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Cyclodextrin-Based Compounds and Their Derived 1,2,3-Triazoles: Recent Aspects, Synthesis, Overview and Applications

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Abstract

Cyclodextrin and related compounds acquired considerable interest in the last decades in chemical and biomedical fields due to the broad spectrum of applications in various fields. The current review shed light on recent aspects related to cyclodextrin structural features, recent applications in polymer chemistry, medical aspects as well as the advanced utility in the drug discovery field. Furthermore, cyclodextrin based 1,2,3-triazole compounds synthesized via click chemistry approach, their synthesis features and applications were also discussed.

Keywords: Cyclodextrin, Biocompatibility, drug delivery, 1,2,3-triazoles, click chemistry, Cancer therapy, anticancer.

1. Introduction

Cyclodextrin is a substance known for more than 130 years and up to the present time. It has become an important motif because of its main advantage in its ability to form supramolecular complexes with a large number of compounds [1]. Villiers published the first description of this substance, later dubbed cyclodextrin in 1891, through the digestion of starch by Bacillus macerans into crystals. The structure of these crystals was defined as $(C_6H_{10}O_5).3H_2$. Following investigations then studied the digestion of starch by microorganisms [2, 3] and isolated materials seemed identical to the cellulose isolated by Villiers, whose research by scientist Schardinger laid the foundations of cyclodextrin chemistry [1]. Interest in CSs has grown over time and continues to this day and acquired considerable interest. They are used in medicine [4], cosmetics [5], as food additives (the European Union has approved the use of β-CD as a food additive E459) [6-8], separation techniques, nanomaterials, sensors, enzymatic catalysis [9] and biomedical applications [1]. Cyclodextrin (CD) has fascinated many scientists since its discovery in 1891, as its captivating structure attracted not only chemists, but also biologists, physicists, engineers and many others, in attempts to take advantage of its unique properties [10].

CDs are large, well-known rich sugars that contain five or more units of α-D-Glucopyranoside linked to α-1,4-glycosidic links component of a lump-shaped cone. In nature, the CDs α, β and γ are three main types of CDs containing six, seven and eight units of glucose respectively [11]. The form of the cone has an internal hydrophobic cavity and the hydrophilic internal surface. This distinctive structure enables them to create complexes with hydrophobic compounds [12]. Through non-covalent interactions, without the need for complex chemical reactions [13]. Under typical conditions for experiments, CDs exhibit stability in alkaline solutions and partially withstand acid hydrolysis, which happens at pH values below 3.5 and temperatures above 60°C [14]. Unlike calixarenes, there are no possible conformational isomers for cyclodextrins, due to the lack of rotation around the bonds to which the glucopyranose units are attached [9], (**Figure.1).**

Cyclodextrins (CDs) are classified depending on the number of glucose units associated with each other in their composition [1]. **(Figure. 2)**

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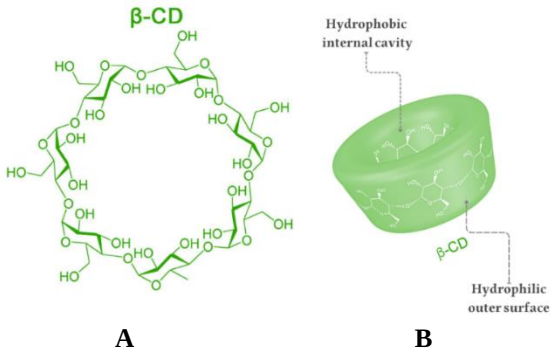


Figure 1. β-CD molecule: (A) chemical structure, and (B) toroidal shape.

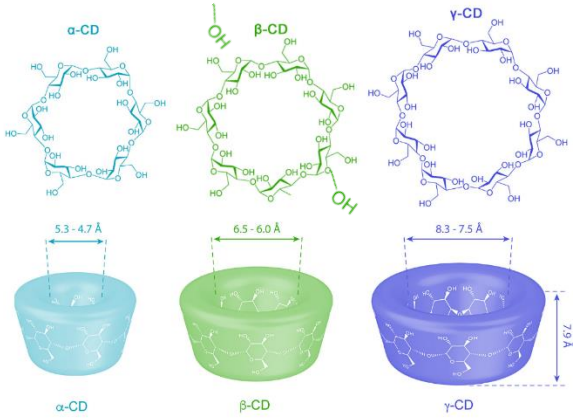


Figure 2. The chemical structure and toroidal shape of α-CD, β-CD, and γ-CD.

α-Cyclodextrin (α-CD) are molecules that contain 6 glucose units [15]. A hydrogen bond is located on the outer edge between the hydroxyl groups (2-OH) and (3-OH) and this reaction is somewhat weak, in which it works 2- OH as a future and 3H as a donor [16]. Medicines cannot be contained in the internal cavity of the α-CD due to their insufficient pain [17].

β-Cyclodextrin (β-CD) in a combination contains 7 glucose units. The hydrogen bond between groups-hydroxyl is stronger than α-CD bonds and weakened than γ-CD [16]. It is frequently used in pharmaceutical applications and this is due because it has a suitable cavity to contain many medications compared to other CDS and also for its availability and access to it [17].

