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Supramolecular Hybrid Hydrogel Based on Host–Guest Interaction and Its Application in Drug Delivery

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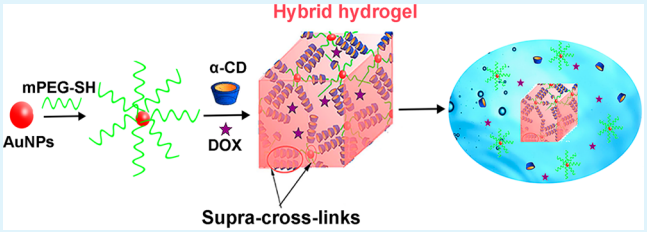
Supporting Information

ABSTRACT: In this work, we developed a simple, novel method for constructing gold nanocomposite supramolecular hybrid hydrogels for drug delivery, in which gold nanocrystals were utilized as building blocks. First, methoxypoly(ethylene glycol) thiol (mPEG-SH, molecular weight (MW) = 5 K) capped gold nanocrystals (nanospheres and nanorods) were prepared via a facile one-step ligand-exchange procedure. Then, the homogeneous supramolecular hybrid hydrogels were formed, after adding α-cyclodextrin (α-CD) into PEG-modified gold nanocrystal solutions, due to the host–guest inclusion. Both gold nanoparticles and inclusion complexes formed between α-CD and PEG chain provided the supra-cross-links, which are beneficial to the gelation formation. The resulting hybrid hydrogels were fully characterized by a combination of techniques including X-ray diffraction, rheology studies, and scanning electron microscopy. Meanwhile, the hybrid hydrogel systems demonstrated unique reversible gel–sol transition properties at a certain temperature caused by the temperature-responsive reversible supramolecular assembly. The drug delivery applications of such hybrid hydrogels were further investigated in which doxorubicin was selected as a model drug for in vitro release, cytotoxicity, and intracellular release studies. We believe that the development of such hybrid hydrogels will provide new and therapeutically useful means for medical applications.



KEYWORDS: *supramolecular hybrid hydrogel, host–guest inclusion, gold nanoparticles, drug delivery*

INTRODUCTION

Biodegradable hydrogels have been actively studied for applications in the biomedical and biotechnological fields.[1,2] To enhance their bioactivity in wound care applications, various inorganic metals have been introduced into hydrogel systems.[3,4] Obviously, application of "organic/inorganic nanocomposites" to the field of polymeric hydrogels has made great successes.[5−8] These materials combine the advantages of both the intrinsic functionalities of inorganic nanoparticles and the properties of tridimensional networks offered by hydrogels.

Gold nanoparticles (AuNPs) are the most stable metal nanoparticles and present many fascinating properties, such as size-related electronic and optical properties.[9,10] AuNPs have been successfully employed in the fields of molecular imaging,[11] surface-enhanced Raman scattering,[12] catalyzing,[13] disease diagnostics,[14] and so on. Inspired by this, researchers have tried to incorporate AuNPs into hydrogels to obtain some unique hydrogels with significant properties. Some strategies, such as physical entrapment, coprecipitation methods, in situ synthesis, and the covalent linkage, have been applied to integrate inorganic AuNPs into hydrogels.[15−17]

Supramolecular hydrogels based on host–guest interaction is of particular interest and has been extensively developed for biomedical applications such as bio/chemo- sensing,[18] controlled drug release,[19] removal of pollutants,[20] and cell culture.[21] Cyclodextrins (CDs) exhibit unique complex-forming ability, based on which they have been devoted to the design and synthesis of self-assembled hydrogels, thus greatly promoting the development of supramolecular systems and their applications in biomedicine and pharmacotherapy.[22−25] In this field, pseudopolyrotaxane (PPR) formed by threading a linear polymer chain into a series of CD cavities is one of the most well-known assemblies,[24−30] and it is also regarded as a classic and successful model applying supramolecular chemistry to self-assembly hydrogels. Strong hydrogen bonds between the adjacent PPR function as physical cross-links and further lead to microcrystalline aggregation, thus promoting physical gel formation. Our previous works have successfully prepared a kind of supramolecular hydrogel for dual cancer drug delivery, in which the PPR formed by poly(ethylene glycol) (PEG) blocks and α-CD were used as supra-cross-links.[24,25] Furthermore, utilizing PPR as supra-cross-links, a series of supramolecular hybrid hydrogels were designed and prepared based on inorganic SiO_2 nanoparticle, nanoplatelets, and so on.[28−30] However, to date, there have no reports in the

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literature on constructing PPR supramolecular hybrid hydrogels based on AuNPs.

