Stimulus Responsive PNIPAM/QD Hybrid Microspheres by Copolymerization with Surface Engineered QDs

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The ultimate integration of Quantum Dots (QDs) into future devices can largely benefit from the availability of precisely engineered designer nanocomposites with stimulus responsive polymers. A frequently used stimulus responsive polymer is poly(*N*-isopropylacrylamide)[1] (PNIPAM), which exhibits a lower critical-solution temperature (LCST) in water around 32 °C (in the region of interest for biological applications) where an abrupt chain collapse and phase separation occur.[2] Direct precipitation polymerization in water at temperatures higher than the LCST allows for controlled synthesis of monodisperse micron and submicron PNIPAM hydrogel particles as described by Pelton.[3] Because of the robust preparation methods and attractive properties, PNIPAM hydrogels are finding their ways into new fields of applications like drug delivery,[4] tissue engineering,[5] sensors,[6] and other advanced materials.[7] On the other hand, QDs are becoming the light emitters of choice in sensing, optoelectronics, and many (bio)nanotechnological applications. Thus, a coupling of QDs and PNIPAM, e.g., in the form of QD loaded PNIPAM microgel particles, holds a great promise in various applications.[8,9]

The methods for introducing presynthesized nanocrystals into polymeric matrices are mainly limited to three general cases,[8] i.e., methods based on covalent bonding, on physical entrapment, or on the exploitation of supramolecular interactions. Among these three cases, covalent binding of QDs to polymers results in the most stable structures and is commonly realized by copolymerization of nanoparticles bearing polymerizable ligands with suitable monomers. In a typical procedure, the polymerizable groups are introduced by a ligand exchange process.[10] This, however, brings about risks of modifying the luminescence properties of the QDs. Moreover, most of the polymerizable ligands are soluble only in nonpolar solvents and do not disperse in water precluding the polymerization of aqueous monomers.

In the context of PNIPAM/QD assemblies, initiation of polymerization from silica-coated nanoparticles was performed.[11] Other literature reports describe introduction of QDs into this thermoresponsive polymer by physical entrapment,[12] by entrapment with thio ligand functionalized PNIPAM,[13] or via hydrogen bond formation.[14]

However, to our knowledge there are no reports on the PNIPAM copolymerization with functionalized water-soluble QDs. This motivated us to tackle effective embedding of QDs in PNIPAM microspheres by a novel, easy-to-perform, and robust synthetic protocol as discussed in this paper.

Inverse miniemulsion photoinitiated polymerization used here is a method which results in high-quality composite microspheres. We synthesized quantum dots by pyrolysis of organometallic precursors at high temperature, yielding nanoparticles coated with hydrophobic ligands (trioctylphosphine oxide (TOPO), *n*-hexadecylamine) covering their surface (for experimental details see ref 15. Initial hydrophobic QDs were first functionalized with a novel designer amphiphilic polymer (Scheme 1) and converted into water-soluble polymerizable assemblies. This approach eliminated the ligand exchange step, as described in previous works.[15,16] The copolymer shown in Scheme 1 furthermore endows the QDs with suitable polymerizable groups. This amphiphilic multifunctional polymer coating was obtained by ring-opening reaction of a polymeric anhydride poly(isobutylene-*alt*-maleic anhydride)[15] with *n*-octylamine and hydroxyethyl acrylate in the presence of *N*,*N*-diisopropylethylamine (DIPEA) as catalyst. As a result, the amphiphilic functional polymer exhibits (a) hydrophobic *n*-octyl chains to interact with the TOPO-capped QDs via hydrophobic/hydrophobic interactions, (b) hydrophilic carboxylic groups in the form of sodium salt for maintaining water dispersibility, and (c) acrylic ester units for use in a polymerization reaction (Scheme 1). Transfer of hydrophobic QDs into water was achieved by previously developed procedures,[15] namely by mixing QD suspensions in THF and aqueous solutions of our amphiphilic polymer. Subsequent evaporation of THF and filtration of the solution results in a clear water suspension of the QD/polymer assemblies.

