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Review

The Role of Macrocyclic Compounds as Supramolecular Drug Delivery Systems: A-Review

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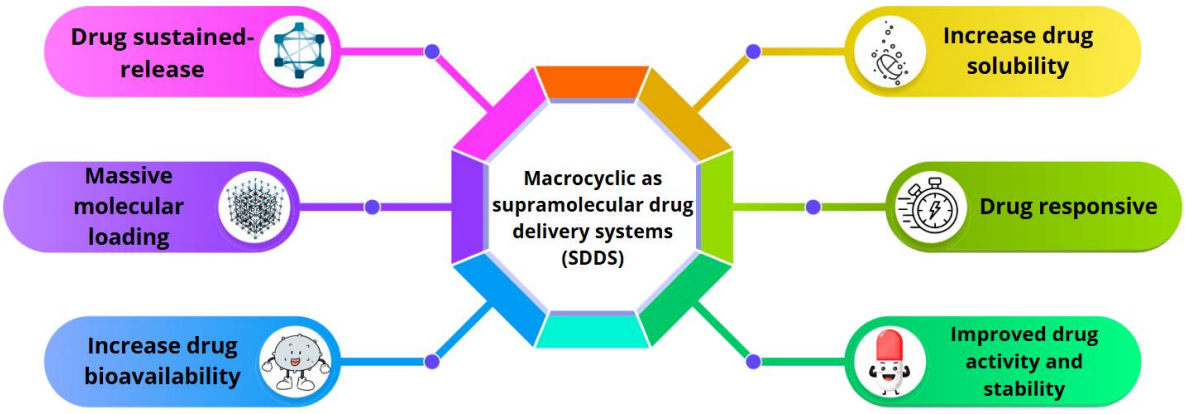
Abstract

In recent decades, significant advances in the development of drug delivery systems have unlocked new possibilities for enhancing therapeutic efficacy. Among the diverse range of innovative materials, macrocyclic-based supramolecular systems have emerged as promising platforms due to their unique physicochemical properties. Macrocyclic compounds such as cyclodextrins and cucurbiturils exhibit a remarkable ability to form stable inclusion complexes with various drug molecules, thereby improving their solubility, chemical stability, bioavailability, and pharmacokinetic profiles. This review highlights the design principles, synthetic strategies, and mechanisms of action underlying macrocyclic drug carriers, with particular emphasis on their responsiveness to environmental stimuli such as pH, temperature, and biomolecular triggers. Recent findings demonstrate that macrocyclic systems can significantly enhance drug loading efficiency, targeted delivery, and cellular uptake, while minimizing systemic toxicity. These advances underscore the potential of macrocyclic supramolecules as foundational elements for the development of next-generation drug delivery systems that are more precise, effective, and adaptable to personalized therapeutic needs.

Keywords: *Drug delivery, macrocyclic, supramolecules*

Graphical Abstract



Introduction

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Supramolecular chemistry is a branch of science that focuses on non-covalent interactions such as hydrogen bonding, π-π interactions, and electrostatic forces, which are used to form complex structures with specific functions [1,2]. In the pharmaceutical field, supramolecular approaches have shown great potential to improve the efficiency and selectivity of drug delivery systems [3-5]. The development of modern drug delivery systems has become a major focus in pharmaceutical research to improve therapeutic efficiency and minimize side effects. One innovative strategy that has gained widespread attention is the utilization of host-guest complex inclusion-based materials [2,3]. Supramolecular materials offer various advantages, such as high stability, structural customizability, and large loading capacity, making supramolecular-based materials an excellent platform for smart drug delivery systems [5].

Among the various supramolecular systems, macrocyclic compounds have emerged as particularly attractive candidates for drug delivery applications [6]. Macrocyclic compounds are currently quite popular in drug delivery applications. Cyclodextrins (CDs), crown ethers (CEs), cucurbit[n]urils (CB[n]s), calix[n]arenes (C[n]As), and pillar[n]arenes (P[n]As) are some of the further developments in the exploration of macrocyclic compounds as drug delivery agents [4]. Specifically, macrocyclic compounds have complex cavity systems that can accommodate various types of guest molecules [5]. Supramolecular-based drug delivery systems (SDDS) with macrocycles are based on dynamic "host-guest" interactions that can have reversible changes in structure, morphology and function [6-7]. This is very beneficial for targeted and controlled drug release, which can reduce damage to normal tissues or cells and improve diagnostic and therapeutic effects. Supramolecular interactions, such as hydrogen bonding and π-π interactions, play an important role in various aspects of drug delivery, including biocompatibility, drug loading, stability, targeting, and controlled release [7-8]. In addition, the use of macrocyclics as host molecules can

Methods

This journal review limits the discussion to macrocyclic compounds such as cyclodextrins (CDs), crown ethers (CE), cucurbit[n]urils (CB[n]s), calix[n]arenes (C[n]As) and pillar[n]arene (P[n]A). This journal review was conducted through a systematic process comprising several stages. First, various references related to macrocyclic supramolecules in drug delivery systems were comprehensively collected. Second, relevant literature was screened and selected based on its significance to the predetermined topic. Third, the content of the selected publications was critically reviewed to gain an in-depth understanding of recent advances in the application of macrocyclic supramolecular compounds as drug delivery systems.

The selection criteria included literature containing the keywords: cyclodextrin, crown ethers, cucurbit[n]urils, calix[n]arenes, and pillar[n]arenes, while excluding studies on compounds lacking host-guest properties and complex binding interactions. The initial search yielded 150 articles, which were subsequently screened to obtain 105 eligible publications and included 50 articles.

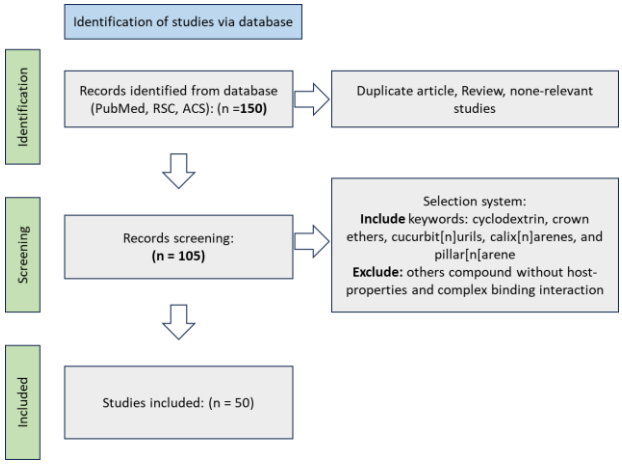


Figure 1. Flow diagram of review study.

The literature analyzed in this review was sourced from reputable scientific journals and publishers, including Nature, ScienceDirect, ACS Publications, MDPI, SciELO, RSC Publishing, AACR, PNAS, PMC Europe, ASCO, Wiley, Chemistry Europe, and SpringerLink.

This review specifically focuses on macrocyclic compounds such as cyclodextrins (CDs), crown ethers (CEs), cucurbit[n]urils (CB[n]s), calix[n]arenes (C[n]As), and pillar[n]arenes (P[n]As), limiting the scope to their structural characteristics, host-guest interactions, and potential for drug delivery applications. keywords. The flow diagram is shown in figure 1.