γ-Cyclodextrin (γ-CD) consists of 8 glucose units, which gives it larger internal cavities and the ability to surround larger molecules, and this gives it a clear advantage over β-CD and α-CD [18]. Hydrogen bonds are stronger between hydroxyl groups compared to other types, and this soil alternates between 2-OH as a donor and 3-OH as an acceptor [16]. Its flexible and non-planar structure gives it maximum solubility in water. This feature makes it a suitable host for improving the solubility of poorly soluble drugs [19]. However, due to its rapid digestion in the gastrointestinal tract and the difficulty of passing through biological membranes, its bioavailability is poor [16]. Additionally, CDs may contain more than eight glucose units. Despite the existence of CDs with tens or even hundreds of units of glucose, their use is still uncommon [20, 21]. The main physical properties of native CDs are presented in **(Table.1)**.

Table 1. *Characteristics of native cyclodextrins.*

Property	**C2**	**C3**	**C6**
D-glucopyranose unites	6	7	8
Molecular weight (g/mol)	972	1135	1297
Solubility in water at 25 ℃ (% w/v)	14.5	1.85	23.2
Outer diameter (Å)	14.6	15.4	17.5
Cavity diameter (Å)	4.7-5.3	6.0-6.5	7.5-8.3
Height (Å)	7.9	7.9	7.9

2. Synthesis of Cyclodextrin derivatives.

CDs contain, in their original structure, a number of hydroxyl groups that are able to react chemically to add different functional groups to their structure, and this leads to the formation of a large variety of CDs derivatives [22]. The substitution of cyclodextrins (CDs) presents a significant challenge for chemists during substitution. The hydroxyl groups at 2, 3, positions and 6 compete with one another, complicating the processThe most basic, least acidic, and most accessible hydroxyl groups are found at position 6 [23, 24], while those at position 2 are the most acidic, and those at position 3 are the least accessible and is most sterically hindered. Cyclodextrins (CDs) can undergo selective modification due to the varying reactivity of their three hydroxyl groups [1, 23, 25, 26] **(Table. 2 and Figure. 3)**.

Table 2. *Summary of hydroxyl groups in CD [26]*

OH-group positions	**C2**	**C3**	**C6**
Features	•OH-group attached to the second carbon atoms of each glucose unit • Points towards the wide rim of CD cone • Most acidic and least nucleophilic •Low reactivity • High steric hindrance	• OH-group attached to the third carbon atom of each glucose unit • Points towards the narrow rim of CD cone • Least accessible • Least reactivity • Low nucleophilicity • High steric hindrance	• OH-group attached to the sixth carbon atom of each glucose unit • Most accessible • Most reactive • High nucleophilicity • Low steric hindrance

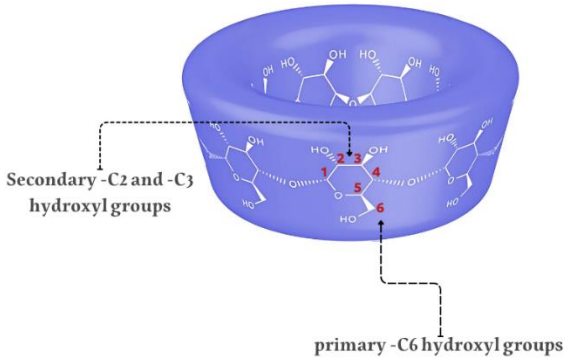


Figure 3. Structure showing positions of OH- groups.

2.1. Replacement methods (CDs).

Methods for the substitution of cyclodextrins are categorized into two types based on the approach used: direct and indirect [1].

a1) A "**direct**" method involves performing a non-regiospecific substitution, after which the resulting cyclodextrin (CD) derivatives are purified using separation techniques such as chromatography [27].

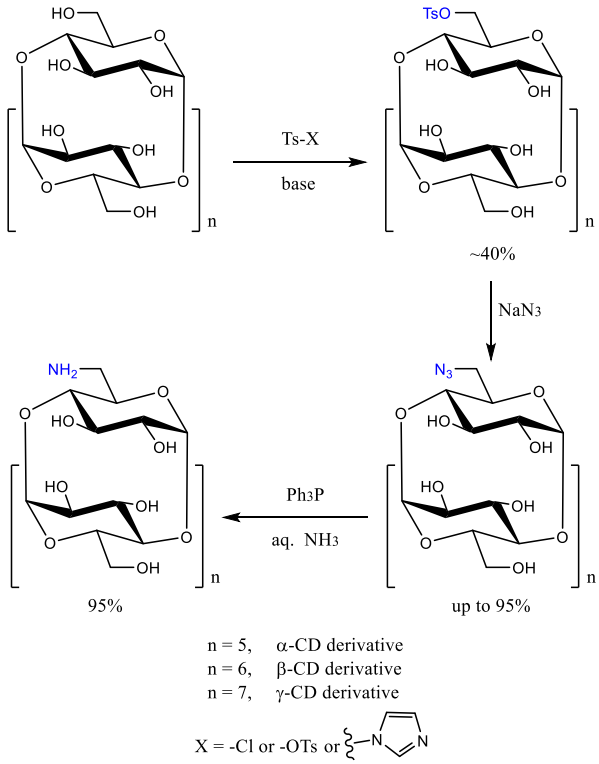
a2) A "**smart-direct**" method – this approach utilizes the distinctive physicochemical properties of a cyclodextrin and a substituent to facilitate a one-step, high-yield substitution reaction , like When an excess of NaOH is employed in relation to the number of hydroxy groups in the CD, the synthesis of 6A-O-allyl,-cinnamyl, and -propargyl CD derivatives produces the greatest results [28]. Jiajing Guo et al used click chemistry reactions in the synthesis of mono-6-azido ß-Cyclodextrin Derivatives by microwave radiation. The results led to high selectivity and high yield [29] **(Schem. 1)**.

