Stimuli-Responsive Gels

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γ-Ray-Responsive Supramolecular Hydrogel Based on a Diselenide-Containing Polymer and a Peptide**

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Stimuli-responsive hydrogels have developed greatly in recent years as a result of the demand for such gels in nanotechnology and for biomedical applications.[1] The regulated transition between gel and solution states can provide tunable release rates for clinical use.[2] Supramolecular hydrogels, which rely on noncovalent interactions to drive the self-assembly of small molecules in water to form supramolecular architectures and encapsulate water, possess excellent biocompatibility and biodegradability.[3] The exploration of supramolecular hydrogels based on derivatives of commercially available therapeutic agents is an emerging research area because of their importance in public health and their potential in drug "self-delivery" systems.[4] Recent research efforts have yielded many stimuli-responsive supramolecular hydrogels, including redox-,[5] light-,[6] and other chemically responsive systems.[7] However, the development of stimuli-responsive supramolecular gel systems that are practical in clinical applications remains challenging. We are interested in using γ rays to modulate the gel–sol transition, because γ rays are used clinically for antitumor radiotherapy. Gels that can be cleaved with γ rays might enable the development of smart systems that combine chemo- and radiotherapy.

Selenium is an essential human trace element,[8] and selenium-containing polymers have recently received wide attention as new redox-responsive biomaterials.[9] Selenium possesses unique chemical properties: the Se–Se bond has a bond energy of 172 kJ mol^{-1} and is weak in comparison with the C–C bond (346 kJ mol^{-1}) and commonly used dynamic covalent S–S bond (240 kJ mol^{-1}).[10] Numerous functional systems based on selenium-containing polymers with different topologies have been developed; these systems act as new biomaterials for innovative drug delivery and efficient enzyme mimics.[8g,h] However, multi-stimuli-responsive hydrogels based on diselenide-containing polymers have not been reported. Herein, we describe a γ-ray-responsive hydrogel based on a diselenide-containing polymer and a peptide amphiphile (Figure 1). The supramolecular hydrogel exhibits a γ-radiation-induced gel–sol transition, including a disruption of the network structure, which facilitates its application as a smart hydrogel. Moreover, we also demonstrate that the system responds to other stimuli (UV radiation) to release the clinically used drug naproxen and thus acts as a drug self-delivery system.

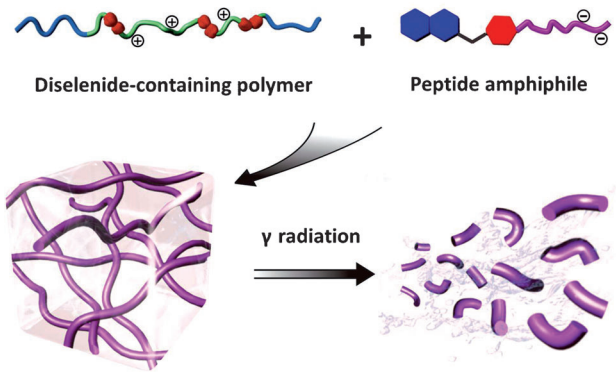

Figure 1. γ-Ray responsive supramolecular hydrogel formed from a diselenide-containing polymer and a peptide amphiphile.

The hydrogel in this study can be cleaved by γ radiation. After exposure to a ^{60}Co source for a 0.5 kGy dose of radiation, a distinct gel–sol transition was observed (Figure 2a). The mechanical properties and the viscosity of the sample decreased significantly, in agreement with the γ-radiation-induced gel–sol transition (for a detailed characterization, see the Supporting Information). To the best of our knowledge, no γ-radiation-cleavable gel has been reported previously. As γ rays are used in clinical radiotherapy, this finding may open a new avenue for combined radio- and chemotherapies. The system was fabricated through the design of two building blocks: the peptide amphiphile and the diselenide-containing polymer. Gelators usually possess a delicate hydrophobic–hydrophilic balance.[11] It is possible to fabricate a self-assembly precursor that affords a hydrogel after complexation with the positively charged diselenide-

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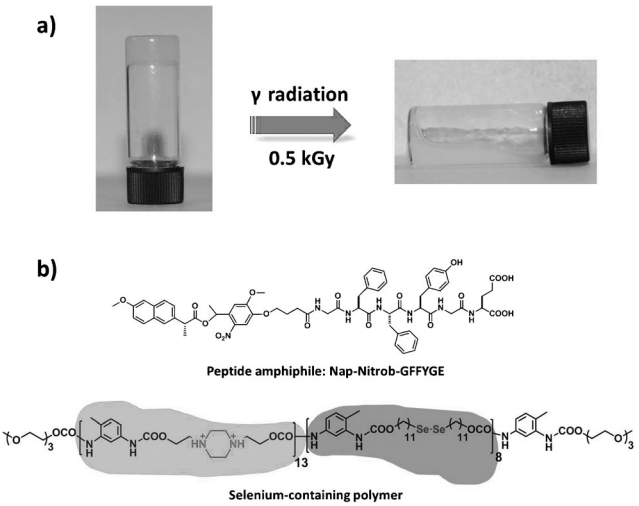