Result and Discussion

Cyclodextrin (CD)-based SDDS

Cyclodextrins (CDs) constitute a prominent class of macrocyclic oligosaccharides that have garnered substantial attention as versatile supramolecular carriers in advanced drug delivery systems [9-10]. Structurally, CDs are toroidal (truncated cone-shaped) cyclic oligomers, each comprising D-glucopyranose units linked via α-1,4-glycosidic bonds. This distinctive molecular architecture gives rise to a hydrophobic internal cavity juxtaposed with a hydrophilic external surface, a duality that underpins their remarkable host–guest inclusion capabilities (Figure 2).

Among the naturally occurring CDs, α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin, containing six, seven, and eight glucose residues respectively (Table 1), are the most extensively characterized. Each variant exhibits a unique cavity diameter, which dictates the selectivity and affinity toward guest molecules of diverse molecular dimensions, polarities, and conformations. In addition to native forms, a plethora of chemically modified derivatives—such as hydroxypropyl-β-cyclodextrin and methylated CDs—have been developed to further optimize solubility, complexation efficiency, and biocompatibility [10-11].

The amphiphilic nature of CDs confers a suite of pharmaceutical advantages. The hydrophobic cavity facilitates non-covalent encapsulation of poorly water-soluble bioactive compounds through van der Waals forces and hydrophobic interactions, thereby substantially enhancing their apparent aqueous solubility, chemical stability, and dissolution rate. Simultaneously, the hydrophilic outer surface promotes favorable dispersion and wettability in biological media, improving formulation performance [9,12].

Beyond solubilization, cyclodextrin inclusion complexes can shield labile or photosensitive drugs from environmental degradation, mitigate undesirable organoleptic properties (e.g., bitter taste or odor), and enable controlled or sustained release profiles. Such multifaceted benefits contribute to improved pharmacokinetic predictability, enhanced bioavailability, and potentially superior therapeutic outcomes. Consequently, CDs have emerged as indispensable excipients and enabling technologies in contemporary pharmaceutical science and nanomedicine [12-16].

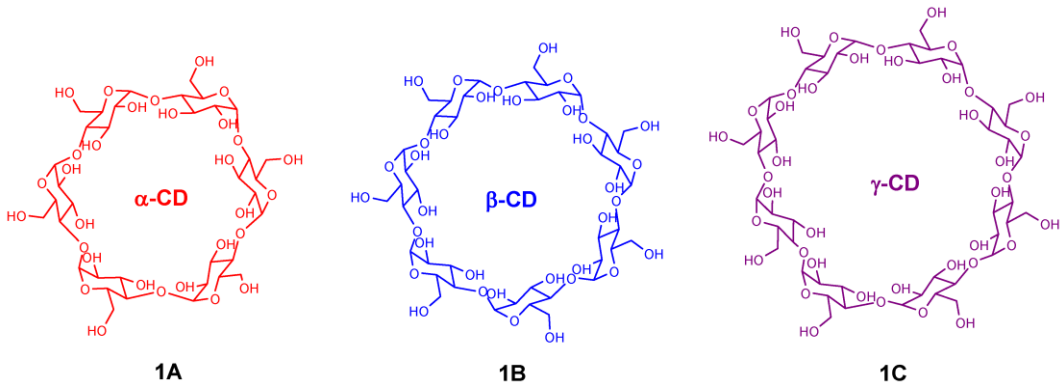
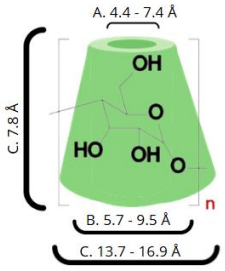


Figure 2. Molecular structure of α-, β-, γ-CDs [11] (Reprinted with permission)

In addition to improving solubility and bioavailability, CDs have been employed to reduce local irritation and systemic toxicity by limiting direct drug interaction with biological membranes. Furthermore, CDs can be functionalized or conjugated with targeting ligands, polymers, or other responsive moieties to develop advanced delivery platforms capable of site-specific drug release or stimuli-responsive behavior. For example, hydroxypropyl-β-

cyclodextrin and sulfobutyl ether-β-cyclodextrin are widely used derivatives approved in various parenteral formulations due to their favorable safety profiles and superior solubilizing capacity. Overall, cyclodextrins exhibit remarkable versatility as supramolecular drug delivery vehicles, offering opportunities to address challenges associated with the formulation of hydrophobic drugs, improve therapeutic efficacy, and enable the development of innovative dosage forms with controlled or targeted delivery properties [17-18].

Table 1. Physical properties of CDs [7]



Properties	α-CD	β-CD	γ-CD
Empirical formulas	$C_{36}H_{60}O_{30}$	$C_{42}H_{70}O_{35}$	$C_{48}H_{80}O_{40}$
Glucose unit total	6	7	8
Molecular weight (g/mol)	972	1135	1297
Inner diameter (A)	4.4 Å	5.8 Å	7.4 Å
Sec. Inner (B)	5.7 Å	7.8 Å	9.5 Å
Outer diameter (C)	13.7 Å	15.3 Å	16.9 Å
Height (h)	7.8 Å	7.8 Å	7.8 Å
Capacity	174 $Å^3$	262 $Å^3$	427 $Å^3$
Aqueous solubility (g/L)	129.5	18.4	249.2
Temperature of degradation (°C)	278	298	267

Table 2. Comparison of cyclodextrin-based drug delivery

Types	Drugs (Guest)	Studies	Findings	Ref.
2-hydroxypropyl-β-cyclodextrin (HP-β-CD)	Budesonide (BUD)	*In vitro* release assay using membrane model with regular intervals from 30 min until 48 h, then drug content was monitored by HPLC	The developed formulation significantly improved the solubility of budesonide, which in turn contributed to enhanced bioavailability and therapeutic effectiveness in managing ulcerative colitis.	[12]
sulfobutylether—cyclodextrin (SBE-β-CD)	Resveratrol (RSV) / solfobutyl	*In vitro,* MTT assay was conducted to evaluate the cytotoxic activity of RSV integrated to SBE-β-CD	The improved formulation led to a significant increase in the solubility of resveratrol, which subsequently enhanced its anticancer efficacy.	[13]
CPT-PEG-α-CD (Cyclodextrin)	Camptothechin (CPT)	*In vitro* release study of 5-FU-loaded CPT-PEG hydrogels in PBS at 37 °C; drug release quantified by HPLC with UV detection (265 nm for 5-FU, 372 nm for CPT-PEG).	Control drug release, temperature- responsive, improved bioavailability and significant temperature-dependent properties for anticancer activity.	[14]
Hydroxypropyl-β-cyclodextrin (HPCD)	Meropenem (MP)	*In vitro* release study using dialysis	Improved solubility and stability in aqueous solution	[15]

