

A ROS-Sensitive Diselenide-Crosslinked Polymeric Nanogel for NIR Controlled Release

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Electronic Supplementary Information

Abstract Here we report a novel polymeric nanogel with stable loading cargo and near-infrared (NIR) controlled release properties. The nanogels are crosslinked by quaternization reactions of biocompatible poly(β -amino esters) and diselenide-bonded crosslinker (DSeDCI) in microemulsions. The hydrophobic cavities of the nanogels have the property of stably encapsulating the hydrophobic guest molecules, resulted from the crosslinked network structure. Due to the redox responsiveness of the diselenide bonds on the DSeDCI crosslinker, the nanogels can respond to oxidant H_2O_2 causing the disintegration of the crosslinked network structure, thus the encapsulated guest cargo molecules will be released. It is noted that, upon loading the photosensitizer IR780, the nanogels can generate reactive oxygen species (ROS) under NIR irradiation to release the cargo. The advantages of encapsulated cargo stability enhanced by chemical cross-linking and remote stimulation response performance via NIR offer great potential of nanogels for applications of cargo controlled release.

Keywords Nanogels; NIR responsiveness; Diselenide-crosslinked; Controlled release

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INTRODUCTION

For the last few decades, smart polymer-based nanomaterials have attracted widespread attention because they provide excellent carriers for cargo delivery systems, in particular self-assembling nanomicelles with intelligent responsiveness.^[1–6] The nanomicelles could undergo volume expansion or collapse, even dissociation, triggering the carrier to unload the encapsulated guest cargo under different stimuli including pH, light, temperature, redox reactions, etc.

Recently, selenium-containing polymeric nanomaterials have attracted increasing attention due to their special electronegativity and atomic structure for their superior redox properties. A series of selenium-containing polymeric nanomicelles have been designed, which could be activated by redox substances, light or ultrasound to achieve controlled drug release.^[7–17] Shi *et al.* developed a nonionic gemini nanomicelle containing diselenide bonds that could be programmed to release loaded drugs when the micelles were exposed to H_2O_2 or 1,4-dithiothreitol in simulated tumor environments.^[8] Li *et al.* developed a selenium-containing nanomicelle, in which the diselenide bonds could be broken under γ -rays due to the production of ROS in aqueous solu-

tion.^[16] Sun *et al.* designed a hyperbranched polymer containing diselenide/porphyrin that could self-assemble into nanoparticles by emulsification, which would rupture under visible light irradiation due to the cleavage of diselenide bonds by ROS generated from porphyrins.^[17] However, there are few studies on selenium-containing polymeric nanomaterials activated by NIR light, which can penetrate deeper into tissues and is more friendly to the human body.^[18–20] Additionally, the carriers formed by self-assembled polymeric nanomicelles usually face the problem of burst release, especially below the critical micelle concentration, which may seriously limit the practical application of polymeric nanomicelles.^[21–23] In contrast, nanogels chemically cross-linked as nanocarriers could overcome the shortages. Li *et al.* designed a pH-sensitive composite nanogel for the delivery of curcumin, which had good stability before stimulation and displayed sustained release profile under low pH conditions.^[24] Qu *et al.* reported redox/pH dual-stimuli responsive camptothecin prodrug nanogels for on-demand drug delivery.^[25] In addition, our group has prepared a series of nanogels for controlled release under different stimuli such as UV light, pH, temperature, and redox.^[26,27] Yet there are few studies on nanogels stimulated by NIR light for controlled release. The construction of selenium-containing crosslinked nanoparticles activated by NIR light would be beneficial for their wide applications.

Bearing all of these in mind, here we report a novel seleni-

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um-containing crosslinked polymer nanogel PDSeNGs, which possesses the advantages of stable encapsulation of guest molecules and efficient release in response to H_2O_2 and NIR stimuli (Scheme 1). The nanogels PDSeNGs were synthesized by quaternization of biocompatible polymeric poly(β -amino ester) (PAE) and diselenide-bonded crosslinker (DSeDCI) in an oil-in-water microemulsion. The PDSeNGs have redox-responsive properties, since the diselenide bonds in the system could be chemically cleaved to generate seleninic acid in the presence of oxidant H_2O_2 , leading to the collapse of the gel and then the eventual release of the cargo. When the photosensitizer IR780 was encapsulated in the nanogels through simple hydrophobic interaction, the system could generate ROS upon irradiation with NIR to release the guest cargo. Such a NIR-controlled selenium-containing polymer nanogel may be applied widely in the field of smart drug delivery and controlled release.

EXPERIMENTAL

Materials

Selenocystamine dihydrochloride (Innochem, 97%), chloroacetyl chloride (Alfa Aesar, 99%), triethylamine (Et_3N , Innochem, 99%), hexamethylene diacrylate (HD, Energy Chemical, 99%), 1,3-bis(4-piperidyl)propane (BPP, Energy Chemical, 99%), coumarin 102 (Sigma-Aldrich, 97%), IR 780 photosensitizer (Sigma-Aldrich, 95%), sodium dodecyl sulfate (SDS, 99%) and 1,3-diphenylisobenzofuran (DPBF, Energy Chemical, 97%) were used as received without further purification.

