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Review

Polysaccharide-based supramolecular drug delivery systems mediated *via* host-guest interactions of cucurbiturils

Yiyun Gao[a,b,1], Yan Gao[c,1], Yuanfu Ding[c], Huaping Tan[a], Aihua Zou[b,d,**], Shengke Li[a,*]

[a] School of Materials Science and Engineering, Nanjing University of Science and Technology, Nanjing 210094, China
[b] Shanghai Key Laboratory of Functional Materials Chemistry, State Key Laboratory of Bioreactor Engineering and Institute of Applied Chemistry, School of Chemistry and Molecular Engineering, East China University of Science and Technology, Shanghai 200237, China
[c] State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macau, China
[d] College of Chemistry and Materials Science, Shanghai Normal University, Shanghai 200234, China

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ABSTRACT

With excellent biocompatibility and biodegradability, natural polysaccharides and their derivatives have exhibited great potential in constructing drug delivery vehicles for tissue engineering and therapeutics. Cucurbit[*n*]uril (CB[*n*])-mediated reversible crosslinking of polysaccharides possess intrinsic stimuli-responsiveness towards competitive guests and have been extensively investigated to fabricate various particles and hydrogels for multiple stimuli-responsive drug release by incorporation with other stimuli including photo, redox, and enzyme. Through host-guest interactions between CB[6] and aliphatic diamines, functional tags covalently connected with CB[6] can be readily anchored into polysaccharide-based hydrogels, realizing multiple functionalization. The rheological property and drug release profile of polysaccharide-based supramolecular hydrogels can be facilely tuned through CB[8]-mediated dynamic homo or hetero crosslinking of polysaccharides and/or other polymers. In this review, we introduce and summarize recent progress regarding polysaccharide-based supramolecular drug delivery systems mediated *via* host-guest interactions of CB[6] and CB[8], covering both bulk hydrogels and particular systems. At the end, possible utilization of CB[7]-based host-guest interactions in constructing polysaccharide-based drug delivery systems and future perspectives of this research direction are also discussed.

1. Introduction

Polysaccharides are a family of biopolymers isolated from natural sources, which are endowed with biocompatible advantages over synthetic polymers, suitable for biomedical applications (Fig. 1). Due to their excellent biocompatibility and biodegradability, polysaccharides, for instance, chitosan, sodium alginate, hyaluronic acid, cellulose *etc.*, have been extensively utilized to construct drug delivery vehicles (hydrogels, particles) for tissue engineering and therapeutics [1–3]. Some polysaccharides (hyaluronic acid, pectin, *etc.*) even have natural biological receptors that can drive targeted delivery, and others are susceptible to enzymatic degradation that may facilitate controlled drug release at specific site [4]. Moreover, with abundant active groups (hydroxyl, amino, carboxylic group) in the polymer chain of polysaccharides, chemical modification of polysaccharides to construct drug delivery vehicles can also be readily achieved [5]. Usually, polysaccharides often need to be crosslinked to improve the physical and chemical properties when forming drug delivery vehicles. The most commonly employed covalent crosslinking methods include alkenyl chemistry, click chemistry, and cleavable covalent bonding (Schiff base, disulfide chemistry, *etc.*) [2,6,7]. Although covalent crosslinking offers polysaccharide-based drug delivery vehicles with robustness, the irreversible chemical bonds often make it complicated to tune the crosslinking degree. In addition, the overall biocompatibility of covalently crosslinked polysaccharides might be affected by synthetic conditions and potentially toxic degradation products or byproducts such as glutaraldehyde [7,8]. Thereby, noncovalent supramolecular crosslinking strategy is often more favorable than covalent crosslinking,

* Corresponding author.
** Corresponding author at: Shanghai Key Laboratory of Functional Materials Chemistry, State Key Laboratory of Bioreactor Engineering and Institute of Applied Chemistry, School of Chemistry and Molecular Engineering, East China University of Science and Technology, Shanghai 200237, China.
E-mail addresses: aihuazou@ecust.edu.cn (A. Zou), lisk@njust.edu.cn (S. Li).
[1] These two authors contributed equally to this work.

