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Review

Supramolecular nano drug delivery systems mediated *via* host-guest chemistry of cucurbit[*n*]uril (*n* = 6 and 7)

Shengke Li[a,*,1], Yan Gao[b,1], Yuanfu Ding[b], Anni Xu[a], Huaping Tan[a]

[a] School of Materials Science and Engineering, Nanjing University of Science and Technology, Nanjing 210094, China
[b] State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macau, China

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ABSTRACT

As a novel family of macrocyclic molecules, cucurbit[*n*]urils (CB[*n*]s) have emerged as promising building blocks of supramolecular nano drug delivery systems (SNDDS) in recent years. Direct encapsulation of amphiphilic guests by CB[6] and CB[7] can modulate their amphiphilicity, resulting in formation of supramolecular amphiphiles that self-assemble into supramolecular nanoparticles for drug delivery. Additionally, CB[*n*]'s host-guest chemistry on the surface of mesoporous nanoparticles makes CB[*n*] an ideal blocking agent to control drug release from delivery vehicles. These SNDDS possess intrinsic stimuli responsiveness towards external guest or host, which can further incorporate responsiveness to a variety of other stimuli including pH, thermal, redox, photo and enzyme, to realize multiple stimuli-responsive drug release. Moreover, the recent breakthrough in direct functionalization of CB[*n*]s has provided a feasible method for preparing superior CB[6] and CB[7] derivatives that can be employed to build multifunctional SNDDS with unoccupied macrocycles located on surface, which could be decorated with various functional "tags" through host-guest chemistry. In this review, we summarized the recent progress of CB[6] and CB[7] based SNDDS through formation of supramolecular amphiphiles, supramolecular nanovalves as well as supramolecularly tailorable surface, which we hope to further promote the development of CB[*n*]s family as building blocks for advanced SNDDS.

1. Introduction

Supramolecular architectures often rely on dynamic non-covalent interactions, including hydrogen bonding, electrostatic interaction, ion-dipole/dipole-dipole interactions, hydrophobic interaction, π-π stacking, and host-guest interaction [1–3]. Among them, macrocycle based host-guest interaction has been considered as a versatile solution to construct multifunctional, reversible supramolecular assemblies for various fascinating applications [4–8]. Cucurbit[*n*]urils (CB[*n*]s, *n* = 5–8, 10) are condensation products between glycoluril and formaldehyde in strong acidic solutions, forming rigid macrocycles with *n* glycoluril units linked by 2*n* methylene groups at each side [9–11]. The rigidity of CB[*n*] macrocycles endows CB[*n*]s remarkable thermal and chemical stability, however it also makes it challenging to introduce functional groups onto CB[*n*]s molecules [12]. The most attracting feature of CB[*n*]s is their strikingly high affinity and selectivity towards encapsulated guests in an aqueous solution, resulting from synergistic contributions of hydrophobic effect inside cavity and ion-dipole interactions adjacent to carbonyl portal [10,13,14]. Zhang *et al.* and Xu *et al.* have developed a plethora of inspiring supramolecular assemblies for efficient supramolecular chemotherapy of cancer *via* CB[*n*]-mediated host-guest chemistry [15–17]. In addition, CB[*n*]-based supramolecular antibiotics were also pioneered with a great success [18–20]. CB[*n*]-mediated host-guest chemistry also has been extensively investigated in construction of supramolecular nano drug delivery systems (SNDDS) [4,10,14,21–23]. For instance, CB[6]'s encapsulation of an amphiphilic molecule was found to significantly decrease its critical micelle concentration (CMC), resulting in the formation of supramolecular nanoparticles for drug delivery at much lower concentrations [24]. Additionally, CB[7]-mediated supramolecular (pseudo)rotaxanes were also employed to build responsive nanovalves for the controlled release of cargoes from mesoporous nanoparticles [25]. The unique ability of CB[8] in forming stable ternary complexes by simultaneous encapsulation of two guests into its cavity makes CB[8] an ideal molecular "glue or handcuff" to construct various supramolecular drug delivery vehicles including supramolecular vesicles, supramolecular organic framework and

* Corresponding author.
E-mail address: lisk@njust.edu.cn (S. Li).
[1] These two authors contributed equally to this work.

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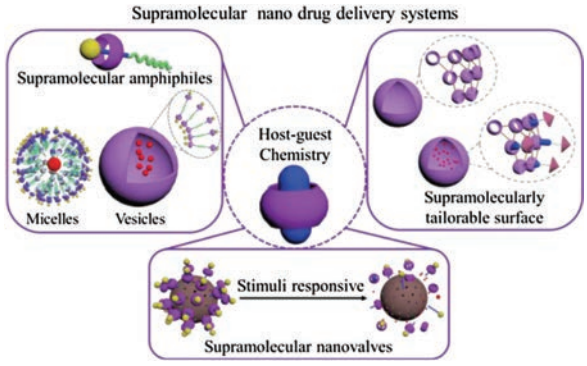
supramolecular nanocapsules [26–28]. Moreover, with CB[6] and CB[7] derivatives, nanocapsules with unoccupied macrocycles on the surface were prepared, which can be further decorated with targeting groups, imaging groups, and sheath groups through host-guest chemistry [29]. In this review, we summarized the recent advances in constructing SNDDS mediated *via* host-guest chemistry of CB[6] and CB[7] (Scheme 1). As this summary was only focused on the inclusion host-guest complex of CB[6] and CB[7] for SNDDS, nano-assemblies formed through ion-dipole interactions between cations and carbonyl portal of CB[*n*]s were not covered in this discussion [30–33]. To have a strategic focus on binary host-guest complexation based SNDDS, CB[8] based SNDDS are excluded from the current review. At the end of this article, a summary about the endeavors to promote the development of CB[*n*]s family as building blocks for advanced SNDDS as well as an outlook discussion about the possible future direction of this research area are presented.

