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β-Cyclodextrins-based nano carriers for cancer therapy

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Abstract

Gene therapy uses oligonucleotides against genetic disorders to interact with the source of the disease; it can be used to decrease the unwanted side effects of commonly used chemotherapy drugs. Naked oligonucleotides have a short half-life in human plasma (usually less than an hour); therefore, it is essential to choose a suitable carrier platform with excellent biodegradation and tailoring properties. Consequently, non-viral vectors are good candidates to increase the lifetime and improve their therapeutic efficacy. β-Cyclodextrins (CDs) are one of the natural cyclic oligosaccharides that provide the desired goals. Additionally, their appropriate sizes form supramolecular inclusion bodies capable of encapsulating the selected genes. This review focuses on some recent applications of β-CD based nano carriers for gene therapy, specifically the cationic polymers and amphiphilic complexes based on β-CDs used to design the nano systems against different cancer types.

Keywords: Cationic polymers, Targeted delivery, Non-viral vector, Amphiphilic CDs, β-cyclodextrin

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1. Introduction

Gene therapy holds tremendous promise for patients as it can transfer the genetic ingredients into the defective cell in order to cure the disease. The clinical trial results confirmed that gene therapy has high rates of complete cancer treatment response.
Many researchers studied gene delivery as an effective method for crossing the gene through the cell membrane. The next generation of medicines will be based on gene delivery systems, and many trial therapeutics which gain approval will launch within the next few years [1]. Specifically, gene delivery is divided into two substantial categories, including viral and non-viral. According to their immunogenic properties and possibilities to cause mutational infection in human bodies, non-viral vectors in comparison to viral vectors are cost-effective with more excellent reproducibility [2].
nanoparticles (NPs) entitled non-viral vectors have been introduced as favorable gene carriers with the ability to encapsulate and quickly circulate in the bloodstream. [3].
In this aspect, cyclodextrin is one of the best supramolecular structures used in sustained gene delivery systems due to its biocompatibility, biodegradation properties and also tunable gene release rate by merely controlling the CD concentrations [4]. Cyclodextrins (CDs) are a family of cyclic oligosaccharides composed of α-(1,4)-linked D-(+)-glucopyranoside units through glycoside bonding. One advantage of CDs is that they can be acquired from starch and non-fossil resources via a simple enzymatic conversion; thus, they are practically nontoxic for therapeutic application. They have a cone structure with a hydrophilic outer surface thus have water solubility properties and a hydrophobic cavity which can make inclusion complexes with many chemical compounds matched in different shapes and sizes [5]. The water solubility can be influenced by the number of the hydroxyl group present in the outer surface, on the other hand due to strong intramolecular hydrogen bonding, it can become more hydrophobic than before. conclusively random substitution of the hydroxy groups make dramatic improvements in their solubility. The commonly used natural CDs consist of six, seven, and eight glucopyranose units are known as α-cyclodextrin (α-CD), β-cyclodextrin (β-CD), and γ-cyclodextrin (γ-CD), respectively. The chemical structures of α, β and γ cyclodextrins have shown in Figure 1.

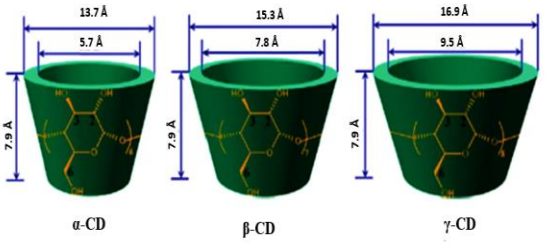

Figure 1. Molecular structures and dimensions of α-, β- and γ-CDs. [6]