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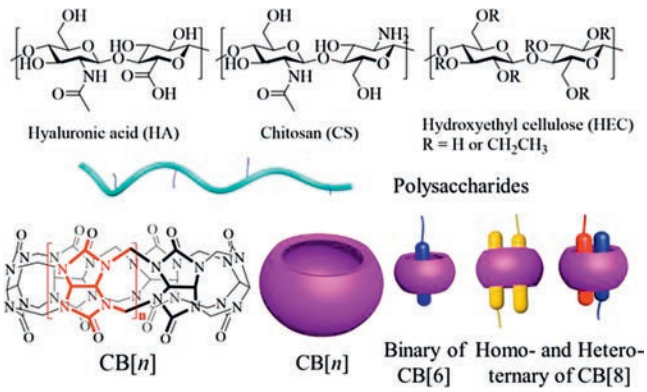

Fig. 1. Chemical structures and schematic diagram of representative polysaccharides, CB[*n*] and host-guest complex of CB[6] and CB[8], respectively.

because the biological properties of polysaccharides can be well maintained, and the crosslinking degree is more facilely adjusted *via* crosslinking [2]. Moreover, the dynamic noncovalent crosslinking of polysaccharides often endows the obtained hydrogels with self-healing property and responsiveness. For instance, positively charged polysaccharides (*e.g.*, protonated amino groups on chitosan) and negatively charged polysaccharides (*e.g.*, deprotonated carboxylic groups on hyaluronic acid and alginate) are often crosslinked with the help of oppositely charged polyelectrolytes or multivalent ions [9,10]. The obtained hydrogels are often pH-responsive, due to the protonation/deprotonation effect of amino groups and carboxylic groups on polysaccharides. Notably, along with the evolution of supramolecular host-guest chemistry studies from initial molecular recognition in organic solvents to more challenging recognition and self-assemblies in water, macrocyclic host-guest interactions are particularly appealing as driving forces for noncovalent crosslinking of polymers under aqueous solutions in recent years, especially for constructing drug delivery vehicles for biomedical applications [11–15]. The dynamic host-guest interactions not only endow drug delivery vehicles intrinsic stimuli responsiveness towards competitive guests, but also pave a promising way to readily achieve multiple functionalization through host-guest complexation [16,17]. Moreover, by incorporation with responsiveness towards other stimuli, including photo, redox, and enzyme, polysaccharide-based particles and hydrogels mediated *via* host-guest interactions may achieve more specific drug release [16].

Cucurbit[*n*]urils (CB[*n*]s, *n* = 5–8, 10) are a family of macrocyclic host molecules composed of n glycoluril units linked by 2n methylene groups (Fig. 1) [18,19]. As intrinsic water-soluble and biologically-inert macrocycles, CB[*n*]s have received particular interest in biomedical research field, since they can form ultrastrong host-guest complexes with binding affinities largely exceed other macrocycle-based (for instance, cyclodextrin) supramolecular systems in aqueous solution [20–22]. CB[6] and CB[7] homologues form binary host-guest complexes with aliphatic and aromatic derivatives, while unique CB[8] homologue is large enough to simultaneously accommodate two guests inside its cavity, forming homo-ternary complexes with phenylalanine terminated guests, and hetero-ternary complexes with electronically complementary guests [20,21]. CB[*n*] homologues have been extensively utilized to construct various supramolecular assemblies for drug delivery applications [11,20,21,23–25]. For instance, a plenty of CB[*n*]-based supramolecular prodrugs were developed *via* direct encapsulation of drug molecules either to improve their therapeutic performance towards various diseases and/or inhibit/reverse undesired side effects [26–30]. Supramolecular nano assemblies (micelles/vesicles, organic framework, nanocapsules) mediated *via* host-guest interactions of CB[*n*]s have also been extensively investigated for efficient drug delivery applications [31–33]. In particular, through host-guest interactions between CB[6] and aliphatic diamines, functional tags covalently connected with CB[6] can be readily anchored into polysaccharide-based hydrogels, realizing multiple functionalization [34–36]. The rheological property and drug release profile of polysaccharide-based supramolecular hydrogels can be facilely tuned through CB[8]-mediated dynamic homo or hetero crosslinking of polysaccharides and/or other polymers [37,38]. In this review, we introduce and summarize recent progress regarding polysaccharide-based supramolecular drug delivery systems mediated *via* host-guest interactions of CB[6] and CB[8], covering both bulk hydrogels and particular systems. Acyclic CB[*n*] conjugated polysaccharides for direct drug loading was not detailed discussed [39]. Moreover, possible utilization of CB[7]-mediated host-guest interactions to construct polysaccharide-based drug delivery vehicles is also included at the end of this article, and future perspectives of this research direction is also discussed.

