Review

Non-Viral Nanovectors Based on Cyclodextrins for siRNA Delivery: An Update to Current Technologies

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Non-Viral Nanovectors Based on Cyclodextrins for siRNA Delivery: An Update to Current Technologies

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Abstract

Gene delivery/administration and, in particular, small interfering RNA (siRNA) delivery represents a therapeutic challenge and very effective carriers have yet to be identified. Cyclodextrins (CDs) are cyclic oligosaccharides with unique host–guest inclusion capabilities, widely recognized in the pharmaceutical field for their ability to enhance drug solubility and bioavailability. Their excellent biocompatibility and chemical versatility make them powerful building blocks for the design of supramolecular nanovectors (NVs). Thanks to their facility of functionalization, CDs are highly versatile and have found numerous applications across various fields. In this contest CD based NVs are currently explored as non-viral agents to transport and release siRNA. Recent studies suggest that self-assembled NVs based on CDs can improve the transfection and safety of siRNA delivery systems. This review provides a comprehensive overview of the most recent advances in the design of NVs based on CDs and their use for delivery of siRNA, discussing the ins and outs of structural differences and chemical functionalization.

Keywords: cyclodextrins; modified-CD ; siRNA ; gene delivery; nanovectors

1. Introduction

Gene therapy is a promising medical approach to achieve the accurate and personalized cure for diverse severe pathologies. The discovery of RNA interference (RNAi) by Fire and Mello in 1998 laid the bases for a new gene therapy approach, recognized with the Nobel Prize in Physiology or Medicine in 2006 [1]. RNAi is a post-transcriptional gene silencing RNA, which acts against endogenous parasitic and exogenous pathogenic nucleic acids, with consequent regulation of the expression of protein-coding genes. RNAi is mediated by short non-coding (approximately 22 nucleotides) RNA, the small interfering RNA (siRNA) and the microRNA (miRNA). From the perspective of therapeutics development, siRNA is very interesting due to its specificity which minimize off-target effects and by 2001, synthetic siRNAs have been developed, providing the foundation for therapeutic applications [2], as reflected by the numerous number of clinical trials rapidly developed in recent years [3] and the approved siRNA medicines on the market of USA and Europe [4,5]. CDs are cyclic oligosaccharides composed of α-(1→4)-linked glucopyranose units, most commonly naturally existing as α-, β-, and γ-CDs containing six, seven, and eight glucose units, respectively. Due to their unique toroidal structure with a hydrophilic outer surface and a hydrophobic inner cavity, CDs can form host–guest inclusion complexes with a wide variety of molecules, ranging from small organic compounds to macromolecular assemblies. This supramolecular capability has made CDs valuable tools in fields such as drug delivery, catalysis, food technology, and environmental remediation [6]. In pharmaceutical sciences, CDs have mainly been largely employed to enhance solubility, stability, and bioavailability of poorly soluble drugs, as well as to control release profiles and reduce drug toxicity. Their high biocompatibility, low immunogenicity, and great chemical versatility have further expanded their application scope from small-molecule encapsulation to the design of advanced nanostructured materials for biomedical purposes. Chemical modification of hydroxyl groups on CD rims allows for the introduction of

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functional moieties (cationic, amphiphilic, targeting ligands, or stimuli-responsive groups), thereby tailoring their physicochemical and biological properties [7–9]. In recent years, these features have been exploited in the development of CD-based supramolecular systems for gene delivery, including DNA and siRNA vectors. CDs can serve as non-viral carriers that condense, protect, and deliver nucleic acids to target cells while minimizing cytotoxicity and immunogenic responses. A first review on the use of CDs for siRNA delivery was written by Chaturvedi et al. about 15 years ago [10]. More recently Mousazadeh et al, have evidenced the potential of cyclodextrins as effective non-viral siRNA delivery systems for cancer gene therapy [11] suggesting that modification of CDs can improve transfection and safety of delivery systems. In addition, the review by Qu et al. (2023) further highlighted the dual diagnostic and therapeutic potential of CD-based systems. In particular, it discussed how functionalized CDs can serve not only as siRNA carriers but also as multifunctional platforms for imaging, controlled release, and targeted cancer therapy, bridging the gap between nanomedicine and theragnostic [12]. Taken together, these studies underscore the versatility of CDs architectures as robust and adaptable frameworks for next-generation gene delivery technologies.

