Cucurbituril Containing Supramolecular Nanomaterials

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7.1 Introduction

Smart functional nanostructures that are adaptive and responsive to different external stimuli (light, heat, pH, competitive guests, redox *etc.*) could be assembled in aqueous milieus by making use of supramolecular chemistry, which basically relies on reversible noncovalent interactions, including hydrogen bonding, π - π stacking, van der Waals forces or hydrophobic interactions.^{1,2} Host-guest inclusion complex formation is particularly appealing as high selectivity between the host and guest molecules provides dynamic but strong interactions and offers a number of possibilities in the design of supramolecular nanostructures with desirable topological diversity and programmable functions for specific applications.³⁻⁷ The macrocycles most commonly used as host molecules are cyclodextrins,⁸⁻¹⁰ pillarenes,¹¹ calixarenes¹² and cucurbiturils,¹³⁻¹⁷ and they can accommodate guest molecules in their cavities on the basis of shape and size complementariness. Among them, cucurbit[n]urils (CB[n]) are a relatively new class of macrocycles with versatile recognition properties and an ability to accommodate different organic guest molecules in aqueous solution with exceptionally high binding constants.¹³⁻¹⁷

In recent years, CB[*n*]-containing functional nanomaterials have been receiving increasing attention due to their versatile applications in areas including but not limited to theranostics, photonics, sensing and catalysis.^{18–22} CB[*n*]s can be employed in the preparation of these materials by making use of their host–guest complexation abilities with a variety of guests^{14–17,23–46} or by the conjugation of their functionalized derivatives to platforms having appropriate functional groups that will allow them to form nanomaterials.^{18,19,47–49}

This chapter provides an overview of the preparation and application of CB[*n*]-containing supramolecular nanomaterials. In Section 7.2, we discuss supramolecular nanostructures (*e.g.*, nanoparticles, micelles, vesicles and capsules) constructed through the host–guest chemistry of cucurbiturils, and in Section 7.3, we discuss nanostructures formed through the conjugation of functionalized CBs to appropriate platforms.

7.2 CB Containing Functional Nanostructures: Through Host–Guest Chemistry of CBs

Properly functionalized amphiphilic molecules consisting of hydrophobic and hydrophilic groups can self-assemble into various nanostructures in aqueous media.^{5,7,50} Depending on the nature of an amphiphile, whether it is a small molecule or a polymeric material, and on the ratio of hydrophilic to hydrophobic parts, the nanostructure could take the form of nanoparticles, micelles or higher-ordered aggregates such as vesicles.

These structures are also characterized by a packing parameter *P*, which is expressed mathematically as $P = V/AL$, where *V* is the volume, *L* the length of the hydrophobic part of the amphiphile and *A* the hydrophobic–hydrophilic interfacial area. As the value of *P* increases, spherical ($P = 1/3$), cylindrical ($P = 1/2$) and planar structures ($P = 1$) are formed.^{50a}

Amphiphilic molecules obtained through host–guest interactions of host macrocyclic molecules, such as calixarene, cyclodextrin and cucurbituril with suitable guest molecules called supra-amphiphiles, proved to be a promising building block for designing a new generation of smart delivery systems because of their dynamic nature that allows their reversibility as well as their biocompatibility and versatility.^{5,7}

Lately, by taking advantage of the abundant host–guest chemistry of CB homologues, a variety of functional and smart supramolecular aggregates have been prepared. Among the CB homologues, CB[7] for its good water solubility and CB[8] for its large cavity have been utilized extensively for these purposes. CB[8] is capable of simultaneously accommodating two guests inside its hydrophobic cavity, forming a ternary complex with methyl viologen (MV) and an electron-rich second guest, including naphthalene, pyrene and tryptophan (see Scheme 7.1).^{23–28} The charge transfer (CT) interaction between the electron deficient–MV and the electron-rich second

Scheme 7.1 Molecular structures of CB[8], 2,6-dihydroxynaphthalene and alkylated methyl viologen (MV) and their ternary complex formation.²³

guests, as well as the hydrophobic interaction, facilitates the formation of the ternary complex.

In this regard, the ability of CB[8] to form ternary complexes with suitably sized and functionalized guests have been extensively explored in the preparation of single-chain nanoparticles, of stimuli-responsive, reversible micelles and of pH-responsive prodrug micelles for the encapsulation, delivery and controlled release of drugs and bioactive nanostructures based on peptide amphiphile vesicles. In this section, the CB-assisted formation of nanostructures including micelles, vesicles, nanoparticles and colloidosomes is discussed.