Synthesis of Poly(β -amino ester) (PAE)

The polymer PAE was synthesized via Michael addition reaction. HD (2.26 g, 10 mmol) and BPP (2.31 g, 11 mmol) were dissolved in 40 mL of chloroform under stirring at 50 °C for 48 h. Then, the compounds were concentrated via vacuum rotary evaporator and precipitated into ice ether to remove unreacted monomers and oligomers. Finally, the polymer was placed in vacuum drying oven at 45 °C and dried for 24 h to obtain a white solid polymer of PAE (2.54 g, yield 56%).

Synthesis of ROS-Sensitive Diselenide Crosslinker DSeDCI

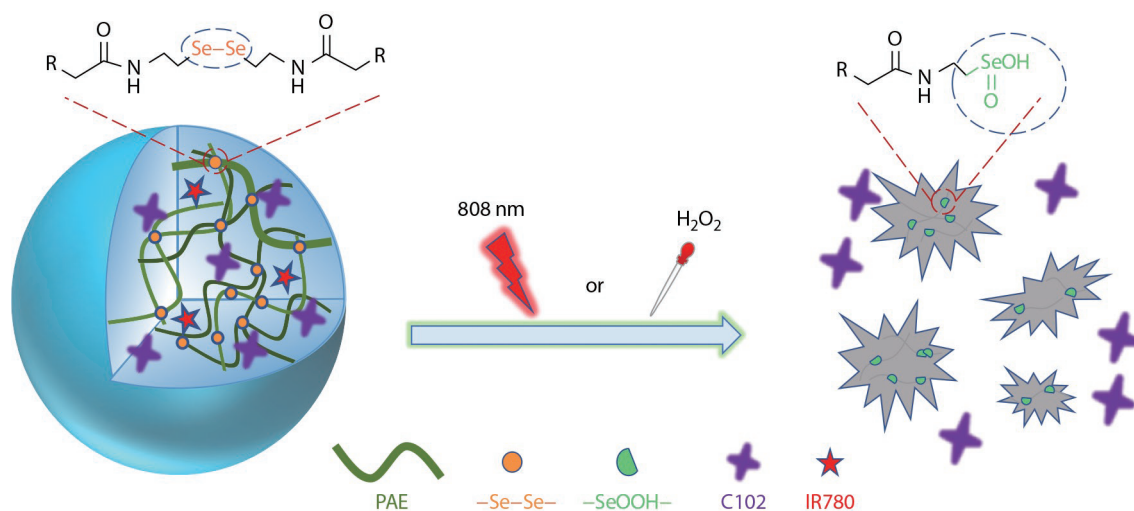
Selenocystamine dihydrochloride (0.64 g, 2 mmol) and Et_3N (0.88 g, 8.8 mmol) were dissolved in dry dichloromethane (20 mL) in a 50 mL flask and stirred for 12 h to remove the hydrochloride. Then the solution of chloroacetyl chloride (0.48 g, 4.4 mmol) in dry dichloromethane (5 mL) was added dropwise into the flask which placed in an ice/water bath over 10 min and stirring for 48 h at 25 °C. The reaction mixture was concentrated under reduced pressure via rotary evaporation. The crude product was further purified by column chromatography with mixtures of 5/1 ethyl acetate/normal hexane. After vacuum drying at 50 °C for 48 h, the neat ROS-sensitive DSeDCI crosslinker was obtained (0.34 g, yield 43%).

Preparation of Diselenide-Crosslinked Nanogels PDSeNGs

Diselenide-crosslinked PDSeNGs were prepared through a modified oil-in-water (O/W) miniemulsion method.^[26] DSeDCI (24 mg) and PAE (131 mg) were dissolved in 4 mL of toluene as the oil phase at 70 °C as per the expected 10% crosslinking pitch. SDS (40 mg) was dissolved in 30 mL of deionized water at 70 °C as the water phase. The SDS aqueous solution was dropped into the heated and stirred toluene solution under the liquid surface, and then sonicated for 2 min to form a stable oil-in-water microemulsion. After stirring the reaction at 70 °C for 24 h, the prepared PDSeNGs were purified through dialysis (cellulose membrane, molecular weight cutoff: 10k Da) against deionized water at room temperature for 48 h. Finally, the PDSeNGs product was obtained by freeze-drying (105 mg, yield 68%).

Encapsulation and Controlled Release of Coumarin 102 in Diselenide-Crosslinked Nanogels PDSeNGs

PDSeNGs (5 mg) was added to 1 mL of coumarin 102 solution (1 mg/mL in tetrahydrofuran (THF)) with constant stirring for 4 h to sufficiently dissolve and mix well. Then, 5 mL deionized water was slowly added to the above solution. The solution was continuously stirred for 72 h and filtered with 0.45 μL to give the solution contained uniform nanogels C102@PDSeNGs. Aqueous solutions of C102@PDSeNGs with H_2O_2 concentrations of 0.1,



Scheme 1 Schematic illustration of the prepared nanogel and H_2O_2 and NIR controlled release of the encapsulated guest cargo.

