Sugercoted pillararenes for drug delivery applications

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Abstract: Supramolecular drug delivery systems (SDDSs) provide a useful platform for smart and functional drug carriers owing to their high selectivity towards various guest molecules and stimulus-responsive properties. Pillar[n]arenes represent a new generation of macrocyclic hosts with unique structures and chemical properties. In recent times pillar[n]arenes have attracted considerable attention as ideal scaffolds for the construction of SDDSs. Since sugar functionalized pillar[n]arenes have good water solubility and excellent biocompatibility, they have been widely applied in supramolecular systems construction, such as nanoparticles, vesicles, and gels by non-covalent interactions, so as to meet the requirements of their applications in biomedicine. These SDDSs present good responsiveness, not only realizing targeted delivery and controllable release of drugs, but also improving drug solubility and reducing its toxic and side effects. Here, according to the different structure of the assembly, the SDDSs constructed by the sugar functionalized pillar[n]arenes are summarized, and the development prospect of the system is prospected.

1 Introduction

With the global health industry surging ahead, the pharmaceutical industry, as an important pillar of the medical and health industry, has ushered in great development opportunities. As the core driving force of pharmaceutical industry, drug R&D has been confronted by tougher demands[1,2] and increasing challenges, including instability in vivo and in vitro (prone to degradation), severe adverse reactions despite drug efficiency, and limited transport capacity due to biological barriers such as blood-brain barrier[3]. Therefore, how to solve these problems has become the difficulty and challenge for future studies on drug R&D. With the continuous progress and rapid development of new technologies, processes, equipment and materials, new drug delivery system has been served as a potential approach to these issues[4].

So far, multiple types of drug delivery systems have been developed, including organic drug delivery system[5], inorganic drug delivery system[6] and biological drug delivery systems[7,8]. Compared with traditional drug delivery system, supramolecular drug delivery systems (SDDSs)[9] mainly constructed by non-covalent interactions such as π-π molecular stacking[10], metal chelation[11], hydrogen bonding[12], Van der Waals force[13], electrostatic interaction[14], which have attracted more and more interests due to their excellent stimuli responsive features and infinite possibilities[15-23]. The SDDSs, such as micelles, vesicles, nanoparticles and gels[24-32], not only improves the stability of the drug, but also delivers the drug to the appropriate site of action, thereby enhancing the therapeutic effect and reducing its toxic and side effects. Moreover, it can also overcome obstacles both in vitro and in vivo, improve its bioavailability, and control the drug release to maintain stable and effective blood drug concentration[33].

Macrocyclic molecules provide ideal scaffolds for the fabrication of SDDSs. As a new generation of macrocycles, pillar[n]arenes (PA) represent a kind of cyclic oligomer consisting of hydroquinone structural units connected by methylene group at the 2, 5 position and forming a unique rigid structure with a hydrophobic cavity. Their homologs with n=5–13 have already been synthesized, but the cyclic pentamers (pillar[5]arenes) and cyclic hexamers (pillar[6]arenes) have been widely studied[34] (as shown in Figure 1). Due to the unique pillar architecture, easy functionalization, and outstanding properties in host–guest chemistry, which make them promising candidates for applications in chemistry, materials, life science and other fields[35-38].

Fig.1. Chemical structure of the Pillar[n]arene.
Recently, water-soluble PA derivatives\cite{39} exhibited a good biocompatibility, strong binding affinity with various kinds of guest molecules and targeting property which could be beneficial for the development of SDDSs\cite{40}. To fabricate smarter SDDSs, it is essential to introduce targeting and hydrophilic functional groups into the PA. Among various reported targeting ligands, glycoderivatives contribute to many biological phenomena such as adhesion, cancer cell metastasis, cellular recognition, or infection of pathogens by protein–carbohydrate interaction\cite{41}, which play an irreplaceable role in targeted drug delivery system\cite{42}. Therefore, introducing the glycosyl groups on PA\cite{43} can improve their biocompatibility and endow them with active targeting abilities via “sugar cluster effect”. This paper reviews the latest research on sugar-coated PA in drug delivery system in recent years.

2 Drug Delivery System of Sugar-functionalized Pillar[n]arene Based on Host-Guest Interaction

Host–guest interactions are attracting more and more attention arising from their distinctive properties in the construction of supramolecular assemblies. Furthermore, functional groups can be easily integrated into SDDSs by simply modifying the building blocks, such as targeting ligands, imaging agents or even therapeutic drugs, endowing them with multi-functional theranostic properties. Sugar-functionalized PA have a strong affinity for various guest molecules, providing a good module for designing and constructing SDDSs that can not only selectively recognize cancer cells, but also can efficiently release the anticancer drugs triggered by the tumor microenvironment.

