Formation and Size Tuning of Colloidal Microcapsules via Host-Guest Molecular Recognition at the Liquid-Liquid Interface

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Introduction

Self-assembled microcapsules have great potential as multifunctional scaffolds for microreactors and carriers for catalysts, enzymes, and drugs. The essential prerequisite for these applications is the fabrication of robust and stable microcapsules. Various types of microcapsules (such as polymeric microcapsules, vesicles, and colloidal microcapsules) have been synthesized so far for these applications. Colloidal microcapsules are particularly interesting systems, exhibiting unique features including mechanical stability and tunable permeability, as well as the ability to integrate the physical properties of their precursor particle building blocks.

The general approach to designing colloidal microcapsules is to use emulsion droplets as a template to self-assemble and cross-function of the water–oil interface. Recently, significant advances have been made in the area of colloidal microcapsule engineering through covalent cross-linking of the particles.

Molecular recognition mediated self-assembly is an attractive alternative to these covalent strategies, introducing the potential for dynamic systems. Molecular recognition provides a unique opportunity for creating microcapsules with stimuli-responsive properties. Specifically, we cross-link β-cyclodextrin (β-CD, “host”) and adamantane (ADA, “guest”) functionalized gold nanoparticles at the oil–water interface to create microcapsules. The size of these microcapsules is tunable via recognition-induced coalescence of the capsules.

Herein, we report the fabrication of colloidal microcapsules via “host–guest” molecular recognition at the oil–water interface. Specifically, we cross-link β-cyclodextrin (β-CD, “host”) and adamantane (ADA, “guest”) functionalized gold nanoparticles at the oil–water interface to create microcapsules. The size of these microcapsules is tunable via recognition-induced coalescence of the capsules.

Experimental Section

Chemicals. Chemicals were obtained from commercial sources and were used as received unless otherwise stated. Millipore-Q water with a resistivity greater than 18 MΩ·cm was used in all experiments. Tetraethylene glycol mono-adamantyl ether and β-CD functionalized Au nanoparticles were synthesized as described before. NMR spectra were recorded on Varian spectrometers.
Patra et al. Letter

400 MHz spectrometer. Elemental analysis results were obtained on a FlashEA 1112 CHNS analyzer.

Synthesis of ADA-Disulfide Ligand. To a solution of tetraethylene glycol mono-adamantyl ether (205 mg, 0.63 mmol) and thioctic acid (103 mg, 0.50 mmol) in dry CH$_2$Cl$_2$ (5 mL) were added 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC, 105 mg, 0.55 mmol) and 4-dimethylaminopyridine (DMAP, 24 mg, 0.20 mmol). The reaction mixture was allowed to stir under argon overnight. The solvent was concentrated under reduced pressure, and the residue was purified by column chromatography (40% EtOAc in hexane) to afford the ADA ligand as a yellow oil (196 mg, yield 76%). $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) = 4.20 (2H, t), 3.67 (2H, t), 3.63 (8H, s), 3.56 (5H, m), 3.12 (2H, m), 2.43 (1H, m), 2.33 (2H, t), 2.11 (3H, s), 1.88 (1H, m), 1.72 (6H, s), 1.63 (10H, m), 1.44 (2H, m). $^{13}$C NMR (400 MHz, CDCl$_3$) δ (ppm): 173.43, 72.23, 71.27, 70.63, 70.58, 70.57, 70.55, 69.15, 63.46, 59.23, 56.30, 41.45, 40.19, 36.44, 34.57, 33.92, 30.48, 28.71, 24.59. Anal. Calcd for C$_{26}$H$_{44}$O$_6$S$_2$: C, 60.43; H, 8.58; S, 12.41. Found: C, 60.61; H, 8.62; S, 12.37.

Ligand Exchange Reaction. Reduction of ADA-disulfide to ADA-dithiol was performed before place exchange reaction. In the next step, dodecanethiol-coated Au NPs (10 mg) were dissolved in 5 mL of CH$_2$Cl$_2$ and 50 mg of ADA-dithiol was added to the NP solution. Reaction mixture was purged with argon and stirred for 2 days at room temperature in a closed vial. The mixture was precipitated with ethanol and centrifuged. Purification of the NPs was achieved through redispersion in toluene.