0.2 and 1 mmol/L were configured and tested for changes in UV-Vis spectra and fluorescence spectra immediately at 30 min intervals.

Encapsulation and Controlled Release of Coumarin 102 in Diselenide-Crosslinked Nanogels PDSeNGs with IR780

(C102+IR780)@PDSeNGs were prepared using a procedure similar to C102@PDSeNGs. The UV-Vis absorption spectra and fluorescence spectra were measured every 1 min, when (C102+IR780)@PDSeNGs was irradiated by NIR laser (808 nm, 1.5 W). Then the UV-Vis absorption spectra and fluorescence spectra were tested every 30 min after stopping irradiation.

Characterization

Proton and selenic nuclear magnetic resonance (^1H - and ^{77}Se -NMR) spectra were recorded using a Bruker Avance III (600 MHz) spectrometer in deuterated solvent. Fourier transform infrared spectroscopy (FTIR) were measured on a PerkinElmer spectrophotometer. The average molecular weight and molecular weight distribution of the polymeric PAE was recorded by gel permeation chromatography (GPC) (Waters 1515) using chloroform (HPLC grade) as the mobile phase. UV-Vis absorption spectra and fluorescence spectra were measured by T9S and F-4500 fluorescence spectrophotometer, respectively. The transmission electron microscopy (TEM) images were obtained by a JEM-2010 EX/S microscope. The dynamic light scattering (DLS) data were determined by a Zetasizer Nano ZS90 instrument. For NIR light experiments, an infrared laser (WG1233B1 fiber coupled laser system,

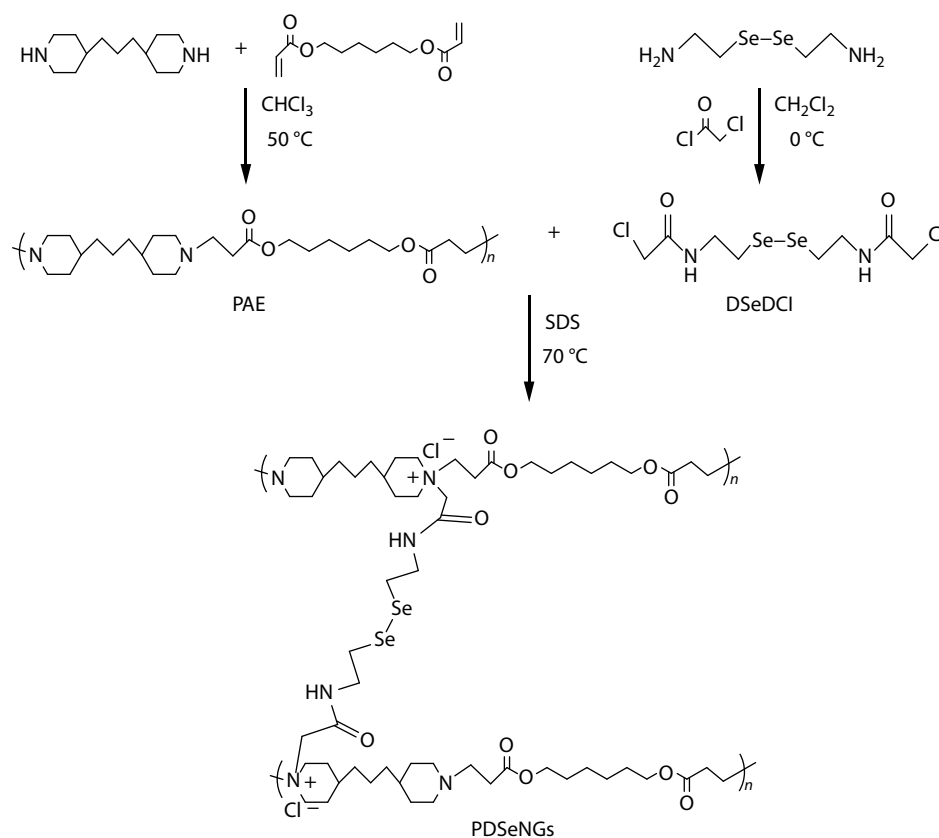
wavelength: 808 nm; power: 1.5 W/cm^2) was used.

RESULTS AND DISCUSSION

Synthesis of the ROS-Responsive Nanogels

The synthesis strategy of PDSeNGs is illustrated in Scheme 2. Firstly, the polymer PAE was synthesized from hexamethylene diacrylate and 1,3-bis(4-piperidyl)propane by Michael addition reaction. The chemical structure of PAE was confirmed by ^1H -NMR (Fig. S1 in electronic supplementary information, ESI). The number average molecular weight (M_n) and polydispersity index (PDI) of PAE were determined by GPC for $3.60 \times 10^3 \text{ g/mol}$ and 1.82, respectively (Fig. S2 in ESI). The ROS-responsive crosslinker DSeDCI was synthesized by the *N*-acylation reaction of selenocystamine dihydrochloride and chloroacetyl chloride. The chemical structure of DSeDCI was confirmed by ^1H -NMR (Fig. S3 in ESI). Finally, the final product nanogels were obtained by quaternization reaction between polymer PAE and crosslinker DSeDCI.