A3) A "**bio-direct**" method involves synthesizing a substituted cyclodextrin (CD) via an enzymatic reaction [30].

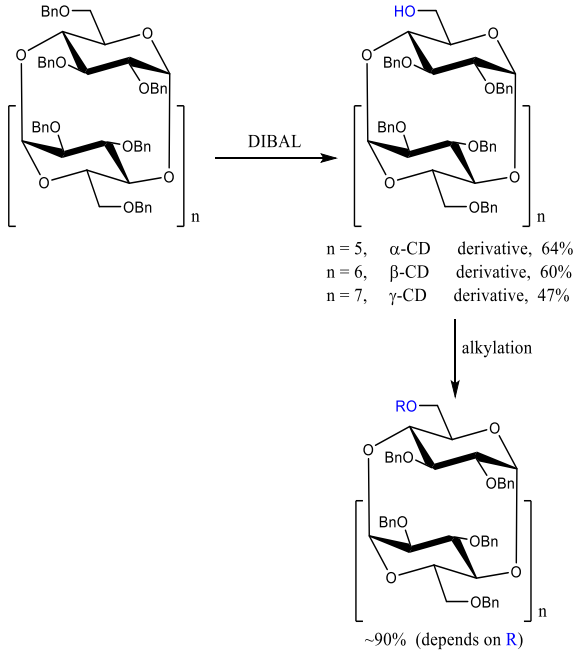
b1) An "**indirect**" method involves multiple protection/deprotection steps to ensure the key substitution step yields high results [31].

b2) A "**smart-indirect**" method involves the selective high-yielding deprotection of monosubstituted cyclodextrins [32] **(Scheme. 2)**.

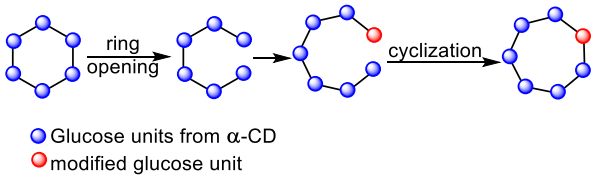
b3) A "**cyclisation-indirect**" method involves synthesizing a monosubstituted cyclodextrin through the cyclisation of an oligosaccharide. Because of the intricacy of the synthesis, the approach is regarded as the most difficult variation. The usual procedure involves opening the α-CD ring, adding a fresh monosubstituted glucose unit to the hexasaccharide, and then closing the ring once more [1] (**Scheme. 3).**



Scheme 1. Synthesis of nomosubstituted CDs by a "smart-direct" method.



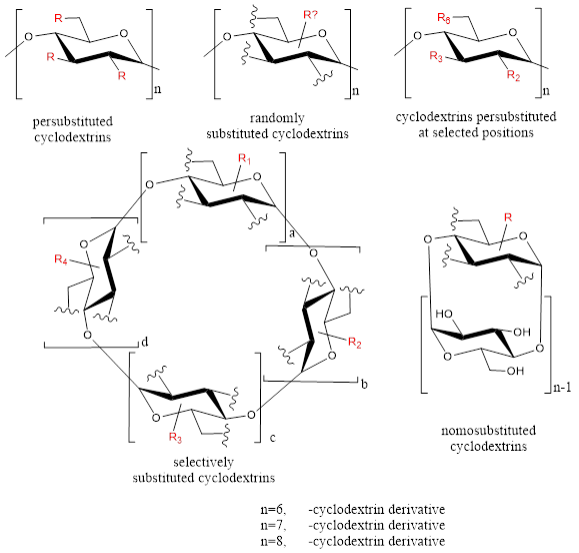
Scheme 2. Synthesis of monosubstituted CDs by a "smart-indirect" method.



Scheme 3. Synthesis of nomosubstituted CDs by the "cyclisation" method.

Furthermore, the CD cavity often interferes with the substituting agent, adding complexity to the functionalization; Solvents serve a crucial role in substitution reactions, influencing the nucleophilicity of oxyanions [32]. **(Scheme. 4)** shows the different types of derivatives cyclodextrin can form.

The many types of exchangeable atoms on CDs lead to many different forms of derivatives with different properties.



Scheme 4. Schematic representation of cyclodextrin derivatives types.