2.1 Supramolecular nanoparticles

Nanoparticles (NPs), which can penetrate tissues and small capillaries offering advantages including long circulation time, improvements in the target-to-non-target concentration ratio, increased residence at target site and improved cellular uptake, are small colloidal particles made of biodegradable or nonbiodegradable materials. To enhance drug accumulation and release at the site of interest from NP which is encapsulated to NP matrix, different strategies have been used. Stimulus-responsive cleavable cross-linking of NPs are of particular interest for efficiency and targeted intracellular drug delivery.

Due to the intracellular glutathione (GSH) level of cancer cells is much higher than that of normal cells. NPs containing reducible disulfide bonds can be degraded easily by thiol/disulfide exchange with GSH, and achieve the efficient intracellular delivery of drug molecules. Hu XiaoYu, et al.\cite{44} modified the two rims of PA with D-galactose via triazole linkage (GalP5). Camptothecin produg molecules with disulfide bonds and trimethylammonium groups can strongly bind to GalP5, and further form higher-order supramolecular vesica in water which could release the anticancer drug efficiently in a tumor cell with high GSH concentration (as shown in Figure 2). They proved that the disulfide bonds modified supramolecular nanoparticle can target tumors and lead to significant drug accumulation in cancer cells via receptor-mediated endocytosis.

Fig.2. GSH-responsive spherical nanoparticles SDDS\cite{44} (Copyright 2017 The Royal Society of Chemistry)

Compared with GSH-responsive NPs, near-infrared (NIR) light-responsive NPs, which has reached clinical trials, can penetrate deeply with negligible attenuation into biological tissues and minimal photodamage to cells. As a semiconductor, copper(II) sulfide nanoparticles (CuS-NPs) can absorb NIR light converting it into heat due to the excitation of direct (band-to-band) transitions, indirect transitions, and plasmonic photoexcitation. However, construction of CuS-NP for synergistic therapies with other functional components as well as anticancer drugs involves complex and tedious synthetic procedures. The introduction of supramolecular macrocycles is an effective method to generate multifunctional CuS-NP. Yu Jihong et al.\cite{45} constructed hydrophilic CuS-NP drug delivery system (CuS@CPG) for targeted cancer chemotherapy and photothermal therapy, employing carboxylatopillar[5]arene sodium salts (CP[5]A) and assembling pyridinium salt moiety of galactose derivative on its surface via the host–guest interaction. Finally, doxorubicin hydrochloride (DOX) was loaded on the surface of CuS@CPG through electrostatic interaction (as shown in Figure 3). This work opens a new perspective on using facile supramolecular strategy to construct multifunctional NPs for cancer therapeutic applications.

Fig.3. NIR Photothermal responsive Nanoparticles SDDSs\cite{45} (Copyright 2018 American Chemical Society)
2.2 Supramolecular nanorods

CeO₂ nanoparticles (CeONPs), which enable to be a considerable candidate for synergistic drug delivery, can facilitate the oxidation of intracellular and extracellular components to induce cell apoptosis in acidic microenvironment. How to immobilize biocompatible macrocyclic molecule that may be also easily removed under microenvironments in cancer cells on CeONPs, to maximally exerted the synergistic antitumor effect on cancer cells caused by CeONPs is still a big challenge.

Pei Zhichao, et al. [46] constructed a smart SDDSs by immobilizing a galactose-functionalized pillar[5]arene (GP5) on pyridine-functionalized nano-rods (CeONRs) with a disulfide linkage through host–guest interactions for synergistic efficacy. The DOX loaded CeONRs capped with GP5 released DOX quickly upon the cleavage of its cap triggered by GSH in cancer cells and exhibited cancer cell targeting ability, because of disulfide units and the galactose on the rim of the PA, respectively (as shown in Figure 4). This study provides a new strategy for the rational design and construction of CeONRs which can synergistically enhance the cytotoxicity for cancer chemotherapies.

![Fig.4. GSH-responsive nano rods SDDS](Copyright 2017 The Royal Society of Chemistry).

2.3 Supramolecular gels

Supramolecular gels, where non-covalent interactions lead to gelation and are generally characterized by their structural reversibility and stimuli-responsiveness, could be a better choice for drug delivery applications. Using stimuli sensitive gels as drug delivery agents to achieve the site-specific controlled release of drugs is still an important issue. A few efforts have been made to solve this problem, active targeting strategies were developed, which could result in significantly higher efficiency and improve accumulation in the tumor site. Among them, the surface of nanogels modification is based on host–guest interactions, which improve the interaction of nanocarriers with receptors on the surface of the desired cells, without additional synthetic efforts.