2. Challenge and Strategies in siRNA Delivery

Although the ideally promising scenarios for siRNA therapeutic applications, several intracellular and extracellular barriers limit siRNA clinical use. These are mainly inadequate stability and limited pharmacokinetic profile, together with the possible stimulation of unwanted side effects. Indeed, RNases and phosphatases can degrade the phosphodiester bond, while enzymes found in serum and tissues can prevent its accumulation in the targeted tissue. Naked siRNA-based drugs can only represent an effective strategy for local delivery as in the case of eye treatments. Additionally, the size of siRNAs (about 7–8 nm in length and 2–3 nm in diameter), their hydrophilicity and polyanionic nature present some difficulties in penetrating the membrane lipid-bilayer. Therefore, siRNA can be easily cleared by glomeruli and excreted in a time lapse from several minutes to one hour [13]. A further intracellular difficult step is the endosomal escape, and innate immune activation can occur when naked siRNA is used. Naked siRNAs leaving the bloodstream, are accumulated in the bladder and quickly excreted from the body, (few minutes to half an hour), which prevents their accumulation in the target tissues or cells. Various chemical modifications have been proposed to obtain clinically efficient medicines, together with the use of cationic cell-penetrating peptides. Additionally, N-acetylgalactosamine conjugated siRNA has been largely used to enhance metabolic stability and nowadays many drugs such as givosiran, lumasiran, inclisiran, vutrisiran, and nedosiran have been approved by the FDA for this purpose. However, this strategy is very successful for liver targeting by the asialoglycoprotein receptor. By contrast, the use of drug delivery systems, in particular NVs, is an exciting prospect to avoid quick renal clearance and, more importantly, to obtain selective targeting of cells and tissues. Due to many limitations of virus-based vectors, drug delivery systems using lipids and cationic polymers which provide the electrostatic binding of negatively charged siRNA are suitable vectors [14]. Lipid nanoparticles (LNPs) transport of siRNA has become one of the most advanced approaches in the field of RNAi therapeutics [13]. The first approved drug employing this technology is Patisiran (ONPATTRO®), recommended for the treatment of hereditary transthyretin amyloidosis (hATTR) [15]. Since then, several candidates have entered clinical development, including BMS-986263 (Bristol-Myers Squibb), an LNP formulation carrying siRNA targeting HSP47 for the treatment of hepatic fibrosis [16]. Cationic micelles have also been used for the transport of small oligonucleodides and in particular siRNA [17,18]. Due to the possibility of monomer exchange, micelles present relatively flexible structures that can be squeezed or loosened to allow different modalities for cargo loading and delivery. Moreover, their simple architecture can be modelled by computational methods and the obtained insights transferred to more complex systems based on other soft matter aggregates.

CDs are natural cyclic oligosaccharides derived from starch, characterized by a ring structure with hydrophilic primary and secondary sides and a hydrophobic cavity. Due to the presence of hydroxyl groups, CDs can be easily functionalized to impart a positive charge to the molecule [19].

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More generally, chemical functionalization is able to produce an unlimited number and variety of CD derivatives, including cationic, amphiphilic and PEGylated compounds. In particular, the electrostatic interactions between nucleic acid and cationic CDs allow for additional self-assembly structures. Haley et al. (2020) provide a comprehensive overview of CDs as modular carriers in drug and gene delivery systems [20]. Their review illustrates how the chemical versatility of CDs allows for the complexation and protection of DNA and RNA, reduction of immunogenicity, and facilitation of interaction with cell membranes. It highlights the ability of CDs to serve as platforms for combined systems—including chemotherapeutics, RNAi, and peptides—with potential applications in personalized therapies. However, the analysis focuses on studies up to 2020, leaving room for an update that includes more recent evidence on self-assembling and targeted systems for siRNA delivery. Table 1 summarizes previous reviews on CD-mediated gene delivery.