In this work, two kinds of AuNPs were introduced as building blocks to construct hybrid hydrogels. Methoxypoly(ethylene glycol) (mPEG) chains (molecular weight (MW) = 5 K) were first anchored onto the surface of gold nanospheres (AuNS) and nanorods (AuNR) via a facile one-step ligand-exchange procedure by capping the end of mPEG with a sulfydryl group (mPEG-SH). Thus, the chains were oriented away from the surface. Such mPEG brushes were then able to thread into CDs and consequently formed hybrid PPR hydrogel. Both AuNPs and PPR all provided the supra-cross-links, which are beneficial to the hydrogel formation. The resultant hybrid hydrogels exhibit the same basic characteristics, especially shear-thinning poperty, as supramolecular physical hydrogels. In addition, the PPR hybrid hydrogels displayed a temperature-responsive gel−sol transition behavior, which is fully based on supramolecular principle. The drug-delivery applications of this hybrid hydrogels were further investigated in which doxorubicin (DOX) was selected as a model drug.

EXPERIMENTAL SECTION

Materials and Instrumentation. Methoxypoly(ethylene glycol) thiol (mPEG-SH) with a molecular weight (MW) of 5000 and polydispersity index (PDI) of 1.05 was purchased from XiaMen Sinopeg Biotech Co., Ltd. α-CD was purchased from Aladdin chemistry Co., Ltd. Hydrogen tetrachloroaurate (III) tetrahydrate ($HAuCl_4{\cdot}4H_2O$) was obtained from Shanghai Chemical Reagent CO., Ltd. Cetyltrimethylammonium bromide (CTAB, 99%) and sodium borohydride (96%) were purchased from Sinopharm Chemical Reagent CO., Ltd. Silver nitrate (99%) was purchased from Shanghai Shenbo Chemical CO., Ltd. Ascorbic acid (99%) was purchased from Tianjin Obokai Chemical CO., Ltd. Other reagents were analytical pure and used directly without further purified.

The UV−vis spectra were recorded with Lambda 35 spectrophotometer (PerkinElmer). X-ray diffraction (XRD) patterns were recorded on powdered samples of freeze-dried hydrogels by using Cu Kα irradiation with PHILIPS X'Pert PRO. The transmission electron microscopy (TEM) image was taken on an FEI-Tecnai G^2 transmission electron microscope. The dynamic and steady rheology measurements were carried out by a hakke, rs6000 rotational rheometer. The morphology of hydrogels was observed by scanning electron microscopy (SEM), and the specimens were prepared according to our previously reported method prior to analysis.[24,25] High-performance liquid chromatographic (HPLC) analysis was done to determine the cumulative percent release of DOX from hydrogels on an Agilent 1260 HPLC system that consisted of a binary solvent delivery pump, a photodiode array detector (PDA), a manual injector, and Chemstation software.

Synthesis of Gold Nanospheres (AuNS). Uniform AuNS were prepared by literature procedure.[31] Briefly, 2 mL of sodium citrate aqueous solution (51 mg/mL) was rapidly injected into a 200 mL of boiling aqueous $HAuCl_4$ (36 mg) solution under vigorous stirring. After it boiled for 15 min, the solution was cooled to room temperature. The structure of the obtained AuNS was confirmed by TEM analysis.

Synthesis of Gold Nanorods (AuNR). CTAB-stabilized AuNR (AuNR@CTAB) were synthesized by a seed-mediated growth method at 30 °C through reduction of $HAuCl_4$ with ascorbic acid in the presence of CTAB and $AgNO_3$ according to the method reported previously.[32] The solution of AuNR was purified by centrifugation (10000 rpm, 20 min) three times to remove excess CTAB, and AuNR@CTAB was collected and resuspended in an appropriate volume of distilled and deionized water for further use. The structure of the obtained AuNR was confirmed by TEM analysis.

Synthesis of AuNS-PEG. For AuNS PEGylation, a solution of mPEG-SH (100 mg) in dimethylformamide (DMF) (2 mL) was slowly added into 10 mL of the concentrated AuNS in water. The solution was stirred for 24 h at room temperature to allow the polymer to bind onto the AuNS surfaces. Then, the obtained AuNS-PEG was recovered by centrifugation at 10 000 rpm for 20 min.

Synthesis of AuNR-PEG. AuNR-PEG was prepared according to the literature procedure with a simple modification.[33] In brief, 3 mL of mPEG-SH (100 mg) water solution was added slowly into 6 mL of the concentrated AuNR@CTAB in water and stirred for 24 h at room temperature. Then, the PEG-coated gold nanorods were purified and collected by repeated centrifugation.

Formation of Hydrogels. The formation process of hybrid hydrogels is as follows: 100 mg of α-CD was added to a 0.5 mL aqueous solution of AuNS-PEG5K or AuNR-PEG5K. For encapsulating DOX, 1.0 mg of DOX, 70 mg of α-CD, and 7 mg of mPEG-SH were added into 1.0 mL of an aqueous solution of AuNS-PEG or AuNR-PEG. For all samples, the mixed solutions were ultrasonicated for 5 min and then left to stand for 72 h at room temperature prior to the measurements.[24,25,28] The encapsulation efficiency (EE) and loading efficiency (LE) of DOX on hybrid hydrogels were calculated using eqs 1 and 2, respectively.

$$EE = (m_1 - m_2)/m_1 \times 100\% \quad (1)$$

$$LE = (m_1 - m_2)/(m_1 - m_2 + m_3) \times 100\% \quad (2)$$

where m_1 is the amount of initial drug loaded in the hydrogel, m_2 is the amount of free DOX, and m_3 is the amount of hydrogel.

