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# Responsive Single-Chain Polymer Nanoparticles with Host-Guest Features

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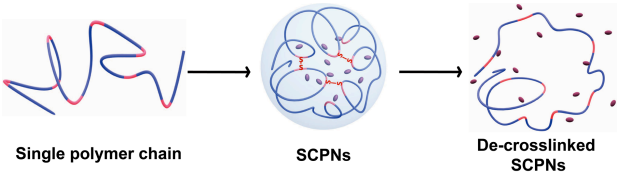
We report a facile approach to form ultra-fine single-chain polymer nanoparticles (SCPNs) *via* disulfide-based intrachain crosslinking of single polymer chains of a random copolymer poly(HEMA-*co*-PDSEMA). The SCPNs, which were prepared under mild reaction conditions and normal reaction concentrations (up to 10 mg $mL^{-1}$), have been characterized by $^{1}H$ nuclear magnetic resonance ($^{1}H$ NMR), atomic force microscopy (AFM), differential scanning calorimetry (DSC), gel permeation chromatography (GPC), and dynamic light scattering (DLS). The influence of crosslinking density, molecular weight and the initial concentration of the polymer upon the formation of SCPNs are also reported. In order to investigate hydrophobic interior of SCPNs, we trace the emission spectrum of pyrene probe. We highlight that these SCPNs exhibit host-guest properties to stably encapsulate hydrophobic guest molecules and release them in response to a redox stimulus.

## Introduction

Access to well-defined polymeric nanoparticles is interesting, as these materials have attracted much attention in the areas of nanomedicine, sensing, and catalysis.[1-5] Traditional synthetic techniques, such as through self-assembly of amphiphiles or miniemulsion polymerization, allowed for achieving polymeric nanoparticles in the 20-200 nm size range.[6-8] Smaller nanoparticles, however, were mainly accessed through iterative covalent synthesis of spherical macromolecules, such as dendrimers.[9,10] There has been an enhanced interest in obtaining ultra-fine nanoparticles in the size range of 5-20 nm with traditional synthetic polymerization techniques. Inspired by folding of proteins to generate well-defined three-dimensional tertiary structures,[11] strategies to fold and collapse single polymer chains to form the so-called single-chain polymer nanoparticles (SCPNs) are being developed.[12,13] These strategies, which often involve high-dilution conditions, include chain collapse using intrachain covalent bonds,[14-18] dynamic covalent chemistry,[19-21] and non-covalent interactions.[22-24] Many of the methods toward stable SCPNs also require high temperatures,[25,26] metal catalysts,[27-29] and non-trivial monomer structures.[30,31] We have been interested in developing a strategy that uses simple polymers that can be collapsed under mild reaction conditions and normal reaction concentrations. Moreover, we also stipulated that the resultant SCPNs be unraveled in the presence of a specific stimulus.

In our previous researches, random copolymers based on pyridyldisulfide ethyl methacrylate (PDSEMA) and oligoethyleneglycol methacrylate have been previously used to generate well-defined, self-crosslinked polymer nanogels.[32-35] The key feature that controls the formation of the polymer nanogel is the hydrophilic lipophilic balance, resulting in the aggregates of multiple polymer chains. We envisaged the possibility that if we were to significantly change this balance, the hydrophobicity based aggregates might not be so dramatic that we could generate single chain nanostructures via disulfide-based intrachain crosslinking of single polymer chains. Aided by this finding, a new approach to the preparation of redox-responsive SCPNs is conceived. Herein, hydroxyethyl methacrylate (HEMA) monomer and PDSEMA monomer were employed to synthesize random copolymer P(HEMA-*co*-PDSEMA) via reversible addition−fragmentation chain-transfer (RAFT) polymerization. Folding/collapse of single polymer chain of P(HEMA-*co*-PDSEMA) was driven by disulfide-based intrachain crosslinking, *via* the PDSEMA units. We utilized the SCPNs to non-covalently encapsulate guest molecules and observed that the release of loaded dyes could be induced by reductants through the cleavage of the crosslinking disulfide bonds, as illustrated in Scheme 1.