2.1.1. Cyclodextrin Polymers.

2.1.1.1. Cyclodextrin-based nanosponges (CD-NS)

The term "nanosponge" originated in 1998 with DeQuan Li and Min Ma, who created it by cross-linking β-cyclodextrin with diisocyanates [33]. This bonding leads to the formation of a three-dimensional porous nanostructure with a network of covalent bonds; this cross-linking is accomplished through cross-linking agents such as diisocyanate, dianhydride, diglycidyl ethers, or other highly reactive compounds containing two electrophilic sites capable of reacting with a nucleophilic hydroxyl group on cyclodextrin [34]. The lipophilic cavities in cyclodextrin monomers and the hydrophilic channels in the porous structure of CD-NS enable the incorporation of a diverse range of compounds [35], The CD-NS drug delivery system has a range of applications in treating ailments like cancer, autoimmune diseases, and theranostic applications, and it offers enhanced bioavailability and stability, etc [36] (**Figure. 4** and **Figure. 5).**

2.1.1.2. Cyclodextrin-based polyrotaxane (CD-NS)

A typical supramolecular polymer is cyclodextrin polyrotaxane (PRX), which has many CDs connected along a linear polymer chain and cross-linked on the polymer axis by capping with big capping molecules [37].

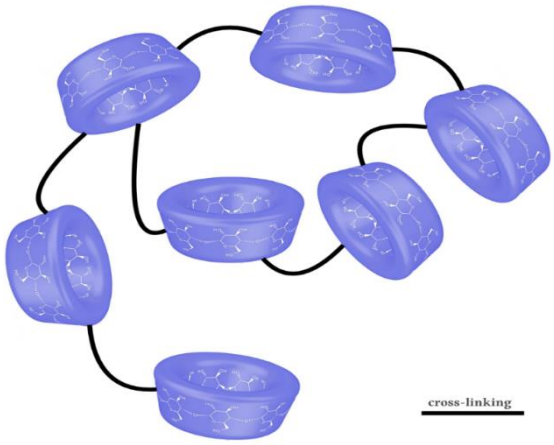


Figure 4. Cyclodextrins are linked with cross-liking polymer from cyclodextrin nanosponge.

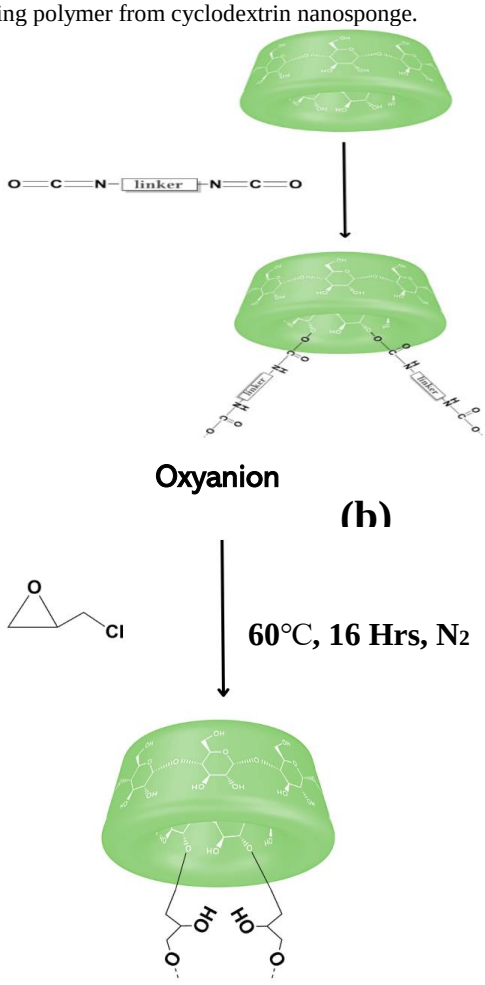


Figure 5. Synthesis of cyclodextrin polymer using (a) diisocyanate as cross-linker and (b) epichlorhydrin as cross-linker

The disassembly or separation of the CD rings from the filament is restricted by the plug until it is prepared for release [26]. In reaction to a variety of chemical

and physical stimuli, including pH, light, reducing chemicals, and reactive oxygen species (ROS), the generated PRXs easily split into their native molecules when cleavable chemical bonds are added to the axis polymers [38-41].

2.1.2. Amphiphilic Cyclodextrin

Amphiphilic cyclodextrins are a unique class of cyclodextrin derivativesThe primary and/or secondary faces of the cyclodextrin rings in these derivatives are joined by hydrophobic (aliphatic) chains [42]. There are two main types including polysubstituted amphiphilic cyclodextrins, which are created by substituting the primary or secondary hydroxyl groups, and monosubstituted amphiphilic cyclodextrins, which are formed by attaching a single hydrophobic anchor. The polysubstituted type can be further categorized into sub-groups like medusa-like, skirt-shaped, and bouquet-like, while the monosubstituted type includes sub-groups such as Cup and Ball,Lollipop and lipid-like. The purpose of these modifications is to enhance cell targeting [12, 43]. **(Figure. 6 and Table. 3).**