Schubert, et al. [47] introduced carbohydrates-pillar[5]arene on the surface of 6-acryloyloxyhexylopyridinium chloride (AHPC) modified nanogel that based on cross-coupling of acrylamide and pyridine salt (as shown in Figure 5), endowing the pH-sensitive gel system with the ability to target concanavalin A (Con. A). This system opens a convenient and straightforward routes to fabricate reversible targeting nanocarriers, which enables fast and easy high-throughput screening of various targeting units combinations.

![Fig.5. The Nanogels SDDS](Copyright 2020 American Chemical Society).

2.4 pH/GSH/ Redox-responsive supramolecular vesicles

Owing to the fascinating stimuli responsiveness, supramolecular vesicles driven by host-guest interactions have received much attention in the field of drug delivery. They possess closed bilayers with hydrophilic cavities as both the internal and hydrophobic shells as the outer layers that can be exploited in the incorporation of two different drugs, thus performing dual drug delivery. Meanwhile, the cavity of the host molecular also can encapsulate bioactive agents or targeting ligand by forming an inclusion host–guest complex, facilitating the synergistically. Furthermore, the vesicles are capable of undergoing reversible assembly and disassembly under specific external stimuli, such as pH, temperature, light, enzymes, and redox agents.

To the best of our knowledge, the pH of the tumor cells is relatively lower than that of normal cells, otherwise the intracellular GSH level of cancer cells than higher that of normal cells. Therefore, the functional moieties which can respond to these stimuli existing at targeted sites and thus lead to SDDSs disassembly as well as cargo release should be integrated into the hosts or guests.

Pei Yuxin, et al. [48] developed a functionalized supramolecular vesicle (as shown in Figure 6) based on the host-guest interaction between galactose capped pillar[5]arene (GALWP5) and n-decyl triphenylphosphine (D-TPP), where the cancer cell targetability caused by the galactose unit of GALWP5, while the mitochondria-targeting ability caused by the triphenylphosphonium group of D-TPP. Loaded DOX, vesicle is helpful to improve drug to accumulate in mitochondria after entering cancer cells. Meanwhile, the SDDSs also feature redox and pH responsiveness. This
work serves as a good example for rational design and construction of dual-targeted supramolecular vesicles for drug delivery, which have potential applications for precise chemotherapy.

**Fig. 6.** Dual targeted glycolvesicle SDDS\(^{[48]}\) (Copyright 2018 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim).

Several functional moieties can be introduced to the pyridine, while the cavity of functionalized PA facilitates the complexation of pyridine derivatives for the construction of supramolecular vesicle. The generated vesicles were target specific and able to simultaneously achieve continuous and controllable drug release upon multi-stimuli responsiveness. As mentioned above, carbohydrates are attractive building blocks in the design of targeted molecules for biomedical applications. By including a structural unit of galactose in the guest pyridinium, the cancer cell targeted supramolecular vesicle was established based on host-guest inclusion of the PA and galactose derivative which showed preferential accumulation in cancer cell. The PA also can be further designed to construct the supramolecular vesicle respond to external stimuli by complexing galactose derivatives guest molecule. Thus, to achieve PA-based multifunctional SDDSs, special or specifically motifs which can respond to unique stimuli existing at targeted sites and thus lead to SDDSs disassembly as well as cargo release must be integrated into the PA.

Tryptophan (Trp), an essential amino acid in the human diet, is known for its interactions with DNA via the indole ring in the molecule. By the host-guest complex of Trp-modified pillar[5]arene and galactose derivatives, the supramolecular vesicle is constructed to encapsulate and deliver the anticancer drug DOX\(\cdot\)HCl (as shown in Figure 7)\(^{[49]}\), which can interact with cellular DNA while showed the ability to overcome DOX-resistant hepatoma cells due to the synergistic effect. As expected, this SDDS exhibits excellent pH responsiveness and quick releases of DOX at acidic environment, enabling them for controlled drug release.

**Fig. 7.** The pH-responsive vesicle SDDS\(^{[49]}\) (Copyright 2016 American Chemical Society)

Ferrocenecarboxylic acid (FA) is responsive to GSH and low pH. The supramolecular vesicles based on the host–guest complexation of FA capped pillar[5]arene (FACP5) and galactose derivative were assembled where DOX was successfully encapsulated (as shown in Figure 8). The vesicle, which exhibited quick release of DOX upon GSH in acidic solution, significantly enhances anticancer efficiency for cancer cells while effectively reduces side effects to normal cells.