2. Polysaccharide-based supramolecular drug delivery systems mediated *via* CB[6]-guest interactions

As the first identified homologue, CB[6] has a portal diameter of only 3.9 Å, which is commonly known to selectively encapsulate aliphatic amines, and the strongest binary host-guest interactions of CB[6] occurs when complexing with pentano- and hexano-bridged α,ω-diammonium functionalities (K_a up to 10^{10} L/mol) [20,40]. With two identical carbonyl portal located on both sides, CB[6] was employed to regulate the aggregation behavior of polysaccharides, resulting in formation of polysaccharide-based particles for drug delivery. Tan *et al.* firstly observed nano sized micelle-like aggregation of sodium alginate upon addition of CB[6] in an aqueous solution, resulting from the Coulombic forces between the carbonyl portal of CB[6] and sodium alginate, with sodium as bridge [41]. Subsequently, they successfully fabricated CB[6]/alginate hydrogel beads with a uniform size (with diameter of *ca.* 2.5 mm) for the controlled release of a model drug 5-fluorouracil [42].

CB[6] derivatives have also been built into polysaccharide-based biomaterials for drug delivery and related applications [34,36,43]. In particular, CB[6] and aliphatic diamines are firstly pre-modified on two polysaccharides, respectively. The strong host-guest interactions between CB[6] and aliphatic diamines served as the main driving force for dynamic crosslinking of polysaccharides, resulting in the formation of hydrogels or particles for drug delivery [34–36]. Furthermore, the un-complexed aliphatic diamines can be employed for further functionalization *via* host-guest interactions between CB[6]-conjugated functional tags and un-complexed aliphatic diamines

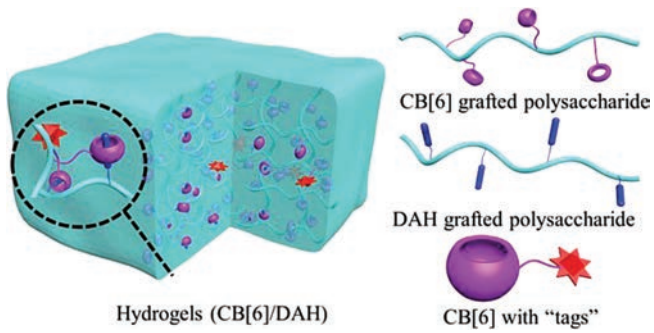

Fig. 2. Polysaccharide-based supramolecular hydrogels mediated *via* CB[6] guest interactions.

(Fig. 2) [36]. In 2012, Kim *et al.* reported supramolecular hyaluronic acid (HA) hydrogel prepared *in situ* and its successful application for cell tissue engineering *in vivo* [36]. CB[6] modified HA (CB[6]-HA) and diaminohexane grafted HA (HA-DAH) could assemble into biocompatible hydrogel (CB[6]/HA-DAH) in the presence of cells with tunable mechanical property through the strong and selective encapsulation of DAH by CB[6] [36]. The hydrogel was modularly modified with various functional tags covalently connected with CB[6] such as fluorescent-dye-conjugated CB[6] (FITC-CB[6]) and peptide conjugated CB[6] *via* host-guest complexation with unoccupied DAH moieties. Cell proliferation results suggested that the treatment of CB[6]/HA-DAH hydrogels with c(RGDyK)-CB[6] (a cyclic derivative of RGD having a high affinity for $\alpha v\beta 3$ integrin, RGD for arginylglycylaspartic acid) not only led to the capture of c(RGDyK) peptides but also reconstructed a stable RGD environment for cellular adhesion and proliferation with high efficiency. *In vivo* experiments suggested that CB[6]/HA-DAH hydrogel was *in-situ* formed under nude mice's skin within a few minutes post-administration and its shape was kept for more than two weeks. After *in-situ* modification of FITC-CB[6], the hydrogel inside the mouse emitted fluorescence for 11 days, while hydrogel modified with carboxyfluorescein without CB[6] conjugation lost fluorescence within a day [36]. This strategy was subsequently employed to prepare CB[6]/HA-DAH hydrogel modified with drug-CB[6] conjugate for the facial chondrogenesis control of human mesenchymal stem cells, and long-term mesenchymal stem cell cancer therapy *in vitro* and *in vivo* [34,43].