Microcapsule Fabrication. In a typical procedure, 300 μL solution of NP2 (0.4 μM) in toluene was taken in an Eppendorf tube. In the next step, 10 μL aqueous solution (11 μM) of NP1 (final concentration 0.4 μM) and FITC dextran (fluorescein isothiocyanate functionalized dextran polymer; $M_w = 500$ 000 g mol$^{-1}$) was added. The heterogeneous mixture was vigorously shaken for 15 s using Amalgamator (blending speed: 4000 rpm). As a result, the solution appeared to be cloudy due to the formation of microemulsions. After 10–15 min, emulsions settled at the bottom of the tube and the supernatant liquid was washed several times with toluene prior to characterization.

Microcapsule Characterization. TEM images were acquired on a JEOL 100CX operating at 100 keV. Samples were drop-cast onto a carbon-coated copper grid, dried, and imaged. Both optical and fluorescence microscope images were taken on an Olympus IX51 microscope. For fluorescence images, an excitation wavelength of 470 nm and emission wavelength of >515 nm (green fluorescence) were used.

Results and Discussion

Cyclodextrins (CDs) are well-known molecular hosts capable of including small hydrophobic molecules inside their cavities in aqueous media. In particular, β-CDs have cavities of ∼7 Å in size and can selectively incorporate ADA molecules (∼7 Å) inside the hydrophobic cavity via host–guest recognition. Both CD and ADA functionalized nanoparticles (NPs) can act as

Microcapsules were created through standard water-in-oil emulsion methods. As an example, NP2 was dissolved in toluene, and then, an aqueous solution of NP1 and fluorescent dye was added. Vigorous shaking for 15 s resulted in the formation of stable emulsions. The supernatant liquid was washed several times with toluene, and microcapsules were analyzed both by optical and fluorescence microscope (Figure 1a,b). The size of the microcapsules fabricated by this procedure was 18.3 ± 9.3 μm. Emulsions formed using the particles separately provided unstable emulsions that rapidly coalesced, whereas cross-linked emulsions are stable for several days. Thus, the formation of stable emulsions (Figure 1a) confirmed sufficient and extended cross-linking between NP1 and NP2 at the oil–water interface via host–guest recognition.

To determine the nanostructure of these droplets, the microcapsules were drop-cast on carbon-coated grids for transmission electron microscope (TEM) analysis. Low-resolution TEM imaging (Figure 1c) depicts the dried capsule structure, whereas high-resolution TEM imaging (Figure 1d) revealed that the capsule is composed of a multilayer of closely packed cross-linked NPs.

An important aspect of host–guest chemistry is that the interactions can be disrupted by competing ligands, a possible means for weakening the assembly and potentially controlling microcapsule size. Size tunability of the colloidal microcapsule (Figure 2a) was demonstrated by sequential addition of an external amphiphilic “guest” ADA-TEG-OH (Scheme 1d) to the microcapsule in toluene. Addition of ADA-TEG-OH to the NP1-NP2 microcapsules interferes with the “host–guest” recognition between NP1 and NP2. As a result, interfacial cross-linking is disrupted and microcapsules coalesce with each other forming larger droplets (Figure 2b–e).

Conclusions

In summary, we have developed a noncovalent approach to fabricating colloidal microcapsule at the liquid–liquid interface based on molecular recognition. The reversible and dynamic nature of the specific recognition process provides a tool for structural manipulation, specially tuning the size of the microcapsules. Further studies aimed at controlling the size and release profile by external stimuli (i.e., temperature, redox potential) are under investigation and will be reported in due course.

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Supporting Information Available: Additional figures. This material is available free of charge via the Internet at http://pubs.acs.org.

Figure 2. (a) Size tunability of the colloidal microcapsule at different ADA-TEG-OH concentrations in the presence of stable microspheres, with overall NP1 and NP2 concentrations of 0.4 μM. Representative fluorescence microscopy images of different-sized microcapsules with varying ADA-TEG-OH concentrations (b) 0 mM, (c) 26 mM, (d) 37 mM, and (e) 47 mM.

multisite hosts/guests for molecular recognition,14 generating supramolecular assemblies.15 In the present study, we have synthesized hydrophilic β-CD functionalized Au NPs (NP1, size ~3 nm; Scheme 1d) as a functional host according to the literature reported procedure.16 The guest-functionalized hydrophobic NPs (NP2, size ~6 nm; Scheme 1d) were prepared by ligand exchange reaction of ADA-dithiol with 6 nm Au NPs.17

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