Table 1. Review on CDs for Gene Delivery.

Authors	Year	Title	References
Chaturvedi, K.	2011	Cyclodextrin-Based siRNA Delivery Nanocarriers: A State-of-the-Art Review.	10
Xu, C.	2019	Cyclodextrin-Based Sustained Gene Release Systems: A Supramolecular Solution towards Clinical Applications.	8
Haley, R.M.	2020	Cyclodextrins in Drug Delivery: Applications in Gene and Combination Therapy.	20
Mousazadeh, H.	2021	Cyclodextrin-Based Natural Nanostructured Carbohydrate Polymers as Effective Non-Viral siRNA Delivery Systems for Cancer Gene Therapy.	11
Castillo Cruz, B.	2022	A Fresh Look at the Potential of Cyclodextrins for Improving the Delivery of siRNA Encapsulated in Liposome Nanocarriers	33
Nazli, A.	2025	Cationic Cyclodextrin-Based Carriers for Drug and Nucleic Acid Delivery	[21]

3. NVs Based on Modified CD for siRNA Delivery

CD based NVs have gained increasing attention due to their biocompatibility, their ability to form stable complexes with siRNA and their potential for targeted functionalization. Moreover, it has also been reported that the combination of CDs with cationic polymers can promote cell penetration [17,18].

The main portions of CD that are modified are the hydroxyl groups at positions 2 and 3, and the CH_2OH group at position 6 (Figure 1).

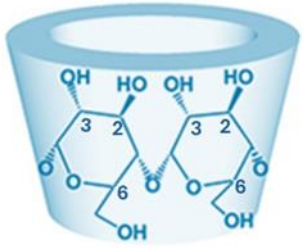

Figure 1. Modifible groups of β-CDs.

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Therefore, it appears that modification of the native CD structure is highly recommended for internalization. As an example, amphiphilic cationic CDs have been studied for siRNA release showing success in mediating gene silencing both in vitro and in vivo. Malhotra et al. present the first example of CD-siRNA conjugates for gene silencing applications [22]. In this study, β-CD was covalently attached to the sense strand of siRNAs via both reducible (disulfide) and non-reducible (sulfanyl) linkers. The conjugates maintained gene silencing efficacy comparable to unconjugated siRNAs when delivered via polycationic lipids such as Lipofectamine 2000 and amphiphilic cationic CDs (Figure 2).