In Vitro Drug Release Kinetics Studies. The DOX-loaded hybrid hydrogels were prepared in l.5 mL cuvettes. For comparison, free DOX (1.0 mg) samples were also placed in 1.5 mL cuvettes under the same conditions. All cuvettes were filled with buffer solution and placed upside-down in a test tube with 30 mL of acetate buffer solution (pH 5.7) or phosphate buffer solution (PBS, pH 7.4.) and incubated in a 37 °C water bath. The buffer solution was changed in determined intervals of time. The concentrations of the DOX released were analyzed at 233 nm using an HPLC. Chromatographic separation of the DOX was achieved on an Agilent ZORBAX SB-C18 column (4.6 × 150 mm, 5 μm) at 25 °C; the mobile phase consisted of methanol−0.1% acetic acid aqueous solutions (60:40, v/v). The separation was run in isocratic mode at a flow rate of 1.0 mL/min.

Cytotoxicity Assays. The cytotoxicity of hybrid hydrogels loading DOX (1.0 mg) against A549 human lung cancer cell line was evaluated by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.[25] Briefly, cells at the exponential growth phase were harvested and seeded into a flat-bottom 96-well plate at an initial density of 5×10^4 cells/well and cultured in a 5% humidified CO_2 incubator at 37 °C for 24 h. Thereafter, the cells were treated with the lyophilized native DOX-free hybrid hydrogels and DOX-loaded hybrid hydrogels at various concentrations, in which DOX was used as a positive control. After incubation for 24 h, 20 μL of MTT solution was added to each well to continue incubating for 4 h at 37 °C. The cell viability was obtained by scanning with a microplate reader at 570 nm. The relative cell viability (%) was expressed as a percentage of that of the control culture. The experiments were carried out six times. The results presented are the average data.

RESULTS AND DISCUSSION

Synthesis of PEG-Modified Gold Nanoparticles. Uniform 14 nm AuNS were prepared by citrate reduction of $HAuCl_4$ in aqueous phase. AuNR@CTAB was synthesized by a seed-mediated growth method through reduction of $HAuCl_4$ with ascorbic acid in the presence of CTAB and $AgNO_3$ according to the well-known method.[32] The obtained nanorods have an average aspect ratio of 2.7 and a diameter of 22.2 nm. The morphology of two kinds of AuNPs was characterized by TEM (Figure 1) and UV−vis spectra (Supporting Information, Figure S1).

AuNPs with PEG brushes were synthesized through a ligand exchange reaction in which PEG were attached to gold

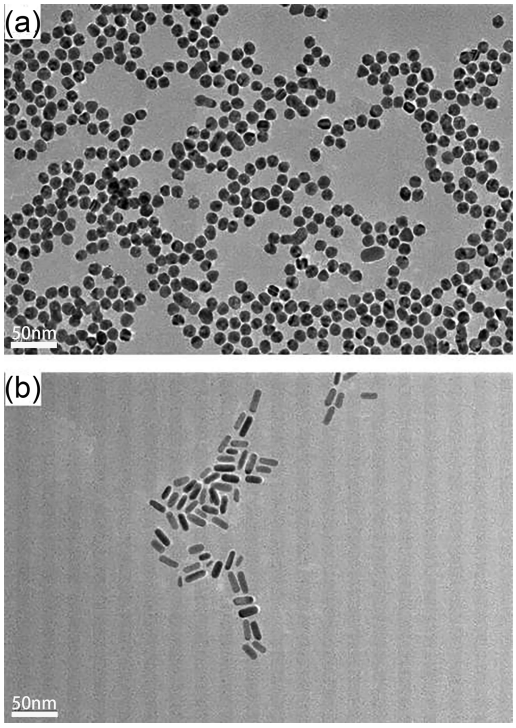

Figure 1. TEM images of gold nanospheres (a) and gold nanorod (b).