One important and interesting subgroup of CDs is β-CD which has 1135 Dalton molecular weights with approximately 1 nm height and width [6]. These remarkable structures can result in the formation of inclusion complexes to solve hydrophobic guest compounds in water. Practically, the non-expensive industrial process and β-CDs' nontoxicity leads to utilizing these compounds in various fields such as flavors in medicine [7-11]. Furthermore, scientists use these β-CD features in drug and gene delivery, and many scientific articles are published in this area each year [12-14]. β-CDs are used to increase the solubility of therapeutic agents in aqueous media and prevent the crystallization of drugs.
Besides the natural CDs, many derivatives have been designed to enhance the basic CD properties. Improved CDs generally have three major categories containing cationic, anionic, and non-ionic. A fundamental subgroup of CD derivatives is amphiphilic, which emerged to extend their usage in pharmaceutical applications. In the last two decades, most studies were done about the synthesis and development of gene delivery systems focusing on cationic polymers or amphiphilic complexes based on CDs [15]. In conclusion, this review covers the recent supramolecular structures based on β-cyclodextrin in the terms of cationic and amphiphilic structures as well as their unique properties in gene therapy applications. Also, it provides the frontiers of material chemistry in β-CD and its various polymeric structures in gene delivery.

2. Cationic Polymers based on CD nanoparticles for gene delivery

Cationic CDs with various properties such as low toxicity, sufficient condensation ability, highly stable

structure, and biodegradability are valuable in gene delivery systems. The incorporation of CDs into cationic polymers like polyethyleneimine and polylysine could provide an electrostatic interaction between the polymers and any nucleic acids with a negative charge. This interaction leads to polymer and nucleic acid condensation into complexes known as polyplexes [16]. The ability of efficient compaction of large volume free plasmids DNA to smaller particles is one of the first steps in designing the gene delivery vectors. Several cationic CD-based polymers have been reported recently that improved DNA condensation by a novel design. A star-shaped β-CD polymer designed by Yin et al. demonstrated a high efficiency to condense pDNA. In this study, the core of β-CD had designed by multiple branched oligoethylenimine (OEI) arms and a reductive amination between β-CD-OEI star polymer and hyaluronic acid (HA) conducted [17]. In another research a β-CD-based supramolecular system could sufficiently compact pDNA to form NPs with the size range around 100-200 nm. In this study, the supramolecular system prepared by PEGylation of polyethylenimine (PEI) -β-CD conjugated to achieve fibroblast growth factor receptors-targeted gene delivery of a complementary peptide with FGFRs via adamantyl-SS-PEG [18].

CD-derivatives nanoparticles generally exhibit improved condensation over PEI polymer alone at a low N/P ratio [19]. In 2016, Qin et al. reported vectors for gene delivery that showed satisfactory pDNA condensation property. They engineered and fabricated two novel scutellarin-grafted cationic polyrotaxanes (PR-EDA-SCU and PR-DETA-SCU), which scutellarin (SCU) were conjugated on β-CD of those. In addition to electrostatic interactions, it is thought, the planar structure of SCU has been effective in condensing pDNA through the intercalation of SCU planar ring into pDNA grooves [20]. Cationic CDs are very customizable for the type of genetic materials which have been used in gene delivery. As well as pDNA, microRNA (mRNA), small interfering RNA (siRNA), messenger RNA (mRNA), and even CRISPR-associated protein-9 (cas9) plasmid or oral DNA vaccine with cationic CDs have been used for delivery purposes. In 2018 Zhang et al. utilized PEI- β-CD as a vector for CRISPR/Cas9 plasmid delivery for in vitro gene editing. The successful transfection of these editing tools had demonstrated by loss of green fluorescent protein (GFP) function in HeLa-EGFP cell line (a stablished cell line by infecting HeLa cells with lentivirus in which express enhanced green fluorescent protein) when the genome editing was mediated by β-CD based nano carrier gEGFP transfection targeting EGFP gene.Additionally, the efficient transfection of CRISPR/Cas9 plasmid by this delivery vector into cells was explored in two genome loci named hemoglobin subunit beta (HBB) (19.1%) and rhomboid 5 homologs 1 (RHBDF1) (7.0%) [21].

Their team previously managed to engineer an oral DNA vaccine by the use of Salmonellae attenuated bacteria coated with this nanoparticle. In fact, in this study they served both bacteria and cationic β-CD-based polymer as a hybrid vector to deliver DNA vaccine for cancer immunotherapy.Coating attenuated Salmonellae with PEI-β-CD, lead to facilitate phagosomal escape of Salmonellae. This DNA vaccine encoded autologous vascular endothelial growth factor receptor 2 (VEGFR2) which can induce T cell activation and cytokine production as well as ultimately activation of anti-tumor activity [22].