Figure 2. a) γ-Radiation-responsive behavior of the hydrogel. b) Chemical structures of the components of the γ-radiation-responsive hydrogel: the peptide amphiphile Nap–Nitrob–GFFYGE based on the clinically used therapeutic agent naproxen, and a diselenide-containing random copolymer with positive charges in the main chain.

containing polymer. A peptide amphiphile with precisely manipulated amphiphilicity was designed and synthesized. This small molecule, Nap–Nitrob–GFFYGE, is capable of self-assembly and UV response (Figure 2b). The hexapeptide and Nap–Nitrob sections were designed as the hydrophilic and hydrophobic parts, respectively. Naproxen ("Nap") is a clinically used painkiller and was selected as a model drug. It was connected with 4-(4-(1-hydroxyethyl)-2-methoxy-5-nitrophenoxy)butanoic acid ("Nitrob") through an ester linkage, which could be cleaved by exposure to UV radiation.[6a] As expected, hydrogelation failed to occur in a phosphate-buffered saline (PBS, pH 7.4) solution containing up to 28 wt% of this peptide amphiphile at room temperature. Only irregular aggregates were observed by transmission electron microscopy (TEM; see Figure S6 in the Supporting Information).

A diselenide-containing polymer with positive charges located in the main chain was synthesized to promote the supramolecular hydrogelation process (Figure 2b). Positively charged 2,2′-(piperazine-1,4-diyl)diethanol and diselenide-containing 11,11′-diselanediylbis(undecan-1-ol) were used as the monomers and were copolymerized with a slight excess of toluene diisocyanate (TDI) through stepwise polymerization in THF. The active ends were terminated with triethylene glycol monomethyl ether to provide the desired solubility (for the detailed synthetic procedure, see the Supporting Information). The resulting diselenide-containing random copolymer had a molecular weight of 1.1×10^4 g mol^{-1}, as estimated from ^{1}H NMR spectra. The M_n value of the polymer was also determined by gel permeation chromatography (GPC) in *N*,*N*-dimethylformamide ($M_w = 1.6\times10^4$ g mol^{-1}, $M_w/M_n = 2.0$). Cryo-TEM images indicated that the polymer self-assembled into spherical micelles (see Figure S7 in the Supporting Information).

As hypothesized, gelation occurred after the addition of a suspension of the diselenide-containing polymer to a solution of the peptide amphiphile. The resulting suspension appeared milky at first and overnight formed a self-supporting hydrogel without any heating or cooling cycles (final concentration of the peptide amphiphile: 1.02 wt%; final concentration of the polymer: 0.06 wt%). Gelation can be ascribed to the electrostatic and hydrogen-bonding interactions between the negatively charged peptide amphiphile and the positively charged polymer. The hydrogel was formed at a physiological pH value.

Hydrogel formation was confirmed by detailed analysis. Rheological measurements (Figure 3a) showed that the value of the storage modulus, G′, was invariant with frequency and

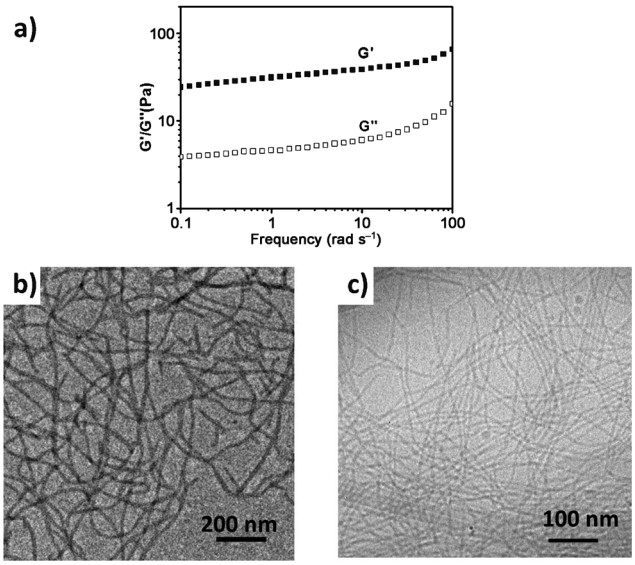

Figure 3. Evidence of hydrogel formation. a) Rheological properties indicating the formation of a self-supporting hydrogel. b) TEM image obtained by positive staining. c) Cryo-TEM image revealing the fibrous nature of the hydrogel.

exceeded that of the loss modulus, G″. These values indicated that the sample was viscoelastic and behaved like a typical gel. To better understand the self-assembly process, we characterized the hydrogel by TEM. Self-assembled nanofibers with a diameter of about 9 nm were formed. Samples stained with a solution of uranium acetate gave negatively stained images (see Figure S8 in the Supporting Information), whereas those stained with a solution of phosphotungstic acid gave positively stained images (Figure 3b). Both types of images indicated the fibrous nature of the hydrogel. To exclude an effect of staining and air drying on the nanostructure, we used cryo-TEM to observe the hydrogel in its native environment (Figure 3c). The long nanofibers were physically cross-linked to form an entangled network.