An inverse water-in-oil emulsion UV photopolymerization process was employed to obtain QD/PNIPAM composite microspheres.[17] The reaction was carried out at ambient temperature (below the LCST), i.e., both PNIPAM chains and QDs were hydrophilic; thus, phase separation was prevented. Different types of surfactants were tested for the formation of the emulsion, namely poly(ethylene glycol) block copolymers (Brij 58, Brij 78, Brij 80) and modified sorbitol surfactants (Span 20, Span 80). The best emulsion stability was achieved using (a) sorbitan monooleate (Span 80) in paraffin oil and (b) NIPAM, cross-linker (*N*,*N*′-methylenebis(acrylamide)), and QDs coated with our amphiphilic polymer in water. No photoinitiator was needed as UV irradiation was sufficient to initiate polymerization directly from the reaction mixture.[18] The inverse emulsion polymerization reaction resulted in micron and submicron PNIPAM spheres featuring QDs copolymerized into the polymer matrix. A control sample of PNIPAM spheres without embedded QDs was also obtained by polymerization of pure NIPAM using the same conditions. Figure 2 displays a SEM image of QD/PNIPAM nanocomposites obtained, exhibiting also the distribution of the diameter values (inset). After purification the TEM images revealed that all PNIPAM spheres carried QDs in their interior. A zoomed-in image of an edge area of a larger sphere with embedded QDs is shown in Figure 2b. The QDs are distributed throughout the microsphere volume. Since TEM image is a 2D projection of a 3D distribution of QDs inside the sphere, it is difficult to judge on the degree of aggregation of the QDs. Some aggregation may however happen during the polymerization process and cannot be excluded.

Since the polymerization reaction was carried out by irradia-

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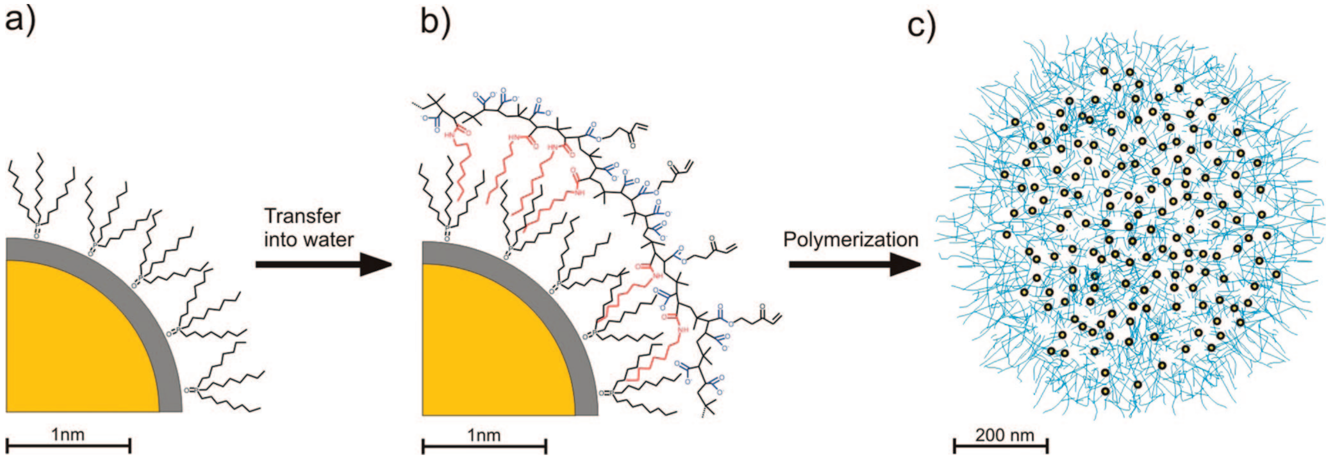


Figure 1. Strategy for the formation of PNIPAM microspheres with embedded QDs: (a) CdSe/ZnS QD coated with hydrophobic trioctylphosphine oxide ligands, soluble in organic solvents; (b) water-soluble QD coated with the amphiphilic polymer; (c) schematic structure of a QD/polymer microsphere.