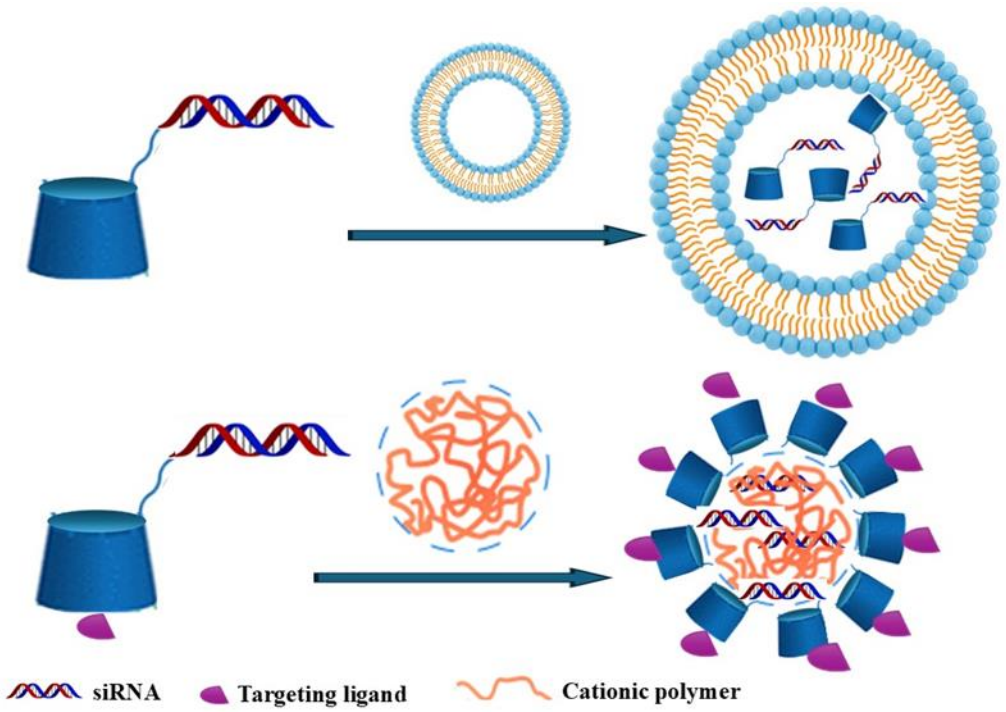

Figure 2. NVs developed by Malhotra et al.

CD NVs are also able to overcome physiological barriers such as the blood brain barrier (BBB) and deliver siRNA to malignant or genetically affected tissues, underscoring their promise for the treatment of neurodegenerative diseases [23]. The system utilized amine-functionalized β-CDs, which facilitated electrostatic complexation with siRNA and promoted endosomal escape. These nanoparticles demonstrated efficient transcytosis across the BBB, along with significant gene silencing effects in neuronal cells. Different approaches can be used to improve the interactions between CDs and siRNA, and in addition targeting ligands can be added to improve siRNA transfection. Specifically, the PEGylation process can be used as passive targeting as well as means for prolonging systemic circulation time. Following this idea amantane-transferrin and adamantane-PEG derivatives of CDs have been produced, enhancing the performance of CD-based platforms by double functionalization with one targeting moiety. Moreover, amphiphilic CDs, which possess both hydrophilic and hydrophobic domains due to substitution with aliphatic or aromatic chains, can undergo hydrophobic-driven self-assembly into core–shell structures or micelle-like NVs. CD-based siRNA release NVs are typically formed by self-assembly under mild aqueous conditions. This self-assembling behavior is particularly advantageous for siRNA delivery, as it enables formulation under physiological conditions without harsh organic solvents or high-energy processes, while allowing for size control, targeting moiety integration, and siRNA protection in a single-step process. In such configurations, siRNA is either electrostatically adsorbed to the particle surface or co-condensed within the hydrophilic shell. These amphiphilic assemblies improve NVs stability in physiological conditions and promote membrane fusion or cellular endocytosis. This process may

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involve the complexation of cationic CDs with the anionic siRNA. In this case, the encapsulating CD superstructure can preserve the native siRNA conformation through a vast network of hydrogen bonds between the positively charged side arms of the c-CD and the negatively charged siRNA skeleton. Additionally, CDs can participate in supramolecular self-assembly via host–guest interactions, such as the inclusion of hydrophobic guest molecules (e.g., adamantane, cholesterol) within the CD cavity. This approach has been widely exploited to construct modular NVs by linking targeting ligands (e.g., transferrin, folic acid), PEG, or additional stabilizing elements via guest moieties, resulting in highly customizable delivery platforms [24]. In systems where CDs are functionalized with cationic side chains (e.g., amino, guanidinium, or polyethyleneimine-like moieties), electrostatic complexation with the negatively charged phosphate backbone of siRNA can drive spontaneous nano-condensation into stable nanoparticles. The resulting complexes can actually preserve the conformational integrity of siRNA, protecting it from serum nucleases and enhancing cellular uptake.