**Scheme 1**. Cartoon illustration of assembly-disassembly of single-chain polymer nanoparticles (SCPNs) by means of disulfide bonds.

## Experimental

### Materials and methods

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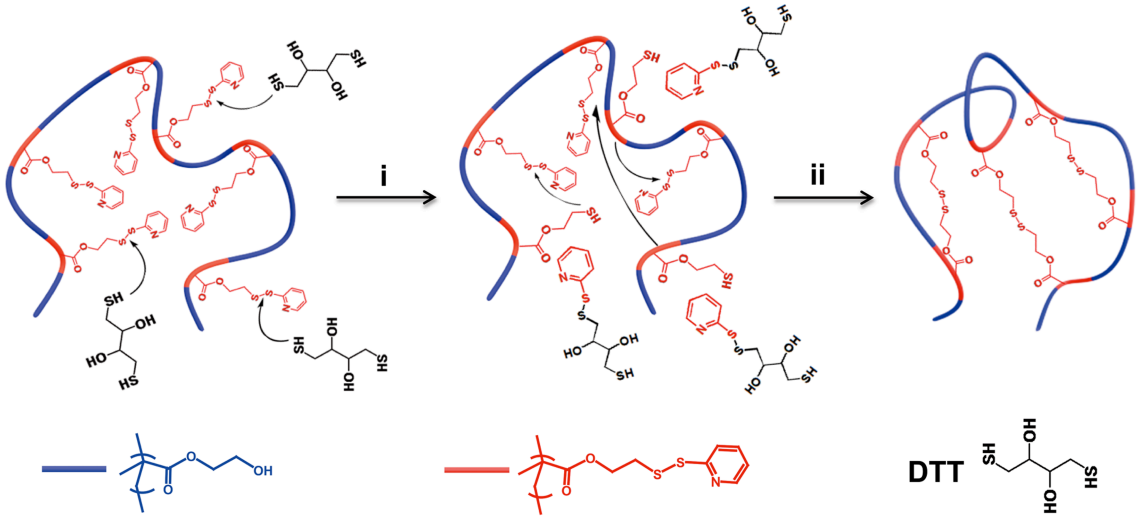


**Fig. 1** General synthetic scheme for the preparation of SCPNs: *i*) DTT attacks PDS groups to generate a reactive thiol unit; *ii*) The reactive thiols react with the remaining PDS groups to form the SCPNs.

2,2-Dithiodipyridine, 2-mercaptoethanol, 2-hydroxyethyl methacrylate (HEMA), D,L-dithiothreitol (DTT), pyrene, Nile red, 4-Cyano-4-(phenylcarbonothioylthio)-pentanoic acid were obtained from Sigma-Aldrich and were used as received without further purification. Pyridyl disulfide ethyl methacrylate (PDSEMA) was prepared using a previously reported procedure.[36] The 2,2'-azobisisobutyronitrile (AIBN) was purified by recrystallization from ethanol. $^1$H NMR spectra were recorded on a 400 MHz Bruker NMR spectrometer. Atomic force microscopy (AFM) images were collected on Dimension 3000 under ambient conditions by use of silicon cantilevers. Molecular weights of the polymers were estimated by gel permeation chromatography (GPC, DMF) using PMMA standards with a refractive index detector. Dynamic light scattering (DLS) measurements were performed using a Malvern Nanozetasizer. The emission spectra were obtained from a JASCO FP-6500 spectrofluorimeter.

### Synthesis of random copolymer P(HEMA-*co*-PDSEMA)

The random copolymer P(HEMA-*co*-PDSEMA) was polymerized by RAFT. The process was as follows: to a Schlenk flask, PDSEMA (256 mg, 1 mmol), HEMA (910 mg, 7 mmol), AIBN (0.41 mg, 0.0025 mmol), and 4-cyano-4-(phenylcarbonothioylthio)-pentanoic acid (3.5 mg, 0.0125 mmol) were dissolved in 1.5 mL dry DMF. The solution mixture was subjected to three freeze-pump-thaw cycles. The sealed flask was immersed in a preheated oil bath at 65 °C. The polymerization reaction was allowed to proceed for 12 h (to polymer **1**), 20 h (to polymer **2**), 32 h (to polymer **3**), respectively. The polymerization was quenched by cooling down the flask to ambient temperature. The polymer was purified by precipitation in ethyl ether for three times.