7.2.1 Supramolecular Micelles and Vesicles

Micelle and vesicle formation through the ternary host–guest–guest interaction of CB[8], 2,6-dihydroxynaphthalene and alkylated methyl viologen (MV) (Scheme 7.1) was first reported by Kim *et al.* in 2002.²³ In this work, first supra-amphiphiles formed in water from the heteroternary complexation of CB[8] with MV derivatives and 2,6-dihydroxynaphthalene, and subsequently these supra-amphiphiles self-assembled into vesicles due to hydrophobic interactions between long alkyl chains. The length of the hydrophobic alkyl chains of MV was observed to be affecting the size and dispersion of the vesicles. While relatively monodisperse vesicles with a 20-nm diameter were obtained by MV-dodecyl, vesicles ranging in diameter from 20 nm to 1.2 μm were attained by MV-hexadecyl. In the absence of CB[8] and 2,6-dihydroxynaphthalene, only micelle formation of the MV derivative was observed.

Since the landmark paper by Kim *et al.*, the ternary complex formation ability of CB[8] has been utilized extensively in the construction of smart, self-assembled nanostructures, whose applications have been demonstrated in the stimuli-responsive nanocarriers of therapeutic cargos. For instance, supramolecular stimuli-responsive, reversible micelles²⁹ have been reported that are responsive to multiple external triggers, including temperature, pH and the addition of a competitive guest, and that can be used for the encapsulation of anticancer drug and controlled drug release.³⁰ To construct this nanocarrier, two types of copolymers were prepared; one of them was a pH-responsive poly(dimethylaminoethyl methacrylate) (PDMAEMA)-terminated naphthalene guest, and the second was a temperature-responsive poly(*N*-isopropylacrylamide) (PNIPAAm) terminated with a methyl viologen guest (Figure 7.1). These two polymers were allowed to form a ternary complex with CB[8] in water, and subsequently this supra-amphiphile self-assembled in water to form micelles. These micelles were loaded with the chemotherapeutic drug doxorubicin (DOX), and controlled drug release was achieved through a pH-triggered release within endosomal and lysosomal vesicles at around pH 4. Also possible was the controlled release of drugs *via* remote heating methods, such as infrared irradiation because of the temperature-responsiveness nature of DOX.

Figure 7.1 (a) Chemical structures of poly(*N*-isopropylacrylamide) (PNIPAAm), terminated with methyl viologen guest (1), poly(dimethyl-aminoethyl methacrylate) (PDMAEMA), terminated with naphthalene guest (2) adamantaneamine (Ad) (3); (b) supra-amphiphile formation through ternary complex of CB[8] and 1 and 2; (c) subsequent assembly into a micellar superstructure, hierarchical self-assembly of the supramolecular entity under different conditions and its subsequent mode of drug release after being exposed to different triggers.

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When drugs are loaded into the nanocarriers by noncovalent interactions, they could be prematurely released, which is not desirable for efficient drug delivery. Thus, conjugating the drugs to the carriers through a covalent bond, which can be cleaved under an appropriate stimulus, could improve the effectiveness of the delivery systems. To circumvent this drawback, pH-responsive supramolecular prodrug micelles based on CB[8] for intracellular drug delivery was prepared (Figure 7.2).³¹ Methyl viologen was conjugated to doxorubicin (MV-DOX) through hydrazone bonds that could be cleaved under an acidic medium, and, as a second block, naphthalene-terminated poly(ethylene glycol) (PEG-Np) was prepared. First, a ternary complex was obtained by mixing PEO-Np, MV-DOX and CB[8] in an equimolar ratio, and subsequently this amphiphilic ternary complex self-assembled into micelles in water. By hydrolyzing the hydrazone linkage, DOX molecules were cleaved from the micelles, and a faster drug release was observed at pH 5 than at the physiological pH 7.4.

Bioactive nanostructures could also be constructed through the self-assembly of supra-amphiphiles based on the ternary complexes of CB[8]. These nanostructures are of great interest in many biomedical applications, including tissue engineering, regenerative medicine and drug delivery.