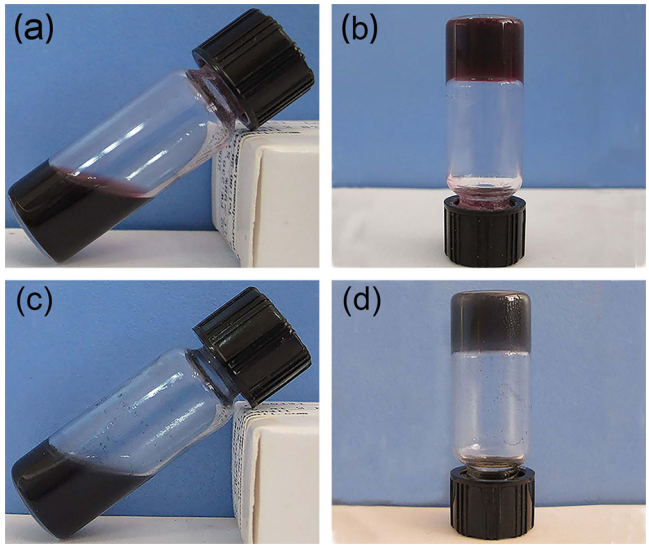

Figure 2. Optical photo of (a) AuNS-PEG5K/α-CD sols before converted to gels, (b) AuNS-PEG5K/α-CD supramolecular hydrogels, (c) AuNR-PEG5K/α-CD sols before converted to gels, (d) AuNR-PEG5K/α-CD supramolecular hydrogels. For all samples [α-CD] = (200 mg/mL).

nanocrystals (AuNS and AuNR) through covalent Au−S bonds. The surface plasmon resonance (SPR) of AuNPs is extremely sensitive to changes in the local environment surrounding the particles and to the interparticle distances. In UV−vis spectra (Supporting Information, Figure S1), the SPR band of AuNS@PEG and AuNR@PEG both have no additional broadening compared with native AuNS and AuNR, which exclude any possible aggregation of the particles upon polymer adsorption.

Formation of Hybrid Hydrogels. It is well-known that when α-CD was added to solutions of low MW mPEG, precipitation rather than a homogeneous hydrogel was formed. This precipitation has been extensively demonstrated to consist of crystalline complexes of the PEG/α-CD PPR.[25,28] Recently, it has been reported that homogeneous hydrogel could be obtained by adding α-CD to that of hydrophobic group modified low MW mPEG. It has been proven that the introduction of the hydrophobic group could partially prevent the threading of CD and may additionally provide physical cross-links based on hydrophobic aggregation.[24,25,28] In this work, we further succeeded in constructing invertible gold nanocomposites PPR hybrid hydrogels just by adding α-CD to mPEG-SH modified AuNS and AuNR solutions under the same conditions as those for hydrophobic group modified mPEG (Figure 2),[24,25,28] and the relative content of gold in AuNS and AuNR hybrid hydrogels, determined by flame atomic absorption spectrometry, was 1.9% and 1.4%, respectively. The introduction of the AuNPs is expected to function in three ways (Figure 3): (a) in preventing the complete inclusion of CD on the PEG chain, (b) in providing stable and constant physical cross-links beneficial to the hydrogel formation, and (c) in improving mechanical properties of hybrid PPR hydrogels.

After adding α-CD dilute solution to dilute mPEG5K and AuNS-PEG5K solutions, the change in turbidity of mPEG5K and AuNS-PEG5K solutions with time were investigated (Supporting Information, Figure S2). The turbidity of mPEG5K increased much faster than that of AuNS-PEG5K. The similar trend was observed as that of previously reported for hydrophobic group modified mPEG systems.[25,28] We believed that AuNS could play a similar role with hydrophobic aggregation of hydrophobic group, in which AuNS-PEG chains only could penetrate the α-CD cavities from one end of the chains because AuNS is larger than the α-CD cavities, while free mPEG5K chains do it from two ends, and the formation rate of the PPR could further affect the speed of microcrystals and turbidity increase.[25,28]

In the hydrophobic group modified PEG PPR hydrogel system, it was reported that the stable bulky hydrogel was formed when the concentration of hydrophobic group modified PEG is close to or above the critical micellization concentration (CMC).[24,25,28] That is because the aggregation of the hydrophobic blocks is an indispensable driving force for gelation process due to the fact that each of such hydrophobic domains connects many PEG chains. In this system, the introduction of AuNPs with PEG brushes not only has no effect on inclusion complexation between α-CD and PEG blocks but also provides stable and constant physical cross-links favorable to hybrid hydrogel formation. Therefore, applying PEG-modified AuNPs might be a more efficient strategy for constructing hybrid hydrogels.

Physical Properties of Hybrid Hydrogels. To further confirm the role that PPR played in the formation of hydrogels, XRD powder patterns were used to give additional information on their nanoscale structure. Pure α-CD and blank samples (mPEG5K/α-CD) were also measured by XRD. As shown in Figure 4, the pattern of AuNPs-PEG5K/α-CD hydrogels was similar to that of the mPEG5K/α-CD inclusion complexes exhibiting a sharp diffraction peak at $2\theta = 19.8°$ (in Figure 4B−D), which represents the extended channel-type structure of α-CD.[34−36] As we discussed in our previous work, this result indicated that the AuNPs-PEG5K chains in the hydrogel network are covered with α-CD, and the strong hydrogen-bond