### Pyrene encapsulation

Polymer **1** was dissolved in methanol to make 0.5, 2, 5, 10, 25, and 50 mg mL$^{-1}$ solutions. 1 mL of polymer solution was placed in a glass vial. 1 wt% of pyrene was dissolved in the vial. Then, the requisite amount of DTT (10 mol% compared to PDSEMA moieties), was added to polymer solution under stirring. The crosslinking reaction was allowed to proceed overnight. After that, the solution was dialyzed against water, followed by filtering through the syringe filter (0.45 μm). The final concentration of particles was diluted to 0.5 mg mL$^{-1}$ by adding water.

### Redox-responsive release

The process of encapsulating Nile red was similar to that mentioned above. 10, 20, 30, 40, 50 mol% (compared to PDSEMA moieties) of DTT was respectively added 1 mL of polymer 1 methanolic solution (0.5 mg mL$^{-1}$) which containing 1wt% of Nile red under stirring overnight. Finally, the solution was dialyzed against water followed by filtrate through the syringe filter (0.45 μm). After adding 5 μM or 5 mM reductant, the spectral emission intensity of Nile red was recorded.

## Results and discussion

The formation of the SCPNs, which is illustrated in Fig. 1, was investigated first. For this purpose, we synthesized the random copolymer **1** poly((HEMA)$_x$-*co*-(PDSEMA)$_y$) with an $M_n$=76,900 g mol$^{-1}$, $M_w/M_n$=1.24. The ratio of the two monomers was found to be 7.6:1.0 based on the relative integration of $^1$H NMR peaks d and k in Figure 2. To cause folding and collapse of this polymer, we then added a pre-determined amount of DTT to a methanolic solution of polymer **1** (0.5 mg mL$^{-1}$). When 50% of DTT was added to the polymer, 50% of the pyridyl disulfide (PDS) groups are presumably cleaved to generate a reactive thiol unit in the polymer. These thiols then react with the remaining 50% of the PDS units to generate 100% crosslinked nanoparticles. Analysis of the resultant polymer product by GPC and DLS provided a $M_n$ of 61,500 g mol$^{-1}$ with a particle size of about 8.5 nm (Table 1). Both of these data provided an initial evidence for SCPN formation.

**Table 1** Characteristics of polymer **1** and SCPNs1-5

| Sample | $M_n$[a] (gmol$^{-1}$) | $M_w/M_n$ | $D_h$[b] (nm) | $T_g$[c] (°C) |
|---|---|---|---|---|
| Polymer **1** | 76900 | 1.24 | 9.9 | 76 |
| SCPNs1 | 71900 | 1.29 | 9.1 | 90 |
| SCPNs2 | 67600 | 1.34 | 8.9 | 95 |
| SCPNs3 | 65700 | 1.26 | 8.7 | 99 |
| SCPNs4 | 63400 | 1.26 | 8.6 | 106 |
| SCPNs5 | 61500 | 1.30 | 8.5 | 110 |

[a] Determined by GPC in DMF versus standards. [b] Determined by DLS. [c] Determined by DSC.

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Next, we tested the possibility of generating different degrees of crosslinking. The main reason for carrying out this experiment are: (*i*) to test whether it is the initial crosslinking step that stitches the polymer into a SCPN and (*ii*) to test whether further crosslinking could provide an easily accessible control over the rigidity of the SCPN. Accordingly, we attempted the generation of SCPNs with the crosslink densities of 20%, 40%, 60%, 80%, and 100%, labeled as SCPNs1, SCPNs2, SCPNs3, SCPNs4, and SCPNs5, respectively. We monitored the progress of the reaction with $^1$H NMR (Fig. 2). The peaks at 7.0-8.5 ppm, arising from the thiopyridine groups of PDSEMA units, decrease with increasing amount of DTT and