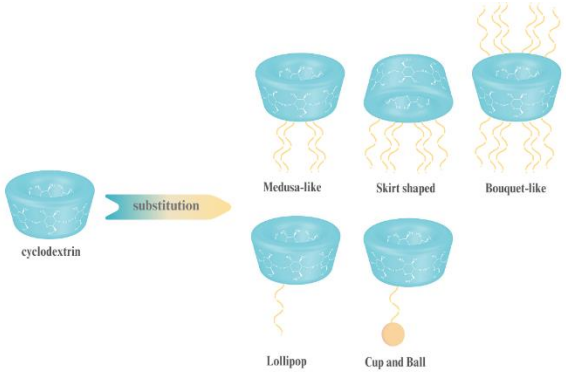


Figure 6. The structure of amphiphilic cyclodextrins substitution

2.1.3. Cyclodextrin inclusion complexes.

Cyclodextrins have the ability to form inclusion complexes with the host in which each

The host molecule is surrounded by a guest (CD). These complexes provide new and useful properties for the host in its chemical structure and physical properties, such as modifying the chemical reactions of the host molecules [44], stabilizing substances that are sensitive to oxygen or light [45, 13], improving their solubility [46], and protecting these materials from degradation by microorganisms [47]. There are different ways to create inclusion complexes:

1. Kneading technique.
2. Supercritical carbon dioxide method
3. Co-precipitation technique
4. Technique of solvent evaporation

Table 3. *Types of amphiphilic cyclodextrins with substituents.*

Type of Amphiphilic Cylodextrin	Subtype	Substituents
Polysubstituted	Medusa-like	Amino-, amido-, thio-alkyl-, or sulfo-chains on the primary side
	Skirt shaped	Modified on the secondary hydroxyl groups with alkyl chains via an ester group
	Bouquet-like	Both sides have hydrocarbon chains, or poly(oxyethylene) and polymethylene chains
Monosubstituted	Cup and Ball	One alkyl chain on the primary side
	Lollipop	Contain a bulky Boc-amino protective group at the end of the alkyl chain
	Lipid-like	phospholipidyl, Cholesteryl or dilauryl moiety

2.2. Drug release systems

Formulations based on cyclodextrin derivatives are capable of improving the pharmacological, physical, and chemical properties of drugs used in biomedical applications, by increasing the loading capacity through the addition of chemical groups to the inner or outer surface of the molecule in order to alter the chemical composition of cyclodextrin. These changes may improve the ability of cyclodextrin to load certain compounds, thereby increasing its interaction with the target chemical. Additionally, by increasing its loading capacity, cyclodextrin can load larger molecules to form inclusion complexes, which can enhance the solubility of the drug in water, facilitating its absorption and increasing its efficacy and bioavailability. It helps in delivering drugs more precisely to targeted sites in the body, reducing side effects and enhancing therapeutic efficacy. Improving stability and bioavailability allows for the use of smaller drug doses to achieve the same therapeutic benefit while reducing the likelihood of negative side effects [48]. Effective site-specific drug administration, however, is dependent on host-guest interactions and the microbial environment of the routes since these systems lack a basic mechanism to govern drug release. In this case, using CD derivatives in conjunction with polymers and nanomaterials can restrict non-specific release and regulate drug distribution by utilizing both external (such as light, magnetic fields, and ultrasound) and internal (such as pH, reducing environments, and enzymes) stimuli [49]. **(Figure. 7).**