Types	Drugs (Guest)	Studies	Findings	Ref.
		membrane then monitored by UV-Vis.		
Mannose-modified γ-cyclodextrin (M-ϒ-CD)	Regorafenib (RG)	Comprehensive study including *in vitro* drug release, MTT cytotoxicity assays against CT26, HT29, SW480, and RKO cells; in vivo efficacy in Balb/c and C57BL/6 tumor-bearing mice; gene expression analysis, ex vivo evaluations, western blotting, and histological assessments.	RG@M-γ-CD nanoparticles suppressed inflammation and TAM activation, improved Regorafenib's anti-tumor effects, optimized pharmacokinetics, and remodeled the tumor microenvironment, showing efficacy in CRC models.	[16]
Hydroxypropyl- β-Cyclodextrin (HP-β-CD)	Dexibuprofen	*In vitro* drug release in phosphate buffer; in vivo acute toxicity evaluation using Wistar albino rats.	Enhanced drug release, and formulation by hydrogel-delivered	[17]
B-cyclodextrin-Carboxymethyl chitosan (β-CD-CMC)	Docetaxel (DTX)	*In vitro* drug release in buffer system; *in vivo* acute toxicity studies using Wistar rats.	Improved water solubility of docetaxel up to 14 times	[18]
γ-cyclodextrin metal-organic frameworks (CD-MOFs) γ-CD- MOF	Paeonol (PAE)	*In vitro release* in phosphate buffer and evaluate anticancer against Human lung cancer through MTT assay; *in vivo* using rats was performed to evaluate activities.	CD-MOF showed biocompatible as a drug carrier, enhanced the permeability of drug and significantly improved PAE release.	[19]
Hydropropyl—cyclodextrin (HP-β-CD)	Brinzolamide (BRZ)	*In vivo* intraocular pressure (IOP) measurement using a calibrated Tono-pen tonometer in rats, supported by *in vitro* BRZ release in simulated tear fluid.	Improve drug release, increase permeability, and enhanced introcular pressure reduction efficacy.	[20]
γ-CD-alg nanoemultion (Cyclodextrin)	Curcumin	Emulsion stability, rheological properties, and gastrointestinal digestion were all	Stable emulsions under harsh conditions with high curcumin bioaccessibility;	[21]

Types	Drugs (Guest)	Studies	Findings	Ref.
		evaluated in vitro, including the standardized INFOGEST digestion model to simulate human gastrointestinal conditions.	promising for bioactive delivery.	

The application of CD as a drug delivery agent has good effectiveness (Figure 3). Cyclodextrins have shown various beneficial applications in the pharmaceutical field, including targeted drug delivery, drug encapsulation, solubility enhancement, and elimination of toxic solvents such as alcohol, propylene glycol, and oil. In addition, cyclodextrin also contributes to improved product stability and shelf life (Table 2). These properties give cyclodextrin the potential to improve drug safety and efficacy [22].

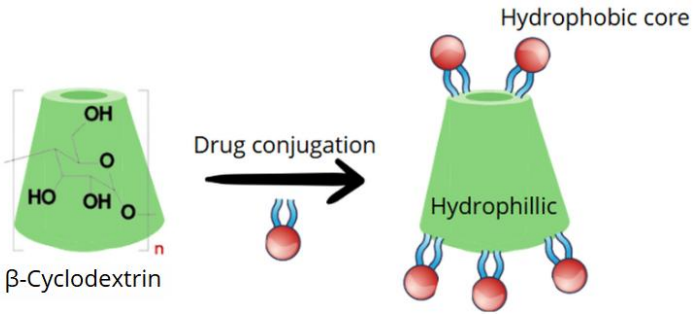
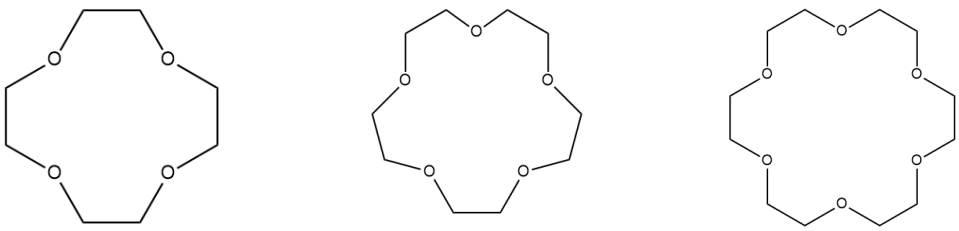


Figure 3. β-CD guest binding mechanism

Crown ether (CEs)-based SDDS

Crown ethers (CEs) are another type of macrocyclic that have great potential as drug delivery agents (Figure 4). CEs were synthesized and published by Pedersen in 1967 [23]. One of the interesting properties of crown ether is the presence of electron pairs on the hetero atoms in its molecular ring, which gives it the ability to form complexes with various cations. The presence of empty spaces in CEs molecules can capture guest molecules [24]. This ability makes CEs a very useful molecule in various chemical applications, including in ion separation, catalysis, and as a component in drug delivery systems. Oxygen atoms in CEs have an important role as complexing agents for other molecules [25].



(A) 12-crown-4 (12C4) (B) 15-crown-5 (15C5) (C) 18-crown-6 (18C6)

Figure 4. Molecular structure of crown ether [6] (Reprinted with permission)

Table 3. Comparison of crown ethers-based drug delivery

Types	Drugs (Guest)	Studies	Findings	Ref.
Fe_3O_4-SiO_2-meso-SiO_2-Crown-ethers	Doxorubicin (DOX)	*In vitro* drug release was perfomed in buffer systems; MTT assay was carried out to determine cytotoxicity against cancer cells.	Controlled release, ultrasound-triggered delivery, high loading, and strong MRI contrast for theranostics.	[26]
Poly(N-isopropylacrylamide-co-benzo-18-crown-6-acrylamide) (PNB)	Doxorubicin (DOX)	Drug release was characterized using UV-Vis in simulated extracellular and intracellular fluids.	Improve drug release behaviors with K^+ followed enhancing the safety and efficacy of cancer therapy.	[27]
1,2-O-dioleoyl-3-O-{2-[(12-crown-4)methoxy]ethyl}-sn-glycerol and 1,2-O-dioleoyl-3-O-{2-[(15-crown-5)methoxy]ethyl}-sn-glycerol (Crown Eter)	DNA	*In vitro* assay was carried out to chacterize drug-incorporated	Could improve DNA delivered by liposomes	[28]
2-aminomethyl-18-crown-6 (Crown Eter)	Clyndamicin	*In vitro* assay was performed to evaluate drug release.	Improve drug release of clyndamicin through liposomes	[29]
Aza-crown ethers (Crown Eter)	Curcumin	Preparation of curcumin–nido-carborane polymers (SA-CBC and CBC); characterization by fluorescence lifetime measurement, transmission electron microscopy, and particle size analysis; in vitro drug release studies; and bioactivity assays evaluating tumor cell inhibition.	Enhance water soluble of curcumin. Morevoer two curcumin–nido-carborane delivery systems (SA-CBC and CBC) were developed to enhance curcumin's stability, bioavailability, and targeting	[30]
DDP@18-crown-6 (Crown Eter)	Cisplatin	In vitro for antitumor activity agains Lung Cancer	Improve solubility, stability and antitumor activity	[31]
TiO_2 / 15-crown-5 ether matrix	Dopamine	Evaluation of dopamine stability when encapsulated in TiO_2 and TiO_2/15-crown-5 ether composites; characterization using XRD, SEM, and thermogravimetric	Demonstrated improved thermal stability and sustained encapsulation of dopamine within the hybrid matrix, suggesting potential	[32]