Seripracharat et al. (2022) describe the development of a supramolecular siRNA delivery system based on the host–guest assembly between cationic β CD derivatives (cCDs) and an adamantane-functionalized poly(vinyl alcohol)-poly(ethylene glycol) (Ad PVA PEG) polymer [25]. Three distinct amino-substituted cCDs—bearing putrescine, spermidine, or spermine moieties—were synthesized and confirmed via ^{1}H NMR and mass spectrometry. These cCDs spontaneously form spherical nanoparticles with Ad PVA PEG and siRNA, as shown by ^{1}H NMR and SEM, with particle sizes below 300 nm and a negative zeta potential at physiological pH. Gel electrophoresis demonstrated efficient siRNA loading (≈90%), while DLS analysis confirmed stable complexation. In vitro assays in A549 cells indicated effective GFP gene silencing, comparable to Lipofectamine™ 2000, with minimal cytotoxicity. Kont et al. 2022 report a novel strategy for siRNA delivery using co-formulated amphiphilic cationic and anionic β-CDs to treat acute myeloid leukemia (AML)[26]. A newly synthesized anionic amphiphilic CD was blended with a cationic CD complexed with siRNA targeting the epigenetic regulator KAT2a. The resulting nanoparticles displayed reduced surface charge (from +34 mV to +24 mV) and improved polydispersity, without compromising particle size or siRNA uptake (~60% in HL-60 AML cells). Despite a slightly slower endosomal escape for the co-formulated NVs, both formulations achieved comparable gene silencing (~21–29% KAT2a knockdown). These findings highlight the potential of charge-balanced CD nanocarriers to minimize toxicity while maintaining therapeutic efficacy for non-viral gene delivery in hematological malignancies. Sun et al. (2023) report the development of sialic acid-functionalized CD-based nanoparticles for targeted delivery of CSF-1R siRNA to tumor-associated macrophages (TAMs) in prostate cancer [27]. The sialic acid ligand enables selective binding to Siglec-1 (CD169), highly expressed on M2-like TAMs, facilitating efficient uptake and significant CSF-1R gene silencing (42–58% knockdown vs. 19–39% for non-targeted controls; $p < 0.01$). The suppression of CSF-1R expression induces macrophage repolarization from the immunosuppressive M2 phenotype to pro-inflammatory M1, demonstrated by increased CD86+/CD68+ populations (~72%) and reduced CD206+/CD68+ (~25%). In co-culture models with prostate cancer cell lines (PC-3, TRAMP-C1), this macrophage reprogramming leads to enhanced cancer cell apoptosis (49–69% vs. 38–44%; $p < 0.01$). Hao et al. (2024) describe a hybrid nanoparticle system combining AS1411 aptamer–PD L1 siRNA chimera with glutamine-modified carboxymethyl-β-CD (Gln CM-β CD) and polyethylenimine/doxorubicin for combinatorial chemo-immunotherapy against lung squamous cell carcinoma [28]. The AS1411 aptamer directs selective binding and internalization into NSCLC cells, achieving effective PD L1 silencing and stimulation of T cell and $CD8^{+}$ cytotoxic responses. SEM imaging revealed conical nanoparticles (~250–500 nm), while glutamine modification enhanced doxorubicin uptake and apoptotic induction in tumour cells. In vivo studies demonstrated superior tumour inhibition (reduced volume and Ki 67 index, increased apoptosis) and elevated intra-tumoral T cell infiltration (1.34 to 1.41 fold increase in $CD8^{+}$ T cells), with reduced systemic toxicity compared to aptamer-only or chemotherapy-alone controls. Even if any CD NVs -based siRNA therapeutics have reached market approval so far, they represent an important area of preclinical research, with

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promising applications in oncology, neurology, and inflammatory diseases, underscoring their potential role in the future of non-viral gene therapy. Some formulations based on CD NVs are currently in clinical trials: such as for example CALAA-01, a self-assembling CD NVs (CALANDO) functionalized with transferrin for tumour targeting. This system was designed for delivering siRNA against the RRM2 gene. The designed clinical trial product is a combination of siRNA (USP # 7427605, 23 September 2008) and RONDEL (United States Patent (USP) # 7807198, 5 October 2010) [9]. The Phase I clinical trial has provided the first evidence of siRNA-mediated gene silencing in human tissues following systemic administration and represents a significant milestone in RNAi therapeutics [29]. Another example issiG12D-LODER, a biodegradable intratumoral implant based on CD NVs, that has advanced to Phase II for the treatment of pancreatic cancer, demonstrating sustained siRNA release directly within the tumour microenvironment [30].

In Figure 3 are evidenced the main types of functionalization of CDs explored in this review.