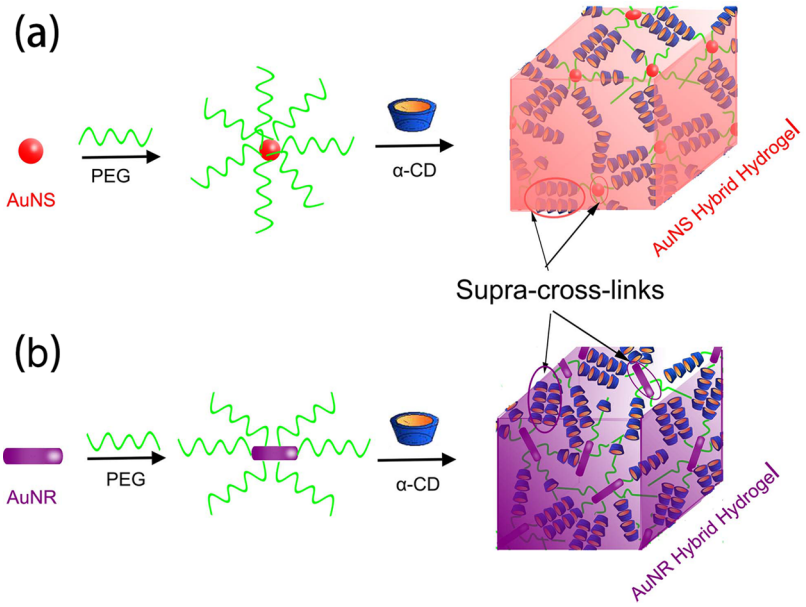

Figure 3. Schematic representation of the hybrid hydrogels made of AuNS-PEG5K/α-CD (a) and AuNR-PEG5K/α-CD (b).

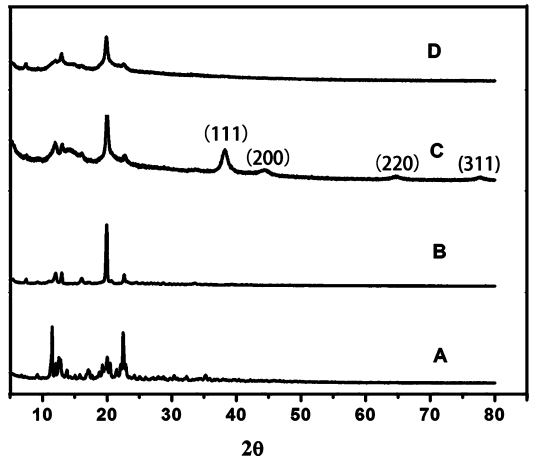

Figure 4. X-ray diffraction patterns for dried (A) pure α-CD, (B) mPEG5K/α-CD, (C) AuNS-PEG5K/α-CD hydrogels, (D) AuNR-PEG5K/α-CD hydrogels.

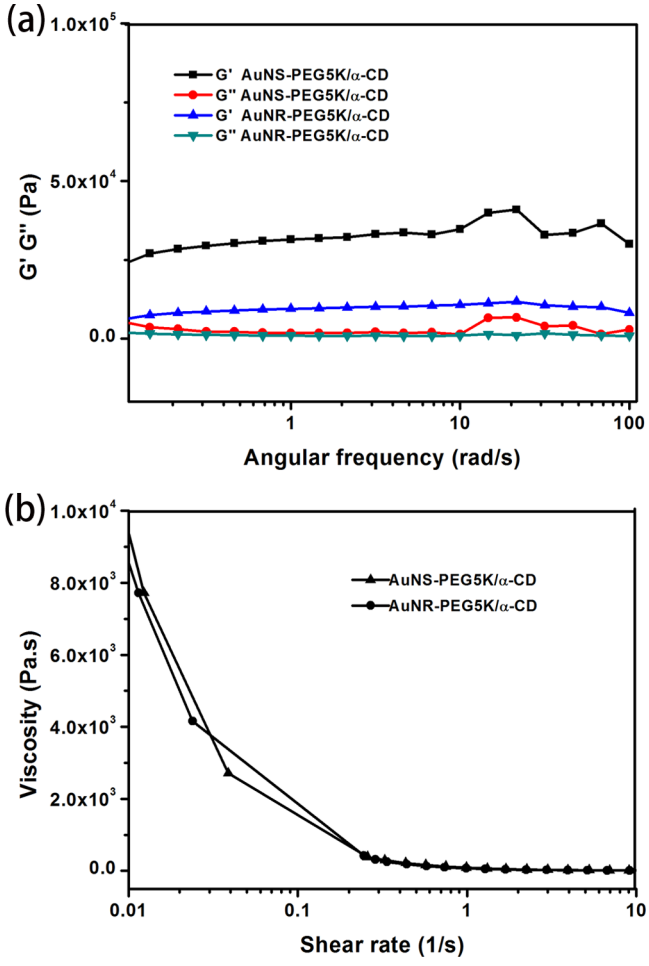

Figure 5. (a) Dynamic and (b) steady rheological behaviors of AuNS-PEG5K/α-CD and AuNR-PEG5K/α-CD hydrogels.

interaction between each PPR complex can provide supra-cross-links, which are necessary for the hydrogel formation (Figure 3).[24,25] Furthermore, in the pattern of AuNS-PEG5K/α-CD hybrid hydrogel, it showed clear peaks of AuNPs in the faced-centered cubic (fcc) structures. The peaks at 2θ = 38.1, 44.1, 64.6, and 78.7° corresponded to the reflections of crystal planes (111), (200), (220), and (311), respectively (Figure 4C). It indicated that AuNS-PEG/α-CD hybrid hydrogel consists of AuNPs.[37] However, the characteristic peaks that belong to AuNR were not found in the XRD pattern of AuNR-PEG5K/α-CD hybrid hydrogel, which may be ascribed to a relative lower content of AuNR in AuNR-PEG/α-CD hybrid hydrogel.

