.
- [70] X. Zhang, H. Qi, S. Wang, L. Feng, Y. Ji, L. Tao, S. Li, Y. Wei, Cellular responses of aniline oligomers: a preliminary study, *Toxicol. Res.* 1 (2012) 201-205.
- [71] X. Zhang, S. Wang, M. Liu, J. Hui, B. Yang, L. Tao, Y. Wei, Surfactant-dispersed Nanodiamond: Biocompatibility Evaluation and Drug Delivery Applications, *Toxicol. Res.* 2 (2013) 335-346.
- [72] X. Zhang, M. Liu, X. Zhang, F. Deng, C. Zhou, J. Hui, W. Liu, Y. Wei, Interaction of Tannic Acid with Carbon Nanotubes: Enhancement of Dispersibility and Biocompatibility, *Toxicol. Res.* 4 (2015) 160-168.
- [73] S. Lowe, N.M. O'Brien-Simpson, L.A. Connal, Antibiofouling polymer interfaces: poly(ethylene glycol) and other promising candidates, *Polym. Chem.* 6 (2015) 198-212.
- [74] Z. Liu, C. Davis, W. Cai, L. He, X. Chen, H. Dai, Circulation and long-term fate of functionalized, biocompatible single-walled carbon nanotubes in mice probed by Raman spectroscopy, *Proc. Natl. Acad. Sci. U.S.A.* 105 (2008) 1410-1415.
- [75] K. Kataoka, A. Harada, Y. Nagasaki, Block copolymer micelles for drug delivery: design, characterization and biological significance, *Adv Drug Deliver Rev* 47 (2001) 113-131.

Biocompatible silica nanoparticles based multifunctional therapeutic systems were fabricated via a “one-step” bioinspired method and utilized for controlled drug delivery application