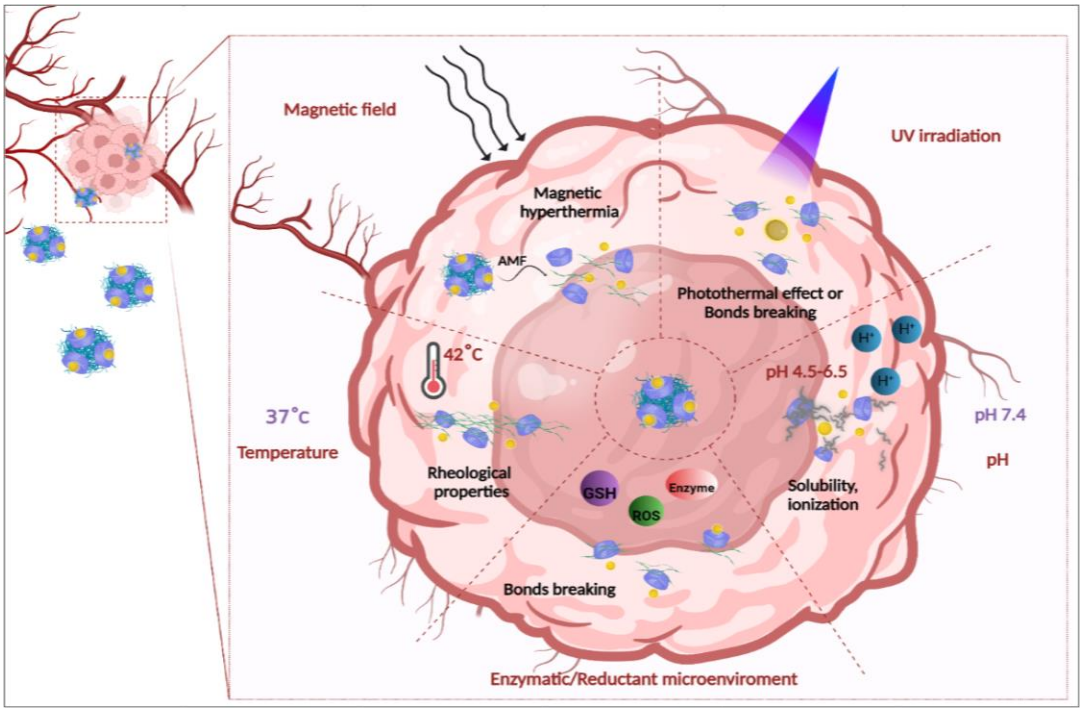


Figure 7. Stimuli-controlled drug release from CD

2.2.1. pH-responsive CDs.

These systems are made of pH-sensitive polymers that release the compound or drug within specific ranges of acidity or alkalinity.

Examples of supramolecular assemblies that utilize pH- and esterase-dependent release include hyaluronic acid-modified β-cyclodextrin (HA-CD) and curcumin-oxoplatin (Cur-Pt) guest conjugates. Curcumin serves not only as a chemotherapeutic agent but also as a guest molecule, that the inclusion reaction established by Bai et al. In vitro drug release experiments conducted under various conditions showcased the pH- and esterase-responsive release behaviors, with an enhanced release of 83% Curcumin and 85% Oxoplatin in esterase and acidic environments. Additionally, cellular experiments revealed the conjugates' active targeting capabilities and effective cytotoxicity against A549 and PC3 cells, which express high levels of the CD44 receptor, while sparing normal LO-2 cells from cytotoxic effects [50]. A molecular-level hybrid hydrogel based on poly(N-(4-aminophenyl)methacrylamide), onion carbon nanoparticles (PAPMA-CNOs = f-CNOs), and γ-CD/DOX-methacryloyl-reinforced gelatin/f-CNOs/CD was proposed by Mamedi and colleagues. Over a period of 18 days, these composites demonstrated superior mechanical, hygroscopic, thermal, and swelling characteristics as well as increased DOX drug release at acidic circumstances (pH 4.5 = 99%, pH 6.0 = 82%) in comparison to physiological pH (pH 7.4) [51]. In a different study, Maqbool and associates created a celecoxib-βCD inclusion complex that was loaded with Eudragit® S100 nanoparticles, which are a combination of methyl methacrylate and methacrylic acid, to treat chronic rheumatoid arthritis. In contrast to absorption in the stomach and small intestine, the medication in this trial was intended to be delivered into the colon, which lengthens its retention period. Nanoparticles showed high drug entrapment efficiency ranging between 68.47% and 91.65%. Gastric and intestinal fluid simulations were used to assess the medication release pattern in vitro. It was discovered that drug release was first delayed at intestinal and gastric pHs (pH = 6.8 and 1.2, respectively), and then rapidly released in the colonic environment (pH = 7.4). The prospect of oral medication administration with colonic absorption after five hours after administration is presented in this study [52].

2.2.2. Temperature-responsive CDs.

Heat-sensitive materials are used to release drugs, and their physical properties change at a certain temperature, leading to the release of the loaded active ingredient. For instance, Okubo and associates created a heat-responsive injectable hydrogel in 2020 to treat diabetes. It was built on hydroxypropylmethylcellulose and βCD that had been altered to be hydrophobic. This hydrogel was able to adjust its viscosity based on body temperature. Interestingly, the proposed hydrogel turns into a gel at body temperature (37 °C). Insulin incorporated into

the hydrogel formulation showed a prolonged effect on blood sugar level, due to the gradual release of insulin from the hydrogel [53].

2.2.3. Concentration-responsive CDs.

A smart trigger is also used to manage drug release, such as a high concentration of certain biomolecules to stimulate drug release. For example, studies such as those by Wang et al [54] and Xu et al, show that modulation of insulin bound to βCD leads to its release when high glucose concentrations are present. Both studies showed that these formulations are safe and designed for glucose-responsive drug carriers, enabling their use in the treatment of diabetes [55, 56].

2.2.4. Light-responsive CDs.

Techniques that use outside stimuli can improve the therapeutic benefits of nanocarriers. Wu et al. have reported a novel material for cancer treatment that is sensitive to light and redox conditions. It consists of mesoporous silica nanoparticles functionalized with a polymer that is azobenzene/galactose-grafted and βCD to release DOX. According to their study, the dissociation of azobenzene groups from the βCD complex during UV irradiation and the subsequent reducing action of glutathione, an endogenous metabolite, caused the release of DOX. Through in vitro tests, this dual redox and UV-responsive release of DOX was confirmed [57].

2.2.5. Electromagnetic fields -responsive CDs.

Drug release has been controlled on demand using pH as an internal promoter and electromagnetic fields as external stimulation. For example, Enoch and associates created a novel pH-sensitive magnetic hydrogel that and is made of carboxymethyl cellulose, β-cyclodextrin, chitosan and incorporates magnetic Fe3O4 nanoparticles. When subjected to an alternating magnetic field (AMF), this hydrogel enabled the controlled release of methotrexate (MTX), achieving a 93% release rate at pH 7.4, suggesting possible use in the treatment of cancer [58].