**Fig. 8.** pH and GSH-responsive vesicle SDDS\(^{[50]}\) (Copyright 2016 the Royal Society of Chemistry).
The cystamine dihydrochloride (CA), an important pharmaceutical intermediate that sensitive to GSH stem from a disulfide bond, while sensitive to pH stem from amino groups. Most importantly, CA can not only inhibit the formation of gastric and mammary tumors that were induced chemically or after irradiation and also enhance the cytotoxicity of DOX. Pei Zhichao, et al. [51] successfully constructed supramolecular vesicles (CAAP5G) based on the host-guest complexation of CA capped pillar[5]arene (CAAP5) and galactose derivative which not only exhibited excellent dual stimuli responsiveness and rapid release of DOX in cancer cells but also possesses targeting ability to ASGP-R overexpressing HepG2 cells (as shown in Figure 9). As expected, the vesicles under high concentration of GSH would release cysteamine, which could enhance the anticancer efficiency of DOX and reduce the drug resistance of cancer cells.

Inspired by the fascinating host–guest properties of PA, researchers have been exerting great effort to the synthesis of novel PA with rationally designed functional groups in order to endow PA-based SDDSs with desired properties. With the rapid development of nanotechnology, supramolecular nanostructures mediated by host–guest interactions are expected to gain increasing attention for their potential in drug delivery.

3 Application of Sugar- Functionalized Pillar[n]arenes in Antibacterial and Antiviral Activities

Sugar functionalized PA has recently come to the fore is the development of anti-adhesive molecules against pathogen infections through the glycoside cluster effect because they provide decavalent scaffolds on a minimal molecular architecture leading to dense presentation of carbohydrate epitopes on their periphery. The first antimicrobial glyoclusters of pillar[5]arene was develop by using a deca-mannose functionalised pillar[5]arene scaffolds (as shown in Figure 10a) that shown the ability of inhibiting adhesion of Escherichia coli to red blood cells through interaction with the FimH adhesin[52]. Subsequently, multivalency improved the binding to lectins and a higher affinity have been obtained by increasing to a certain limit the length of the spacer arm between the carbohydrate subunits and the central pillar[5]arene core (as shown in Figure 10b) [53]. Meanwhile, it is proved that steric interactions were demonstrated to be a key factor in achieving good binding to LecA with more flexible galactose glyoclusters showing enhanced activity (as shown in Figure 10c) [54].

In order to mimic the multivalent presentation of carbohydrates on glycoprotein or cell surfaces, sugar-coated pillar[5]arene-containing [2]rotaxanes have been built (as shown in Figure 11) [55]. And it proved that they can combine with pathogenic bacterial lectin. This study developed an effective synthetic approach combining recent concepts for the preparation of multifunctional nanomolecules with self-assembly to prepare rotaxane allowing the synthesis of sophisticated supramolecular heteroglycoclusters for biological applications.

Similarly, pillar[5]arene based glyoclusters, featuring five galactose moieties, facilitated agglutination of E. coli which can reduce the infection to normal cells and inhibit the spread of diseases, although the specific lectin interactions were not identified (as shown in Figure 12)[56]. This study shows that supramolecular self-assembly driven by noncovalent interactions can be used as a unique chemical tool to capture living bacteria in solution.
4 Conclusion and Outlook

The potential of PA scaffolds for the development of SDDSs have their own unique advantages but are still in their infancy. Considering the outstanding advantages of biomolecules (such as carbohydrate, proteins, enzymes, and siRNA/DNA) in curing diseases, it can be used to modified the PA endowing the SDDSs with good targeting property and biocompatibility. In this account, sugar coated PA-based SDDSs with stimuli responsiveness have been summarized which are formed directly via supramolecular host–guest complexation of a sugar coated PA as the host and suitable guests containing recognizable motifs. Through responsiveness to specific stimuli, specific location targeting, and site-specific controllable release, sugar coated pillar[n]arene-based SDDSs can complete customer-oriented tasks due to the unique characteristic features of PA in structures and host–guest interactions. However, despite these advances, the use of sugar functionalized PA in the construction of SDDSs is still limited. One of the main issues is their poor stability and early burst release. The other concern is how to achieve the successful transition of SDDSs from lab to clinical applications, which is also the ultimate goal of developing SDDSs. Therefore, much more efforts are still necessary to improve the biocompatibility, targeting efficacy, stimuli -responsiveness and in vivo stability of the SDDS, and to further evaluate their biodistribution, long-term toxicity effects, and circulation properties.

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