As shown in Fig. 1(a), the ^1H -NMR of PDSeNGs exhibited the characteristic peaks of PAE at 1.2–2.0, 2.8–3.0, 3.3, 3.5 and 4.0–4.2 ppm. Meanwhile, the characteristic peaks of DSeDCI at 3.0, 3.7 and 4.0 ppm were also observed. The crosslinked nanogels were achieved by nucleophilic substitution of the tertiary amine group on the polymer PAE and the chlorine group on the DSeDCI. By comparing the integrated areas of 3.7 (–NHCH₂–CH₂Se–) and 3.5 ppm (–NCH₂CH₂CO–), a crosslinking degree of 9.8% could be obtained accordingly. Compared to PAE, FTIR spectrum of the nanogel PDSeNGs



Scheme 2 Synthesis route to PDSeNGs.

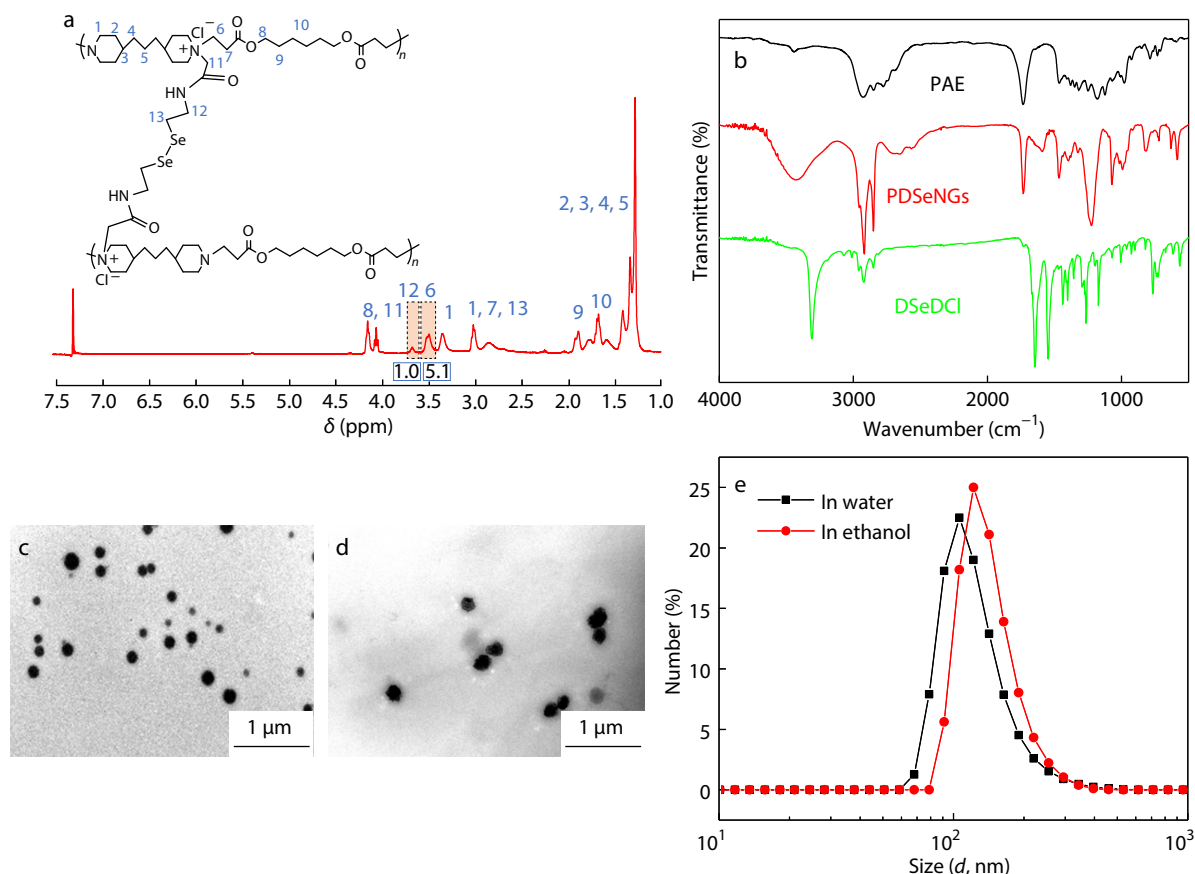


Fig. 1 (a) ¹H-NMR spectrum of PDSeNGs in CDCl₃; (b) FTIR spectra of PAE, DSeDCI and PDSeNGs; (c, d) TEM images of PDSeNGs in (c) water and (d) ethanol, respectively; (e) Hydrodynamic radius distributions of PDSeNGs in deionized water and in ethanol.

showed a strong stretching vibration band at 3400 cm⁻¹ that could be attributed to the $\text{—N}^+(\text{CH}_2)_2\text{—}$ group. The stretching vibration band at 770 cm⁻¹ of DSeDCI, which could be attributed to $\text{—CH}_2\text{Cl—}$, disappeared at the corresponding position on the nanogels after the quaternization reaction (Fig. 1b). These results proved the successful crosslinking of the polymer PAE by the diselenide-bonded crosslinker.