The siRNA is widely studied in gene delivery via cationic CDs. Effective delivery of therapeutic siRNAs into cells requires several chemico-physical properties of vector such as charge, stability, and functionalization on the surface for active targeting [23]. Taking into the count of these properties, cationic β-CDs could consider a valuable delivery vector for siRNA. Unlike pDNA, siRNAs possess the small size and relative simplicity that lead to preserve their native conformation through encapsulating cationic CDs. In 2018 a research explored the self-assembly of cationic β-CDs for siRNA delivery by both simulation and experimental approaches. It has demonstrated that CD derivatives possess lipid-like behavior in solution and the negative charges of siRNAs drive the cationic molecules to assemble rapidly into steady supra-structures [24]. Besides the highly stable polyplexes, cationic nano carriers provide a buffering capacity which is a beneficial capability for effective cytosolic release of siRNA. The proton buffering capacity of polyplex set up an osmosis-driven process that leads to rupture of the endosomal membrane. This mechanism is known as the “proton sponge effect”. It has proven that in nano particles with highly branched and rigid cationic polymers like PEI, the proton sponge effect is positively considered [16]. Introducing CDs into traditional cationic polymers with strong charge density also considerably reduces their toxicity [25]. However, the IC50 value of β-CD polymers is linked to their polymeric structure and molecular weight [26]. In general, cationic polymers like PEI can result in extreme cytotoxicity if there is a too high positive charge on their surface. By binding with negatively charge serum protein and red blood cells, they can affect instant toxicity in the body [27, 28]. Research

showed that low molecular weight (LMW) PEI (PEI-600 Da) cross-linked with β-CD is a valuable nano carrier with no cytotoxicity reported both in vitro and in vivo [29]. In an innovative design, Lv. et al. tailored a supramolecular carrier based on β-CD-LMW PEI polymer that showed less cytotoxicity than branched PEI without falling the efficiency of transfection. By grafting Poly-L-lysine on succinicate-grafted-β-cyclodextrin-LMW PEI, they tailored a complex that an adamatane-functionilized PEG encapsulated into this to form a highly stable delivery system [30]. Another challenge is designing gene delivery systems with high transfection efficiency. Cationic liposomes e similar polyplexes without β-CD. Under UV radiation, these polyplexes could release DNA segments into cell nuclei to increase the gene transfection [35]. In terms of biodegradability of cationic β-CD polymers, numerous common cationic polymers like PEI, PDMAEMA and PLL possess non-degradable vinyl (-C-C-) and amide bonds that are unable to break into low molecular weight residues in the cell environment [36]. However, incorporating them into the backbone of the β-CD polymer is mostly by disulfide, imine, carbamate, amide, and ketal bonds that are biodegradable and lead to further body clearance [37]. Table 1 indicates some structures for gene delivery purposes based on degradable polycationic CDs that were introduced for cancer therapy.

Table 1. Some selected major degradable polycationic CDs as gene carriers and their medical application. [37]

Gene carrier	DNA/RNA	Target disease	Characters
TF-containing CD-based polymer	EWS-FL1 siRNA	Ewing's sarcoma (metastatic Ewing's sarcoma mouse model)	– Cancer targeting by transferrin – Suppression of Ewing's family tumors
	RRM2 siRNA	Head and neck tumor (xenograft model)	– Cancer targeting by transferrin – Suppression of malignant Progression
FA–HP–β-CD–PEI	Vascular endothelial growth factor protein siRNA	Cancer (xenograft model)	– Cancer targeting by folic acid – Suppression of tumor growth
MC-10–HP–γ-CD–PEI	IFN-α	Breast and ovary cancer (xenograft model)	– Cancer targeting by MC-10 peptide that binds to human epidermal growth factor receptor 2 – Suppression of tumor growth and improvement of survival time
YC21–β-CD–PEI	Acetylcholinesterase Gene	Liver cancer (xenograft model)	– Cancer targeting by YC21 peptide that binds to EGFR – Suppression of tumor growth by controlling cell proliferation