2. Supramolecular amphiphiles mediated *via* host-guest chemistry of CB[*n*]

CB[6] and CB[7] are often employed to modulate the amphiphilicity of surfactants or act as a hydrophobic or hydrophilic end through direct encapsulation of guests. CB[6] is poorly soluble in water, while CB[7] possesses superior water solubility among CB[*n*]s family [9]. Therefore, CB[6] plays different roles from CB[7] in forming supramolecular amphiphiles. SNDDS constructed from self-assemblies of supramolecular amphiphiles possess intrinsic stimuli-responsiveness towards competitive guests or hosts, as competitive host-guest binding would impact the stability of nanostructures by dissociating the original host-guest interaction (Scheme 2).

2.1. CB[6] based supramolecular amphiphiles

Supramolecular encapsulation of amphiphiles by CB[6] often decreases their CMC value, resulting in the formation of supramolecular nanostructures at lower concentrations. With this principle, Zhou and Zhang *et al*. reported the construction of supramolecular vesicles through encapsulation of surfactants *N,N′*-hexamethylenebis (1-octyl-4-carbamoyl pyridinium bromide) (HBPB-8) by CB[6] [34]. Later, they reported the transformation of micelles solely formed by surfactant into stable supramolecular vesicles by involving the simultaneous inclusion of the surfactant by CB[6] and CB[7], where CB[7] acted as a hydrophilic head while CB[6] played a role in increasing the hydrophobicity of the tail [35]. A model drug 5-carboxyfluorescein (CF) was loaded into the relatively stable vesicles, nearly no premature release was observed even at temperature up to 95 °C. In 2016, Liu and co-workers demonstrated the loading of doxorubicin (DOX) into supramolecular nanoparticles constructed from self-assembly of the host-guest complexes between CB[6] and an alkyl chain-modified polyamine surfactant named DTA. The release of DOX could be triggered upon addition of a host α-cyclodextrin (α-CD) that could strongly bind the alkyl chain of DTA [24].



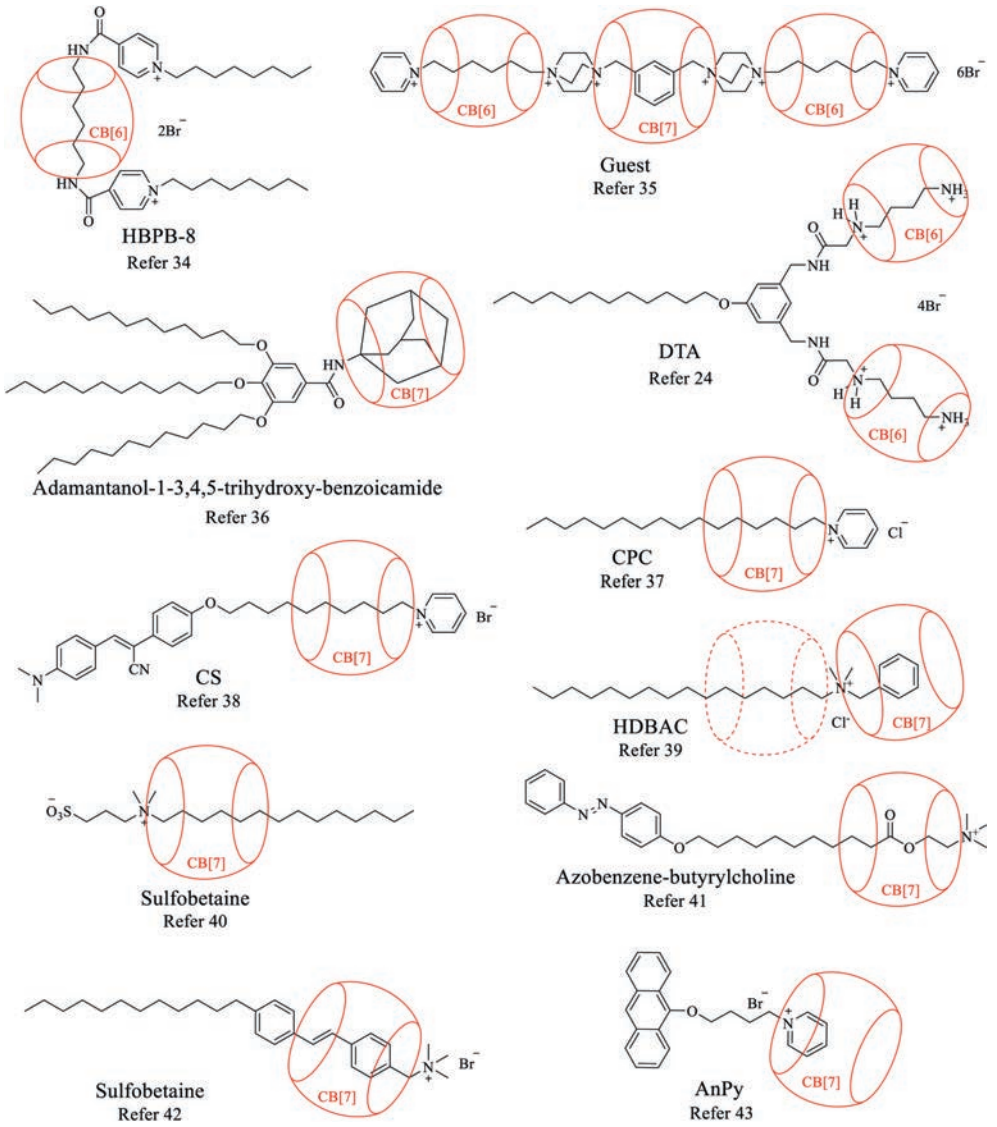
Scheme 1. CB[6] and CB[7] based supramolecular nano drug delivery systems through formation of supramolecular amphiphiles, supramolecular nanovalves as well as supramolecularly tailorable surface.