The morphology and size of the prepared nanogel PDSeNGs were characterized by TEM and DLS. Fig. 1(c) shows the morphology of PDSeNGs in aqueous solution as dispersed spheres with an approximate size of 95 nm. Fig. 1(d) shows the morphology of PDSeNGs in ethanol with an approximate size of 110 nm, which was slightly larger than in aqueous solution because of the better solubility of PDSeNGs in ethanol. DLS data of the nanogels in aqueous and in ethanol (Fig. 2e) show that the sizes distribution in the range of 80–160 and 90–180 nm, respectively. The sizes were larger than those measured by TEM, which could be caused by the swelling effect of nanogels in solution.

ROS Responsiveness of Selenium-Containing PDSeNGs upon H₂O₂ and NIR Stimulation

It is known that the diselenide bonds could be broken by oxidation of ROS to generate seleninic acid.^[8,11,12,14] Thus the crosslinkers of PDSeNGs containing diselenide bonds units could be activated by ROS stimulation. As shown in Fig. 2(a), ⁷⁷Se-NMR spectra of PDSeNGs indicated that the chemical shift

of PDSeNGs changed from 283 ppm to 999 ppm in the presence of H₂O₂, confirming the cleavage of the diselenide bonds to form seleninic acid. The changes of morphological and particle size of the nanogels after adding H₂O₂ were characterized by TEM and DLS, shown in Fig. 2(b), from which it can be seen that the PDSeNGs spheres could be collapsed after adding 1 mmol/L H₂O₂ and the particle size decreased to 30–60 nm. It is also well known that IR780 is a hydrophobic NIR photosensitizer, which can generate ROS under 808 nm NIR irradiation.^[28] The prepared nanogel could be imparted with NIR responsiveness by encapsulating IR780 into the hydrophobic cavity of PDSeNGs. Determined by UV-Vis spectrum, the loading content of IR780 in PDSeNGs was 5.7% (Fig. S4 in ESI). The nanogels loaded with IR780, IR780@PDSeNGs were also uniformly dispersed spheres with a diameter of approximately 120 nm (Fig. S5 in ESI). After NIR irradiation, as shown in Fig. 2(c), the nanogels underwent rupture and the particle size decreased to 30–80 nm, which could attribute to the breakage of diselenide bonds induced by ROS generated by IR780 upon NIR irradiation. The ability of IR780@PDSeNGs to generate ROS was evaluated by employing DPBF as a ROS probe. As shown in Fig. 2(d), the absorption band of DPBF centered at 410 nm gradually decreased with increasing NIR irradiation time, implying the continuous generation of ROS. As for the comparison group, the peak at 410 nm of DPBF in the absence of IR780 remained essentially unchanged (Fig. S6 in ESI). Simultaneously, the absorption band of IR780 centered at 795 nm decreased