The hydrogel formed could be cleaved by γ radiation. Long nanofibers were gradually broken down in a process that coincided with the macroscopic gel–sol transition. TEM images showed virtually no cross-linked networks on the copper grid (Figure 4a) after exposure to a 0.5 kGy dose of γ radiation. The entire field was covered with short fibers. As the γ-radiation dose reached 0.8 kGy, the fibers became shorter (see Figure S9 in the Supporting Information).

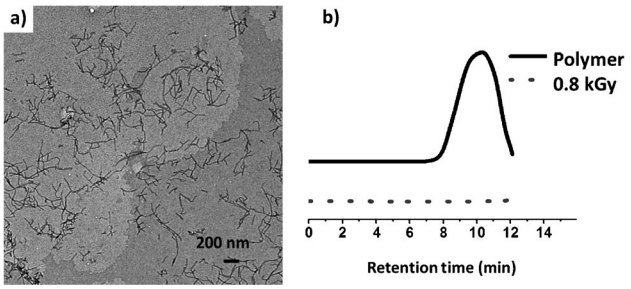

Figure 4. Evidence for the γ-radiation response of the hydrogel. a) TEM image of the hydrogel morphology after exposure to a dose of 0.5 kGy of γ radiation. b) GPC plot before and after exposure to a dose of 0.8 kGy of γ radiation.

The reason for the γ-radiation-triggered gel cleavage is ascribed to the cleavage of the diselenide-containing polymer by oxidative species generated upon irradiation, owing to the active nature of the Se–Se bond. Water can generate oxidative species, including ·OH, $\cdot HO_2$, and H_2O_2, upon exposure to γ radiation.[12] We explored the capacity of the diselenide-containing polymer to react with free radicals. The radical signals in the ESR spectra were about 60% lower in the polymer solution than in the pure-water control; this result indicates that the polymer could efficiently clear the free radicals and decrease the concentration of free radicals (see Figure S10 in the Supporting Information). To confirm the γ-radiation-induced chemical transformation, we examined the hydrogel composition by GPC after irradiation with γ rays. The peak corresponding to the polymer component disappeared after exposure to a 0.8 kGy dose of γ radiation (Figure 4b). This observation suggests that oxidative free radicals produced by γ radiation could cleave the diselenide bonds in the polymer and thus promote the subsequent gel–sol transition.

To further demonstrate that the diselenide-containing polymer plays an essential role in the γ-radiation-responsive behavior of the gel, we replaced the diselenide-containing polymer with a disulfide-containing polymer. The disulfide-containing polymer was synthesized by a similar procedure (see the Supporting Information). An analogous hydrogel based on the disulfide-containing polymer and peptide amphiphile was prepared according to the same procedure. The disulfide bond is a dynamic covalent bond because of its low bond energy. We wondered if the disulfide-containing gel could also be cleaved by γ radiation; however, it failed to degrade after exposure to a dose of 0.8 kGy (see Figure S11 in the Supporting Information). The hydrogel still showed no obvious change even after exposure to a radiation dose of 5 kGy (see Figure S12 in the Supporting Information). The nonresponse of the disulfide-containing hydrogel further suggested that the γ-radiation-induced gel–sol transition was due to the cleavage of the diselenide-containing polymer. These observations confirm that the diselenide bond is more sensitive to γ radiation than the disulfide bond, and that selenium-containing polymers may play an important role in the molecular self-assembly of next-generation biomaterials and soft devices.

The hydrogel can act as a UV-mediated drug self-delivery system. It is capable of translating the UV-triggered degradation of the *o*-nitrobenzyl moiety in the peptide into a macroscopic gel–sol transition. To investigate its photoresponse, we irradiated the hydrogel in a UV photochemical reactor. The hydrogel became a viscous solution within 1.5 h (Figure 5c). The macroscopic transition of the hydrogel