3. Polysaccharide-based supramolecular drug delivery systems mediated *via* CB[8]-guest interactions

The unique ability of CB[8] in forming stable ternary host-guest complexes by simultaneous encapsulation of two guests into its cavity has greatly expanded the molecular recognition of CB[8]. The sequential encapsulation of an electron deficient guest (such as methyl viologen dication, MV) and an electron rich guest (such as naphthyl (Nap) derivatives) by CB[8] results in formation of hetero-ternary complexes, stabilized by charge-transfer interactions (K_a up to 10^{14} L^2 mol^{-2}) [44,45]. A compound with both electron deficient and electron rich moieties (such as 2-anthracene ammonium (Ant), coumarin), or one that could be reduced to radical cation species (such as $MV^{+\bullet}$), often experiences a double encapsulation by CB[8], forming homo-ternary complexes [46–48]. It is worthy to note that some specific peptide sequences containing tryptophan (Trp) or phenylalanine (Phe) residues could also be dimerized by CB[8] through double encapsulation of Trp or Phe residues (K_a up to 10^{11} L^2 mol^{-2}) [49,50]. With such unique strong ternary host-guest interactions of CB[8], the applications of CB[8] as a supramolecular "glue or handcuff" for polymer crosslinking to fabricate polysaccharides-based drug delivery vehicles have been extensively studied, because only guests need to be pre-modified on polysaccharides when using CB[8] for crosslinking, avoiding challenging preparation of CB[*n*] derivatives. Polysaccharide-based supramolecular drug delivery vehicles constructed through ternary host-guest interactions of CB[8] exhibit intrinsic stimuli responsive property, as the controlled release of cargoes from hydrogels and particles can be readily achieved upon addition of a competitive guest of CB[8] with a higher binding affinity.

3.1. Homo-ternary host-guest interactions of CB[8]

Wang *et al.* reported the preparation of chitosan (CS)-based supramolecular nanostructures mediated *via* homo-ternary host-guest interactions of CB[8] [51]. CS was first modified with Phenylalanine (Phe) through amidation reaction to obtain CS-Phe, and the addition of CB[8] into CS-Phe aqueous solution resulted in formation of CS nanoparticles (CB[8]/CS-Phe) driving by homo-ternary complexation between CB[8] and 2Phe. A model drug doxorubicin was loaded into CB[8]/CS-Phe nanoparticles and was found to exhibit selective release towards endogenous and exogenous competitive guest, spermine and amantadine, respectively (Fig. 3). With the help of microfluidic technique, Scherman *et al.* developed supramolecular cargo delivery microcapsules by employing CB[8]-mediated crosslinking of Ant modified hydroxyethyl cellulose (HEC-Ant) as supramolecular skins of microcapsules [52]. The permeability of the skin was tunable through UV-triggered [4 + 4]-photo-dimerization of two Ant moieties inside CB[8]'s cavity. Upon addition of competitive guests for disassembling CB[8]/2Ant complexes, the skin of the microcapsule was readily destructed, resulting in the release of the loaded cargoes. This microfluidic strategy to prepare microcapsules for controlled drug delivery was also successfully demonstrated by using CB[8]-mediated hetero-ternary complexation between Nap modified HEC and MV functionalized poly((vinylbenzyl)trimethylammonium chloride) [53].

Additionally, the homo-ternary host-guest interactions of CB[8] and 2Phe was employed to fabricate polysaccharide-based supramolecular hydrogel with self-healing property and stimuli-responsiveness (Fig. 3). Scherman and co-works developed a facile reproducible methodology to prepare a variety of polysaccharide-based supramolecular hydrogels by CB[8]-mediated crosslinking of Phe-grafted polysaccharides including HA, HEC, carboxymethyl cellulose (CMC), and guar, respectively [54]. CB[8]/CMC-Phe supramolecular network can be further interpenetrated with supramolecular DNA network to obtain double network hydrogels with complementary mechanical property of each hydrogel [55]. The hybrid hydrogel possessed selective degradability towards specific enzymes, geared for applications of drug-controlled release and tissue engineering. In 2018, Scherman *et al.* demonstrated the application of high water content (98%) CB[8]/HA-Phe supramolecular hydrogel for efficiently delivering chemotherapies for glioblastoma treatment *in vitro* and *ex vivo* [37]. The optimized supramolecular hydrogel was injectable and adjusted less stiff than brain tissue, thereby implantable after surgery resection, and the contact surface area was increased than that of commercially used Gliadel® wafers. By replacing Phe with coumarin, the stiffness of CB[8]/HA-coumarin supramolecular hydrogel was reversibly modulated through light-controlled [2 + 2] cycloaddition of coumarin [38]. Very recently, Wang *et al.* reported the fabrication of berberine (BBR)-loaded supramolecular konjac glucomannan (KGM) hydrogel (CB[8]/KGM-Phe) with tunable crosslinking degree for ulcerative colitis (UC) therapy [56]. The supramolecular hydrogel was stable in gastric area and can be degraded by colon-specific enzymes, resulting in burst drug release at the colon site. *In*