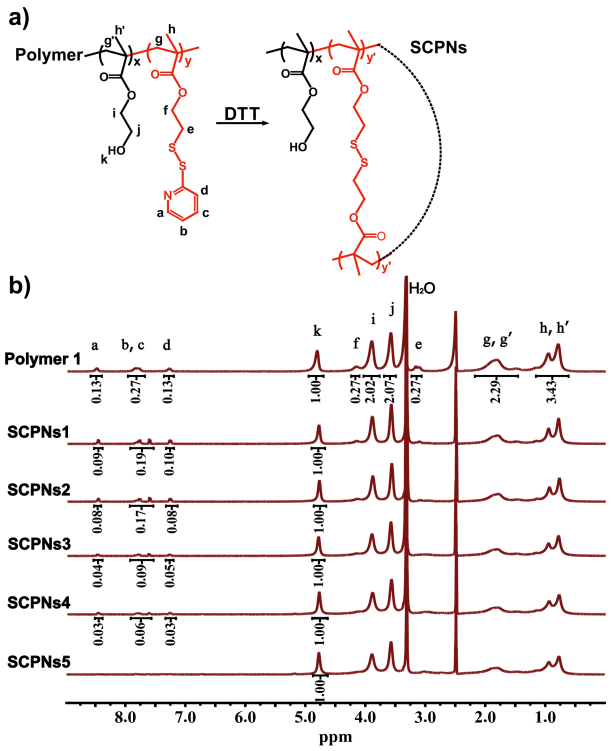


**Fig. 2** (a) Design and preparation of SCPNs via disulfide-based intrachain crosslinking. (b) $^1$H NMR of polymer **1** and SCPNs1-5 in (CD3)2SO.

completely disappear at 100% crosslinking. This observation, combined with the fact that there are no discernible new peaks in the NMR, suggests that the crosslink density has a tight correlation with the amount of DTT added to the reaction mixture.

A series of experiments were performed to test whether it is indeed the intrachain crosslinking and not interchain crosslinking (Table 1). GPC has proved to be a convenient method to monitor volume changes in SCPNs,[37,38] as these systems should exhibit volume changes that will be shown as an apparent change in the molecular weight. Since interchain crosslinking will have to show a necessary increase in molecular weight, the observation of a decrease in $M_n$ can be taken to be an indicator of SCPN formation. In Fig. 3a, the crosslinked NPs showed a significant increase in retention times of the SCPNs compared with polymer **1**, which indicates a reduction of hydrodynamic volume. This increased retention time systematically increased with increasing crosslink density, attributed to the increased crosslinking-induced chain folding in the SCPN formation process. Subtle shoulder appears when the crosslink density is low. This could be attributed to the possible reaction of adjacent PDS groups in some of the polymer chains, which results in the indistinguishable reduction of hydrodynamic volume. The lack of peaks at lower retention times

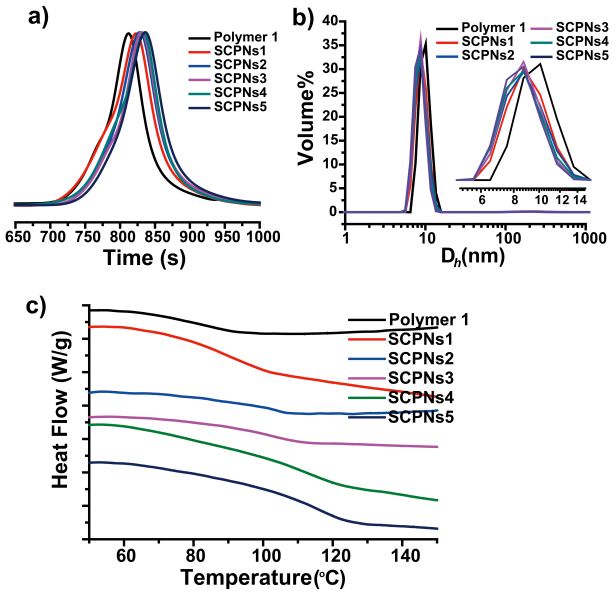


**Fig. 3** (a) GPC of polymer **1** and SCNPs1-5. (b) DLS measurement of polymer **1** and SCNPs1-5 in water. (c) DSC of polymer **1** and SCPNs1-5.

discounted the possibility of interchain cross-linking in these reactions.