The introduction of AuNPs positively affects the strength of PPR hydrogels. To confirm this positive effect, the obtained hybrid hydrogel samples were measured after standing for 72 h at room temperature. As shown in Figure 5a, for both of the two hybrid hydrogels, their storage modulus (G') were greater than loss modulus (G'') indicating the formation of hybrid hydrogels. The G' of AuNS-PEG5K/α-CD and AuNR-PEG5K/α-CD hybrid hydrogels were ~30 and 10 kPa, which is ~100 orders of magnitude higher than that of reported hydrophobic group modified PEG/α-CD PPR hydrogels over a

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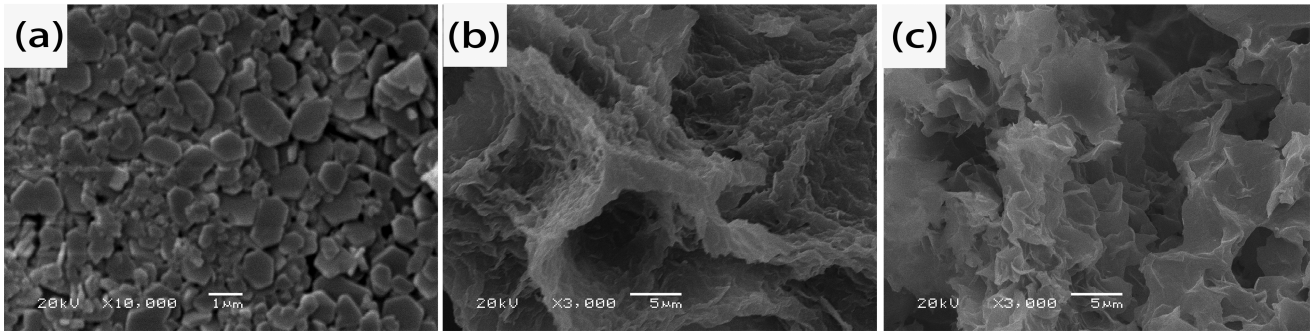

Figure 6. SEM images of (a) mPEG5K/α-CD crystal complex, (b) AuNS-PEG5K/α-CD, and (c) AuNR-PEG5K/α-CD hydrogels.

broad frequency range.[28] Furthermore, the G' of AuNS-PEG5K/α-CD hybrid hydrogels was higher than that of AuNR-PEG5K/α-CD hybrid hydrogel, which might be due to a relative higher content of gold in AuNS-PEG/α-CD hybrid hydrogel. Therefore, it can be concluded that using gold nanoparticles as the constant supra-cross-links not only provide a novel and more simple strategy to construct gold-incorporated hybrid PPR hydrogels, but also greatly improve the mechanical strength of such PPR hydrogels. Meanwhile, both the AuNS-PEG5K/α-CD and AuNR-PEG5K/α-CD hybrid hydrogels exhibit a typical shear-thinning behavior (Figure 5b), which is a required property for injectable hydrogels.[38] This shear-thinning effect can be attributed to the supra-cross-links. Under shearing, that is, partial dissociation of the inclusion complex between the PEG chain and α-CD, leads to a substantial decrease in the degree of cross-links.[24,25,27−30]

The morphology of the resulting hybrid hydrogels was also assessed by SEM using complexes formed by mPEG5K and α-CD as a comparison. Figure 6 illustrates that mPEG5K/α-CD complexes (Figure 6a) exhibit a disklike crystalline structure, while AuNS-PEG5K (Figure 6b) and AuNR-PEG5K/α-CD hydrogels (Figure 6c) display a relatively homogeneous three-dimensional gel structure. Furthermore, the obtained hybrid hydrogels exhibited a typical porous structure with smaller pore size than that of hydrophobic group modified PEG PPR hydrogel. This might be attributed to the fact that the size of AuNPs is smaller than that of hydrophobic aggregates in PPR hydrogels resulting in the increase of network density.