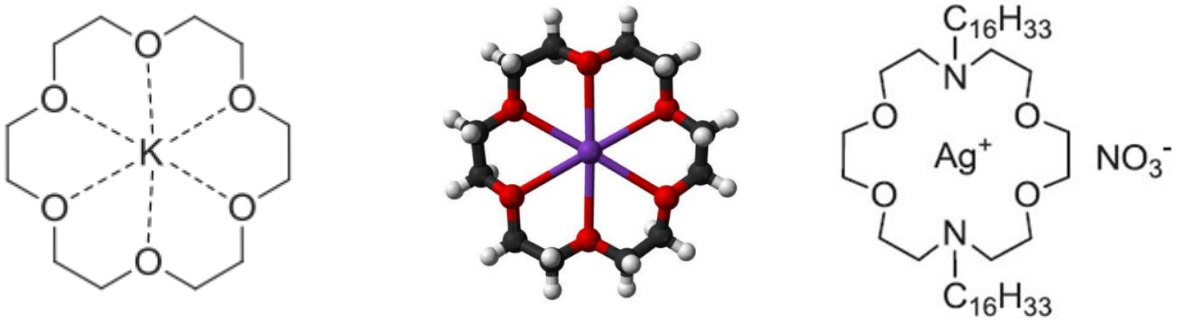
Types	Drugs (Guest)	Studies	Findings	Ref.
		analysis to assess protective effects.	as a controlled release system.	
Fluoro-crown ether phosphate (Cyclic-FP-CEs)	5-Fluoroacil	Investigation of fluoro-crown ether phosphate as a cell-permeable carrier; assessment of membrane permeability enhancement via hydration layer disruption mechanisms in vitro	Exhibited efficient cell penetration and potential for improving intracellular delivery of various therapeutic molecules by altering hydration barriers.	[33]
Crown ether-functionalized fusidic acid butyl ester (FABE-CEs)	Fusidic acid derivate	Synthesis and characterization of crown ether-functionalized fusidic acid ester; biological activity assessment, ADMET prediction, and molecular docking studies against bacterial targets.	Showed enhanced antimicrobial activity, favorable ADMET profile, and strong binding affinity in docking simulations, supporting further exploration as a therapeutic candidate.	[34]
K^+-responsive crown ether-based amphiphilic copolymer	Doxorubicin (DOX)	Synthesis of K^+-responsive amphiphilic copolymer incorporating crown ether moieties; evaluation of controlled drug and nanoparticle release triggered by potassium ion stimuli.	Achieved ion-responsive release behavior for both doxorubicin and gold nanoparticles, demonstrating utility in smart delivery platforms with potential biomedical applications.	[35]

The oxygen atom in the crown ether is in an ideal position to coordinate with the cation on the inside of the ring [36]. Complex formation between crown ethers and cations depends on the suitability of the size of the crown ether to the metal ion, the type of solvent used, as well as the nature of the substituent groups in the crown ether [37]. The naming of crown ethers is based on two numbers, where the first number indicates the total number of atoms in the ring, while the second number indicates the number of oxygen atoms [38]. The oxygen atoms in CEs can be replaced by other atoms that have coordination ability such as nitrogen [39]. Due to the special structure possessed by CEs, the complex formed between CEs and ions is amphiphilic, where ions form a hydrophilic center, while the polyether structure forms a hydrophobic outer part [40]. The amphiphilic nature of these complexes allows CEs to have great potential in macrocyclic-based drug delivery systems (SDDSs) (Table 3). Although CEs are easy to modify, there are some major obstacles that hinder their application in the biomedical field, namely their relatively high price and the presence of a certain degree of toxicity [41]. The formation of complexes between crown ethers and cations is highly dependent on the relative size of the crown ethers. compared to the metal ion, the nature of

the solvent used, and the type of substituent present in the crown ether (Figure 5). The size of the crown ether that matches the size of the metal ion will increase the binding affinity, thus allowing the formation of a stable complex. In addition, solvent properties, such as polarity, also play an important role in facilitating the interaction between the crown ether and the cation [42]. Substituents on the crown ether, either in the form of electron-donating groups or electron-withdrawing groups, can also affect the strength and selectivity of binding with certain metal ions [43].

The ability of CEs to interact with ions makes them good hosts in ion delivery systems. Bell and co-workers [40] developed CEs that act as carriers for certain atoms with therapeutic effects and produce alpha particles, such as the radioisotope Actinium-225 (^{225}Ac). Such compounds can be complexed by heterocyclic CEs with 18 rings and are referred to as macropa. Research by Monserrat and co-workers [44] successfully synthesized spherical vesicles from aza crown ether. The synthesis of the compound involves the interaction between aza crown ether which is like a surfactant with silver (I) ions, producing a complex in aqueous solution.

The development of drug delivery systems based on CEs is an interesting study in modern pharmacy. CEs are known to be developed as delivery systems that are responsive to several variables [45]. Lee and his co-workers [26] developed the material Fe_3O_4@SiO_2@meso-SiO_2@ crown ether (CE) based CEs for transporting the hydrophobic drug doxorubicin (DOX). Initially, DOX is deposited in mesoporous silicon, CEs prevent its release by the interaction of exogenous cations such as Na^+ and Cs^+. However, when subjected to ultrasound waves or in an acidic environment (pH 4.0), the interaction between CEs and cations is disrupted, allowing controlled release of DOX. Crown ether has also been reported to be successfully complexed with bioactive compounds. Echegoyen and co-workers [46] developed non-ionic liposomes based on CEs with cholesterol-derived compounds. The addition of cholesterol to the crown ether aims to ensure that when the monomer is sonicated in water, stable niosomes can be formed which are then named cholestanyl. These studies have uncovered a new chapter in macrocyclic supramolecule-based delivery systems such as CEs. CEs also play a major role in the potential utilization of supramolecular-based materials in drug delivery applications.



(A) Compleks of 18C6 with K (B) 3D model 18C6 binding K^+ (C) Aza-crown ether

Figure 5. Structure and modeling of 18C6 complex with Potassium [10], aza-crown ether with silver(I) (Reprinted with permission

SDDS based on Cucurbit[n]urils (CB[n]s)

Cucurbit[n]urils (CB[n]s) are a type of macrocyclic that serve as molecular carriers with various unique properties. CB[n]s are synthesized through an acid-catalyzed condensation process between glycoluryl and formaldehyde. The CB[n]s compound was first synthesized by Behrend and co-workers (1905) [48], after which Freeman and co-workers (1981) [49] confirmed its structure. The characteristic of CB[n]s structure is its highly symmetrical shape resembling a flask, with negatively charged

carbonyl cavities at both ends and a hydrophobic central cavity.