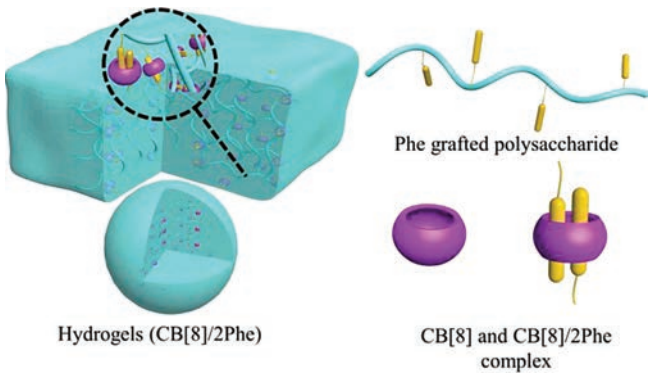

Fig. 3. Polysaccharide-based supramolecular hydrogels and particles constructed by homo-ternary host-guest interactions of CB[8].

vivo mice model study with dextran sulfate sodium induced UC demonstrated that BBR-loaded CB[8]/KGM-Phe hydrogel significantly improved the therapeutic efficacy of BBR without causing systematic toxicity.

3.2. Hetero-ternary host-guest interactions of CB[8]

Compared with homo-ternary complexation, hetero-ternary host-guest interactions of CB[8] are more favorable to crosslink polysaccharides with different biopolymers or synthetic polymers, mostly for the purpose of performance complementation, providing a facile and tunable method for constructing superior drug delivery vehicles [57–59]. In 2012, Scherman *et al*. prepared a high water content supramolecular hydrogel *via* CB[8]-mediated crosslinking between Nap modified HEC (HEC-Nap) and MV modified poly(vinylalcohol) (PVA-MV) under biologically relevant temperatures [58]. The high biocompatibility of this hydrogel was benefited from the combination of HEC polysaccharides. The mechanical properties of the CB[8]/HEC-Nap/PVA-MV hydrogel were readily tuned through varying the ratios of each constituents, to suppress the initial burst release of proteins from hydrogel as well as to realize highly sustainable release of proteins with well-preserved activity. Later, the multiple stimuli-responsive property of this supramolecular hydrogel towards temperature, competitive guests, specific organic solvents, and MV reducing agent was successfully demonstrated, because these external stimuli can disassemble CB[8]/Nap/MV hetero-ternary complexes, resulting in collapse of the supramolecular hydrogel [59]. Light-triggered "activation" and "de-activation" of photo-responsive competitive guest (azobenzene (Azo) imidazolium derivative) in CB[8]/Nap/MV-mediated polysaccharide-based supramolecular hydrogel was also investigated to facilely photo-modulate its rheological properties [60].

Incorporation of nanoparticles into polysaccharides matrix *via* CB[8]-mediated hetero-ternary host-guest interactions was also developed to improve their respective drawbacks (Fig. 4). For instance, to inhibit initial burst release of cargoes from hydroxylpropyl cellulose (HPC)-based hydrogels, virus nanocages were integrated into HPC hydrogel network *via* CB[8]-mediated crosslinking of HPC and virus that are respectively pre-modified with MV and Nap [61]. The virus compartments inside hydrogel not only improved the solubility of the loaded model drug tetrasulfonated zinc phthalocyanine, but also facilitated its quantification inside the hydrogel. In contrast, very recently, Wang *et al*. reported the "turn-off" of non-specific toxicity of MV functionalized polylactic acid nanoparticles by CB[8]-mediated supramolecular coating of Azo grafted HA (HA-Azo) [62]. This toxicity shielding strategy was validated by using *in vitro* and *in vivo* models. Notably, upon remote photo-irradiation, the configuration change of Azo from *trans* to *cis* would disassemble the CB[8]/Azo/MV hetero-ternary complexes, resulting in falling off of HA-Azo from the nanoparticles, thereby activating the toxicity of nanoparticles, which can be applied for smart and safe antibacterial and anticancer therapy.