2.2. CB[7] based supramolecular amphiphiles

As mentioned above, with superior water solubility, the encapsulation of surfactants by CB[7] often leads to an increase of CMC value of the surfactants. CB[7] may also act as a hydrophilic head of supramolecular amphiphiles. In 2012, Liu and Luo *et al*. reported the construction of a supramolecular amphiphile *via* host-guest chemistry between CB[7] and an adamantanol-terminated hydrophobic chain, which subsequently self-assembled into supramolecular vesicles as promising SNDDS for controlled release of Rhodamine B [36]. The CMC value of a frequently used cationic surfactant cetylpyridinium chloride (CPC) was increased from 1.0 mmol/L to 1.63 mmol/L after forming guest-host complex with CB[7]. CB[7] was thus employed to disassemble Nile Red loaded micelles formed from CB[5]/CPC mixture with CMC value of 0.57 mmol/L [37]. CB[7] was also utilized to disassemble amphiphilic cyanostilbene (CS) based non-emissive vesicles through forming CB[7]-CS complex, giving a strong blue emission [38]. Interestingly, after CB[7]'s encapsulation of hexadecyl dimethyl benzyl ammonium chloride (HDBAC) with selective binding site at different equivalents, CB[7] was demonstrated to induce a transformation of HDBAC micelles into mixed morphologies including micelles, nanorods and nanosheets [39]. In addition, the addition of CB[7] into zwitterionic surfactants such as sulfobetaines was also found to shift up their CMC values without affecting surface tension. CB[7]-sulfobetaines host-guest complex formed very stable supramolecular nanoparticles with an average diameter of 172 nm, with negatively charged surface, and the controlled release of pre-loaded model drug CF was achieved upon addition of a competitive guest, tetraethylammonium chloride [40]. More importantly, supramolecular amphiphiles constructed from CB[7] and amphiphilic guest molecules with inherent stimuli responsive groups can self-assemble into multiple stimuli-responsive supramolecular nano-assemblies. For instance, Jiang and Zhou *et al*. reported the construction of photo- and enzyme-responsive SNDDS by incorporating azobenzene and butyrylcholine groups into supramolecular amphiphiles, resulting in the controlled release of DOX upon photo-irradiation, *via* enzyme hydrolysis, and addition of a competitive host, α-CD, respectively [41]. Yang and Hua *et al*. also reported photo triggered collapses of calcein loaded supramolecular vesicles self-assembled from supramolecular amphiphiles containing azobenzene group [42]. Moreover, the complexation of CB[7] with amphiphilic pyridinium-functionalized anthracene (AnPy) self-assembled into nanoparticles at high concentrations, which was found to be responsive towards temperature change and UV irradiation, suggesting the good potential for drug delivery applications [43].

3. Supramolecular nanovalves mediated *via* host-guest chemistry of CB[*n*]

CB[*n*]s can be used as gating agents on the surface of nanoparticles, *via* formation of host-guest complexes (*e.g.*, pseudorotaxanes, rotaxanes). CB[*n*] based (pseudo)rotaxane systems could be employed as nanovalves of inorganic nanoparticles for the controlled release of cargoes. CB[6] and CB[7] have been

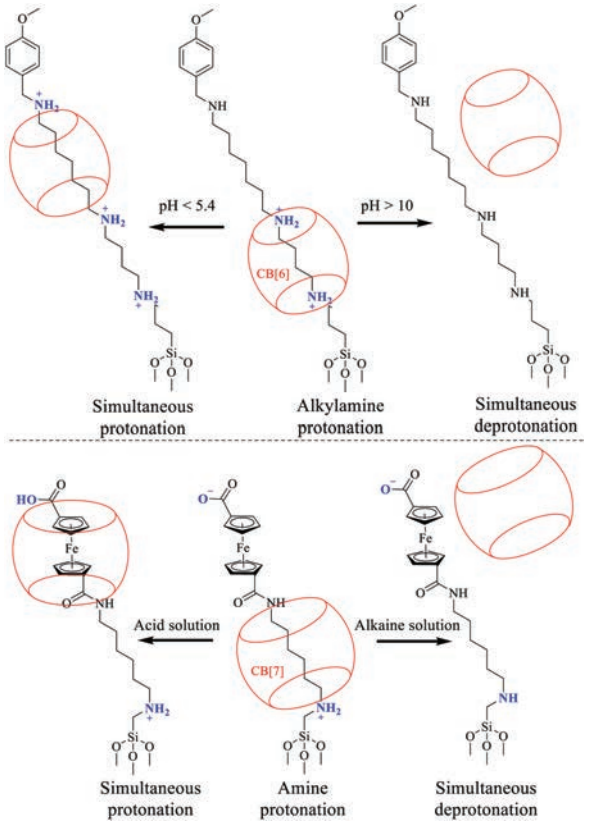


Scheme 2. Chemical structures of amphiphilic guests and the reported binding sites of CB[6] and CB[7] during formation of supramolecular amphiphiles. CB[7] with dashed line means the second sequential binding site.