Table 4. Comparison of cucurbit[n]urils-based drug delivery

Types	Drugs (Guest)	Studies	Findings	Ref.
CB[7] (Cucurbit[7]uril)	Triamterene	In vivo pharmacokinetic study evaluating the delivery of triamterene encapsulated by CB[7], assessing solubility, stability, and bioavailability.	Improved solubility, bioavailability, and drug stability; exhibited pH-responsive release behavior.	[50]
CB[8] (Cucurbit[8]uril)	Doxorubicin (DOX)	Preparation of supramolecular nanomedicine from CB[8]-based amphiphilic brush copolymer; evaluation of self-imaging capability and in vitro drug release.	Enabled self-imaging and controllable drug release for cancer therapy applications.	[51]
CB[7] (Cucurbit[7]uril)	Nabumetone, Naproxen	In vitro spectroscopic, calorimetric, and computational studies of host–guest inclusion complexes in aqueous solution.	Enhanced solubility and formation of stable inclusion complexes with both drugs.	[52]
CB[6]-polymer (Cucurbit[6]uril)	Galactose-spmd	Synthesis of stimuli-responsive polymer nanocapsules based on CB[6]; evaluation of cargo encapsulation and controlled release triggered by environmental stimuli.	Stimuli-responsive polymer system enabled controlled release of encapsulated cargo.	[53]
CB[7]-PEG (Cucurbit[7]uril)	Insulin	In vitro studies on supramolecular PEGylation to modify insulin properties and stability.	Improved protein stability and modified pharmacokinetic behavior of insulin.	[54]
CB[7]-PEG-polymer (Cucurbit[7]uril)	Oxaliplatin	Development of supramolecular polymeric chemotherapy formulations; assessment	Demonstrated low cytotoxicity and prolonged circulation performance, enhancing anticancer potential.	[55]

Types	Drugs (Guest)	Studies	Findings	Ref.
		of cytotoxicity and pharmacokinetics.		
CB[7]-Fe_3O_4 (Cucurbit[7]uril)	FA-ADA	Preparation of CB[7]-functionalized magnetic nanoparticles; evaluation of imaging-guided cancer therapy efficacy.	Improved therapeutic efficacy through targeted delivery and imaging-guided treatment.	[56]
CB[7]-PEG-DSPE (Cucurbit[7]uril)	Mannose-ADA	Construction of supramolecular artificial receptor-modified macrophages incorporating CB[7]; assessment of antibacterial function and selective delivery.	Exhibited powerful antibacterial activity and selective delivery to target sites.	[57]
CB[7]-HA (Crown Ether)	Curcumin	Development of hyaluronic acid-based supramolecular formulations; evaluation of anti-psoriasis activity and controlled release properties.	Enhanced anti-psoriasis activity and provided controlled release of curcumin.	[58]
Cy2-CB[8], Me4-CB[8] (Cucurbit[8]uril)	Amiodarone, Tamoxifen, β-Estradiol, Albendazole	In vitro inclusion studies to assess the solubility enhancement of poorly soluble drugs in water using CB[8] derivatives.	Significantly improved aqueous solubility of multiple hydrophobic drugs via host–guest complex formation.	[59]

CB[n]s are capable of forming host-guest complexes in 1:1 or 1:2 ratios with various organic and inorganic guest molecules, where the guest molecules are encapsulated in their hydrophobic cavities (Figure 6). The stability of these complexes is supported by various types of non-covalent interactions, including hydrogen bonding, Van der Waals forces, as well as ion-dipole interactions occurring in the CB[n]s cavity [29]. Cucurbit[n]urils CB[n]s are a type of macrocyclic that is quite similar to cyclodextrin (CD) but has different properties [10]. The binding of guest molecules to CDs relies on hydrophobic interactions, where the hydroxyl groups at the cavity end of CDs face outward and rarely interact with guest molecules. In contrast, the binding of guest molecules to CB[n]s depends on multiple interactions, such as ion-dipole interactions and hydrophobic interactions [60-61].

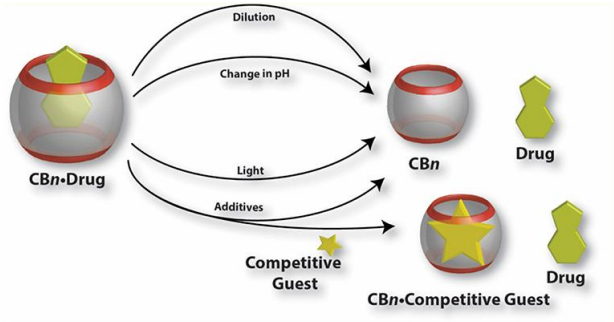


Figure 6. Loading mechanism of cucurbit(7)uril guest

In the field of drug delivery, cucurbit[n]uril (CB[n]s) generally act as delivery media with controlled release, detoxification agents, and targeted drug or gene delivery systems. In addition, CB[n]s can also be assembled into biomacromolecular structures and have broad potential applications in biosensors and treatment of various diseases [61]. However, one of the main obstacles in the development of CB[n]s is their relatively low solubility and difficult-to-modify structure. CB[n]s have hydrophilic surfaces and hydrophobic cavities, which allow them to form inclusion complexes with lipophilic drugs to improve their solubility and stability. CB[5] has a limited cavity size, making it interact only with small molecules and is often used as an ion container medium [63]. Meanwhile, CB[7] is the most widely used type because it has an ideal cavity size, excellent water solubility, and low toxicity [64]. For example, CB[7] is known to encapsulate triamterene, thereby improving the stability of the drug [50]. In addition, CB[7] can also increase the cholesterol solubility of β-estradiol, potentially enhancing its pharmacological effectiveness [65]. CB[n]s are also reported to have successfully enhanced the effectiveness of platinum-based chemotherapy with cisplatin. Plumb and co-workers [66] in their study successfully encapsulated cisplatin in CB[7] to increase its anticancer effectiveness against human ovarian cancer cells. In vivo studies show that the CB[7]Cisplatin complex has the potential to be used in the treatment of drug-resistant cancers (Table 4).

(CB[n]) can also serve as an antidote to prevent or reduce the toxic side effects of the guest molecules it encapsulates. For example, CB[7] was shown to reduce paraquat toxicity by lowering its concentration in plasma and major organs in paraquat-poisoned test animals [67].