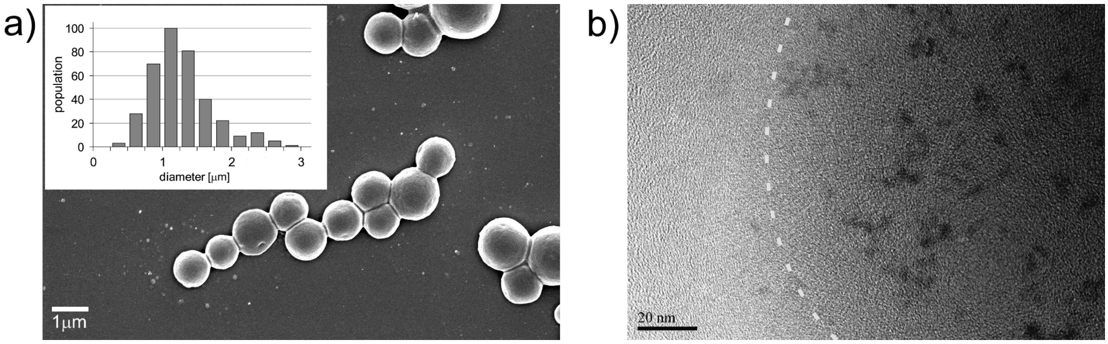
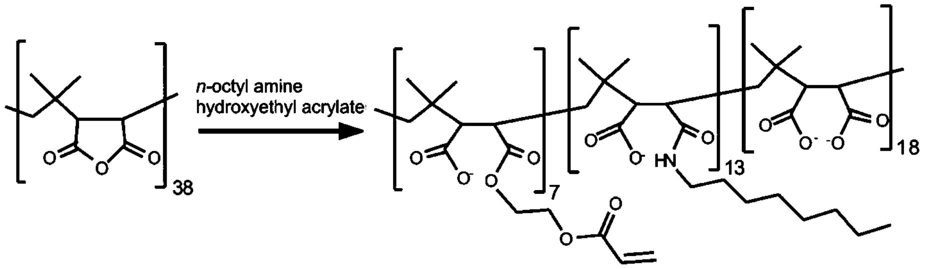


Figure 2. (a) SEM image of PNIPAM/QDs microspheres synthesized by inverse emulsion photopolymerization. The inset shows a histogram of diameter values of PNIPAM/QD microspheres. (b) TEM image of an edge of a larger PNIPAM sphere (darker right part of the picture) with QDs embedded in the polymer matrix. The dashed line representing the projected microsphere boundary is drawn to guide the eye.

Scheme 1. Synthesis and Structure of an Amphiphilic Polymer Bearing Hydrophobic Octylamine Chains, Hydrophilic COO$^-$ Groups, and Polymerizable Acrylic Functional Groups



tion with UV without a photoinitiator, the question arises whether the nanocrystals could be responsible for the radical initiation. Cases of polymerization initiated by QDs were reported previously.[19] In the present case, however, the polymerization takes place irrespective of the presence of the QDs in the water phase of the emulsion (control experiment with NIPAM polymerization also yields PNIPAM spheres). Taking into account that the reduction of the NIPAM/QD ratio leads to poorer quality of the spheres (probably related to a lower degree of polymerization), we conclude that the polymerization in this particular case is initiated from the *N*-isopropylacrylamide molecule rather than from the QDs.

Confocal microscopy imaging was used to check whether the luminescence properties of the QDs were preserved upon incorporation into the PNIPAM spheres. Luminescence images of PNIPAM/QD spheres dispersed on a glass cover slide are shown in Figure 3. One can observe that the QDs are solely present inside the PNIPAM spheres. Cross-sectional confocal imaging taken at 200 nm depth steps through a single PNIPAM/QD sphere (Figure 2b) reveals that the QDs are uniformly distributed within the bead volume and that no migration of the nanoparticles to the edge of the growing PNIPAM sphere occurred.