A biodegradable cationic polymeric vector with the aim of gene silencing application was fabricated by Ghodke et al. In this research by the use of PEG and sebacic acid (SA), a biodegradable linear aliphatic polyester was synthesized and incorporated on the β-CD-based polyrotaxane [38] β-CD-based polyrotaxane is a supramolecular polymer that its structure consists of a linear axis that CD rings threaded over it and entrapped by two bulky molecules at each end of the axis [39]. This degradable polymer backbone can widely apply in biomedical applications like transfecting therapeutic genes [40].

3. Amphiphilic Cyclodextrins for gene delivery purposes

There are some obstacles related to native cyclodextrins (CDs) that limit their usage in cancer therapy and other pharmaceutical applications. To solve such problems, many derivatives were developed by chemical modification of CDs to obtain the appropriate properties. Meanwhile, a new group named Amphiphilic CDs was developed. It was expected by designing of this type, some drawbacks of parent CDs will be solved. For example, the interactions between CDs with different biological membrane will boost and make self-assembly in aqueous solutions [41, 42]. Amphiphilic CDs can be self-assembly designed or incorporated in lipid membranes. The most crucial property of amphiphilic CDs is their self-assembly that leads to build many nano carrier systems naturally without using any surfactants. Then, different types of supramolecular structures can be obtained using amphiphilic CDs such as micelles, vesicles, and nano particles to use in gene delivery systems [43]. Amphiphilic CDs are build using grafting of 6C aliphatic chains that bind ester or/and amide groups with various length on primary/secondary face of the glucopyranose [42]. They are divided into three subgroups based on their

surface charge as non-ionic, cationic, and anionic amphiphilic CDs.

3.1 NON-IONIC AMPHIPHILIC CDs

In this subgroup of amphiphilic CDs, aliphatic chains with various lengths are grafted onto the primary and/or secondary face of the vital glucopyranose part of the CD. Figure 2 shows different structures of this group of amphiphilics are synthesized and reported in the literature such as Lollipop, Cup-and-ball, Medusa-like CD, Skirt-shaped CD and Bouquet-shaped CD. Table 2 indicates structural description of these types of amphiphilic CDs [41-44].

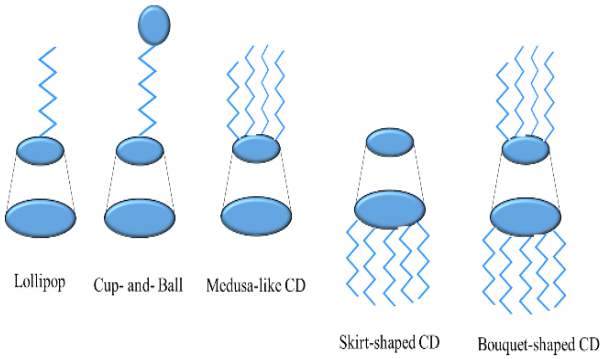

Figure 2**.** Various structures of nonionic amphiphilic CDs. [5]

Table 2. Various types of nonionic amphiphilic CDs. [5]

Different nonionic amphiphilic CDs	**Description**
Lollipop	It is achieved when just one alkyl chain has grafted to 6-amino β-CD. Because of the weak solubility of this structure, it prefers to be trapped into the hydrophobic cavity of CD. As a result an intramolecular self-inclusion will be achieved.
Cup-and-ball	It is achieved when amino group are subjoined at the tailing of the alkyl chain. It leads to avoid self-inclusion of the hanging downward.
Medusa-like CD	It is achieved when amino-, amido-, sulfo-, or thioalkyl chains (with length between C10 and C16) is grafted to whole primary hydroxyls of the CD.
Skirt-shaped CD	It is achieved by modification of CD structure by alkyl chains using aliphatic ester link (C2 to C14) on the secondary alcohol groups.
Bouquet-shaped CD	It is achieved when a poly(oxyethylene) or polymethylene and O-alkul chain are grafted on each face of CD ring molecule.