As an additional confirmation of the decrease in the hydrodynamic volume, we also attempted to quantify the change by measuring the change in hydrodynamic sizes ($D_h$) using dynamic light scattering (DLS). Fig. 3b shows the $D_h$ decreased from 9.9 nm (for polymer **1**) to 9.1 nm (for SCPNs1). The entire DLS profile of up to 1 μm is shown first of all to illustrate that there are no discernible large size particles, indicating the lack of interchain crosslinking. The rather subtle decrease in $D_h$ is not readily obvious and therefore a zoomed-in version of the DLS profile is also shown in Fig. 3b. These data indicate that there is an obvious change from polymer **1** to SCPNs1, but the differences among different crosslink densities are very small. The size decrease at different crosslink densities can be considered to be real, only when coupled with the GPC data.

The reduced segmental mobility of the crosslinked SCPNs

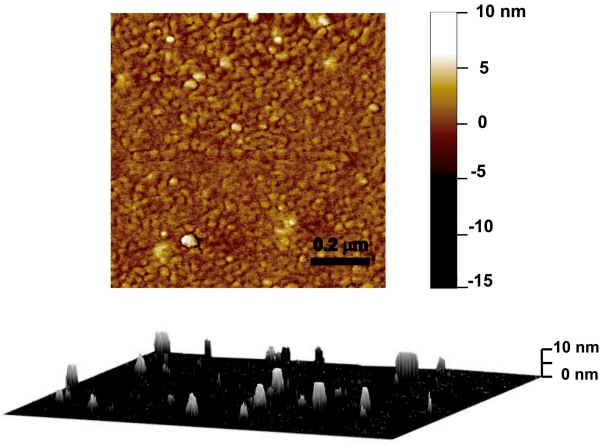


**Fig. 4** AFM height images of SCPNs1 (top: 2D and bottom: 3D model).

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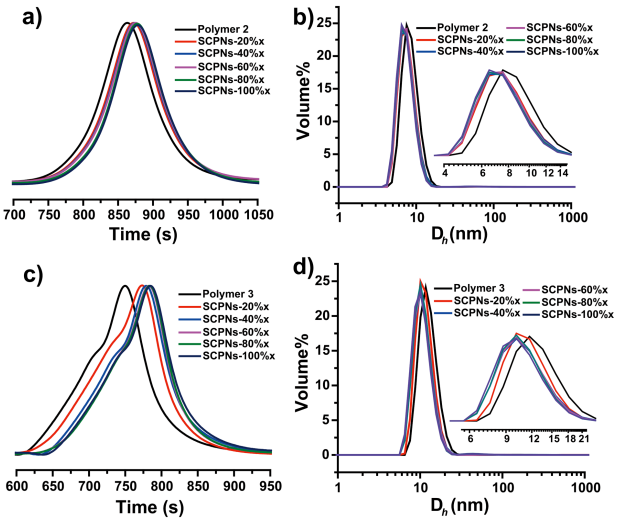


**Fig. 5** (a, c) GPC and (b, d) DLS of polymer **2**, polymer **3**, and the corresponding SCPNs.

should have a significant impact on the glass transition temperature ($T_g$).[39] To test this possibility, DSC of the polymer samples were recorded and indeed the $T_g$ value gradually increased from an initial value of 76 °C for polymer **1** to 110 °C for SCPNs5 (Fig. 3c). In fact, the $T_g$ also increased from 90 °C for SCPNs1 to 110 °C for SCPNs5, showing that segmental chain mobility decreased with the increasing crosslinking density. AFM analysis of SCPNs1 in Fig. 4, drop-cast from methanol solution at 1 μg mL$^{-1}$, also revealed a relatively uniform distribution of SCPNs with size of 10 nm on the silicon wafer.