Supramolecular peptide vesicles were reported by Sherman and coworkers that was prepared through the host-guest complexation of CB[8]^{32a} with a peptide sequence terminated with pyrene, which acted as one of the guests for CB[8] as well as a fluorescent sensor. A second-guest, viologen unit was

Figure 7.2 Schematic presentation of pH-responsive supramolecular prodrug micelle formation through ternary complexation of CB[8] with methyl viologen-conjugated doxorubicin (MV-DOX) and naphthalene-terminated poly(ethylene glycol) (PEO-Np) for intracellular drug delivery. Reproduced from ref. 31 with permission from the Royal Society of Chemistry.

conjugated to a long hydrophobic linker. Vesicle formation was achieved by the self-assembly of suprapeptide amphiphiles resulting from the ternary complex of pyrene- and viologen-containing blocks (Figure 7.3). These vesicles exhibit a stimuli-responsive behavior and can undergo disassembly in the presence of competitive guests, such as 2,6-dihydroxynaphthalene and 1-adamantylamine. The assembly and disassembly processes can be monitored through the changes in the emission intensity of pyrene units as the emission of pyrene is quenched upon formation of vesicles but is recovered when the vesicles undergo disassembly in the presence of the competitive guests. It was also shown *in vitro* that these vesicles were effectively internalized by HeLa cells and that their toxicities could be regulated using an appropriate stimulus. The same group also demonstrated CB[8] ternary complexation-mediated formation of the polymeric peptide-amphiphile-based vesicle at the physiological temperature for the encapsulation and release of the basic fibroblast growth factor (bFGF).^{32b}

A systematic study of the ternary complex formation process for aromatic amino acids using CB[8] and a viologen amphiphile shows that the affinity of the amino acid needs to be higher or in a comparable range to that of CB[8] for the amphiphile to form the ternary complex.³³ By taking these results into account, a supramolecular peptide amphiphile was prepared containing an azobenzene group at the N-terminus of the peptide to serve as a second guest for CB[8]. The vesicles formed by the self-assembly of this peptide amphiphile exhibit stimuli-responsive behavior toward a number of external stimuli such as light and competitive guests. Azobenzene groups can respond to the light through *cis-trans* isomerism; *trans*-isomer fits well in the cavity of CB[8], but *cis* isomer does not. Thus, irradiation of vesicles with UV-light at 365 nm causes their disassembly through *cis* isomer formation of azobenzene. Assembly and disassembly of the vesicles can be controlled by using an appropriate wavelength as well as the addition of the guest 1-adamantylamine or 2,6-dihydroxynaphthalene, both of which are known to have a high affinity toward CB[8].

It was also demonstrated by Jonkheijm *et al.* that CB[8]-based supramolecular amphiphiles-based vesicles can be employed for the encapsulation of proteins and their delivery into cells.³⁴ Vesicles about 200 nm in diameter were formed by the self-assembly of ternary complexes of CB[8], an alkylated paraquat derivative and a tetraethylene glycol-functionalized azobenzene (Figure 7.4). Their outer surfaces were functionalized with cell-targeting ligands, and these vesicles were utilized as supramolecular nanocarriers.

Liu *et al.* very recently reported highly stable giant supramolecular vesicles constructed by hierarchical self-assembly of CB[8]-based supra-amphiphiles for photoresponsive and targeted intracellular drug delivery.³⁵ Again, first a supra-amphiphile was constructed through the ternary complex formation of CB[8] with hydrophilic and hydrophobic blocks containing the guests' methyl viologen and photoresponsive azo moiety (Figure 7.5). This amphiphile simultaneously forms vesicles in water through self-assembly. The size and morphologies of these vesicles are determined by light microscopy and

Figure 7.3 The chemical structures of pyrene-imidazolium-labeled peptide and viologen-functionalized PNIPAAm; their ternary complex with CB[8] and the subsequent temperature-induced formation of a supramolecular polymeric peptide vesicle. Reproduced from ref. 32a with permission from John Wiley & Sons, Copyright © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

Figure 7.4 (a) Formation of a supramolecular amphiphile through a ternary complex of CB[8] with methyl viologen linked to a hydrophobic alkyl chain (MV) and azobenzene linked to a hydrophilic oligo(ethylene glycol) chain (azo); (b) vesicles loaded with teal, yellow and red fluorescent proteins (TFP, YFP, TagRFP) as cargo and decorated with azoRGD peptide ligands for targeting; (c) molecular structures of MV, azo, azoRGD and CB[8]. Reproduced from ref. 34 with permission from the Royal Society of Chemistry.

