REVIEW ARTICLE

Supramolecular nano-drug delivery systems

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Kapoor J. Supramolecular nano-drug delivery systems. J Nanosci Nanomed 2022;6(5): 01-03.

ABSTRACT

Anti-cancer drugs have many limitations including solubility, dosage limitation, targeting issues, and so forth, which results in a low level of efficacy in the treatment of cancer. Nano drug delivery systems have a strong hand in resolving all these limitations. It is known that supramolecular interactions are reversible, so these interactions can be used to make nano-drug delivery systems. Supramolecular hosts such as calixarene, cucurbituril, cyclodextrin, and pillararenes were used to synthesize these systems. Normal cells and tumor cells have different microenvironments, which influence drug binding and release from the host.

Key Words: *Supramolecular Drug; Metastasis; Cucurbituril*

INTRODUCTION

According to studies providing insight into cancer statistics, the number of cancer cases was estimated to be 19.3 million in 2020, and the number of cancer deaths to be 10 million, excluding non-melanoma cancers [1]. It is the tumor cells' ability to control what happens in the environment, co-opting complex signaling networks for their own benefit, causing multidrug resistance, metastasis, and tumor progression which makes cancer treatment difficult [2]. Chemotherapy is one of the treatments that emerge as a cure for cancer. The last few decades have seen the use of drugs such as cisplatin, oxaliplatin, and carboplatin to treat cancer, but these drugs have a number of side effects, such as nephrotoxicity, neurotoxicity, ototoxicity, emetogenesis, and dose-limiting side effects as well. Furthermore, these drugs are also associated with many defects, such as hydrophobicity, poor solubility, poor stability in physiological environments, and poor efficacy [3-6].

As a cancer treatment tool, nanomedicine has many benefits, including improving the pharmacokinetics of drugs, reducing side effects, increasing therapeutic efficacy, extending retention and action time in the bloodstream, increasing cell uptake, and reducing systemic toxicity. Drug delivery to the desired tumor site is very important. Supramolecular chemistry provides the most effective way to release drugs to the tumor by taking advantage of the differences between normal and tumor microenvironments including the difference in temperatures, ions, pH, and enzyme levels that act as stimulants for drug release.

Supramolecular chemistry is something different as this chemistry is beyond the molecules, it consists of non-covalent and reversible interactions between molecules, these supramolecular interactions involve ion-ion, ion-dipole, dipole-dipole, π-π, cation-π interaction, hydrogen bonding, and metal-ligand coordination. Crown ethers, cyclodextrins, calixarenes, pillararenes, and cucurbiturils are macrocyclic hosts that usually have hydrophobic cavities for embedding partners; these guest compounds contain the active agents that fight cancer. The aim of this review is to summarize the recent work where supramolecular chemistry and nanomedicine have been combined to provide cancer treatment systems by improving drug delivery.

CALIXARENE AS THE HOST

A calixarene is a macrocyclic compound that consists of phenol units linked by methylene bridges in the ortho position [7]. In calixarene, the number of phenol units determines the cavity size, which accommodates the guest as a result of a host-guest complexation occurring within the cavity. A calixarene-integrated nano-drug delivery system consisting of azocalix arena, RhB, and DOX has been synthesized that can deliver and track anticancer drugs in vivo to tumors [4]. Sulfonated azocalix[4] arena act as a responsive supramolecular host. The CalixareneRhB complex gets stability as a result of electrostatic interactions between the sulfonate and positively charged RhB, but inside the calixarene cavity, RhB loses its fluorescence due to the PET process. Similarly, the Calixarene-DOX complex is getting stability as a result of π-πinteractions. Inside the cancer cells, the azo bond gets reduced due to the hypoxic environment resulting in the weakening of host-guest interactions, enabling DOX and RhB to reach inside cancer cells, where RhB regains its fluorescence and confirmed the drug delivery. Researchers used this calixarene-integrated nano-drug delivery system to deliver DOX to the tumor site in mice, and the studies show that DOX stimulates cell apoptosis, inhibits cancer cell proliferation, reduces systemic toxicity, and enhances its anti-cancer activity (Figure 1) [8].