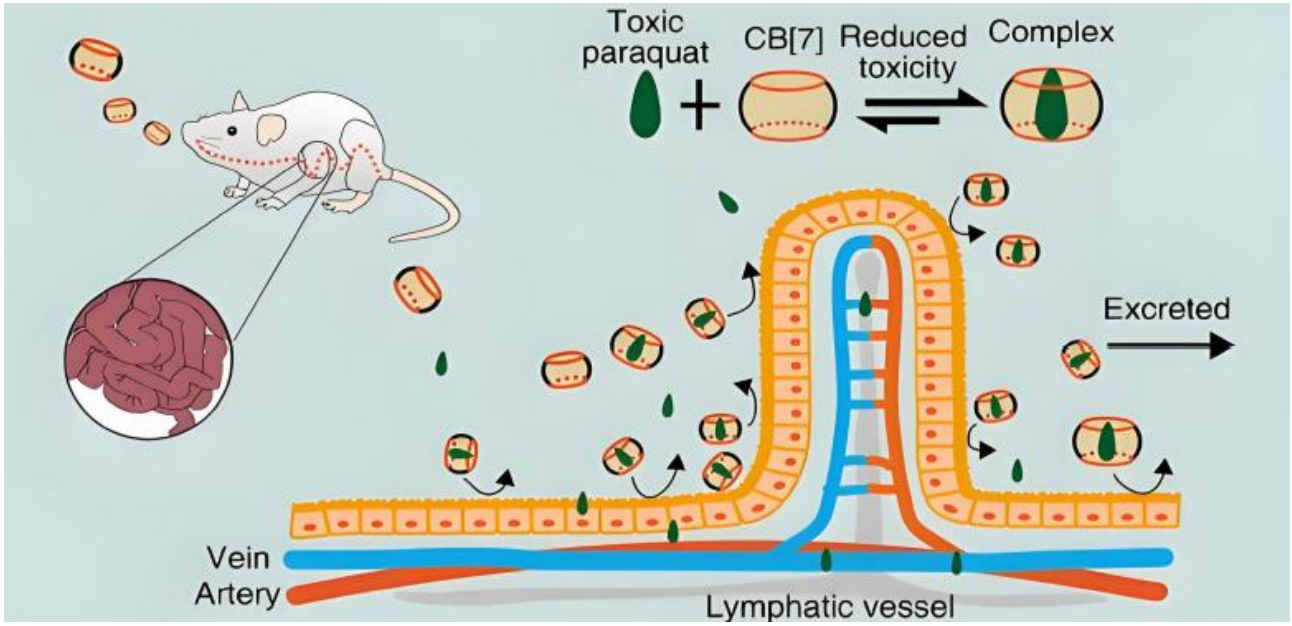


Figure 7. Illustration of CB-based antidotes [7] in overcoming paraquat (PQ) toxicity [37] (Reprinted with permission)

In addition, CB[7] also has the potential to be used as an antidote to neuromuscular blocking agents. One of the most commonly used neuromuscular blocking agents is succinylcholine, but its use often causes serious side effects. Through the host-guest encapsulation mechanism, CB[7] can reduce the toxicity of succinylcholine, thus potentially improving the safety of therapy for patients who are require this drug [67]. Kuok and co-workers [68] successfully developed a CB[7]-bedaquiline-based tuberculosis therapy. Bedaquiline is an antituberculosis drug that has cardiotoxicity effects and low water solubility. However, through the encapsulation process with CB [7], the solubility of bedaquiline has increased significantly.

Data from both in vitro and in vivo tests show that bedaquiline's cardiotoxicity is reduced, while its antimycobacterial activity remains unchanged. This makes the use of CB [7] a promising strategy to improve the safety and effectiveness of this drug in tuberculosis therapy.

SDDS based on Calix[n]arenes (C[n]As)

Calix[n]arenes (C[n]As) are macrocyclic compounds composed of phenol units connected by methylene bridges (Figure 8), with a cup-like structure [69]. In general, C[n]As can be synthesized through the reaction between phenol and formaldehyde, with the phenolic unit connected by a methylene group at the meta position. C[n]As has variable hydrophobic voids (depending on the phenolic unit) as well as two edges on the primary and secondary sides (Figure 8). C[n]As and its derivatives have been reported to have anticancer, antibacterial and antiviral activity [70], antituberculosis, and antifungal [71] activities. As therapeutic drug carriers, water-soluble C[n]As are synthesized through sulfonation reactions at the top edge, incorporation of carboxylic groups at the bottom edge, or addition of polar functional groups at the molecular edge [72]. Various small molecules and biomolecules can be incorporated into the voids at both edges of C[n]As, including ions, carbohydrates, proteins, amino acids, peptides, hormones, and nucleic acids [73-75]. These inclusion complexes are stabilized by various interaction forces, such as hydrophobic effects, ion-dipole interactions, and hydrogen bonding.

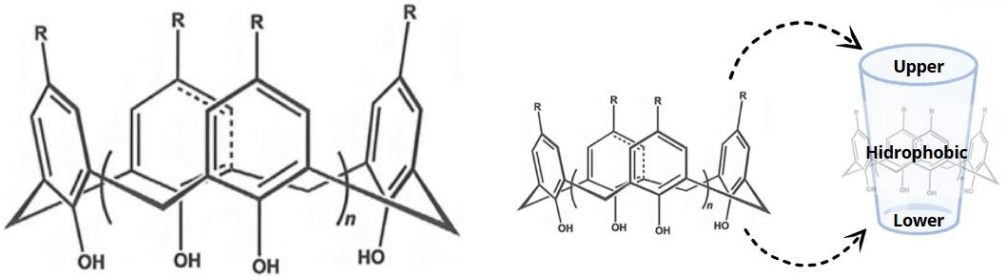
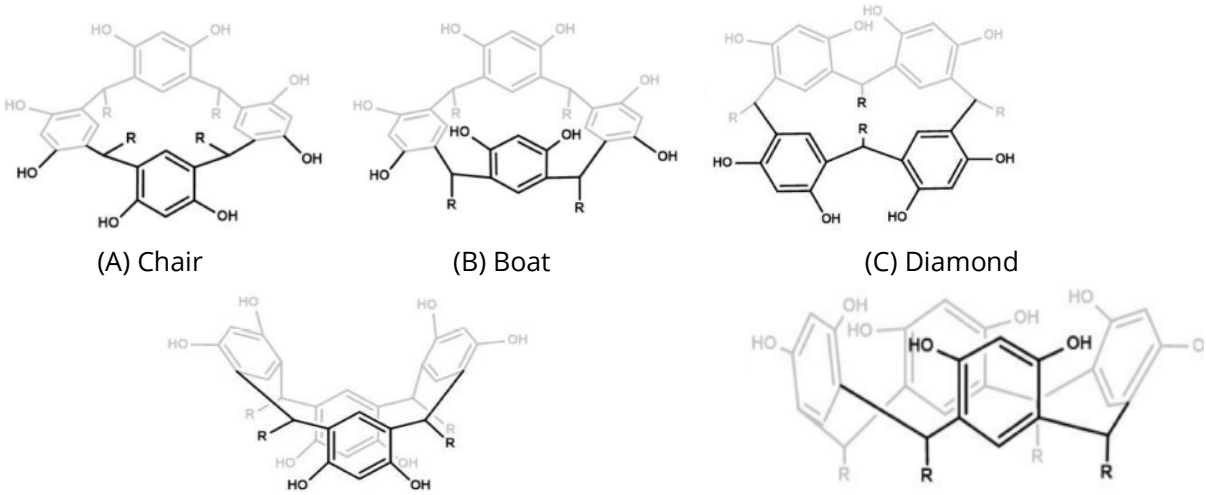


Figure 8. Molecular structures of (C[n]As) and (P[n]As)

The unique structure makes C[n]As have a variety of different isomeric conformations that are customized based on the phenol unit. Previous study explained about calix[4]resorcinarenes as a drug delivery application [76]. Calix[4]resorcinarenes is a macrocyclic C[4]As derivative that has 4 resorcinol units connected with a methylene bridge, creating the molecule to have 5 different conformations (Figure 9).