To check the temperature responsive behavior of the PNIPAM/QD spheres, we performed temperature-variable light absorption measurements (λ_{ex} = 500 nm). In these experiments the absorption of the PNIPAM/QD solution is monitored while crossing the LCST temperature of the PNIPAM. The optical absorbance as a function of temperature is shown in Figure 4. An abrupt jump upon increasing the temperature of the PNIPAM solution is clearly visible on the graph, which corresponds to

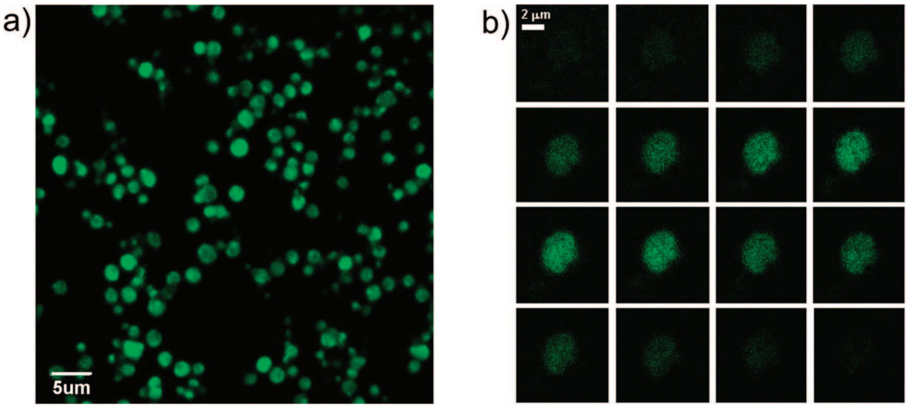


Figure 3. (a) A 50 × 50 μm^2 scanning confocal fluorescence image of PNIPAM/QD spheres deposited on glass cover slides. (b) Scanning confocal cross-sectional z-scan of a single PNIPAM/QD microsphere. The QDs are uniformly distributed throughout the bead volume.

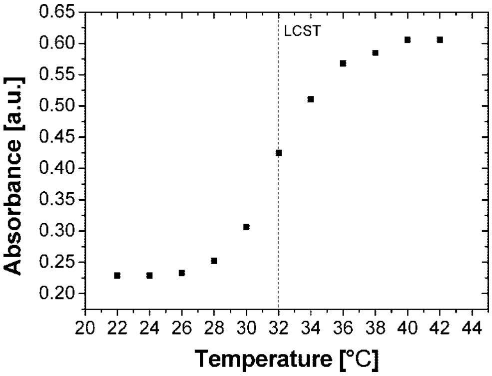


Figure 4. Absorbance (λ_{ex} = 500 nm) of PNIPAM/QD microspheres as a function of temperature. The LCST temperature is determined to be 32 °C by plotting the first derivative of the data.

the signature of the LCST transition of the polymer.

The increase of the absorbance is related to the structural modifications of the PNIPAM latex. When heating the solution and crossing LCST, water is expelled from the particles interior and the polymer microgel collapses and shrinks, increasing the refractive index and thus the scattering of light.

The LCST temperature determined by plotting the first derivative of the data obtained was equal to 32 °C (same value as the LCST of PNIPAM spheres without QDs), indicating that the QDs do not interfere with the LCST behavior of the polymer and that the temperature responsiveness of the assemblies is retained.

In conclusion, a method for effective incorporation of QDs into PNIPAM polymeric matrix by water-based copolymerization was presented. A novel, designer polymeric coating for hydrophobic QDs was synthesized and used to transfer the QDs from a nonpolar to aqueous medium. Inverse miniemulsion photopolymerization without initiator and using a modified sorbitol surfactant Span 80 resulted in full incorporation of QDs inside the PNIPAM spheres. TEM and confocal images showed that the QDs are uniformly distributed inside the microspheres and that the luminescence properties of the QDs are preserved. Upon incorporation of the QDs inside the spheres, the PNIPAM retained its temperature responsive behavior. The thermoresponsive PNIPAM/QD assemblies presented in this study may be explored in the context of their applications in thermometry, biosensing, and temperature-modulated bioimaging and as temperature-controlled drug delivery systems. We believe that our method has a generic use, i.e., that it can be used for the introduction of QDs into other vinyl polymer networks. Thus, a wide spectrum of different functionalities may be investigated, omitting the critical step of ligand exchange and overcoming problems of luminescence stability of the QDs.

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Supporting Information Available: Experimental details for synthesis of the amphiphilic polymer bearing acrylic ester functional groups, ^{1}H NMR spectra of the amphiphilic polymer, suspension of the QDs with amphiphilic polymer, copolymerization of functional QDs with PNIPAM, technical details of spectroscopy and microscopy. This material is available free of charge via the Internet at http://pubs.acs.org/.

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