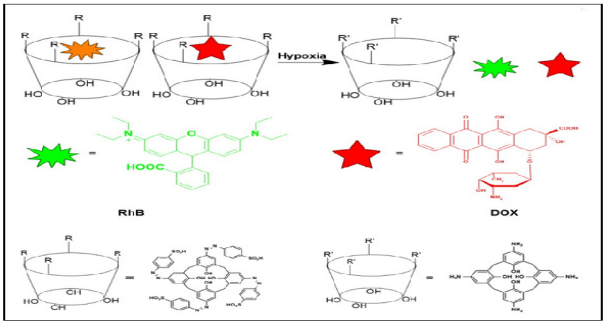

Figure 1) *Showing the drug release in hypoxic conditions [9].*

CUCURBITURIL AS THE HOST

Cucurbituril is a macro-cycle formed when the glycoluril monomer is linked by methylene bridges. A targeted drug delivery system designed to treat PSMA (prostate-specific membrane antigen) positive prostate cancer. Two polymers as Methyl Viologen (MV) linked with poly (ε- caprolactone) (PCL-MV) and naphthalene linked with Polyethylene Glycol (Nap-PEG) form a supramolecular amphiphile by ternary host-guest complexation with CB[8]. A Supramolecular Drug Delivery System (SDDS) was prepared by embedding naphthalene attached PSMA-617 (a prostate cancer targeting ligand) into a supramolecular amphiphile with the aid of CB[8]-naphthalene -interactions. DOX was loaded to this SDDS successfully, and studies show that it was capable of releasing excessive DOX in acidic tumor microenvironments and intracellular lysosomes thereby enhancing drug concentration as shown in Figure 2 [9]. It was seen that using CB as host, CB[7]-DOX, and CB-CPT nanomedicine increases the solubility of DOX and CPT and was able to efficiently induce apoptosis in U87 cells and demonstrated good anticancer effects on glioma [7,10].

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Received: 27-June-2022, Manuscript No. PULJNN-22-5103; Editor assigned: 29-June-2022, Pre QC No. PULJNN-22-5103 (PQ); Reviewed: 12-July-2022, QC No. PULJNN-22-5103 (Q); Revised: 25-July-2022, Manuscript No. PULJNN-22-5103 (R); Published: 30-Sep-2022, DOI: 10.37532/ puljnn.2022.6(5).01-03.

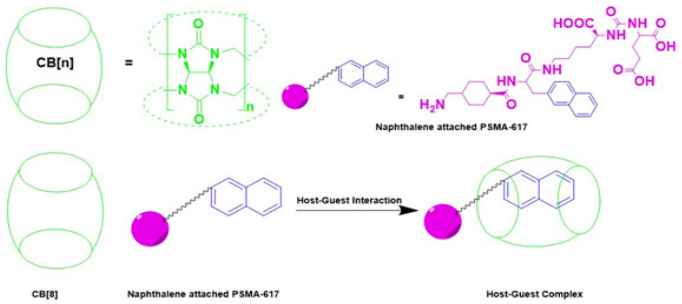

Figure 2) *Host-Guest interaction between PSMA and CB[8] [11].*

CYCLODEXTRIN AS THE HOST

Cyclodextrins are ring-shaped oligosaccharides containing glucose units held together by α- 1,4-glycosidic bonds, cyclodextrins containing six, seven, or eight glucose units are also called α-, β-,-cyclodextrin respectively. There are many problems associated with cis-platin as it is susceptible to drug resistance due to high levels of Glutathione (GSH) in cancer cells and also shows dose limiting side effects, to overcome these limitations, researchers have synthesized a platinum-based supramolecular nanosystem for drug delivery, by taking the advantage of the high affinity of β-cyclodextrin (β-CD) for the adamantyl group. This nanosystem constitutes poly β-cyclodextrin and adamantyl-modified platinum(IV) as host and guest respectively. After accumulating in tumor tissues with high GSH levels through the Enhanced Permeability and Retention effect (EPR), and being absorbed by cancer cells, this modified platinum(IV) converts into cisplatin due to a high reducing environment and shows a redox-responsive behavior and is able to inhibit in vivo tumor growth (Figure 3) [11].