The majority of studies on stimuli-triggered drug release are centered on cancer therapy, owing to the distinct hallmarks of cancerous tissues compared to healthy ones, such as elevated temperatures, acidic pH levels, reductive environments, and the presence of particular enzymes/metabolites [59, 60], **(Figure. 7)**. Illustrates the stimuli-driven drug release for cancer treatment using polymer-CD conjugates. In contrast to healthy cells, which normally have a normal temperature of 37°C, the higher temperature at tumor locations can be used to change the rheological characteristics of the polymers, releasing medications when the local temperature reaches 42°C [61]. Conversely, the acidic pH within cells facilitates alterations in the solubility of polymer-CD conjugates, thereby initiating the release of drugs. This is because the acidic microenvironment of cancer cells, with a pH ranging from 4.5 to 6.5, is distinct from the neutral pH of 7.4 found in normal cells [48]. The presence of reducing agents, like glutathione—which is found in higher concentrations at tumor sites—could facilitate the breaking of bonds, primarily S-S bonds, and the release of drugs at the targeted site [62]. Additionally, the use of externally controlled laser irradiation and ultrasound waves enhances drug delivery strategies. This is primarily

The conjugates reach the tumor sites by passive/active targeting, then an external stimulus (alternating magnetic field, AMF, or UV irradiation) and/or an internal stimulus (temperature, intracellular metabolites, or acidic pH) triggers the drug release from the conjugates achieved by integrating with a photosensitizer or magnetic agents, which raises the local temperature, facilitating bond disruption and inducing cell death through hyperthermia [57, 58]. **(Table. 4)** shows the biological performances as well as the effective catalysts and target applications of various modern CD-based nanocarriers [50].

2.3. Applications of CDs

Cyclodextrins (CDs) and their derivatives serve as controlled drug release systems, leveraging their unique cavity to form reversible complexes with drugs. This allows the gradual release of the host molecule from the cavity, preserving the drugs' physical, chemical, and biological properties. CDs also extend the molecules' residence time in the diffusion medium, enhancing efficiency and specificity towards target tissues. CDs are also effective solubilizers, physical stabilizers, and protectors of guest molecules against gastrointestinal tract degradation, increasing medication bioavailability [16]. Recognized as biologically inert, CDs are utilized as pharmaceutical excipients in various drug formulations. Cyclodextrins α, β, γ, and the derivative HP-β-CD have been deemed safe by the FDA and the European Pharmacopoeia [13]. Piroxicam/β-CD (Brexin® tablets) became the first pharmaceutical formulation released in Europe in 1977, while itraconazole/2-hydroxypropyl-βCD oral solution (Sporanox®) was the initial formulation to receive US approval [63]. Owing to

theirbiocompatibility and adaptability, nanosponges present a broad spectrum of potential applications in the biomedical field [36]. **(Figure. 8, Figure. 9).**

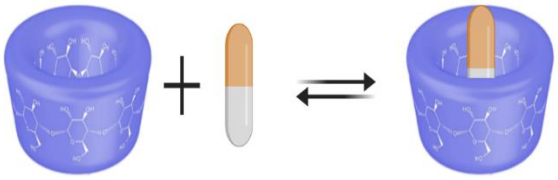


Figure 8. Schematic of some medical applications of cyclodextrin compounds.

Figure 9. Dynamic equilibrium for drug-cyclodextrin complex.

Cyclodextrins may be administered through oral, nasal, dermal, ocular, and intravenous drug delivery systems [72] **(Table. 5).**

2.3.1. Improve solubility

Steroid hormones have become the focus of increasing attention as active pharmaceutical agents for the treatment of endocrine disorders. However, the very low aqueous solubility of many steroid drugs hampers their medical use, reducing their bioavailability. Cyclodextrins are ideal candidates for the development of oral drug delivery systems, as they improve the solubility of hydrophobic steroids and increase their transport rate in aqueous media. In this study, M. Hesler et al synthesized and characterized polymeric derivatives of beta-cyclodextrin, resulting from the interaction of hydrophilic β-CD-thioether with hyaluronic acid. Host–guest complexes were formed using conjugates of hyaluronic acid and β-cyclodextrin with a poorly soluble model steroid (β-estradiol) and compared to monomeric β-cyclodextrin derivatives in terms of solubility and complexation efficiency. Complexes of β-cyclodextrin and drug (host and guest) were evaluated in vitro to determine their suitability (cytotoxicity and transport rate) as enteral drug carriers for steroids. The results showed that in the case of β-estradiol, much higher solubility can be achieved by complexation with complex β-cyclodextrin derivatives, leading to higher intestinal transport rates in vitro compared to monomeric β-cyclodextrin derivatives [64]. Quercetin (Que) has many pharmacological benefits, such as anticancer properties, antioxidants, cardiovascular protection, and lowering blood pressure and lipids.