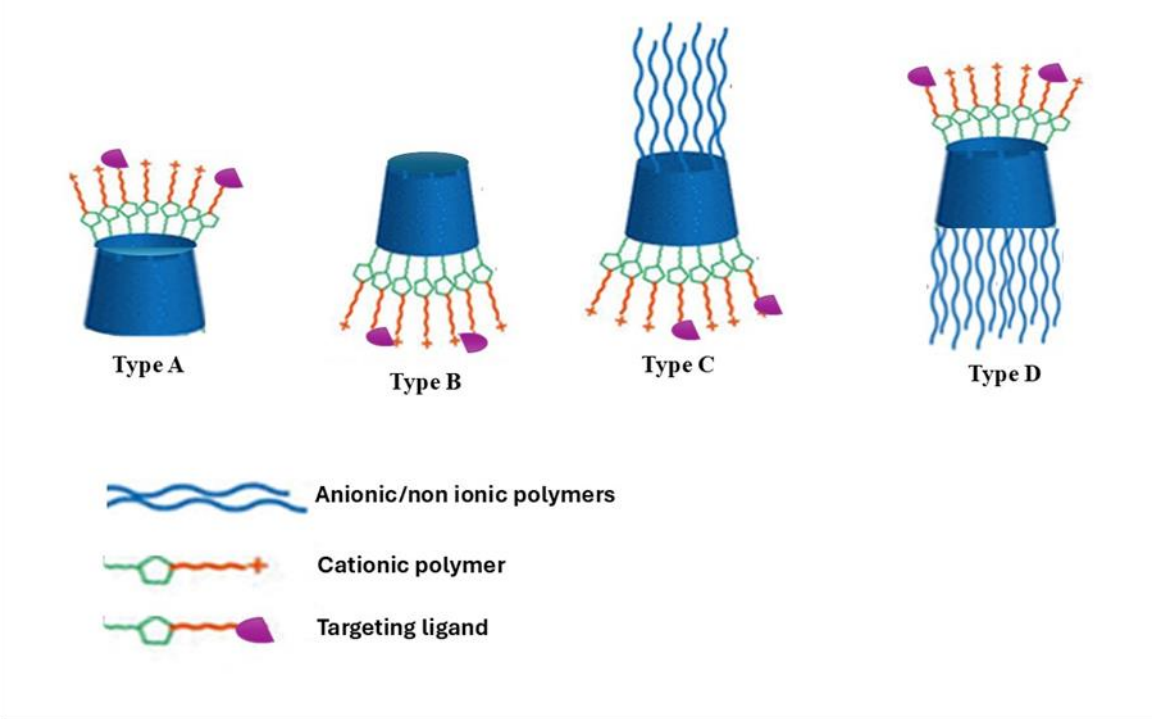

Figure 3. Functionalization of CD derivatives.

3.1. Stimuli Responsive and Thermodynamics in CD-Mediated Gene Delivery

NVs CDs can be formulated in order to selectively release siRNA in conditions such as temperature, light, pH, redox microenvironment [11]. Recent advances in CD-based supramolecular systems have underscored the central role of both thermodynamic stability and kinetic accessibility in the design of effective gene-delivery platforms. The review of Zhang et al. (2020) highlights how host–guest interactions, threading or sliding of CD rings, and stimuli-responsive triggers (pH, redox, enzyme, light) enable rapid morphological and functional transitions of CD Nanocarriers, thereby influencing both the rate of assembly/disassembly and the release kinetics of the cargo) under physiological conditions [31]. In parallel, the review of Mousazadeh H. et al. (2021) discusses how CD-based carbohydrate polymers (including CD-cationic polymers, CD-polyrotaxanes, CD-dendrimers and CD-modified targeting ligands) can be finely tuned in terms of degree of functionalization, N/P ratio, ionic microenvironment and presence of co-polymers to modulate both binding affinity and complex formation/release behavior of siRNA delivery systems[11]. Overall, these works suggest that the thermodynamics and kinetics of the self-assembly process in CD-based siRNA delivery systems are critically governed by multiple physicochemical parameters, including the CD substitution pattern and degree of functionalization, the ionic strength and pH of the