Figure 7.5 Chemical structure of azo and viologen attached guests, their ternary complex formation with CB[8] and the schematic representation of photoresponsive giant vesicles from the supra-amphiphiles. Reproduced from ref. 35 with permission from American Chemical Society, Copyright 2018.

electron microscopies (SEM and TEM). It was observed that they had a spherical shape with a uniform size in the range of 0.8–1 μm (Figure 7.6). It was demonstrated that these vesicles can encapsulate drug molecules in high loading capacity, and light-triggered drug delivery can be achieved using these nanocarriers. Moreover, through the maleimide units on the surface of the vesicles, several biomolecules can be attached as a targeting group for the control drug delivery.

Recently, Yu Liu and coworkers demonstrated that the morphology of supramolecular aggregates can be controlled by suitable external stimuli.³⁶ They constructed lamellar and helical supramolecular assemblies using CBs and a naphthalene diimide derivative and showed that the formation of the lamellar assembly could be reversibly photocontrolled *via* competitive binding with α -cyclodextrin and water-soluble azobenzene (Figure 7.7).

7.2.2 Supramolecular Nanoparticles

If supra-amphiphiles are based on the host–guest chemistry of macrocyclic hosts with large macromolecules decorated with suitable multiple guests, less well defined structures with higher solid contents form, and these aggregates can be called nanoparticles. Their sizes and morphologies can also be controlled by carefully tuning the structure of the macromolecules and the reaction conditions. Their assembly and disassembly can also be easily

Figure 7.6 Microscope images of giant photoresponsive vesicles (a) optical microscope; (b) SEM; (c) TEM; and (d) DLS histogram. Reproduced from ref. 35 with permission from American Chemical Society, Copyright 2018.

controlled by triggering with suitable stimuli if they possess stimuli-responsive features. These stimuli-responsive nanoparticles can be utilized as biomedical delivery vehicles.

To this end, the host-guest chemistry of CB[8] was also successfully utilized in the preparation of single-chain nanoparticles by installing both guests on the same polymer chain. This approach proved to be very convenient for the synthesis of nanoparticles with well-defined shape, size and composition.³⁷ For the preparation of these nanoparticles, poly(*N*-hydroxyethyl acrylamide) polymers were prepared by atom transfer radical polymerization (ATRP) and were functionalized using an isocyanate conjugation with guest moieties (MV^{2+} and Np) for complexation with CB[8]. By tuning the concentration of polymers and CB[8], the size and dispersity can be controlled. When CB[7] was used as a host instead of CB[8], no nanoparticle formation was observed.

Limited examples have been found in literature where the strategy of controlled and reversible host-guest supramolecular chemistry was adapted to prepare core-shell polymeric microspheres. In the following example, CB[8]-based, core-shell polymeric microspheres with a cleavable shell is prepared in water, where CB[8] is used as supramolecular “handcuff” to lock 2-naphthol-functionalized linear acrylate polymers (shell) onto a methyl viologen-functionalized polymeric microsphere (core).³⁸ The polymeric shell

Figure 7.7 Formation of lamellar and helical supramolecular assemblies using CB[7], CB[8] and naphthalene diimide derivatives and the reversibility of the lamellar assembly *via* competitive binding with α -cyclodextrin and water-soluble azobenzene. Reproduced from ref. 36 with permission from the Royal Society of Chemistry.

and the microsphere core are linked *via* CB[8]-mediated ternary complex with the residues of Np and MV^{2+} (Figure 7.8). The strategy of switching the cytotoxicity of the forming microspheres has extended the range of potential applications in cancer therapy.

Huskens *et al.* developed a multicomponent supramolecular nanoparticle fabrication method based on heteroternary CB[8] complexes.²¹ In this method, CB[8] was utilized as a cross-linker to link viologen and naphthol-containing dendrimer and polymers, namely, methyl viologen-poly(ethylene imine) (MV-PEI), naphthol-poly(ethylene glycol) (Np-PEG) and naphthol₈-poly(amidoamine) (Np₈-PAMAM). The formation of nanoparticles was thermodynamically controlled, and time and temperature were noted to affect their formation rate.³⁹ Their sizes can also be controlled by varying the concentrations of multivalent core and monovalent shell-forming stopper molecules while keeping the ratio of MV/Np/CB[8] at 1 : 1 : 1. Disassembly of these nanoparticles was shown to be achieved by using a reducing agent that decreases the dicationic MV species to MV^+ radical cations, which undergo stable homoternary complex formation in one CB[8] by releasing the Np guests; this, in turn, causes the disassembly of the particles. As a follow-up of this work, the same group substituted Np guest units with azo groups to add