extensively investigated to construct supramolecular nanovalves for stimuli-responsive release of cargoes from mesoporous silica nanoparticles (MSNs).

3.1. CB[6] based supramolecular nanovalves

The first example of CB[6] based supramolecular nanovalves was developed by Stoddart and Zink *et al.* [44]. The construction of pseudorotaxanes by CB[6] and bisammonium stalks on the surface of MSNs resulted in the blockage of nanopores of MSNs, thus the cargoes loaded inside MSNs were trapped inside. Under alkaline conditions, deprotonation of bisammonium at pH ~10 took place, leading to disassociation of the CB[6] based pseudorotaxanes, followed by cargoes release from MSNs [44]. After that, several upgraded pH-responsive nanovalves were reported, either to achieve biological pH responsiveness or to improve the biocompatibility/stability of the SNNDS [45–47]. For instance, bistable pseudorotaxanes were constructed between CB[6] and trisammonium stalks on the surface of MSNs (Scheme 3). Under neutral conditions, CB[6] preferred to bind four-carbon alkyl spacer (alkyl-$NH_2^+(CH_2)_4NH_2^+$-alkyl) near the surface with both of the two amino groups protonated, rather than the better matched six-carbon alkyl spacer (alkyl-$NH_2^+(CH_2)_6$NH-phenyl) far from the surface with only one amino group protonated. The shuttle of CB [6] from four-carbon spacer to six-carbon spacer upon protonation of phenylamine (OCH_3 *para* substituted) under mildly acid conditions led to the unblock of the pores of MSNs, resulting in release of cargoes under biological conditions (*e.g.* lysosome) [46]. In 2010, Stoddart and Zink *et al.* constructed rotaxanes by CB[6] and disulfide containing stalks on the surface of MSNs, and realized redox responsive release of the trapped cargoes inside MSNs [48]. Moreover, plasmonic photothermal responsive nanovalves also have been developed through constructing CB[6] based pseudorotaxanes on gold hybridized MSNs [49–51]. Gold nanoparticles in the core of MSNs were synthesized by one-pot method, and the local temperature was increased upon plasmonic heating of the gold inside. The binding constant between CB[6] and the stalks on the surface of MSNs was decreased under high temperature, resulting in cargoes release *via* unblocking the pores in MSNs.



Scheme 3. Chemical structures of bistable pseudorotaxanes constructed (top) between CB[6] and trisammonium, and CB[6]'s shuttling at different pH; (bottom) between CB[7] and ferrocenecarboxylic acid/hexylamine, and CB[7]'s shuttling at different solutions.

3.2. CB[7] based supramolecular nanovalves

With well-explored biocompatibility and good water solubility, CB[7] has advantages over CB[6] in building nanovalves for biomedical applications [52,53]. Du and co-workers designed and constructed CB[7] based pH- and competitive guest-responsive nanovalves for controlled release of anionic calcein from MSNs [25]. CB[7] formed host-guest complex with protonated butanediamine stalks on the surface of MSNs, and the deprotonation of butanediamine led to the disassociation of the assemblies, thus resulted in release of calcein from MSNs. CB[7] based nanovavles were demonstrated to block the nanopores more efficiently than that of CB[6] based nanovalves when encapsulated butanediamine stalks on the surface of MSNs, which was attributed to its lager outer diameter and higher affinity with butanediamine than that of CB[6] [25]. This CB[7] based nanovalves were also unblocked in the presence of competitors such as cetyltrimethylammonium bromide and 1,6-hexanediamine that can be biologically generated. Later, they indeed realized enzyme triggered release of CB[7]-butanediamine nanovalves based on Fe_3O_4 embedded MSNs. Upon hydrolysis of lysine by corresponding decarboxylase, the *in-situ* produced cadaverine disassembled CB[7]-butanediamine host-guest complex, leading to the calcein release. The embedded Fe_3O_4 was to assist site-specific accumulation of MSNs [54]. In 2012, Yang and co-workers developed CB[7] based photo-responsive nanovalves by installing cinnamamide stalks on the surface of MSNs for controlled release of Rhodamine B [55]. Upon UV-irradiation, the *trans*- to *cis*-change of the conformation of cinnamamide led to the disassembling of CB[7]-cinnamamide host-guest complex. Later, Fu and co-workers constructed dual pH-responsive pseudorotaxanes by CB[7] and stalks containing hexylamine units (near the surface) and ferrocenecarboxylic acid units (far from the surface) on the surface of MSNs [56]. Under neutral solutions, CB[7] preferred to bind the protonated hexylamine rather than deprotonated ferrocenecarboxylic acid, thus blocked the nanopores. The simultaneous deprotonation or protonation of hexylamine and ferrocenecarboxylic acid under alkaline conditions and acidic conditions resulted in the release of gemcitabine from the nanopores of MSNs (Scheme 3).