Temperature is one of the most widely used stimuli in environmentally responsive hydrogels system owing to its controllability and a certain practical advantages both in vitro and in vivo.[39−41] Our previous work has proven that the supramolecular hydrogels would be endowed with temperature-sensitive properties by the introduction of PPR.[24] In this work, the temperature-responsive behavior of hybrid hydrogels was also investigated. As shown in Figure 7, AuNS-PEG5K/α-CD (Figure 7a) and AuNR-PEG5K/α-CD (Figure 7b) hybrid hydrogels both exhibited a temperature-induced reversible gel−sol transition behavior with increasing or decreasing temperature. This is because the formation of PPR is a dynamic equilibrium, in which temperature plays a key role. With the change of temperature, there occurred the threading and dethreading of α-CD from PEG blocks thus leading to a reversible supramolecular assembly.

In Vitro Drug Release Kinetics Studies. As a drug carrier, the drug loading efficiency (LE) is an essential factor to evaluate the potential application of materials in drug delivery area.[42] However, in this work, higher concentration of α-CD

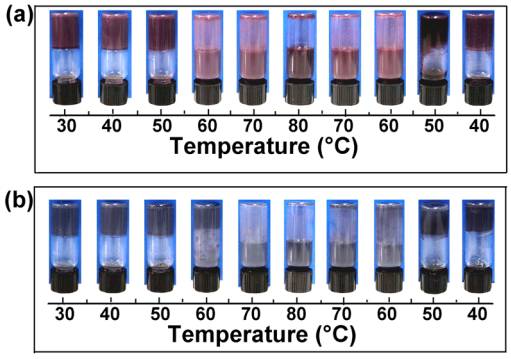

Figure 7. Temperature-induced reversible gel−sol transition observed in (a) AuNS-PEG5K/α-CD and (b) AuNR-PEG5K/α-CD hybrid hydrogels aqueous systems.

(200 mg/mL) was utilized in constructing supramolecular hybrid hydrogels compared with hydrophobic modified low MW mPEG supramolecular hydrogels. It has been reported that the formation of PPR is a dynamic equilibrium in which the movability of PEG chains, the concentration of α-CD, and the temperature all play very important roles in the self-assembly of PPR.[43,44] The size of AuNPs is much smaller than that of hydrophobic aggregates in PPR hydrogels resulting in the increase of movability of PEG chains anchored onto the surface of gold nanoparticles. In this case, a higher α-CD concentration is necessary in this system to ensure more α-CDs could penetrate the PEG chains and provide the additional supra-cross-links (Figure 3). Therefore, as a drug carrier, a small number of free mPEG-SHs was added into the system to lower the concentration of α-CD utilized in constructing hybrid hydrogels. It is surprising that more stable hybrid hydrogels were successfully obtained at low concentration of α-CD (70 mg/1.0 mL) by introducing more PEG chains into the hybrid hydrogel system. This might be accounted for by the fact that increasing PEG chains in the hybrid hydrogels system will promote the hydrogen bond interactions between adjacent PPR, which improves the stability of PPR and further promotes the formation of the hybrid hydrogels. The supramolecular hydrogels with the porous, highly hydrated, hydrophilic microstructures were further utilized for encapsulating DOX, which is a kind of classic water-soluble anticancer drug. When DOX was added into the system during the formation process of hybrid hydrogels, DOX would be entrapped into hybrid hydrogels efficiently after the hybrid hydrogels formed and the introduction of DOX exhibited no effect on the formation of hydrogels. We considered that the leading force between the hybrid hydrogels and DOX is hydrophilic interaction. The

encapsulation efficiency (EE) of DOX in AuNS-PEG/α-CD and AuNR-PEG/α-CD hydrogels was 98.4% and 100%, respectively, and the loading efficiency (LE) was 1.3% and 1.8%, respectively.

In vitro drug release behaviors of the DOX-loaded hydrogels were carried out at different pH value (acetate buffer solution, pH 5.7; PBS, pH 7.4.) at 37 °C. As shown in Figure 8a, both