Next, the impact of molecular weight of random copolymer for the formation of SCPNs was explored. Polymer **2** ($M_n$=42100 g mol$^{-1}$, $M_w/M_n$=1.30) and **3** ($M_n$=118300 g mol$^{-1}$, $M_w/M_n$=1.38) were synthesized for this purpose. It is interesting that the high molecular weight shoulder in polymer **3** is carried over throughout the SNPN formation process. Crosslinking, using various percentages of DTT

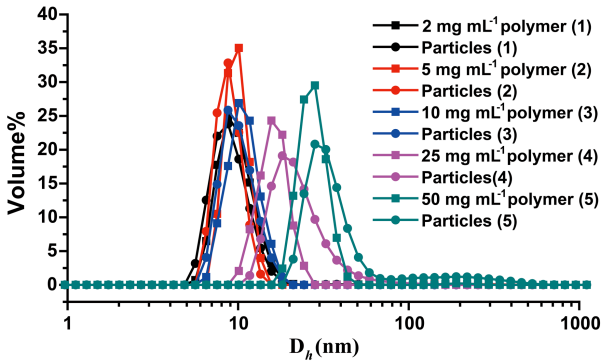


**Fig. 6** DLS of polymer **1** at 2, 5, 10, 25, and 50 mg mL$^{-1}$ and the corresponding particles by adding 10 mol% DTT.

in methanol ($c_{polymer}$=0.5 mg mL$^{-1}$), at ambient temperature afforded SCPNs that are commensurate in size with the polymer molecular weight (Fig. 5). GPS and DLS were similar in the tendency to the forming of SCPNs in polymer **1.** The $D_h$ of the SCPNs was found to be around ~7 nm (from polymer **2**) and 11 nm (from polymer **3**). These results imply that the folding/collapse of single polymer chain is precisely controlled over a considerable molecular weight range.

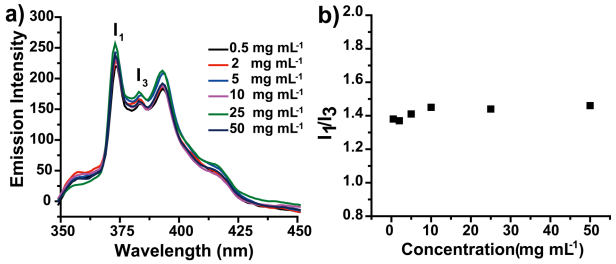


**Fig. 7** (a) The emission spectra of pyrene sequestered in SCPNs. (b) The values of $I_1/I_3$ versus the concentration of SCPNs.

