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Review

Controlled drug delivery systems based on calixarenes

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ABSTRACT

In recent years, cancer has become the number two cause of death around the world, and scientists have exploited various treatment maps. Calixarenes, with diversified features, have been widely applied into drug delivery systems, which can respond to multi-stimuli and exhibit excellent performance. In this mini-review, we summarize the recent advances on controlled drug delivery systems based on calixarenes, in the form of inclusion complexes, amphiphilic self-assembly nanocarriers including micelles, hydrogels, vesicles and liposomes, and supramolecular nanovalves on mesoporous silica nanomaterials.

1. Introduction

Supramolecular approaches have been applied to drug delivery systems [1,2], and have attracted much attention among researchers in various disciplines. Enormous research efforts have been made to enhance the therapeutic efficacy and minimize the side effects of anticancer drugs, satisfying the clinical needs. Stimuli-responsive drug delivery systems with the features of sustained, controlled and targeted drug release are highly desirable [3–5]. Ideal drug carriers, such as host-guest inclusion complexes [6–10], micelles [11,12], hydrogels [13], vesicles [2,4,14], liposomes [15,16], and inorganic nanoparticles [5,17], should be stable and can avoid nonspecific cell uptake, and beyond that they should also be capable of targeting on tumor sites to realize good treatment efficacy in cancer therapy. Different generations of synthetic macrocycles, *i.e.*, cyclodextrins, calixarenes (CAs), cucurbiturils, and pillarenes (or pillar[n]arenes), have been employed for the construction of new drug delivery systems [1,14,18–20].

CAs are a family of bowl or cone shaped synthetic supramolecular macrocycles, composed of phenol units linked by methylene bridges through condensation reaction of a phenol and an aldehyde, and they are capable of forming inclusion complexes with suitable guest molecules through the hydrophobic and electron-rich cavity [21]. Significantly, CAs and their derivatives of water-soluble versions in particular, show good biocompatibility and non-cytotoxicity, which are important prerequisites for application in any practical drug delivery systems [22]. In this mini-review, we present a general overview about CA-based drug delivery systems, which can respond to multifarious external stimuli and achieve appreciable therapeutic effect in disease treatment.

2. Inclusion complexes

Supramolecular host-guest inclusion complexes were formed by hydrophobic interactions, hydrogen bonding, π–π stacking, charge-transfer, and others, which have provoked lots of interest because of their reversible nature (complexation and decomplexation) [23–26]. Numerous research groups have reported CA-based drug delivery systems by loading drugs in different inclusion complexation forms (Fig. 1). In 2009, Wheate *et al.* [6] constructed a vehicle for anticancer drug delivery based on *p*-sulphonatocalix[4]arene (SC[4]A) and dinuclear platinum compound (Fig. 2i) by side-on binding of the two parts. The system would release dinuclear platinum upon *in vivo* administration, due to high content of blood serum existing in body. In order to amplify the applicability of water-soluble CAs in complex systems, Liu *et al.* [7,27] reported the complexation of topotecan and irinotecan (Fig. 2iii and v) with SC[4]A under 1:1 molar ratio, and the inclusion modes were confirmed by means of ^{1}H NMR, DSC, 2D NMR and UV–vis spectroscopy. And then Dong *et al.* [8] constructed the inclusion complex using *p*-sulphonatocalix[6]arene and vitamin B_6

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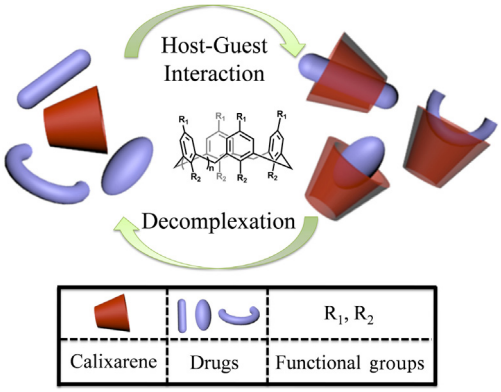

Fig. 1. Schematic representation of the formation of inclusion complexes based on CAs and drugs and their decomplexation.

(Fig. 2ii) in acidic and alkaline media. The complex systems could release cargo through disaggregation of the inclusion complexes under certain conditions, which means they can act as an excellent candidate for drug delivery. For the sake of loading larger cargo, such as norfloxacin (Fig. 2iv) and ciprofloxacin, calix[8]arene was chosen as host macrocyclic compound to encapsulate drug into its cavity [9,28]. Luo *et al.* [9] reported a smart delivery system, which was composed of *p*-sulfoniccalix[8]arene and antimicrobial agent in aqueous solutions and could respond to competitive agent, *i.e.*, bovine serum albumin.