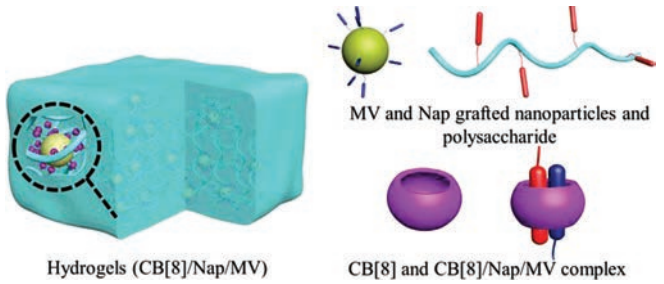

Fig. 4. Polysaccharide-based supramolecular hydrogels constructed by hetero-ternary host-guest interactions of CB[8].

4. Outlook

CB[6] and CB[8]-mediated host-guest interactions have been extensively investigated to construct polysaccharide-based supramolecular particles and hydrogels for drug delivery applications. In addition to particles and hydrogels, CB[6] was also modified on HA chain to prepare HA receptor targeted on demand theranostic systems *via* host-guest interactions between CB[6] and spermidine conjugated functional groups [63]. Despite these successes, the large-scale obtaining of pure mono-substituted CB[*n*]s derivatives bearing active sites remains challengeable, and the low organic solubility of CB[*n*] derivatives and their self-inclusion issues constrain their efficient conjugation with polymeric materials [25]. These obstructions are pretty much the agenda for biomedical applications of CB[*n*]. For instance, the grafting of CB[6] onto polysaccharides requires tedious synthetic steps to obtain allyl- or amino-terminated CB[6] derivatives first, and the relatively poor water solubility of CB[6] derivatives also makes difficult to react with polysaccharides in aqueous solutions that often has to be used for dissolving polysaccharides. Therefore, direct grafting of CB[*n*] onto polysaccharides *via* radical reactions is worthy to be investigated. In addition, as CB[8] derivatives bearing active sites is yet to be synthesized and CB[8] possesses unique ability to form ternary complexes for polymer crosslinking, the pre-modification of guest molecules onto polymer chains is most commonly employed to construct CB[8]-based drug delivery systems. CB[8]-mediated hetero-ternary complexation mostly involves MV or MV modified guests, which raises significant cytotoxicity concerns for biomedical applications, although several particular cases demonstrated that MV modified guests exhibit relatively good biocompatibility [64,65]. Nevertheless, the safety profile also needs to be fully addressed in future studies.

More importantly, the integration of CB[7] with polysaccharides has been rarely investigated. The challenging large-scale synthesis of CB[7] derivatives and the requirement of tedious synthesis for grafting CB[7] onto polysaccharide constrain the use of CB[7] in construction of polysaccharide-based drug delivery systems. With superior water solubility, well-explored safety profile and appropriate cavity size, CB[7] exhibits the greatest potential among CB[*n*] family for drug delivery applications [26,28]. Zhang *et al*. have developed PEG/CB[7] copolymer to complex with anticancer drugs for efficient supramolecular polymeric chemotherapy [29]. Supramolecular PEGylation of biopharmaceutics through CB[7]-mediated host-guest interactions with aromatic amino has achieved great success in improving therapeutic efficacy of insulin and pramlintide [66,67]. Polysaccharides are often considered as potential alternatives of PEG, as they can play similar "stealth" role to PEG for blood circulation prolonging through, for instance, constraining non-specific protein binding [2,68]. Moreover, most polysaccharides have good biocompatibility and low immunogenicity, which can be modified with CB[7] to construct supramolecular assemblies *via* host-guest interactions of CB[7] for drug delivery applications. Meanwhile, the variety of polysaccharides used to construct CB[*n*]-based supramolecular drug delivery systems may also get extended along with the development of CB[*n*]s in the future.