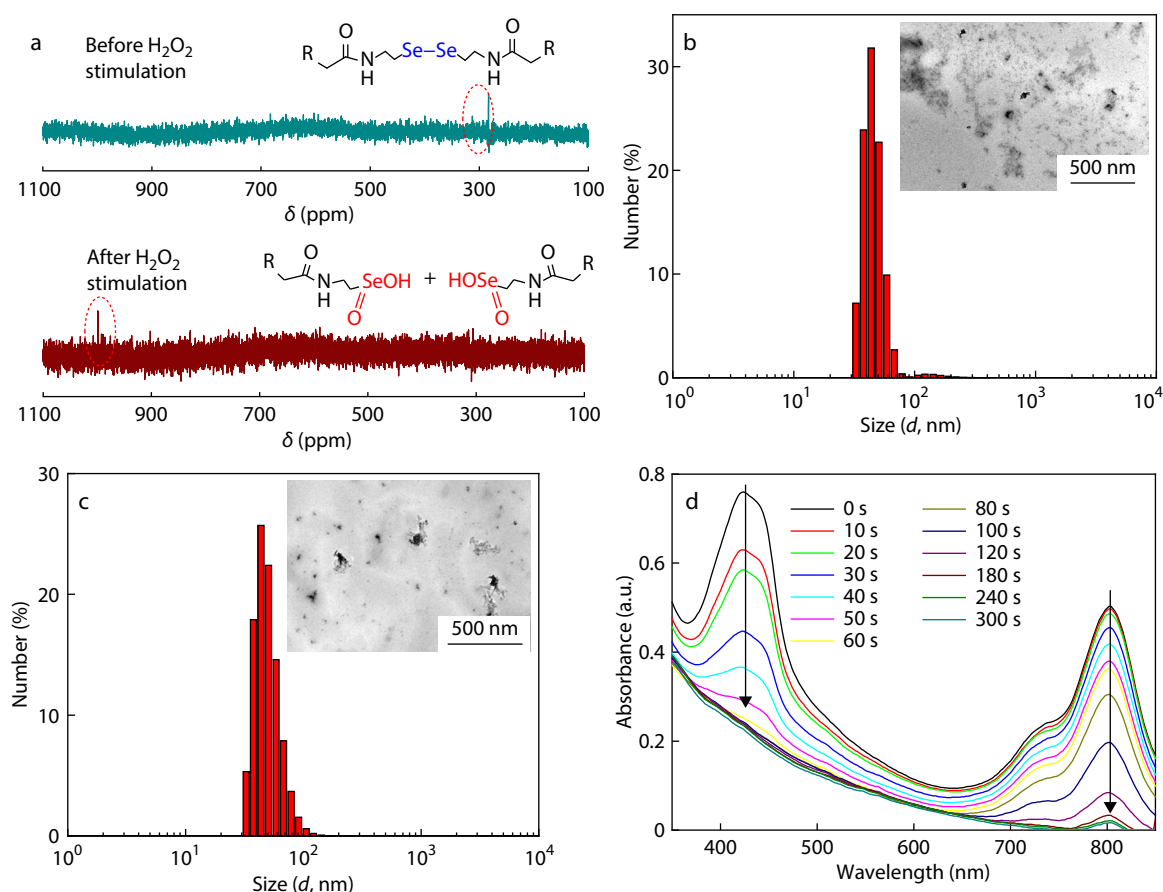


Fig. 2 (a) ^{77}Se -NMR spectra of PDSeNGs before and after H_2O_2 stimulation; (b) Size distribution for PDSeNGs in water obtained by DLS under 1 mmol/L H_2O_2 stimulation for 24 h (inset: TEM image); (c) Size distribution for IR780@PDSeNGs in water obtained by DLS under 808 nm laser irradiation (1.5 W/cm^2) for 6 min then rest for 24 h (inset: TEM image); (d) UV-Vis spectra of the system irradiated at 808 nm with different irradiation time after adding 50 μL of DPBF in THF solution (1 mg/mL) to IR780@PDSeNGs aqueous solution (1.5 W/cm^2).

gradually with increasing NIR irradiation time since IR780 could be also decomposed by the produced ROS.^[29–31]

Controlled Release of Coumarin 102 from PDSeNGs upon H_2O_2 and NIR Stimulation

The H_2O_2 /NIR responsive nanogels system could be used as smart nanocarriers for controlled release owing to the oxidative cleavage of the diselenide bonds and morphological changes upon the stimulation. Using coumarin 102 as a model molecule, the encapsulation and controlled release behaviors of dye-encapsulated nanogels PDSeNGs were investigated. Compared to the blank nanogels PDSeNGs, C102@PDSeNGs showed the absorption peak of coumarin 102 at 390 nm (Fig. S7 in ESI). Determined by UV-Vis spectra, the loading content of hydrophobic cargos was 9.5% (Fig. S4 in ESI). As a control group, the UV-Vis absorption and fluorescence spectra of C102@PDSeNGs without ROS stimulation remained basically unchanged over time (Fig. S8 in ESI). However, the absorption and fluorescence spectra changed greatly upon ROS stimulation, shown in Fig. 3. Figs. 3(a)–3(c) show the UV-Vis absorption spectra of C102@PDSeNGs treated with 0.1, 0.2 and 1 mmol/L H_2O_2 , respectively. The absorption bands of coumarin 102 decreased over time and the decrease enhanced with increasing H_2O_2 concentration. Based on the absorption changes, the release profiles are summarized, shown in Fig. 3(d), from which it can be seen that the release of coumarin 102 after

treatment with 0.1, 0.2 and 1 mmol/L H_2O_2 for 24 h were 44.8%, 61.1% and 84.9%, respectively. The result indicates that the release rate and efficiency of coumarin 102 were positively correlated with the concentration of H_2O_2 . Figs. 3(e)–3(g) show the fluorescence spectra of coumarin 102 after C102@PDSeNGs were treated with 0.1, 0.2 and 1 mmol/L H_2O_2 , respectively. The fluorescence intensity of coumarin 102 also decreased over time due to its release and precipitation in the system. Fig. 3(h) shows the release profiles based on the fluorescence intensity changes of coumarin 102, from which it can be seen that the release of coumarin 102 after treatment with 0.1, 0.2 and 1 mmol/L for 24 h were 50.5%, 66.8% and 98.9%, respectively. It is noted that the release data revealed by fluorescence were higher than those revealed by absorbance, as could be ascribed to the effect of absorbance of PDSeNGs (Fig. S7 in ESI).