Figure 7.8 Reversible preparation of core-shell polymeric microspheres *via* the formation and dissociation of CB[8] ternary complex. Reproduced from ref. 38 with permission from the Royal Society of Chemistry.

to their system photo responsiveness.⁴⁰ Light-triggered *cis-trans* isomerism of azo groups caused self-assembly and disassembly of the nanoparticles. Under UV light (350 nm), *trans*-azo isomer turned into *cis*-isomer by causing a disruption of the nanoparticles (Figure 7.9). In order to increase the stability of the nanoparticles in the biological media, the same group utilized a slightly different strategy in which, instead of PEG, they used zwitterionic motif as an antifouling agent.⁴¹ These nanoparticles exhibit pH-dependent aggregation and photoresponsive disassembly.

Recently the theranostic applications of these nanostructures *in vitro* and *in vivo* have also been demonstrated.^{42,43} Theranostic platforms combine therapeutic and diagnostic agents in one platform and work on the principle of “detect” and “repair”.⁵¹ While therapeutic agents, including drugs, proteins and genetic materials, are delivered, their journey can be followed by imaging agents found in the same system. The use of a nanostructured platform for this purpose provides many opportunities. The nanostructures with diameters smaller than 100 nm, which are much smaller than normal human cells, interact quite strongly with biomolecules such as enzymes, receptors and antibodies, both on the surface and inside the cell. Moreover, attaching suitable targeted groups to these systems would make the targeted delivery of the therapeutic agents possible. This approach provides the efficient delivery of therapeutic agents to the target, can minimize their nonspecific systemic distribution and, in turn, decrease systematic toxicity.

Theranostic nanoparticles were prepared from the self-assembly of an amphiphilic brush copolymer composed of the ternary complex of tetraphenylethene and 4,4'-bipyridinium substituted polymer (PTPE) and PEGylated naphthol (PEG-Np).⁴² These nanoparticles can be used to encapsulate the anticancer drug doxorubicin (DOX) in its hydrophobic core, establishing a Förster resonance energy transfer (FRET) system, in which the tetraphenylethene (TPE) group acts as a donor and the drug molecule DOX acts as an acceptor (Figure 7.10). When the DOX-loaded nanoparticles enter the cells with the help of intracellular reducing agents and a low-pH environment, they are disassembled, and the loaded drug molecules are released. The disassembly process was monitored by the recovery of fluorescent upon the release of the DOX drug molecules when the energy transfer was interrupted. It was shown that DOX-loaded nanoparticles were very effective in killing the HeLa cells. *In vivo* experiments demonstrated that these DOX-loaded nanoparticles accumulated in tumorous regions.

Liu *et al.* reported a two-stage mediated near-infrared (NIR) emissive supramolecular assembly for lysosome-targeted cell imaging.⁴³ For this purpose, 4,4'-anthracene-9,10-diylbis(ethene-2,1-diyl)bis(1-ethylpyridin-1-ium) bromide (ENDT) was synthesized as an organic dye with weak fluorescence emission at 625 nm. When ENDT complexes with CB[8], this binary supramolecular complex assembles into nanorods with a near-infrared fluorescence emission (655 nm) and fluorescence enhancement as the first stage (Figure 7.11). Such supramolecular complexes interact with lower-rim

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Figure 7.10 (a) Doxorubicin (DOX)-loaded nanoparticles prepared from the self-assembly of an amphiphilic brush copolymer composed of the ternary complex of tetraphenylethene and 4,4'-bipyridinium substituted polymer (PTPE) and PEGylated naphthol (PEG-Np); (b) monitoring drug release through an increase in the fluorescent emission. Reproduced from ref. 42 with permission from American Chemical Society, Copyright 2017.

Figure 7.11 Schematic presentation of a two-stage mediated near-infrared (NIR) emissive supramolecular assembly for lysosome-targeted cell imaging. Reproduced from ref. 43 with permission from John Wiley & Sons, Copyright © 2018 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

dodecyl-modified sulfonatocalix-[4]arene (SC4AD) to form nanoparticles for further fluorescence enhancement as the second stage. Furthermore, based on a costaining experiment with LysoTracker™ Blue, such nanoparticles can be applied in NIR lysosome-targeted cell imaging.