4. Supramolecular surface decoration mediated *via* host-guest chemistry of CB[*n*]

SNDDS self-assembled from supramolecular amphiphiles or constructed with supramolecular nanovalves often do not have unoccupied cavity of CB[6] or CB[7] on the surface of these nanomaterials, as hydrophobic interactions inside CB[*n*]'s cavity are the main driving force for the formation of inclusion host-guest complex [12]. Along with the development of functionalized CB[6] and CB[7], novel supramolecular nanostructures for drug delivery related applications have been constructed through self-assembly of CB[6] and CB[7] derivatives. With unoccupied cavity of CB[*n*] macrocycles located on the surface of nanoparticles, SNDDS could be decorated with various functional groups (targeting, imaging, sheath group) *via* host-guest chemistry, leading to multifunctional SNDDS.

4.1. CB[6] based multifunctional SNDDS

There are two types of surface-tailorable drug delivery vehicles derived from CB[6] derivatives. The first type is often derived from self-assembling of amphiphilic CB[6] derivatives or nano emulsion of oil soluble CB[6] derivatives, leading to the formation of supramolecular solid nanoparticles. The second type often involves polymeric covalent crosslinking of CB[6] derivatives, resulting in supramolecular hollow nanocapsules.

4.1.1. Self-assembly of amphiphilic CB[6] derivatives

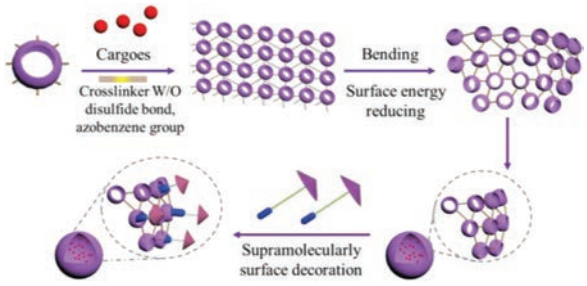
In 2005, Kim and co-workers reported the first surface-tailorable supramolecular vesicles by self-assembly of amphiphilic CB[6] derivatives [57]. The accessibility of unoccupied CB[6] cavity was demonstrated through the successful introduction of spermine-conjugated fluorescein isothiocyanate (FITC) and α-mannose on the surface of the vesicles through host-guest chemistry between CB[6] and spermine. Later, they reported the preparation of CB[6] based nanoparticles through precipitation of CB[6] derivatives, which was employed as drug delivery carriers with high loading capacity and efficiency of hydrophobic drug paclitaxel (PTX) [58]. The surface decoration with folate-spermidine remarkably facilitated the efficient delivery of PTX into cells *via* folate receptor-mediated endocytosis. In 2010, they successfully synthesized amphiphilic CB[6] containing disulfide bond, which was self-assembled into redox-sensitive vesicles [59]. DOX loaded into the multifunctional SNDDS decorated with folate and fluorescence imaging probe (FITC) was delivered into targeted cancer cells *via* receptor-mediated endocytosis with trackability, followed by reduction-triggered release of entrapped drugs into GSH rich cytoplasm. Moreover, in 2018, Wang *et al.* reported the preparation of photo-responsive CB[6] based nano drug delivery system through nano emulsion of perallyloxyCB[6] [60]. The loaded PTX was specifically released in cancerous cells with high GSH concentration upon UV irradiation, although surface decoration of this drug delivery system with functional groups was not investigated.

4.1.2. Self-assembly of covalently crosslinked CB[6] polymers

Another type of CB[6] based SNDDS is hollow nanocapsules formed *via* self-assembly of crosslinked perallyloxyCB[6] by dithiols, which was firstly reported by Kim *et al*. [61]. Upon UV irradiation, the disc-shaped perallyloxyCB[6] was crosslinked to form dimers and trimers, which subsequently grew into 2 dimensional (2D) oligomeric patches linked by thioether. The 2D oligomeric patches started to bend in order to reduce the total energy when reaching to a certain size, resulting in the formation of a hollow loose sphere that was further crosslinked to afford robust nanocapsules with tailorable surface [62]. The drawbacks of the prepared nanocapsules as drug delivery carriers are 1) The *in-situ* formation of cargo loaded nanocapsules forced the cargo being exposed with strong UV irradiation, which might decompose the cargo, especially for UV sensitive cargo; 2) the entrapped cargo was difficult to be released, as the nanocapsules were covalently crosslinked; 3) the nanocapsules were found stable in organic solvents, and would aggregate in an aqueous solution, which greatly limited its real-world biomedical application. To address the first two problems, they subsequently prepared nanocapsules by crosslinking amino terminated CB[6] with *N*-hydroxysuccinimide activated dicarboxylic acid containing disulfide bond in the middle of the chain, thus avoided the UV-irradiation of cargoes, and the obtained nanocapsules with reductive labile bond were specifically collapsed inside cancer cells with high GSH concentration, resulting in the controlled release of cargoes for drug delivery [63]. Additionally, to improve the stability of the nanocapsules in aqueous solutions, methyl iodide (CH_3I) was added after formation of the nanocapsules to form positively charged sulfonium, resulting in improved aqueous stability [64]. Later, Kim and Park *et al*. utilized these surface-charged nanocapsules for cancer-targeted multimodality bioimaging *in vivovia* simultaneous attachment of spermidine-conjugated targeting groups and several imaging tags on the surface of the nanocapsules [29,65]. More recently, Wang *et al*. developed a facile method for preparing CB[6] based nanocapsules *via* direct crosslinking of perhydroxyCB[6] with 1,4-dibromobut-2-ene as a ditopic linker, avoiding laborious and low-yield synthesis of perallyloxyCB[6]. As a proof of concept, targeted photo dynamic therapy was achieved by this novel SNDDS loaded with chlorin e6, with surface decorated with spermidine conjugated folate [66]. Very recently, they further constructed hypoxia-responsive CB[6] based SNDDS by using azobenzene-containing crosslinker for perallyloxyCB[6] [67]. After surface decoration with spermine-conjugated folate through host-guest chemistry *between* CB[6] and spermine, folate receptor targeted control release of the loaded DOX was realized in hypoxia cancerous cellular model and hypoxic zebrafish embryos model (Scheme 4).