3.2 CATIONIC AMPHIPHILIC CDs

Cationic amphiphilic kinds of CDs can develop via two different methods. In the first method, switching ω-amino groups to oligo (ethylene oxide) and in the second method, amido groups on the primary face of CDs are modified with alkyl chains on positions 2 and 3. Consequently, the products are per-6-amino-β-CD 2,3-di-O-alkyl ethers.

Constructive balance between thioalkyl chains and hydrophilic ethylene glycol oligomers has important role to make the properties of cationic amphiphilic CDs. For example, when the nanoaggregates of cationic amphiphilic CDs are constructed, their colloidal stability will boost by ethylene glycol. Literature studies indicated various experiments to find the best cationic amphiphilic CDs that can be used in gene delivery. For instance, Cryan et al. used reduced per-azido moieties (per-amino amphiphiles) as hydrochloride salts in gene delivery. They showed cationic amphiphilic CDs have a higher capacity to bind nucleotides that cause improving gene delivery by vectors. Cationic amphiphilic CD-based nanoparticles significant property is their self-assembly. In another work, Diaz-Moscoso et al. substituted the primary hydroxyl groups with various components including amino [40].

3.3 ANIONIC AMPHIPHILIC CDs

To make anionic property in amphiphilic CDs, a sulfate or carboxyl group must be attached to the CD structure (primary or secondary face). When alkyl is grafted at position 6 and carboxymethyl groups

replaced at positions 2 and 3, carboxyl is constructed that comprises amphiphilic CDs.Dubes et al. and Sukegawa et al. described the synthesis procedure of sulfate containing amphiphilic CDs. They explained that if the CDs esterified at positions 2 and 3 followed by sulfating of 6-hydroxyls group in the structure, then the final sulfate amphiphilic CDs is obtained. Trifluoromethylthio groups are functional compounds that can be used in functionalization at the 6-position of β-CDs structure to build Fluorite-containing anionic β-CDs. They were introduced as an appropriate class of amphiphilic carriers. Some other amphiphilic derivatives are synthesized and reported in literature studies such as prfluorohexyl- and perfluorooctyl-thio-β-CDs and their alkyl analog [41, 43]. Ghania Degobert et al. investigated the sulfated and non-sulfated amphiphilic-CDs to find the impact of their structural properties on the physicochemical characteristics of nano particles. They prepared some nano spheres made of amphiphilic β-CDs by various acylation degrees (DA) at the secondary hydroxyl face (DA= 14 and 21) and then varied the sulfation degrees (DS) at the primary hydroxyl face (DS=0.4 and 7).

They realized there is a correlation between the amphiphilic- β-CD structures and the formation of nano spheres. When sulfated amphiphilic-β-CDs were associated with peracylated amphiphilic- β-CDs, the stability of nano spheres size was boosted. Table 3 stated different physicochemical properties of non-sulfated and sulfated amphiphilic CDs [45].

Table 3. Physicochemical properties of non-sulfated and sulfated amphiphilic cyclodextrins and their influences on the properties of produced nano spheres. [9]

Amphiphilic β-CD	**Characterization of amphiphilic CDs**					**Characterization of nano spheres**		
	Acylation degree	**Sulfatation degree**	**Molecular weight (g/mol)**	**HLB[a] values (µM)**	**CMC (µM)**	**Diameter (nm)**	**P.I.[b]**	**Zeta potential (mV)**
$\beta CD21C_6$	21	0	3193	5.6	-	137.2±3.4[c]	0.04±0.038	-20±1.2
$\beta CD21C_6S_4$		4	3601	7.2	-	132±1.5	0.06±0.03	-50.6±0.7
$\beta CD21C_6S_7$		7	3907	8.2	10	41-92[d]	-	-
$\beta CD14C_6$	14	0	2507	7.1	-	159±5.5	0.09±0.074	-15±1.7
$\beta CD14C_6S_4$		4	2915	9	120	29-86[d]	-	-
$\beta CD14C_6S7$		7	3221	10	110	33-84[d]	-	-

[a]Hydrophile lipophile balance ,[b] Polydispersity index,[c] Unstable preparation and formation of aggregates after keeping it in an aqueous suspension for 1h,[d] We have a bimodal distribution of the size.