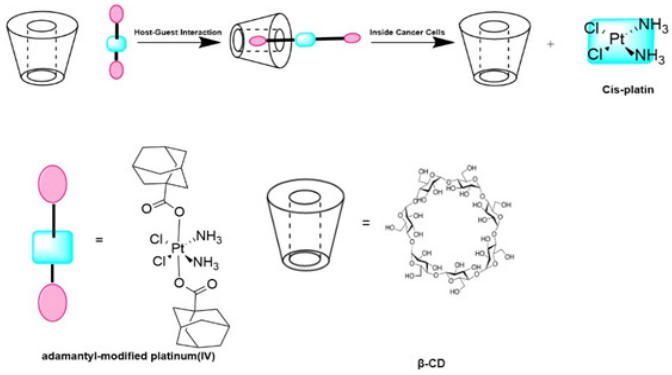

Figure 3) *Adamantyl-modified platinum(IV) interaction with cyclodextrin [13]*

PILLARARENE AS THE HOST

Pillararenes are macrocycles composed of hydroquinone ordialkoxybenzene units linked in the para position by methylene bridges. Based on pillararenes, a supramolecular nanoprodrug was synthesized using host-guest interaction. Through a disulfide coupling reaction between chlorambucil and Near-Infrared (NIR) heptamethine cyanine dye IR806, the guest was obtained, and the ammonium salt of biphenyl-extended-pillar arene acted as host [2,6]. The Host-Guest complexation is the result of hydrophobic interactions between the pillararene cavity and chlorambucil. Due to the high concentration of GSH and acidic environment inside the tumor cells, the disulfide bond of guest breaks, and host-guest interactions get weakened resulting in the release of activated chlorambucil. On the irradiation of near IR, this nanoprodrug releases IR806 resulting in the generation of hyperthermia and ROS generation which kill tumor cells. Based on in vitro and in vivo studies, this supramolecular nanoprodrug exhibits prominent antitumor activity via PDT-PTT-CT with excellent biocompatibility (Figure 4)[12-15]. Depicts a brief summary of the components and hosts discussed in this review for synthesizing drug delivery systems shown in Table 1.

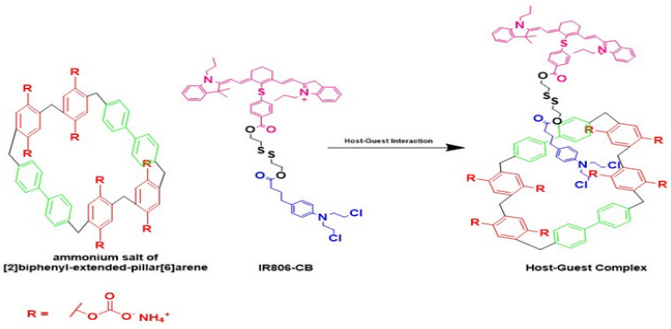

Figure 4) *Host-guest interaction between Pillararene and IR806-CB [15]*

TABLE 1
Drug delivery systems and their major component [1-15]

Drug Delivery System	Components	Summary
Calixarene as the host	Sulfonated azocalix [4] arene	This Drug delivery system has efficient drug loading ability. It delivers the drug to target cancer cells that are indicated by RhB and enhanced the anti-tumor effect of DOX and reduce its systemic toxicity.
	RhB	
	DOX	
Cucurbituril as the host	CB[8]	This Drug Delivery system's major focus is to deliver anti-cancer drugs to the prostate cancer tumor cells. This is achieved by taking the advantage of high binding affinity of naphthalene with CB [8].
	PSMA-617	
	MV	
	PEG	
	DOX	
Cucurbituril as the host	CB[7]	The host-guest complex of CB[7]-DOX and CB[7]-CPT form nanoparticles by self- assembly in the aqueous solution. The water solubility of DOX and CPT has increased. It was found that these two supramolecular nanomedicines could efficiently induce apoptosis in U87 cells and also shows a good anti-cancer effect on glioma.
	DOX	
	CPT	
Cyclodextrin as the host	Polymer β-CD	This drug delivery system overcomes many limitations of cis-platin. A prodrug adamantyl- modified platinum(IV) was synthesized and introduced in polymer cyclodextrin. In the high reducing environment of Cancer cells, the prodrug reduces to active cis-platin.
	adamantyl-modified platinum(IV)	
Pillararene as the host	Biphenyl -extendedpillar[6] arene [2]	The water-soluble [2] biphenyl-extended- pillar[6]arene has a high drug loading capacity and delivers the drug to the cancer cells and shows triple therapeutic effect PDT-PTT-CT.
	IR806-CB	

CONCLUSION AND PERSPECTIVES

There are many problems with chemotherapy drugs for cancer, including solubility, dosage limitation, targeting issues, and so forth, which results in a low level of efficacy in the treatment of cancer. The superiority of supramolecular nano-drug delivery systems lies in their ability to overcome all these problems. This review summarized the latest research on supramolecular nano-drug delivery systems using different supramolecular biocompatible hosts and anti- cancer drugs as guests.

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