4.2. CB[7] based multifunctional SNDDS

Isaacs and co-workers prepared Fujita-type metal organic polyhedron (MOP) through self-assembly of palladium nitrate ($Pd(NO_3)_2$) and bis(pyridine)-CB[7]-hexanediamine host-guest complex [68]. Since endohedral functionalization of alkyl chains inside cage can render MOP hydrophobicity for encapsulating hydrophobic cargoes, they employed host-guest chemistry between CB[7] and alkyl diamine or photo responsive alkyl diamine to endow hydrophobicity inside cages. The loaded hydrophobic Nile Red and DOX could be released upon external stimulation such as competitive guest addition, pH change and photo irradiation. In 2018, Kim *et al*. reported direct vesicle formation of monoallyloxyCB[7], which was photo-responsive *via* light initiated "thiol-ene" reaction of monoallyloxyCB[7] and GSH [69]. *In vitro* studies with cancer cells (GSH enriched inside) indicated that this nano delivery carrier not only facilitated cellular uptake of DOX, but also achieved



Scheme 4. CB[6] based multifunctional SNDDS through self-assembly of covalently crosslinked CB[6] polymers.

controlled cargo release upon light irradiation. However, the large size (~1 μm) and unstable morphology of the vesicles in aqueous solutions make them unsuitable for real-word applications in drug delivery. Recently, Wang *et al*. demonstrated the first CB[7]-decorated poly(lactic acid)/poly(lactic-*co*-glycolic acid) (PLA/PLGA) nanoparticles as a novel and versatile nano drug delivery vehicle with a noncovalently tailorable surface [70]. CB[7] on the surface of nanoparticles allowed facile, modular surface modification based on host-guest chemistry between CB[7] and amantadine (Ad) conjugated tags, including but not limited to folate-Ad (a targeting tag), FITC-Ad (a fluorescent conjugate), and PEG-Ad (a hydrophilic polymer), as well as between CB[7] and a guest drug molecule offering the unique opportunity for synergistic therapy. Very recently, Ni and Xiao *et al*. reported the self-assembly of CB[7]-anchored polyacrylic acid into nano-vesicles, which was demonstrated to be a good delivery vehicle for enhanced photodynamic therapy [71].

5. Outlook

CB[6] and CB[7] have been extensively investigated as building blocks in construction of SNDDS *via* host-guest chemistry. In addition to the intrinsic stimuli responsiveness of SNDDS towards competitive guest or host, pH-, thermal-, redox-, photo- and enzyme-responsiveness could be achieved through incorporation of corresponding responsive groups into supramolecular amphiphiles, supramolecular (*pseudo*)rotaxanes and covalently crosslinked polymeric networks. Furthermore, multifunctional SNDDS can be realized through surface decoration of functional groups (targeting group, imaging group, PEG group) with the assistance of host-guest chemistry of CB[6] and CB[7]. However, special attentions should be paid to the stability of SNDDS under physiological conditions, as host-guest chemistry of CB[*n*]s would be possibly affected by extraneous pH, salts, proteins and other competitors in the circulatory system. Therefore, these SNDDS should be validated by using *in vivo* mammal model rather than *in vitro* cellular model in future studies.

More importantly, the employment of CB[*n*]s in building SNDDS is still at an outset stage, hampered by their difficult derivatization. For the currently reported two methods, CB[*n*] derivatives bearing active sites including a vinyl, an ethynyl, or an azide group often have to be synthesized first through hydroxylated CB[*n*] or CB[*n*] bearing chloride group, followed by post-functionalization through "thiol-ene" and "azide-alkyne" click reaction [72–74]. However, the requirement of nontrivial purification steps and ample organic synthetic skills along with the low yields pose great challenges for the facile large-scale preparation of CB[*n*] derivatives. Moreover, the low activity of hydroxyl group, self-inclusion issues of monofunctionalized CB[*n*]s, and the organic solubility issues always impel researchers to do further explorations regarding the directly azidation, amination, and carboxylation of the "equatorial" hydrogens of CB[*n*]s. With these endeavors, the