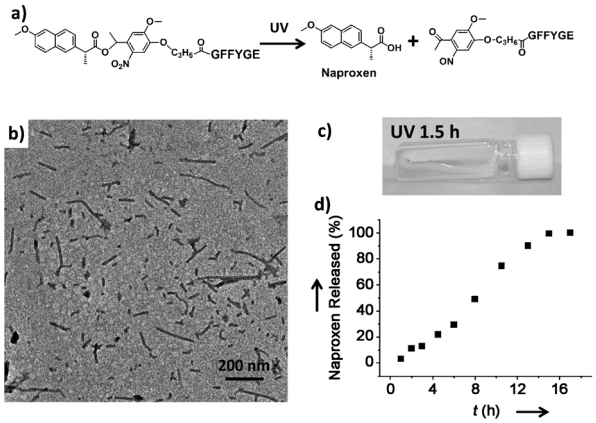

Figure 5. Degradation of the hydrogel upon exposure to UV radiation. a) The chemical reaction induced by UV light. b) TEM image and c) optical photograph of the degraded gel after irradiation for 1.5 h. d) Kinetics for the release of naproxen under irradiation with UV light, as determined by LC–MS.

coincided with microscopic changes in the nanofibers. The long fibers tended to break down, as revealed by TEM images (Figure 5b); this way, the local network cross-linking density was decreased, which resulted in a significant macroscopic change. An extended irradiation time with UV light led to shorter fibers (see Figure S13 in the Supporting Information).

To quantify the photoresponse of the hydrogel, we exposed it to UV light for extended periods of time. The solutions became more fluid and their color deepened during longer irradiation times (see Figure S14 in the Supporting Information). A 30 μL sample was removed after the desired time period for analysis by liquid chromatography–mass spectrometry (LC–MS). Upon irradiation with UV light, the ester group in the *o*-nitrobenzyl moiety was hydrolyzed. The release of naproxen was plotted as a function of time (Figure 5d). The intrinsic driving force for the photoresponse of the hydrogel was the photoinduced hydrolysis of the ester group in the *o*-nitrobenzyl moiety. The cleavage process proceeded over a period of 15 h; almost linear cleavage with time was observed. After 15 h, an equilibrium was reached. The released naproxen is a clinically used therapeutic agent, and its release in the current study may further the development of stimuli-responsive drug self-delivery systems. It is anticipated that UV-responsive systems may be applied in vivo in zebra-fish embryos and other transparent animals.[6e,13]

In summary, we have demonstrated a stimuli-responsive hydrogel formed by combining a diselenide-containing polymer and a peptide amphiphile. The use of γ radiation to control the degradation of the hydrogel components yields a smart gel–sol transition. The diselenide-containing gel is

much more sensitive to γ radiation than its disulfide analogue. We also showed that the gel can serve as a drug self-delivery system, which can release naproxen in a controlled manner under UV irradiation. The diselenide-containing hydrogel could be used to produce biomaterials whose functionality is tailored to a range of applications, for example, programmable responsive systems for combined chemo- and radiotherapy. Further studies on the size control of the hydrogel particles could lead to enhanced sensitivity to external stimuli.

Experimental Section

TEM images were obtained with an H-7650B microscope with an accelerating voltage of 80 kV. The samples were prepared by drop coating the aqueous solution on the carbon-coated copper grid for 15 min and staining with 1.5% uranium acetate or 0.2% phosphotungstic acid before observation. Cryo-TEM samples were prepared in a controlled-environment vitrification system at 28 °C. The vitrified samples were stored in liquid nitrogen until they were transferred to a cryogenic sample holder (Gatan 626) and examined by a JEM2200FS TEM (200 kV) at about −174 °C.

Samples were irradiated with γ rays at Peking University Department of Applied Chemistry with a ^{60}Co radiation source at a dose rate of 0.02 kGy min^{-1} (for a radiation dose of 5 kGy, the dose rate was 0.035 kGy min^{-1}). The unit kGy refers to the radiation energy absorbed by objects of a certain mass: 1 kGy = 1 kJ kg^{-1}. O_2-saturated water (10 μL) was added to the hydrogel (400 μL) before irradiation.

For UV irradiation, samples were contained in a quartz cuvette to ensure good UV transmission and then irradiated by a UV photochemical reactor equipped with a 100 W UV lamp with a peak wavelength of 365 nm.

Electronic spin resonance was recorded on a JEOL JES-FA200 instrument equipped with a UV light source. 5,5-Dimethyl-1-pyrroline *N*-oxide was employed as the spin trap.

LC–MS was conducted with an LCMS-20AD (Shimadzu) system, and rheology was performed with an AR 2000ex (TA instruments) system by using parallel plates (40 mm) at a gap of 500 μm. ^{1}H NMR spectra were recorded on a JEOL JNM-ECA 300 (300 MHz) spectrometer. The size distribution of the aggregates was analyzed with a Malvern ZEN3690 Zetasizer by using a monochromatic coherent He–Ne laser (633 nm) as the light source and a detector that detected the scattered light at an angle of 90°. GPC was performed with Shimadzu LC-20AD pump system with *N*,*N*-dimethylformamide (DMF) as the eluent.

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