3.4 *AMPHIPHILIC CYCLODEXTRIN NANOPARTICLES IN GENE DELIVERY SYSTEM*

Gene therapy is an advanced technology that turned up in cancer treatment concepts. CDs are utilized in treating different types of cancer. The outer hydrophilicity of CDs is a disadvantage for crossing the cell membrane; thus for solving this problem, amphiphilic CDs nano particles have been introduced.These nano particles are self-assembled and designed as gene carriers.Among the studies on viral and non-viral vectors, the non-viral vectors showed lower toxicity in gene therapy, encouraging scientists to work more on this scope. One group of non-viral nanosystems is based on CDs, CD nano particles, CDplexes(polyplexes), rotaxanes, polyrotaxanes, polypseudorotaxanes, and CD-based dendritic systems [42]. In this section, amphiphilic CD-based nano particles as non-viral vectors will be considered as gene delivery systems. A specific and crucial group of amphiphilic CD nano particles are polycationic derivatives used in non-viral gene delivery systems. Different experiments were carried out on polycationic amphiphilic CD-pDNA as CD

plexes. Some details of the selected studies were reported in Table 4.

Table 4. Selected Literature Examples about Amphiphilic Cyclodextrin nanoparticles for Gene Delivery. [6]

Cyclodextrin derivatives	Primary face	Secondary face	Nucleic acids	Structure
Polycationic Amphiphilic Cyclodextrin	14 primary amino groups, 7 thioureido groups	14 hexanoyl chains	pDNA	Folate decorated Nano complex (204–3554 nm)
Polycationic Amphiphilic Cyclodextrin	14 primary amino groups, 7 thioureido groups	14 hexanoyl chains	pDNA	Nano complex
Cationic Amphiphilic Cyclodextrin	guanidino group		siRNA	Nanoparticle
Amphiphilic Cyclodextrin	Cationic amino-terminated PEG500		siRNA	Nanoparticle (281 nm)
Amphiphilic Cyclodextrins	6- or 16-carbon chains	galactose groups	pDNA	Nanoparticle

Interactions between CD and nucleic acids play a key role in gene delivery through building a nano particulate self-assembly system. In fact, the anionic nature of nucleic acids leads to a stable construction of polycationic amphiphilic CDs (paCD) and anionic nucleic acids. So, this group of CDs is the most useful compound in gene delivery systems [42].

Aranda et al. used folate conjugation with polycationic amphiphilic CD-DNA nano particles for active targeting. The characterization of nano systems via in vitro and in vivo studies showed folate conjugation has an effective transfection role. In fact, it improves transfection effectiveness and compared with naked DNA, leading to accumulation in the liver and lung. It was introduced as a non-viral vector for gene treatment in specific determined organ [46].

Generally, the main problem in gene delivery is the involvement of the cellular internalization and endosomal escape of the DNA. Diaz Moscoso et al. investigated the CDplexes with different endocytosis inhibitors, including chlorpromazine, genistein, dynasore and methylated β-CD (MbCD) in order to find their effects on transfection and level of uptake. They worked on a set of CDplexes obtained from the most efficient paCD gene vectors for internalization purposes to use both clathrin-dependent (CDE) and clathrin-independent endocytosis (CIE).

The results showed the most taking up of gene complexes by CDE; however, it was not very relevant for transfection. On the other hand, the smaller fraction of gene complexes that contain internalization by the CIE pathway is significantly responsible for the efficient transfection [47].

Additionally, in cancer therapy, amphiphilic CD nanoparticles were applied in gene silencing as RNA interference carrier systems. Evans et al. examined targeting and non-targeting methods based on cationic amphiphilic $_{\beta CD}$ (heptakis[2-O-(N-(3v-aminopropyl)-10Htriazole-40-yl-methyl)-6-dodecylthio]-β CD) nanoparticles for metastatic prostate cancer therapy. In vitro characterization demonstrated the mean particle sizes of nanoparticles (less than 200 nm), which possessed a cationic charge. Two parallel studies with and without modification of PEG were considered.