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surrounding medium, the N/P ratio (nitrogen in CD to phosphate in siRNA), and the presence of co-polymers or stabilizers such as PEG, hyaluronic acid, or chitosan. Isothermal titration calorimetry (ITC) has emerged as a powerful technique to quantify the binding thermodynamics of CD–siRNA interactions, providing access to parameters such as binding affinity (K_d), enthalpy (ΔH), entropy (ΔS), and Gibbs free energy (ΔG) [32,33]. Studies on self-assembled cationic β-CD nanostructures have demonstrated that the substitution degree of cationic groups markedly influences the electrostatic contribution to ΔH and ΔS, with higher substitution leading to stronger exothermic interactions and reduced entropic penalties during complexation [4]. In particular, the entropic loss in the complexation of self-assembled cationic β-CDs mainly arise from a reduced conformational freedom of both CDs and guest molecules, as well as from the ordering of water molecules and counterions around the complexes. The enthalpic contribution is due to β-CDs stronger binding (ΔH<0) to negatively charged molecules like siRNA when more cationic groups are present in their structures. In this latter case, however, the entropic penalty is reduced, because more water molecules and counterions are released during binding, which partially offsets the loss of flexibility. The ionic strength and pH of the medium further modulate complex stability by altering electrostatic screening and protonation states, shifting the balance between enthalpic and entropic driving forces [6]. From a kinetic perspective, the dynamics of siRNA complexation and release depend strongly on the N/P ratio and the nature of co-stabilizing polymers. Elevated N/P ratios typically enhance complex compactness and reduce dissociation rates, whereas the inclusion of PEG, hyaluronic acid, or chitosan can modulate assembly kinetics and colloidal stability by steric or electrostatic means [34]. ITC combined with molecular dynamics simulations has revealed that self-assembled β-CD/siRNA complexes exhibit favourable binding kinetics driven primarily by electrostatic and dehydration effects [32]. Moreover, differential scanning calorimetry (DSC) and fast-scanning calorimetry (FSC) have been used to probe solid-state transitions and thermal stability, confirming that the substitution pattern and N/P ratio affect not only molecular affinity but also phase behaviour and thermal robustness [6,35]. Overall, the interplay between thermodynamic stability (ΔG, ΔH, ΔS) and kinetic accessibility dictates the efficiency of siRNA complex formation, protection, and intracellular release.

4. Computational-Experimental Design of β-self Assembling CD

Singh et al. (2019) describe the design and characterization of self-assembled cationic β-CD (cCD) nanostructures for siRNA delivery, employing a combined computational and experimental approach [32]. Using extensive molecular dynamics simulations, they demonstrate that cCD molecules spontaneously assemble into supramolecular bilayer-like structures around siRNA, stabilizing its native conformation via extensive electrostatic interactions and hydrogen bonding. Unlike unmodified β-CDs, which form transient, non-specific complexes, cCD derivatives exhibit strong, specific binding to siRNA, mediated by their positively charged side arms and hydrophobic alkyl chains. The simulations reveal lipid-like interdigitated assemblies that encapsulate siRNA, mimicking natural biomembranes and potentially enhancing membrane permeability. Isothermal titration calorimetry experiments validate these findings, confirming a spontaneous, enthalpy-driven complexation process with low dissociation constants.

5. Targeted Delivery

Targeted formulations achieved superior knockdown efficiency compared to non-targeted controls. CD can be modified allowing receptor-mediated delivery particularly useful for cancer therapy. Malhotra et al., 2018, prepared ligand-targeted nanoparticles by exploiting the inclusion complexation capabilities of CD and adamantyl-PEG-modified ligands combined with chitosan, obtaining a good internalization to glioblastoma (U87) and prostate cancer (DU145) cells [22]. This performance has been attributed to the formation of supramolecular structures through interdigitation of aliphatic tails for disulfide-linked conjugates, which demonstrated enhanced gene silencing, likely due to intracellular bioreduction [36]. Li et al. 2023 developed a folic acid-