Next, simultaneous encapsulation of IR780 and coumarin 102 into PDSeNGs and the release of coumarin 102 under NIR irradiation were investigated. The (C102+IR780)@PDSeNGs showed two absorption peaks at 386 and 795 nm corresponding to coumarin 102 and IR780, respectively (Fig. S9 in ESI). Based on the absorption, the loading contents of coumarin 102 and IR 780 were calculated to be 8.5% and 7.5%, respectively. Notably, the photostability of IR780 could be significantly improved when encapsulated in nanogels. Fig. S10(a) (in ESI) shows the UV-Vis absorption spectra of IR780 in

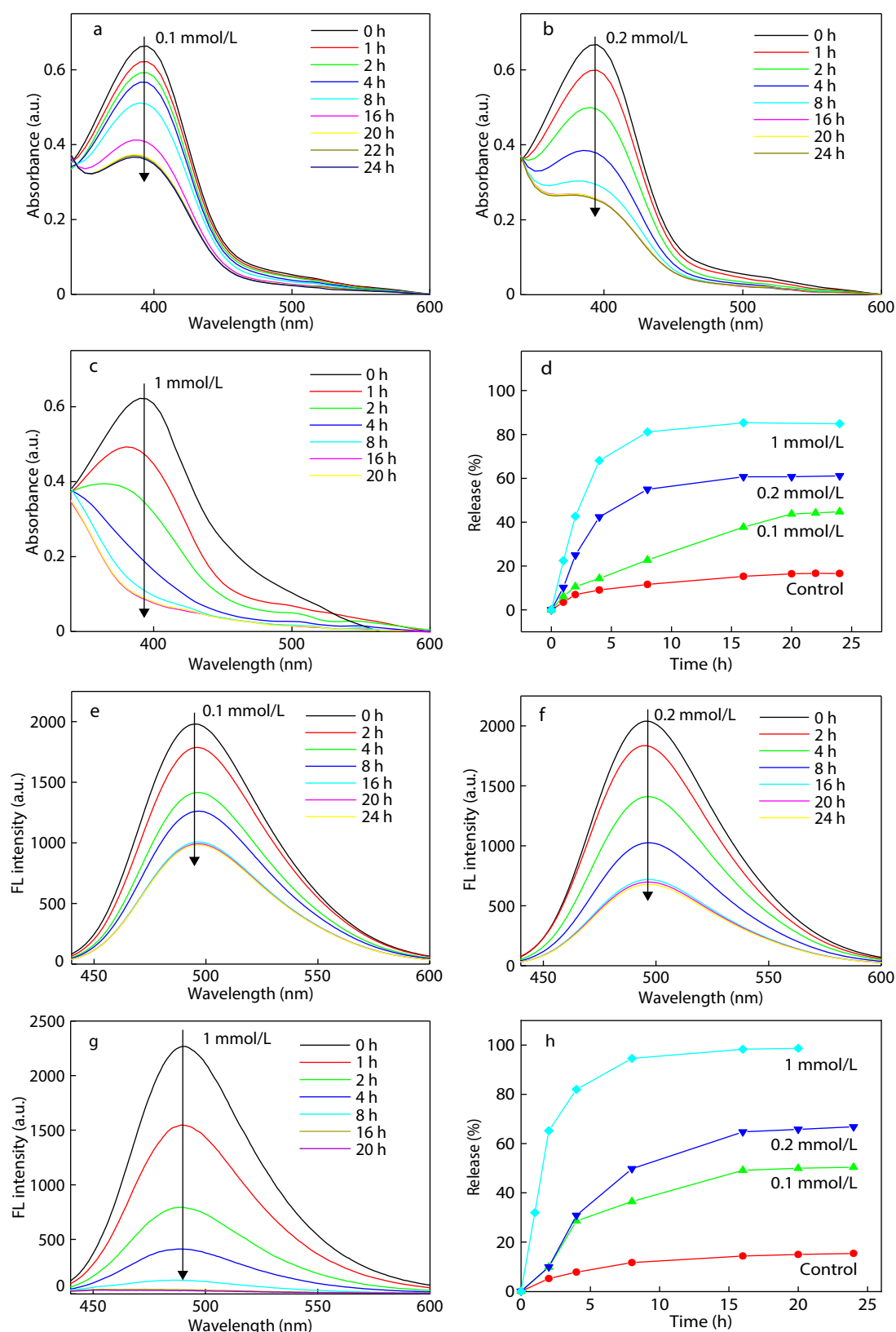


Fig. 3 (a–c) UV-Vis spectra of C102@PDSeNGs treated with 0.1, 0.2 and 1 mmol/L H_2O_2 for 24 h, respectively; (d) Release profiles of coumarin 102 from C102@PDSeNGs treated with different concentrations of H_2O_2 obtained by UV-Vis spectra; (e–g) Fluorescence spectra of C102@PDSeNGs treated with 0.1, 0.2 and 1 mmol/L H_2O_2 for 24 h, respectively; (h) Release profiles of coumarin 102 from C102@PDSeNGs treated with various concentrations of H_2O_2 obtained by fluorescence spectra.