development of CB[*n*]s family in biomedical sciences, particularly as building blocks for advanced SNDDS can be greatly promoted.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] L.F. Lindoy, I.M. Atkinson, Self-assembly in Supramolecular Systems, The Royal Society of Chemistry, Cambridege, 2000.
[2] I.V. Kolesnichenko, E.V. Anslyn, Chem. Soc. Rev. 46 (2017) 2385–2390.
[3] M.J. Webber, R. Langer, Chem. Soc. Rev. 46 (2017) 6600–6620.
[4] X. Ma, Y. Zhao, Chem. Rev. 115 (2015) 7794–7839.
[5] C.B. Rodell, J.E. Mealy, J.A. Burdick, Bioconj. Chem. 26 (2015) 2279–2289.
[6] Z. Liu, S.K.M. Nalluri, J.F. Stoddart, Chem. Soc. Rev. 46 (2017) 2459–2478.
[7] J. Murray, K. Kim, T. Ogoshi, W. Yao, B.C. Gibb, Chem. Soc. Rev. 46 (2017) 2479–2496.
[8] Y. Liu, Y. Chen, H.Y. Zhang, Handbook of Macrocyclic Supramolecular Assembly, Springer, Singapore, 2019.
[9] E. Masson, X. Ling, R. Joseph, L. Kyeremeh-Mensah, X. Lu, RSC Adv. 2 (2012) 1213–1247.
[10] S.J. Barrow, S. Kasera, M.J. Rowland, J. Del Barrio, O.A. Scherman, Chem. Rev. 115 (2015) 12320–12406.
[11] K.I. Assaf, W.M. Nau, Chem. Soc. Rev. 44 (2015) 394–418.
[12] J. Lagona, P. Mukhopadhyay, S. Chakrabarti, L. Isaacs, Angew. Chem. Int. Ed. 44 (2005) 4844–4870.
[13] W.M. Nau, M. Florea, K.I. Assaf, Isr. J. Chem. 51 (2011) 559–577.
[14] D. Shetty, J.K. Khedkar, K.M. Park, K. Kim, Chem. Soc. Rev. 44 (2015) 8747–8761.
[15] Y. Chen, Z. Huang, H. Zhao, et al., ACS Appl. Mater. Interfaces 9 (2017) 8602–8608.
[16] H. Chen, Y. Chen, H. Wu, et al., Biomaterials 178 (2018) 697–705.
[17] B. Tang, W.L. Li, Y. Chang, et al., Angew. Chem. Int. Ed. 58 (2019) 15526–15531.
[18] L. Chen, H. Bai, J.F. Xu, S. Wang, X. Zhang, ACS Appl. Mater. Interfaces 9 (2017) 13950–13957.
[19] Y. Yang, P. He, Y. Wang, et al., Angew. Chem. Int. Ed. 56 (2017) 16239–16242.
[20] L. Chen, Y. Yang, P. Zhang, et al., ACS Appl. Bio Mater. 2 (2019) 2920–2926.
[21] R.H. Gao, L.X. Chen, K. Chen, Z. Tao, X. Xiao, Coord. Chem. Rev. 348 (2017) 1–24.
[22] K.M. Park, M.Y. Hur, S.K. Ghosh, et al., Chem. Commun. 55 (2019) 10654–10664.
[23] D. Tuncel, Cucurbituril-based Functional Materials, The Royal Society of Chemistry, Cambridege, 2019.
[24] X. Wu, Y.M. Zhang, Y. Liu, RSC Adv. 6 (2016) 99729–99734.
[25] J. Liu, X. Du, J. Mater. Chem. 20 (2010) 3642–3649.
[26] C. Gao, Q. Huang, Q. Lan, et al., Nature Commun. 9 (2018) 2967.
[27] J. Tian, C. Yao, W.L. Yang, et al., Chin. Chem. Lett. 28 (2017) 798–806.
[28] C. Hu, N. Ma, F. Li, et al., ACS Appl. Mater. Interfaces 10 (2018) 4603–4613.
[29] S. Kim, G. Yun, S. Khan, et al., Mater. Horiz. 4 (2017) 450–455.
[30] Q.L. Li, Y. Sun, Y.L. Sun, et al., Chem. Mater. 26 (2014) 6418–6431.
[31] Q.L. Li, S.H. Xu, H. Zhou, et al., ACS Appl. Mater. Interfaces 7 (2015) 28656–28664.
[32] F. Ostadhossein, S.K. Misra, P. Mukherjee, et al., Small 12 (2016) 5845–5861.
[33] F. Benyettou, M. Alhashimi, M. O'Connor, et al., ACS Appl. Mater. Interfaces 9 (2017) 40006–40016.
[34] Q. Zhou, H. Wang, T. Gao, et al., Chem. Commun. 47 (2011) 11315–11317.
[35] Q. Zhou, D. Gao, J. Liu, et al., J. Colloid Interface Sci. 410 (2013) 131–139.
[36] J. Li, L. Zhou, Q. Luo, et al., Chin. J. Chem 30 (2012) 2085–2090.
[37] S.D. Choudhury, N. Barooah, V.K. Aswal, et al., Soft Matter 10 (2014) 3485–3493.
[38] P. Xing, H. Chen, M. Ma, et al., Nanoscale 8 (2016) 1892–1896.
[39] J.S. Yu, F.G. Wu, Y. Zhou, Y.Z. Zheng, Z.W. Yu, Phys. Chem. Chem. Phys. 14 (2012) 8506–8510.
[40] J. Fernández-Rosas, M. Pessêgo, A. Acuña, et al., Langmuir 34 (2018) 3485–3493.