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functionalized β-CD-grafted polyethylenimine (β-CD-PEI-FA) nanocarrier for the targeted delivery of miR-34a-5p against Kaposi's sarcoma-associated herpesvirus (KSHV) [37].β-CD-PEI-FA polymer formed stable nanocomplexes with miR-34a-5p via electrostatic interaction, effectively protecting the miRNA from nuclease and serum degradation. The nanocomplex exhibited suitable physicochemical properties (size ~203 nm, zeta potential ~27 mV) for cellular uptake and showed low cytotoxicity and hemolysis in vitro. Functional assays in KSHV-positive BCBL-1 and SK-RG cells demonstrated that β-CD-PEI-FA/miR-34a-5p complexes increased intracellular miR-34a-5p levels, inhibited cell proliferation by arresting cells in the G2 phase, and significantly downregulated KSHV genes (ORF26, LANA, K8.1A). These results suggest that β-CD-PEI-FA represents a promising strategy for folate-receptor-targeted delivery of therapeutic miRNAs in antiviral applications.

In Table 2 the different types of modified CD NV are explored in this review.

Table 2. CD Nanovectors for gene delivery from 2020 to 2025.

NVs Composition	Size (nm)	siRNA	Co-delivery	In vivo/in vitro studies	References
TEPA-βCD polyplexes	332-912	anti-GFP	Plasmid DNA	In vitro	34
βCD derivatives / βCD-Ad-PEG/ anisamide target ligand /amantadine inclusion	<300	targeting PLK1	/	In vitro	19
Surface modified CDs-functionalized with RVG peptide	<200	targeting HTT mRNA	/	In Vitro	23
Modified cationic β-cyclodextrins-Ad-PVA-PEG	<300	anti-GFP	/	In vitro	25
Modified amphiphilic cationic CD-siRNA /coformulated with anionic CD	<200	Anti-KAT2a	/	In vitro	26
Modified CD NPs-sialic acid target ligand	<250	CSF-1R	/	In vitro	27
AS1411 aptamer–PD-L1-siRNA combined with Gln/β-CD-DOX	250-500	PD-L1 siRNA	Doxorubicin	In vivo	28
CD-Polymer-PEG/Tf target ligand	<200	RRM2	/	Clinical Trial	29
Modified cationic β-CD	<300	PLK1	/	In vitro	32
Covalent conjugates β-CD-siRNA	<200	PLK1/ anti GFP	/	In vitro	22
FA-β-CD-PEI	<250	miR-34a-5p	/	In vitro	3

6. Conclusions and Future Prospectives

CD based NVs are versatile and promising platforms for siRNA delivery, thanks to their structural adaptability, biocompatibility, and tunable host–guest interactions. The ability to modulate the physicochemical parameters of CDs, such as degree of substitution, cationic charge density, and functionalization with targeting or stimuli-responsive groups, allows fine control over complex stability, binding thermodynamics, and release kinetics under physiological conditions. Modified CD-based nanocarriers are capable of effectively condensing and protecting siRNA, facilitating its cellular uptake while minimizing cytotoxicity and immune responses.

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Despite the remarkable progress, several challenges remain to be addressed before CD-based siRNA vectors can reach full clinical translation. A deeper understanding of the relationship between molecular structure, supramolecular dynamics, and biological performance is essential to optimize delivery efficiency and specificity. Future studies should focus on integrating multi-responsive or targeted CD architectures, capable of responding to intracellular stimuli such as pH, redox potential, or enzymatic activity, as well as on developing biodegradable and scalable CD-based polymers for safe systemic administration and a deeper elucidation of the mechanisms governing CD–siRNA interactions and optimizing their therapeutic efficacy.

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Conflicts of Interest: The authors declare no conflict of interest.:

Abbreviations

The following abbreviations are used in this manuscript:

siRNA	small interfering RNA
CD	cyclodextrin
NVs	Nanovectors
RNAi	RNA interference
miRNA	microRNA
LNPs	Lipid Nanoparticles
hATTR	hereditary transthyretin amyloidos
BBB	Blood Brain Barrier
cCD	Cationic cyclodextrin
AML	acute myeloid leukaemia
TAMs	tumor-associated macrophages

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