As can be seen from these examples, in the formation of self-assembled supramolecular aggregates, mostly the ternary complex formation ability of CB[8] has been employed. The examples involving CB[7]-mediated supramolecular aggregates are rather limited. Recently, Garcia-Rio *et al.* reported the preparation of supramolecular nanoparticles through the complexation of a zwitterionic surfactant, sulfobetaine, with CB[7].⁴⁴ The size of the nanoparticles was determined as 172 nm by dynamic light scattering (DLS) and cryo-TEM. These nanoparticles are observed to be stable after more than 2 weeks in an aqueous medium. The reversibility of the sulfobetaine/CB[7] host-guest complexes allows SNP disaggregation by adding a competitive guest, as shown by treatment with tetraethylammonium chloride. The addition of this competitive cation triggers an SNP-to-micelle transition. The potential application of these nanoparticles as drug delivery vehicles was investigated using carboxyfluorescein. These experiments revealed that, upon externally induced disruption of the SNPs (by tetraethylammonium chloride), the fluorescent dye was trapped in micellar aggregates that can be further disrupted by cyclodextrin addition.⁴⁴

In another work, Nau *et al.* reported the tunable nanostructure formation using an amphiphilic guest molecule for the differently sized CB[*n*] homologues.⁴⁵ Supramolecular complexation between CB[7] and an amphiphilic pyridinium-functionalized anthracene (AnPy) in aqueous solution led to nanoparticle formation, whereas the complexation of AnPy with CB[8] led to the formation of nanorods (Figure 7.12). Hence, the CB[7] cavity is capable of accommodating the pyridinium moiety, while CB[8] can simultaneously encapsulate both the pyridinium and anthracene moieties. Both assemblies show responsive properties. For example, the CB[7]-AnPy particles can be assembled and disassembled by changing the temperature. This approach can be used to potentially construct various responsive CB[*n*]-based self-assembled materials for drug delivery applications.

7.2.3 Supramolecular Microcapsules

Microcapsules can be utilized in a variety of practical applications such as sequestering biomolecules, storing and delivering drugs, transporting vaccines, as well as being used in self-healing materials. Moreover, they can be used as microreactors to mimic cell-catalyzed biological reactions.⁵²

Although the use of the supramolecular approach, especially host-guest interactions, can offer many additional features such as stimuli-responsive behavior and reversibility, the examples are rather limited. Sherman *et al.* reported a series of seminal works on monodisperse supramolecular microcapsules, fabricated through the integration of traditional microfluidic techniques and interfacial host-guest chemistry, specifically CB-mediated

Figure 7.12 The tunable nanostructure formation using an amphiphilic guest molecule for the differently sized CB[n] homologues. Reproduced from ref. 45 with permission from the Royal Society of Chemistry.

host-guest interactions (Figure 7.13).^{46,53–59} They employed three methods for the microcapsule fabrication: colloidal particle-driven assembly, interfacial condensation-driven assembly and electrostatic interaction-driven assembly. They also studied systematically the design criteria required for structural complexity with the desirable functionality and demonstrated their proof-of-principle applications in cargo delivery. On account of its dynamic nature, the CB-mediated host-guest complexation has demonstrated efficient response toward various external stimuli such as UV light, pH change, redox chemistry and competitive guests. It has also demonstrated different microcapsule modalities, which are engineered with a CB host-guest chemistry and also can be disrupted with the aid of external stimuli, for a triggered release of payloads.

7.3 CB Containing Functional Nanostructures: Through Functionalized-cucurbituril Derivatives

Although functionalized CB-based nanostructures with many interesting properties and features could be suitable in a variety of applications,

Figure 7.13 (a) Schematic illustration of supramolecular polymer microcapsules assembled at the interface of microfluidic droplets. By using a microfluidic flow-focusing device, an aqueous phase carrying CB[8] and first guest-containing polymer 1 intersects with another phase consisting of second guest-containing polymer 2, at flow-focusing microchannel junctions to form a periodic flow of oil-in-water microdroplets. (b) Stepwise formation of a supramolecular heteroternary complexation of CB[8] and guest 1 (electron deficient, such as methyl viologen) and then guest 2 (electron rich, such as naphthol, azobenzene, benzyl, phenylalanine *etc.*). Reproduced from ref. 46 with permission from American Chemical Society, Copyright 2017.

including theragnostic, photonics and catalysis, examples in the literature are rather limited. In this section, we are going to discuss the research efforts on functionalized CB-based nanoparticles, and in Chapter 10, Kim and co-workers discuss the CB[6]-based nanocapsules.