Thus, results showed PEGylation as a crucial modification to prolong the circulation time of amphiphilic CD nanoparticles by reducing the surface charge and non-targeted binding to the serum proteins. Besides, the transfection efficiency of nanoparticles has been determined by 2D and 3D cell culture studies. Comparing the targeted and non-targeted experiments showed no notable difference in the polo-kinase 1 (PLK1) messenger-RNA (mRNA) knockdown levels. Also, 3D cell culture studies indicated higher PLK1 mRNA knockdown levels in targeted nanoparticles [41]. An influential factor in high-performance gene delivery is nucleic acid delivery without applying natural structure changes. Mendez-Ardoy et al. studied a group of paCD and made monodisperse and stable nano systems to use in gene delivery. The comparison study for transfection in vitro and in vivo applied on HeLa and HepG2 cell lines. As a result, they showed amphiphilic CD is a suitable, safe and effective nano system for gene therapy [48]. Ning wan et al. designed and

synthesized two sets of cationic amphiphilic βCD derivatives using 6-mono-OTs-β-CD to be the precursor of an amphiphilic gene delivery vector construction. They considered the transfection and endocytic property of the β-CD derivatives/DNA nanoystems using the replacement of various cationic head groups. The constructed nano systems showed acceptable results of low cytotoxicity and stable nano complexes Among the different synthesized structures, those which had PEI head group showed improved transfection. The endocytic uptake mechanism was primarily through caveolae-mediated endocytosis; thus, it can prevent the lysosomal degradation that happens during the gene loading phase [49].Nano systems consisting of more than one type of amphiphilic CD as nano carriers for gene delivery in cancer therapy, had been studied. For example, O'Mahony et al. considered a co-formulated nano system that carries siRNA composed of a cationic and a PEGylated amphiphilic CD system. They indicated PEGylation has an influential role in stability boosting and reducing the surface charge [50]. In another study, the star-like amphiphilic β-CD-g-PCL-poly(2-(dimethylamino) ethyl methacrylate copolymer exhibited higher encapsulated pDNA compared with PEI-25 kDa, the golden standard for non-viral vector gene delivery [51]. Additionally, co-formulated nano systems, Caitriona M. O'Driscoll et al. worked on gene silencing in brain cancer cells using short interfering RNA (siRNA) for in vitro analysis. They tagged a PEGylated amphiphilic CD-based nanoparticle with a CNS-targeting peptide that is extracted from the rabies virus glycoprotein (RVG).

They believed that based on this preparation method, the siRNA would be protected from degradation and cell-specific uptake will increase as well as the gene silencing performance will improve. They synthesized and formulated nano systems that carry siRNA based on CD structure modification in order to find the best characterization. The synthesized nano system can be a promising nano complex as a systemic delivery method for siRNA targeting brain cancer. However, these co-formulated systems can be excellent options for more gene delivery therapy studies [52].

4. Conclusion

In this review, cationic polymers and amphiphilic complexes with CDs based on the definition of their structures were presented. It was concluded from the literature studies, supramolecular assemblies based on β-CD attracted growing interest as biomaterials for gene delivery purposes over the past decades. The unique properties of CD-based nanomaterials along with the easy modification and biodegradability, addressed them as one of the promising vectors for controlled gene delivery. Cationic polymers and amphiphilic complexes based on β-CDs are two popular subgroups used for various pharmaceutical purposes, especially cancer treatment.

Different complexes of these basic structures were developed and applied in gene delivery nano systems, and main parameters such as toxicity, stability, biodegradability and efficiency were evaluated. It can be concluded that cationic amphiphilic β-CD nanoparticles are fabulous options to be used as nanocarriers in gene delivery systems. Furthermore, research on β-CD as a biodegradable smart material will continue for pharmaceutical applications and designing nanocarriers. Also, it is predicted to provide more useful co-formulated cationic amphiphilic β-CD with the desired structural modifications to achieve lower toxicity and higher performance in gene therapy. It is expected that the nano carriers based on β-CDs could be further developed and contributed to improve the quality of life of the patients and the family.

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