[41] R. Chen, H. Gu, F. Qiu, et al., Tetrahedron 72 (2016) 5290–5294.
[42] L. Shao, B. Hua, J. Sun, et al., Tetrahedron Lett. 58 (2017) 1863–1867.
[43] K.I. Assaf, M.A. Alnajjar, W.M. Nau, Chem. Commun. 54 (2018) 1734–1737.
[44] S. Angelos, Y.W. Yang, K. Patel, J.F. Stoddart, J.I. Zink, Angew. Chem. Int. Ed. 47 (2008) 2222–2226.
[45] N.M. Khashab, M.E. Belowich, A. Trabolsi, et al., Chem. Commun. (2009) 5371–5373.
[46] S. Angelos, N.M. Khashab, Y.W. Yang, et al., J. Am. Chem. Soc. 131 (2009) 12912–12914.
[47] W. Guo, J. Wang, S.J. Lee, et al., Chem. Eur. J. 16 (2010) 8641–8646.
[48] M.W. Ambrogio, T.A. Pecorelli, K. Patel, et al., Org. Lett. 12 (2010) 3304–3307.
[49] J. Croissant, J.I. Zink, J. Am. Chem. Soc. 134 (2012) 7628–7631.
[50] S. Soulé, J. Allouche, J.C. Dupin, et al., Phys. Chem. Chem. Phys. 17 (2015) 28719–28728.
[51] D.T. Marquez, J.C. Scaiano, Langmuir 32 (2016) 13764–13770.
[52] K.I. Kuok, S. Li, I.W. Wyman, R. Wang, Ann. N. Y. Acad. Sci. 1398 (2017) 108–119.
[53] H. Yin, R. Wang, Isr. J. Chem. 58 (2018) 188–198.
[54] J. Liu, X. Du, X. Zhang, Chem. Eur. J. 17 (2011) 810–815.
[55] Y.L. Sun, B.J. Yang, S.X.A. Zhang, Y.W. Yang, Chem. -Eur. J. 18 (2012) 9212–9216.
[56] T. Chen, N. Yang, J. Fu, Chem. Commun. 49 (2013) 6555–6557.
[57] H.K. Lee, K.M. Park, Y.J. Jeon, et al., J. Am. Chem. Soc. 127 (2005) 5006–5007.
[58] K.M. Park, K. Suh, H. Jung, et al., Chem. Commun. (2009) 71–73.
[59] K.M. Park, D.W. Lee, B. Sarkar, et al., Small 6 (2010) 1430–1441.
[60] Q. Cheng, S. Li, C. Sun, L. Yue, R. Wang, Mater. Chem. Front. 3 (2019) 199–202.
[61] D. Kim, E. Kim, J. Kim, et al., Angew. Chem. Int. Ed. 46 (2007) 3471–3474.
[62] D. Kim, E. Kim, J. Lee, et al., J. Am. Chem. Soc. 132 (2010) 9908–9919.
[63] E. Kim, D. Kim, H. Jung, et al., Angew. Chem. Int. Ed. 49 (2010) 4405–4408.
[64] G. Yun, Z. Hassan, J. Lee, et al., Angew. Chem. Int. Ed. 53 (2014) 6414–6418.
[65] S. Kim, M.Y. Hur, J. Kim, K.M. Park, K. Kim, Supramol. Chem. 31 (2019) 289–295.
[66] C. Sun, H. Zhang, L. Yue, et al., ACS Appl. Mater. Interfaces 11 (2019) 22925–22931.
[67] C. Sun, L. Yue, Q. Cheng, Z. Wang, R. Wang, ACS Mater. Lett. 2 (2020) 266–271.
[68] S.K. Samanta, J. Quigley, B. Vinciguerra, V. Briken, L. Isaacs, J. Am. Chem. Soc. 139 (2017) 9066–9074.
[69] K.M. Park, K. Baek, Y.H. Ko, et al., Angew. Chem. Int. Ed. 57 (2018) 3132–3136.
[70] C. Sun, H. Zhang, S. Li, et al., ACS Appl. Mater. Interfaces 10 (2018) 25090–25098.
[71] B. Xiao, Q. Wang, S. Zhang, et al., J. Mater. Chem. B 7 (2019) 5966–5971.
[72] S.Y. Jon, N. Selvapalam, D.H. Oh, et al., J. Am. Chem. Soc. 125 (2003) 10186–10187.
[73] B. Vinciguerra, L. Cao, J.R. Cannon, et al., J. Am. Chem. Soc. 134 (2012) 13133–13140.
[74] M.M. Ayhan, H. Karoui, M. Hardy, et al., J. Am. Chem. Soc. 138 (2016) 2060-2060.

Biography of corresponding author

Dr. Shengke Li received MSc degree in Organic Chemistry from East China University of Science and Technology in 2012. After three years working as a Chemist in cosmetic industry, he joined University of Macau to pursue Ph.D. degree in Biomedical Sciences under the supervision of Professor Ruibing Wang in 2015. Since then, he focused on pharmaceutical applications of cucurbituril-based host-guest chemistry. After graduation in 2018, he joined Nanjing University of Science and Technology as a Lecturer and continued his research on supramolecular biomaterials based on cucurbiturils and their derivatives.