(A) Chair (B) Boat (C) Diamond

(D) (D)

Figure 9. Conformation of calix [4] resorsinaren isomers: (A) Seat; (B) Boat; (C) Diamond; (D) Crown; (E) Saddle [10,76]. (Reprinted wtih permission).

Table 5. Comparison of calix[n]arenes-based drug delivery

Types	Drugs (Guest)	Studies	Findings	Ref.
PTX-CPT-P4C6 (Calixarene)	Carboplatin, Paclitaxel	Development and physicochemical characterization of a pH-responsive complexation-based delivery system; assessment of molecular loading efficiency, biocompatibility, and anticancer efficacy.	Demonstrated efficient molecular loading, enhanced drug activity against tumor cells, and excellent biocompatibility in vitro.	[77]
Calix[8]arenes (Calixarene)	Glycosylation conjugates	Synthesis and biological evaluation of multicomponent self-adjuvant vaccine candidates tethered on a calixarene platform; studies of tumor cell migration and proliferation inhibition.	Effectively prevented tumor cell migration and proliferation, supporting potential applications in cancer immunotherapy.	[78]
P-Sulfocalix[6]arene (Calixarene)	Doxorubicin (DOX)	Formulation of P-sulfocalix[6]arene nanocarriers for Doxorubicin delivery; in vitro evaluation of release kinetics and cytotoxicity against cancer cells.	Provided low toxicity, controlled release behavior, and sustained anticancer efficacy.	[79]
Calix[6]arene hexa-carboxylic acid (Calixarene)	Paclitaxel (PTX)	Preparation and characterization of amphiphilic calixarene nanoparticles as carriers for Paclitaxel; in vitro release and loading capacity assessment.	Achieved slow, sustained release and high drug loading capacity, improving delivery of hydrophobic agents.	[80]
P-Phosphonated-calix[4]arene (Calixarene)	Paclitaxel (PTX)	Design and evaluation of pH-responsive phosphonated calixarene nanovesicles for Paclitaxel delivery; analysis of drug activity enhancement.	Enabled pH-responsive drug release and enhanced anticancer activity.	[81]
βCD-CA4 giant amphiphiles (Calixarene)	Docetaxel	Fabrication of Docetaxel-loaded nanoparticles from β-cyclodextrin/calixarene giant surfactants; studies of solubility, release, and cytotoxic effects in cancer cells.	Demonstrated slow drug release and improved aqueous solubility, contributing to higher cytotoxicity in prostate cancer and glioblastoma cells.	[82]

Types	Drugs (Guest)	Studies	Findings	Ref.
Tetra-para-phosphonomethyl calix[4]arene	Carboplatin	Investigation of shear-induced carboplatin complexation within phospholipid-mimicking calixarene cavities; evaluation of loading efficiency and release profile.	Improved drug loading efficiency and controlled release, enhancing anticancer efficacy.	[83]
P-Sulfonatocalix[4] arene (Calixarene)	Temozolomide	Encapsulation of Temozolomide in calixarene nanocapsules; assessment of stability, encapsulation efficiency, and in vitro/in vivo therapeutic efficacy against glioblastoma.	Significantly increased therapeutic efficacy and improved stability and encapsulation efficiency of Temozolomide.	[84]
P-Sulfonatocalix[4] arene	Chaperone for anticancer drugs	Development of amphiphilic p-sulfonatocalix[4]arene as a supramolecular “drug chaperone”; evaluation of anticancer drug delivery and release kinetics.	Enhanced anticancer activity and enabled controlled release of hydrophobic drugs.	[85]
Mannosylated-calix[4]arene	Doxorubicin (DOX)	Dynamic self-assembly of mannosylated calixarene micelles; characterization of pH-responsive release behavior and drug encapsulation for hydrophobic anticancer agents.	Demonstrated pH-responsive release and significantly improved delivery and solubility of hydrophobic drugs.	[86]

This configuration allows for a complex array of 'host-guest' interactions, where guest molecules can bind to the host through various non-covalent bonding mechanisms, such as hydrophobic interactions, Van der Waals forces, and hydrogen bonding. These properties make this material an efficient drug delivery biomaterial candidate, capable of improving the stability and bioavailability of active compounds in the body. In addition, similar characteristics are also found in the C[n]As units, which are known to have four different possible conformations, allowing high structural flexibility in conforming to different types of guest molecules. This flexibility expands their potential applications in more specific and targeted drug delivery systems, including in cancer therapy, infectious diseases, as well as gene-based therapies.

C[n]As can also be integrated as micelle- and nanoparticle-based delivery. In their research, Li and co-workers [77] synthesized phosphorylated C[4]As that can encapsulate camptothecin and paclitaxel in the form of nanovesicles as an application of tumor inhibition by increasing therapeutic effectiveness. Research by Drakalska and co-workers [87] also synthesized PEGylated tert-butyl C[4]A which was applied as a micelle-based drug carrier and was able to increase the solubility of curcumin. With various types of modifications that exist for C[n]A illustrates that the supramolecular macrocyclic C[n]A-based delivery has enormous potential in the world of

modern drug delivery systems (Figure 10). Bandela and co-workers [88] synthesized cholesterol-modified C[4]arene to improve the delivery and storage efficiency of drugs such as doxorubicin, curcumin, tocopherol. The results showed that molecular loading with cholesterol-modified C[4]arene can provide good reversibility for 4 cycles of use. This is because the transition of C[4]arene synthesis from sol to gel showed high efficiency. C[n]As is also reported to be applicable in gene delivery therapy. Solubility and toxicity are often obstacles in the development of C[n]A-based drug delivery. Modifications are often made to overcome this problem (Table 5). For example, the development of hypoxia-responsive molecular containers based on carboxylated azocalix[4]arene was carried out in tumor therapy applications [89].

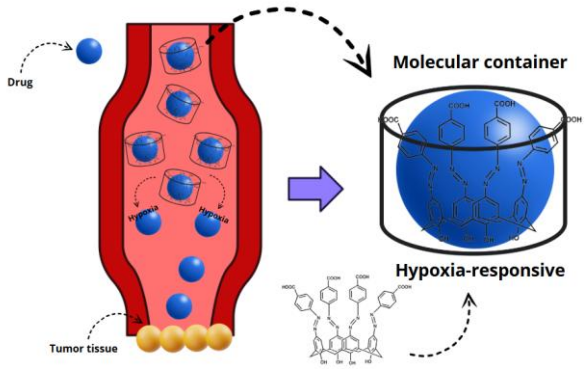


Figure 10. Schematic illustration of hypoxia-responsive drug delivery based on CAC[4]A Modified from Zhang [50]

CAC[4]A showed good ability in the recognition of "host-guest" complexes for 12 chemotherapeutic drugs, showing good versatility in cancer therapy.