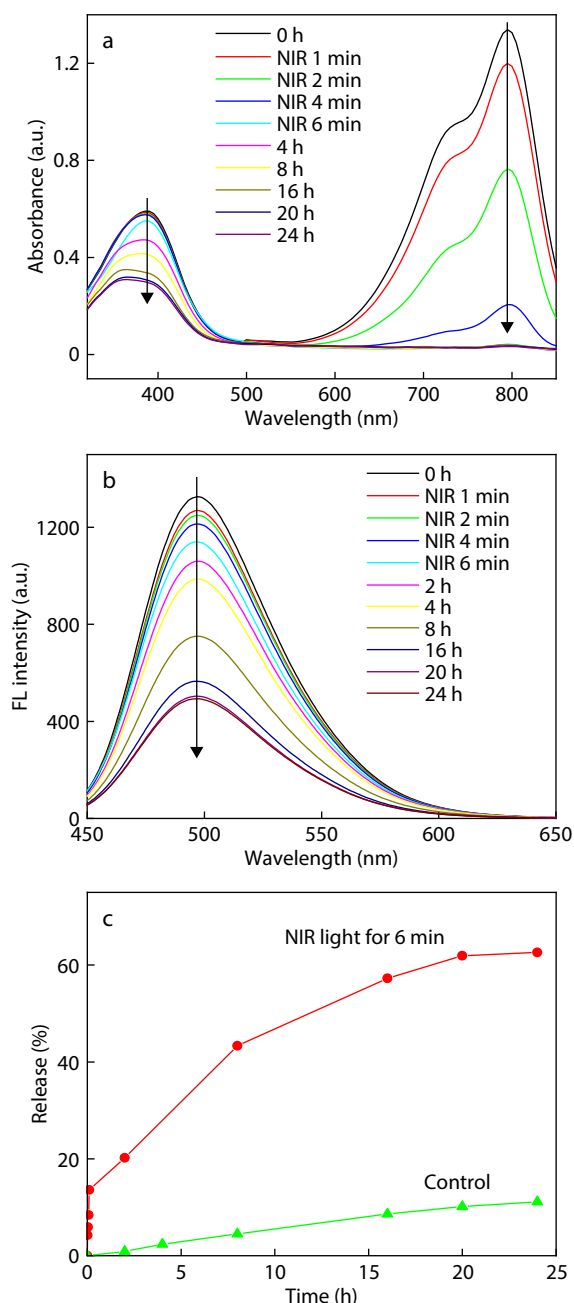


Fig. 4 (a) UV-Vis spectra of (C102+IR780)@PDSeNGs upon 808 nm NIR irradiation treatment (6 min, 1.5 W/cm²) and then kept for 24 h; (b) Fluorescence spectra of (C102+IR780)@PDSeNGs upon 808 nm NIR irradiation treatment (6 min, 1.5 W/cm²) and then kept for 24 h; (c) Release profiles of the guest molecule from nanogels obtained by fluorescence spectra of coumarin 102 without and with NIR irradiation.

aqueous solution with an 85.6% decrease in absorbance within 60 min. In contrast, encapsulation of IR780 into nanogels resulted in only a 3.4% decrease in absorbance within 60 min (Fig. S10b in ESI). Fig. 4(a) shows the UV-Vis absorption spectra of (C102+IR780)@PDSeNGs irradiated by 808 nm laser (6 min, 1.5 W/cm²), from which it can be seen that the absorbance of IR780 centered at 795 nm decreased continuously and disappeared within 6 min of irradiation, resulting from

the decomposition of IR780. The absorbance of coumarin 102 centered at 386 nm kept decreasing in the following 24 h after stopping the irradiation, implying the continuous release of coumarin 102. The obvious fluorescence changes of coumarin 102 after NIR light irradiation are shown in Fig. 4(b). Without NIR irradiation, the control experiments only showed a slight decrease in the absorption and fluorescence of coumarin 102 (Figs. S10b and S10c in ESI). Based on the decrease in fluorescence, the release profiles are summarized, shown in Fig. 4(c), from which it can be seen that 62.6% of coumarin 102 could be released from the nanogel within 24 h after NIR light irradiation treatment. The TEM and DLS characterizations confirmed that the morphological changes of the nanogels with encapsulated cargoes stimulated by H₂O₂/NIR (Fig. S12 in ESI) were generally consistent with those of blank PDSeNGs. The controlled release of the model molecules coumarin 102 from the nanogels upon H₂O₂ and NIR light stimulation can endow the system with great potential for drug delivery.

CONCLUSIONS

In conclusion, we have successfully synthesized a novel diselenium bonded crosslinked polymer nanogel PDSeNGs by microemulsion quaternization reaction. The hydrophobic guest molecules could be wrapped into the hydrophobic inner cavities of PDSeNGs. In the presence of ROS, the diselenide bonds in the PDSeNGs would be broken and oxidized to seleninic acid, which could induce the nanogels collapsed, releasing the encapsulated guest molecules. The release efficiency of the guest molecules is positively correlated with the concentration of oxidant H₂O₂. After encapsulating the photosensitizer IR780 into the nanogels, the diselenide bonds could be broken by the ROS and the nanogels collapsed under NIR irradiation, thus resulting in effective release of the guest molecules. Such a NIR-responsive selenium-containing nanogel system will have great potential in the field of smart drug delivery and controlled release.

NOTES

The authors declare no competing financial interest.

Electronic Supplementary Information

Electronic supplementary information (ESI) is available free of charge in the online version of this article at <http://doi.org/10.1007/s10118-022-2867-1>.

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