3. Micelles and hydrogels

Self-assembly behavior is ubiquitous in living systems. Specific amphiphilic molecules are significant research topics in the fields of materials science and chemical biology because it can be spontaneously developed into micelles (Fig. 3), hydrogels and others. In 2011, Zhu *et al.* [11] took advantage of the host-guest interaction of hydrophilic host molecules, that is, PEGylated calix[4]arene, and hydrophobic chlorin e6 to form supramolecular polymeric micelles, which exhibited more efficient photodynamic therapy efficacy than free chlorin e6. For repairing injury or treating disease in central nervous system (CNS), oxidative stress is a vital element for cell survival. Raston *et al.* [29] established new micellular systems based on phospholipid calix[4]arenes, which exploited the antioxidants of macrocyclic host compounds

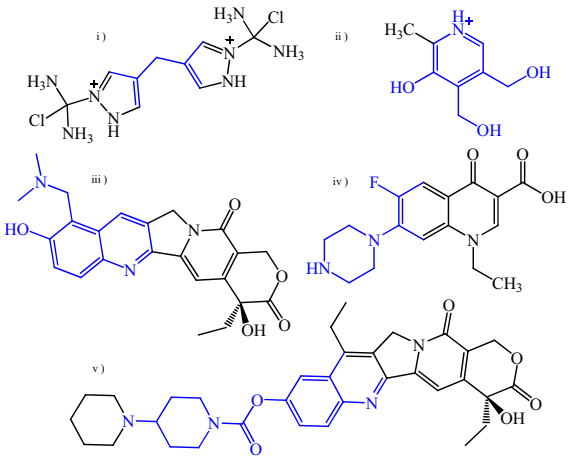

Fig. 2. Chemical structures of the studied drugs. The blue parts are the ones that can inset into the cavity of CAs.

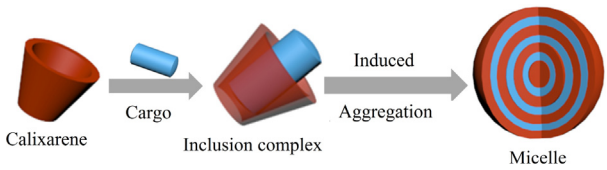

Fig. 3. Schematic illustration of the formation of micelles.

sufficiently. Moreover, they can encapsulate fluorescent antioxidant curcumin to realize cargo release. In order to enhance the loading efficiency, Liu *et al.* [12] made use of drug molecules themselves as an essential unit to form co-assembly nanostructures through simple procedure and subtle design. The amphiphilic assemblies were fabricated *via* different assembling methods, one was directed by inducing aggregation of antipsychotic drug chlorpromazine with SC[4]A, another co-assembly nanostructure was formed between anionic *p*-sulfonatocalix[4]arene tetraheptyl ether (SC[4]AH) and cationic chlorpromazine, which exhibited high loading efficiencies (61% and 46%, respectively). In addition, as designed by Xiao *et al.* [28], the modified amphoteric CAs, with negative and positive charges on each rim, own excellent loading capacity for hydrophobic drug. The amphoteric calix[8]arene can form complexes or multilayers with ciprofloxacin under pH values ranging from 7.05 to 7.58. Furthermore, no matter in acidic medium or basic medium, the assemblies will disaggregate and release drug effectively.

Low molecular weight hydrogels have aroused prodigious attention in many fields. Liu *et al.* [13] designed a series of supramolecular binary gels by two steps. First, *tetra*-proline modified calix[4]arenes (TPC) turned to micelles when the concentration of TPC was above the critical micelle concentration (CMC), and then the complexes translated itself into hydrogels with basic amino acids (arginine, histidine and lysine) in acidic conditions. Meanwhile, anticancer drug, doxorubicin hydrochloride (DOX), was entrapped into the gels (Fig. 4) and the systems released DOX upon immersion of the hydrogels into water.

4. Vesicles and liposomes

Among different forms of nanocarriers for drug delivery and controlled release, lipid vesicles and immune-liposomes exhibited remarkable advantages [2,15,30]. In contrast with micelles, vesicles with the hollow cavities prefer to entrap hydrophilic drugs and can capture more. In 2004, Lee *et al.* [31] constructed the nanocarriers based on CAs backbone, consisting of four hydrophilic dibranched chains with different lengths at the upper border and liphophilic decyl chains at the lower border. Upon increasing the length of hydrophilic chain, large vesicle would transform itself into small spherical micelle. Furthermore, vesicle would also collapse into micelle at acidic conditions thereby realizing cargo release. In 2010, Liu *et al.* [32] constructed a new nanoscale

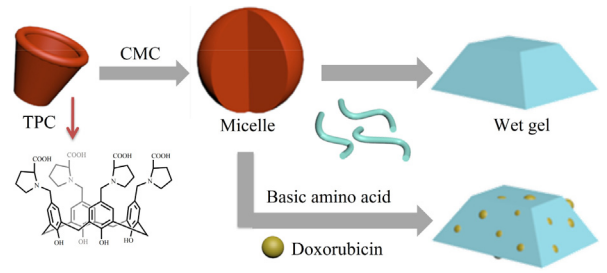

Fig. 4. Schematic depiction of gel generation from TPC gelator induced by basic amino acids.