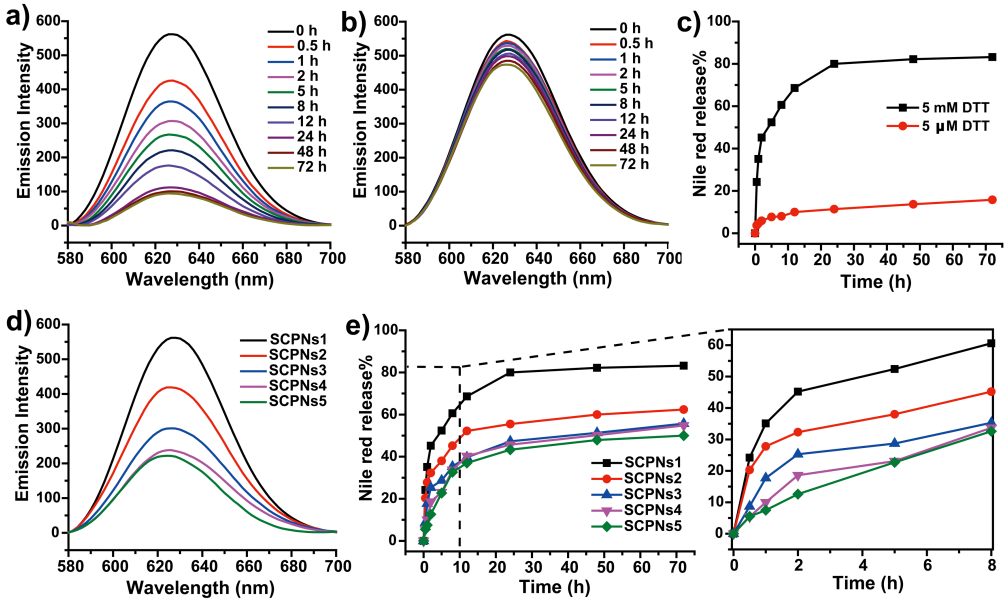


**Fig. 8** Nile red release from SCPNs1 in response to varied DTT concentration, (a) 5 mM, (b) 5 μM. (c) Comparison of Nile red release rate from SCPNs1 under different concentration of DTT. (d) The emission spectra of Nile red sequestered in SCPNs1-5. (e) Comparison of DTT-induced Nile red release rate from SCPNs1-5.

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A key feature of this methodology is that we do not utilize high dilution conditions to achieve the targeted SCPNs. It is then interesting to test the range of concentrations at which this holds true. Therefore, SCPN formation was explored at different concentrations of polymer **1** with 10 mol% DTT (Fig. 6). Upon increasing the concentration to 10 mg $mL^{-1}$, there was no significant change in particle size comparison to the concentration at 0.5 mg $mL^{-1}$, indicating SCPN formation. This is because in the range of concentrations, polymer chains in good organic solvent are isolated to prevent aggregation. However, the presence of peaks at higher $D_h$ at 25 mg $mL^{-1}$ and higher implies that interchain interactions can no longer be ignored at such high concentrations.[40]

The SCPNs were found to be soluble in water upon dialysis. The interior environment of particles was studied in aqueous phase by incorporating hydrophobic environmental probes as guest molecules. It is well-known that pyrene fluorescence is dependent on its microenvironment.[41,42] The ratio of the intensities between the first and the third peaks ($I_1/I_3$) in the pyrene emission spectrum can range from 1.9 in polar solvents to 0.6 in certain hydrocarbon solvents.[43] This ratio was found to be ~1.4 for SCPNs1 (Fig. 7), which suggests a moderately hydrophobic interior and is consistent with the rather small NP that is likely to experience a relatively high degree of solvent exposure.

As mentioned above, we were interested in unraveling these SCPNs in response to a specific trigger. To this end, Nile red was encapsulated into SCPNs1 and the release of this molecule was evaluated in the presence of a large excess of DTT. We envisaged that at a high DTT concentration (5 mM), the thiol-disulfide exchange reaction between DTT and SCPNs1, would cause the crosslinked disulfide bonds to be cleaved. Indeed, the guest molecule was found to be stably encapsulated at low DTT concentrations (5 μM), while it was rapidly released at 5 mM DTT concentration (Fig. 8a-8c).

Encapsulation and release of guest molecules from SCPNs with different crosslink densities were also explored. Fig. 8d shows that the encapsulation capability decreases with increase in crosslinking density. Note that the crosslinked disulfide bonds come at the expense of the hydrophobic PDS units, which presumably leads to decreased hydrophobic encapsulation. Comparing the release rate of SCPNs1-5, under the same concentration of DTT (5 mM), shows that the kinetics of molecular release was understandably slower at higher crosslink densities (Fig. 8e).

## Conclusions

In summary, this manuscript introduced a facile method to reliably prepare SCPNs *via* intrachain crosslinking. We show that: (*i*) the random copolymer poly(HEMA-*co*-PDSEMA) can be converted to SCPNs using the pendent PDS moieties; (*ii*) the SCPNs can be achieved even at mild crosslink densities, but can be locked into a more compact structure by increasing the crosslink density; (*iii*) the size of the SCPNs can be modulated by varying the molecular weight of the polymer; (*iv*) SCPNs can be achieved even at moderately high concentrations, presumably due to chain collapse of the polymer are isolated in good organic solvent to prevent aggregation; and (*v*) guest molecules can be encapsulated within these SCPNs, which can then be released in response to a trigger by unraveling the nanoparticles. The specifically redox-responsive nature of these SCPNs could render these scaffolds useful in applications such as drug delivery.

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## Notes and references

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