The first example of functionalized CB-based nanoparticles was reported by Kim and coworkers after they developed a convenient method for the synthesis of perhydroxylated CBs that opened the possibility of practical applications of CB[6]-based nanomaterials in a variety of applications, such as nanomedicine and catalysis.⁴⁷ Nanoparticles around 200 nm in diameter were prepared from functionalized CB[6]-derivative (3-(6-hydroxyhexanethio)-propan-1-oxy)₁₂CB[6],

Figure 7.14 Schematic presentation of UVA- (sunlight)-triggered, GSH-responsive PTX-loaded nanoparticle prepared from AO₁₂CB[6] and their chemical structures.

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which was synthesized by photoreaction between (allyloxy)₁₂CB[6] (AO₁₂CB[6]) and 6-mercaptohexanol in methanol. They demonstrated that functionalized CB-based nanoparticles could be utilized as an efficient carrier for the delivery of hydrophobic drugs.

Wang *et al.* prepared nanoparticles from perallyloxy-CB[6] (AO₁₂CB[6]) using a mini emulsion method and loaded these nanoparticles with the anticancer drug paclitaxel (PTX) (Figure 7.14). These nanoparticles were observed to be light irradiated, glutathione (GSH) responsive. Under light and in the presence of GSH, allyl groups of CB[6] react with the thiol groups of GSH *via* thiol-ene click reaction, and the resulting functionalized CB[6] becomes more hydrophilic. This, in turn, causes the disassembly of the nanoparticles by the release drug molecules. The authors observed that drug-loaded nanoparticles not only exhibited efficient cellular uptake but also significantly increased the cytotoxicity and apoptosis rate of cancer cells, with remarkably reduced cytotoxicity against noncancerous cells under UVA light irradiation.

Following up on their previous work, Wang *et al.* developed a new strategy for the preparation of biocompatible nanoparticles. For this purpose, functionalized CB[7] was decorated with poly(lactic acid) (PLA)/poly(lactic-co-glycolic acid) (PLGA) and subsequently converted into nanoparticles (Figure 7.15).⁴⁹ The surface of these nanoparticles could be further functionalized due to the available cavity of CB[7] as a host. A variety of guests, including amantadine-conjugated folate, polyethylene glycol, and fluorescein isothiocyanate and drug molecules, were used to demonstrate the application of these nanoparticles as a theranostic platform.

Figure 7.15 (a) Synthesis of CB[7]-PLA; (b) schematic presentation of CB[7]-PLA-based nanoparticle and the noncovalent surface modification of nanoparticles with a variety of functionalities. Reproduced from ref. 49 with permission from American Chemical Society, Copyright 2018.

7.4 Conclusion

In this chapter, we discussed CB-based supramolecular nanostructures. In the first section, nanostructures prepared by taking advantage of the rich-host chemistry of CB homologues were reviewed. Particularly, the ternary complex formation of CB[8] with electron-rich and electron-deficient guests through charge transfer was extensively applied in the preparation of a variety of nanostructures, including micelles, vesicles and nanoparticles. In their preparation, first a supra-amphiphile, formed through the ternary complex formation of CB[8] with two other guests and subsequent self-assembly, turned into micelles, vesicles and nanoparticles in water. Depending on the structures of the supra-amphiphile, a number of different properties are added to these nanostructures. For instance, they can be photo or pH sensitive, and their assembly and disassembly processes can be controlled by triggering light, pH, redox potential and competitive guests. Applications of these nanostructures were also demonstrated in drug delivery and in general theranostics. Microcapsules were also prepared through the ternary complex formation ability of CB[8] and making use of the advantages of microfluidics. Resulting microcapsules were reversible and stimuli responsive.

In the second section of the chapter, nanostructures prepared from functionalized CB derivatives were discussed. Although this approach offers many unprecedented opportunities in the area of nanostructured materials, it is not well explored. Currently there are only a handful of examples in the literature, but we think there will be more to come in the near future.

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