SDDS-based Pillar[n]arenes

Pillar[n]arenes (P[n]As) are cyclic oligomers consisting of hydroquinone or hydroquinone ethers connected at the para position of the benzene ring via a methylene bridge [90]. P[n]As was first introduced by Ogoshi and co-workers (2008) [91]. Compared to the cup-like structure of C[n]As connected via a meta-bridge, P[n]As is composed of methylene bridges (-CH_2-) connecting 1,4-dialoxybenzene units at the para position (Figure 11), forming a unique architecture. which is rigid with a pillar-like shape. Due to its symmetrical structure, P[n]As has been utilized to create various complex supramolecular systems [92].

P[n]As has the ability to improve the stability, solubility, as well as bioavailability of the guest molecules it encapsulates. However, the water solubility of ordinary P[n]As is still limited. The structure on both sides of P[n]As can be well modified, and most of its functionalized derivatives exhibit good water solubility, low toxicity, and selective inetraction to guest molecules [93]. Among these derivatives, carboxyl-modified P[n]As with water-soluble ability (WP[n]As) is widely used in drug delivery applications (Table 6). Shangguan and co-workers [94] performed carboxyl modification on P[6]As (WP[6]As) as an encapsulant for the anticancer drug tamoxifen to improve the bioactivity and solubility of the drug. Research by Wheate and co-workers [95] compared the potential of carboxylated P[n]As with water-soluble (WP[6]As/WP[7]As) in drug delivery and biodiagnostic applications. Both types of WP[n]As are capable of forming host-guest complexes with various drug molecules such as memantine, chlorhexidine hydrochloride, and proflavin. These interactions are stabilized by hydrophobic effects within the molecular cavity, as well as hydrogen bonding and electrostatic interactions at the portals. In addition, WP[n]As shows low toxicity to cells, except in high doses or after prolonged continuous exposure

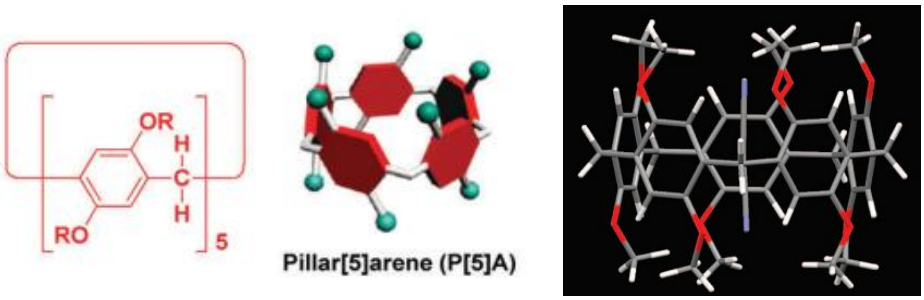


Figure 11. Structure and 3d illustration of P[n]As

Table 6. Comparison of pillar[n]arene-based drug delivery

Type	Drug (Guest)	Studies	Findings	Ref.
deca-carboxylatopillar[5]arene) (pillar[n]arene)	Amikacin	In vitro assay using HepG2 cells; evaluation of endocytosis-mediated uptake and water solubility with fluorescence labeling (CF@4).	Enabled water-soluble delivery and targeted cellular uptake of amikacin, improving potential for intracellular antibiotic therapy.	[97]
WP6 (Pillar[6]arene)	Tamoxifen	Investigation of water-soluble complexation using in vitro release assays and UV spectroscopic analysis.	Improved drug solubility and enhanced bioactivity of tamoxifen in aqueous environments.	[94]
pillar[6]arene	Doxorubicin (DOX)	In vitro release behavior assessed under physiological pH conditions; evaluation of multidrug resistance (MDR) reversal effects.	Provided controlled drug release and demonstrated anti-multidrug resistance properties, enhancing chemotherapeutic potential.	[98]
pillar[5]arene-[2]rotaxane	Doxorubicin (DOX), Prodrug	Responsive behavior assessed under in vitro pH conditions; evaluation of mitochondrial targeting using fluorescence imaging techniques.	Achieved pH-responsive release and specific mitochondrial imaging capability for targeted cancer therapy.	[99]
Trp-pillar[5]arene-galactose	Doxorubicin (DOX)	In vitro MTT assay for cytotoxicity; evaluation of release kinetics and targeting efficiency toward cancer cells.	Enabled synergistic delivery with low cytotoxicity and enhanced targeting of cancer cells.	[100]

Type	Drug (Guest)	Studies	Findings	Ref.
SeSe-[P5]$_2$-Man-NH_3	Doxorubicin (DOX)	n vitro MTT assay evaluating tumor microenvironment (TME)-responsive release and targeted delivery.	Demonstrated TME-responsive behavior and effective targeted delivery for cancer chemotherapy.	[101]
N-methylimidazolium-pillar[5]arene	Doxorubicin (DOX)	In vitro release assay by UV spectroscopy; cytotoxicity evaluation via MTT assay.	Exhibited low cytotoxicity and sustained, slow-release behavior, supporting applications as a controlled release system.	[102]
T-SRNs-carboxylate-pillar[5]arenes	Doxorubicin (DOX)	In vitro evaluation of pH-responsive behavior and sustained release under acidic conditions.	Showed pH-responsive, prolonged release profile suitable for tumor-targeted drug delivery.	[103]
Acetal-pillar[5]arene	Paclitaxel	Cargo encapsulation confirmed by confocal laser scanning microscopy (CLSM); in vitro assays for biological activity assessment.	Increased bioactivity and provided targeted delivery to cancer cells with pH-responsive release.	[104]
2,2'-biphen[4]arene	Palmatine, berberine	*In vitro* fluorescence titration studies; binding complex characterization using NMR spectroscopy.	Induced strong fluorescence enhancement and demonstrated high binding affinity to alkaloid guest molecules, supporting applications in detection and delivery systems.	[105]

CP[5]A can be well used as a pH-responsive based delivery, or competitive interaction between cargo molecules that will create sustained release in drugs such as rhodamine B (RhB), calcein, and doxorubicin hydrochloride (DOX). In addition, P[n]As is also known to have the ability to detoxify by encapsulating toxins, making this delivery system has great potential in its utilization in the modern pharmaceutical field [58]. Various studies have certainly been conducted to identify several uses of macrocyclics as supramolecular-based drug delivery.

Conclusion

The various studies that have been discussed prove that macrocyclic compounds have enormous potential in their utilization as modern drug delivery systems with various unique properties according to their application. Cyclodextrins (CDs), crown ethers (CE), cucurbit[n]urils (CB[n]s), calix[n]arenes (C[n]As)

and pillar[n]arene (P[n]A) are some of the many types of macrocyclic supramolecular modifications that have unique capabilities as drug delivery systems. Properties such as stable host-guest interaction, stability, solubility, surface area and biocompatibility make these compounds play an important role in the modification of drug delivery systems in the modern pharmaceutical world.

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Author Contributions

Conceptualization, M. F. N. S and I. L. T.; Methodology, M. F. N. S.; Validation, I. L. T and Y. N.; Investigation, M. F. N. S.; Resources, I. L. T.; Writing – Original Draft Preparation, M. F. N. S.; Writing – Review & Editing, I. L. T and Y. N.; Visualization, M. F. N. S.; Supervision, I. L. T.; Project Administration, I. L. T. and M. F. N. S.

Conflict of Interest

The authors declare no conflict of interest.

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