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] B. Kang, T. Opatz, K. Landfester, F.R. Wurm, Chem. Soc. Rev. 44 (2015) 8301–8325.
[2] T.G. Barclay, C.M. Day, N. Petrovsky, S. Garg, Carbohydr. Polym. 221 (2019) 94–112.
[3] T.A. Debele, S.L. Mekuria, H.C. Tsai, Mater. Sci. Eng. C 68 (2016) 964–981.
[4] C. Yang, X. Wang, X. Yao, et al., J. Control. Release 205 (2015) 206–217.
[5] X. Hu, Z. Gao, H. Tan, et al., Front. Chem. 7 (2019) 477.
[6] H. Qian, X. Wang, K. Yuan, et al., Biomater. Sci. 2 (2014) 220–232.
[7] T. Zhu, J. Mao, Y. Cheng, et al., Adv. Mater. Interfaces 6 (2019) 1900761.
[8] Z. Liu, Y. Jiao, Y. Wang, C. Zhou, Z. Zhang, Adv. Drug Deliv. Rev. 60 (2008) 1650–1662.
[9] J. Yan, Y. Miao, H. Tan, et al., Mater. Sci. Eng. C 63 (2016) 274–284.
[10] S. Potiwiput, H. Tan, G. Yuan, et al., Mater. Chem. Phys. (2019) 122354.
[11] X. Ma, Y. Zhao, Chem. Rev. 115 (2015) 7794–7839.
[12] C.B. Rodell, J.E. Mealy, J.A. Burdick, Bioconj. Chem. 26 (2015) 2279–2289.
[13] Z. Liu, S.K.M. Nalluri, J.F. Stoddart, Chem. Soc. Rev. 46 (2017) 2459–2478.
[14] J. Murray, K. Kim, T. Ogoshi, W. Yao, B.C. Gibb, Chem. Soc. Rev. 46 (2017) 2479–2496.
[15] Y. Liu, Y. Chen, H.Y. Zhang, Handbook of Macrocyclic Supramolecular Assembly, Springer, Singapore, 2019.
[16] T. Xiao, L. Xu, L. Zhou, et al., J. Mater. Chem. B 7 (2019) 1526–1540.
[17] E.A. Appel, J. del Barrio, X.J. Loh, O.A. Scherman, Chem. Soc. Rev. 41 (2012) 6195–6214.
[18] E. Masson, X. Ling, R. Joseph, L. Kyeremeh-Mensah, X. Lu, RSC Adv. 2 (2012) 1213–1247.
[19] K.I. Assaf, W.M. Nau, Chem. Soc. Rev. 44 (2015) 394–418.
[20] S.J. Barrow, S. Kasera, M.J. Rowland, J. Del Barrio, O.A. Scherman, Chem. Rev. 115 (2015) 12320–12406.
[21] D. Shetty, J.K. Khedkar, K.M. Park, K. Kim, Chem. Soc. Rev. 44 (2015) 8747–8761.
[22] W.M. Nau, M. Florea, K.I. Assaf, Isr. J. Chem. 51 (2011) 559–577.
[23] R.H. Gao, L.X. Chen, K. Chen, Z. Tao, X. Xiao, Coord. Chem. Rev. 348 (2017) 1–24.
[24] K.M. Park, M.Y. Hur, S.K. Ghosh, et al., Chem. Commun. 55 (2019) 10654–10664.
[25] S. Li, Y. Gao, Y. Ding, A. Xu, H. Tan, Chin. Chem. Lett. 32 (2021) 313–318.
[26] K.I. Kuok, S. Li, I.W. Wyman, R. Wang, Ann. N. Y. Acad. Sci. 1398 (2017) 108–119.
[27] Y. Chen, Z. Huang, H. Zhao, et al., ACS Appl. Mater. Interfaces 9 (2017) 8602–8608.
[28] H. Yin, R. Wang, Isr. J. Chem. 58 (2018) 188–198.
[29] H. Chen, Y. Chen, H. Wu, et al., Biomaterials 178 (2018) 697–705.
[30] W.C. Geng, J.L. Sessler, D.S. Guo, Chem. Soc. Rev. 49 (2020) 2303–2315.
[31] J. Tian, C. Yao, W.L. Yang, et al., Chin. Chem. Lett. 28 (2017) 798–806.
[32] C. Gao, Q. Huang, Q. Lan, et al., Nature Commun. 9 (2018) 2967.
[33] C. Hu, N. Ma, F. Li, et al., ACS Appl. Mater. Interfaces 10 (2018) 4603–4613.
[34] J. Yeom, S.J. Kim, H. Jung, et al., Adv. Healthc. Mater. 4 (2015) 237–244.
[35] H. Jung, J.S. Park, J. Yeom, et al., Biomacromolecules 15 (2014) 707–714.