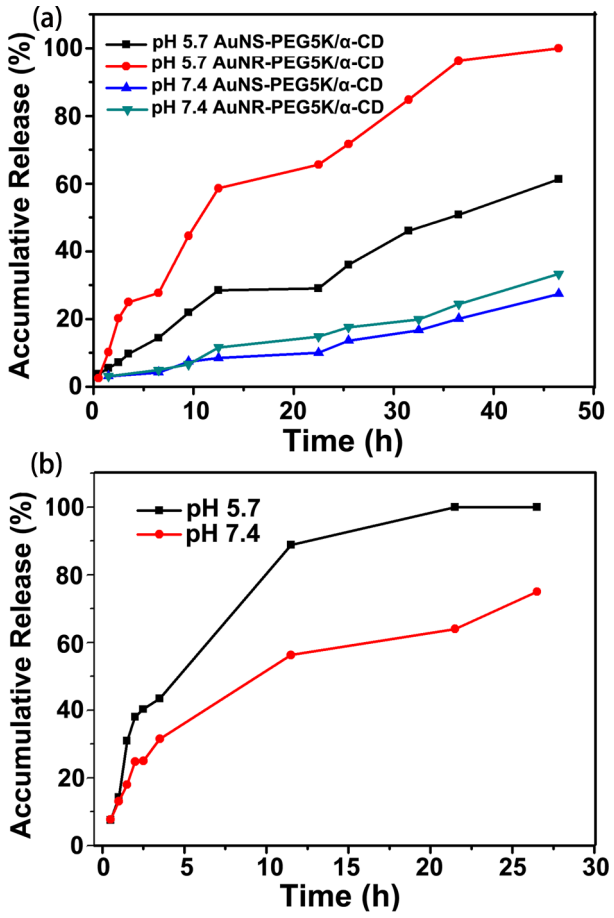

Figure 8. DOX release profiles of (a) DOX-loaded AuNS-PEG5K/α-CD and DOX-loaded AuNR-PEG5K/α-CD hydrogels at pH 5.7 and 7.4, (b) free DOX at pH 5.7 and 7.4.

hybrid hydrogels exhibited a sustained release of DOX during 30 h at pH 5.7, with the total release amount of 85% and 46% from the AuNS-PEG5K/α-CD and AuNR-PEG5K/α-CD hydrogels, respectively. However, less than 20% DOX was released from the AuNS-PEG5K/α-CD and AuNR-PEG5K/α-CD hydrogels in PBS of pH 7.4 during 30 h. DOX was released faster and more completely at lower pH value,[45,46] which showed an advantage to the DOX release from hybrid hydrogels in a acidic environment (tumor tissues). For comparison, the release behavior of free DOX was also investigated. As shown in Figure 8b, free DOX showed significantly faster release behavior at both pH 5.7 and 7.4 compared with DOX-loaded hybrid hydrogels. DOX was released from hydrogel mainly by diffusion and the internal structure change of the hybrid hydrogels. The partial erosion of the supra-cross-links that are formed by strong hydrogen-bond interaction among adjacent PPR complexes was gradually induced by a significant dethreading of α-CD from the mPEG block when the hydrogels were placed into a large amount of buffer solutions for a period of time. Consequently, the partial framework of hydrogel was gradually dissociated accompaniment of the sustained release of DOX from the hydrogel.[24,25,47]

In Vitro Cell Viability of Drug-Loaded Hybrid Hydrogels. MTT assays were employed to evaluate the in vitro cytotoxicity of free DOX, DOX-loaded AuNS-PEG5K/α-CD, and AuNR-PEG5K/α-CD hydrogels on A549 lung cancer cell lines. As shown in Figure 9, at equal doses of DOX, the

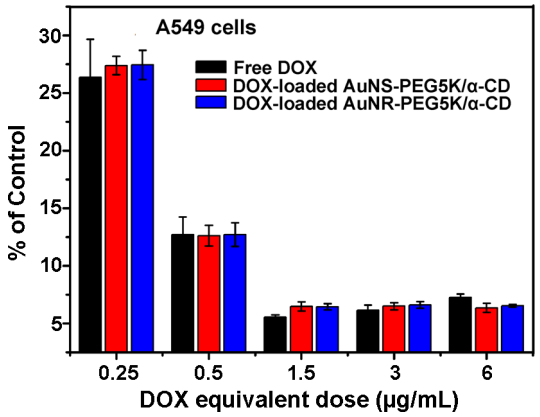

Figure 9. In vitro cytotoxicity of free DOX, DOX-loaded AuNS-PEG5K/α-CD, and DOX-loaded AuNR-PEG5K/α-CD hybrid hydrogels to A549 lung cancer cells determined by MTT assay.

cytotoxicity of DOX-loaded hydrogels was similar to free DOX in all the doses tested in A549 lung cancer cells. It indicated that the materials used for constructing hybrid PPR hydrogels have no effect on the activity of DOX, and the encapsulated DOX can still exert its activity. For comparison, the cytotoxicity of DOX-free hydrogels was also investigated on A549 lung cancer cells. As shown in Figure S3 (Supporting Information), the cell viabilities of A549 lung cancer cells were all above 80%, even the concentration of native hydrogels at 20 μg/mL. Therefore, such hybrid PPR hydrogels have promising potential for drug loading and delivery in cancer therapy.

CONCLUSIONS

In conclusion, we developed a simple, novel method for constructing gold nanocomposite supramolecular hybrid hydrogels for drug delivery. The stable hybrid hydrogels were assembled through inclusion complexation between mPEG-SH modified AuNPs and α-CD. The resultant hybrid hydrogels exhibited the same properties, especially a shear-thinning behavior necessary for drug delivery and controlled release, as supramolecular physical hydrogels. Furthermore, the introduction of AuNPs was proven effective in improving mechanical properties of PPR hydrogels. In view of its interesting temperature responsive gel−sol properties, this system could potentially serve as excellent drug carriers. We believe that the development of such hybrid hydrogels will provide new and therapeutically useful means for medical application.

ASSOCIATED CONTENT

Supporting Information

UV−vis spectra of PEG-modified gold nanoparticles, turbidity experiment, and in vitro cytotoxicity of DOX-free hydrogels. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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