[36] K.M. Park, J.A. Yang, H. Jung, et al., ACS Nano 6 (2012) 2960–2968.
[37] M.J. Rowland, C.C. Parkins, J.H. McAbee, et al., Biomaterials 179 (2018) 199–208.
[38] A. Tabet, R.A. Forster, C.C. Parkins, G. Wu, O.A. Scherman, Polym. Chem. 10 (2019) 467–472.
[39] J. Chen, Y. Liu, D. Mao, D. Ma, Chem. Commun. 53 (2017) 8739–8742.
[40] W.L. Mock, N.Y. Shih, J. Org. Chem. 48 (1983) 3618–3619.
[41] X. Huang, Y. Tan, Q. Zhou, Y. Wang, Y. Che, Carbohydr. Polym. 74 (2008) 685–690.
[42] H. Xiaoling, T. Yebang, Z. Qifeng, W. Yuexia, ePolymers 8 (2008) 095.
[43] H. Jung, J.S. Park, J. Yeom, et al., Biomacromolecules 15 (2014) 707–714.
[44] H.J. Kim, J. Heo, W.S. Jeon, et al., Angew. Chem. Int. Ed. 40 (2001) 1526–1529.
[45] M.E. Bush, N.D. Bouley, A.R. Urbach, J. Am. Chem. Soc. 127 (2005) 14511–14517.
[46] R. Wang, L. Yuan, H. Ihmels, D.H. Macartney, Chem. Eur. J. 13 (2007) 6468–6473.
[47] D. Jiao, F. Biedermann, F. Tian, O.A. Scherman, J. Am. Chem. Soc. 132 (2010) 15734–15743.
[48] F. Biedermann, I. Ross, O.A. Scherman, Polym. Chem. 5 (2014) 5375–5382.
[49] L.M. Heitmann, A.B. Taylor, P.J. Hart, A.R. Urbach, J. Am. Chem. Soc. 128 (2006) 12574–12581.
[50] S. Sonzini, S.T.J. Ryan, O.A. Scherman, Chem. Commun. 49 (2013) 8779–8781.
[51] Y.F. Ding, J. Wei, S. Li, et al., ACS Appl. Mater. Interfaces 11 (2019) 28665–28670.
[52] Z. Yu, J. Zhang, R.J. Coulston, et al., Chem. Sci. 6 (2015) 4929–4933.
[53] X. Xu, E.A. Appel, X. Liu, et al., Biomacromolecules 16 (2015) 2743–2749.
[54] M.J. Rowland, M. Atgie, D. Hoogland, O.A. Scherman, Biomacromolecules 16 (2015) 2436–2443.
[55] C. Li, M.J. Rowland, Y. Shao, et al., Adv. Mater. 27 (2015) 3298–3304.
[56] Y.F. Ding, T. Sun, S. Li, et al., ACS Appl. Bio Mater. 3 (2020) 10–19.
[57] C.S.Y. Tan, J. Liu, A.S. Groombridge, et al., Adv. Funct. Mater. 28 (2018) 1702994.
[58] E.A. Appel, X.J. Loh, S.T. Jones, C.A. Dreiss, O.A. Scherman, Biomaterials 33 (2012) 4646–4652.
[59] E.A. Appel, X.J. Loh, S.T. Jones, et al., J. Am. Chem. Soc. 134 (2012) 11767–11773.
[60] C.S.Y. Tan, J. del Barrio, J. Liu, O.A. Scherman, Polym. Chem. 6 (2015) 7652–7657.
[61] L. Yang, A. Liu, M.V. de Ruiter, et al., Nanoscale 10 (2018) 4123–4129.
[62] C. Gao, C.H.T. Kwong, C. Sun, et al., ACS Appl. Mater. Interfaces (2020), doi: http://dx.doi.org/10.1021/acsami.1020c05013.
[63] H. Jung, K.M. Park, J.A. Yang, et al., Biomaterials 32 (2011) 7687–7694.
[64] E.A. Appel, X.J. Loh, S.T. Jones, C.A. Dreiss, O.A. Scherman, Biomaterials 33 (2012) 4646–4652.
[65] H.Q. Song, W. Pan, R.Q. Li, et al., Small 14 (2018) 1703152.
[66] M.J. Webber, E.A. Appel, B. Vinciguerra, et al., Proc. Natl. Acad. Sci. U. S. A. 113 (2016)14189.
[67] K. Henriksen, M.A. Karsdal, Nat. Biomed. Eng. 4 (2020) 481–482.
[68] X. Yang, S. Kootala, J. Hilborn, D.A. Ossipov, Soft Matter 7 (2011) 7517–7525.

Biography of corresponding author

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.