However, its poor solubility in water restricts its use in medical and food fields. Zhenjiong Wang et al successfully loaded quercetin into cyclodextrin metal-organic frameworks (γ-CD-MOFs), novel porous carriers for functional products. The results showed that the apparent solubility of Que-CD-MOFs was improved by 100-fold compared to pure quercetin, and its free radical scavenging ability was significantly enhanced [65]. Derivatives of 3-Nitro-2H-chromene have shown promising anticancer properties; However, their clinical application is hindered by low water solubility. Neelima et al. conducted a study where they employed a cyclodextrin complexation approach to enhance the solubility and therapeutic effectiveness of the anticancer compound 8-methoxy-2-(4-methoxyphenyl)-3-nitro-2H-chromene (MNC). They prepared solid inclusion complexes of MNC with β-cyclodextrin (β-CD) using co-precipitation and kneading techniques, followed by thorough characterization. The β-CD complex was found to significantly improve MNC's solubility in water. When tested for cytotoxicity against various human cancer cell lines, including breast cancer (MCF-7, MDA-MB-231), lung cancer (A549), and hepatocellular carcinoma (HepG2), the MNC:β-CD complex demonstrated enhanced anticancer efficacy compared to MNC alone [66]. P-coumaric acid is the source of the saccharide molecule comselogoside (COM), which has a variety of potentially advantageous qualities. However, its low stability and low solubility in water restrict its application and study.

Table 4. *Stimuli-responsive CD-based nanocarriers as potent strategy in smart nanomedicine.*

Supramolecular nanocarrier	stimuli mode	Drug	Targeted application	Release efficiency	Therapeutic performances In vitro	Therapeutic performances In vivo	R ef.
Chlorin e6-conjugated β-CD/ Ad-MMP-SPEPs NPs	Visible-light	C e6	Cancer therapy	-	exceptional rate of bactericidal activity (99.4% and 99.997%, respectively, against planktonic P. aeruginosa following 4 and 8 minutes of exposure)	After 7 days of topical administration, mouse corneas with P. aeruginosa-infected keratitis showed high antibacterial efficacy with a mild inflammatory response; after 30 days of treatment, there was little long-term damage to the main organs	[118]
CD-PEG/ Azo-PC carrier	Redox/ light dual	DOX	Cancer therapy	>55% under GHS/UV and >20% in 48 h in standard conditions	Selective cytotoxicity and spontaneous drug release for SCOV3 cancer cells with less harm to healthy HEK293T cells	-	[119]
Star polymer β-CDPNIPAM/BM-PCL micelles	Temp/ pH dual	DOX	Anti-cancer therapy	48.6% at 25 ◦C and 100% at 37 ◦C/ pH 5.2	A dose-dependent lethal impact of DOX on HeLa cells combined with excellent biocompatibility (98% at up to 1.0 mg/m micelles)	-	[120]
HA-β-CD/Cur-Pt (Cur-Pt) NPs	pH/ esterase dual	CUR-PT	Cancer therapy	In 48 hours without esterase, 5% at pH 5 and 16% at pH 7; 85% at pH 5 and esterase	Good biocompatibility on normal LO-2 cells and strong anticancer activity on PC3 and A549 cells	-	[121]
Fc-PCL/β-CD-LasPOEGMA micelles	Dual-redox ROS/ GSH	DOX	Cancer therapy	20% under standard conditions and 95% under DTT and NaClO in 72 hours	High cytotoxicity in Bel-7402 cells; excellent biocompatibility and hemocompatibility	Three times as much DOX was found in the tumor, it was poorly distributed in the other main organs, and 16 days after therapy, Bel-7402 BALB/c mice with tumors showed effective tumor inhibition	[122]

The solubility and photostability of COM may be enhanced by the development of an inclusion complex with (β-CD), according to Fatima et al. The freeze-drying method was used for the first time to study the complexation of COM with β-CD in aqueous solution, and the results demonstrated good encapsulation yield and efficiency. According to solubility studies, COM's aqueous solubility increased by 100%. Additionally, complexing COM with β-CD increased its stability when exposed to UV light at 254 nm [67]. According to the Solubility and Permeability Drug Classification System (BCS), drugs in Class II have a high degree of permeability and low aqueous solubility. These medications frequently have disorganized or not enough absorption characteristics. Syed Haroon et al. conducted a study with the goal of forecasting how β-cyclodextrin and various hydrophilic polymers, including Soloplus (SOLO), Poloxamer 188 (PXM-188), and polyvinylpyrrolidone (PVP), would influence the dissolution profile of the model hydrophobic drug rivaroxaban (RIV). The kneading (KN) and solvent evaporation (SE) methods were used to create binary inclusion complexes with βCD, with drug to cyclodextrin weight molar ratios of 1:1, 1:2, and 1:4. When compared to the pure drug, the binary complex (Drug:βCD with a molar ratio of 1:2 w/w) performed best in terms of improved solubility

and drug release. Furthermore, the hydrophilic polymers SOLO, PVP K-30, and PXM-188 were used in various ratios to create ternary inclusion complexes together with ideal binary formula RIV:βCD (1:2). The findings demonstrated that the ternary formulations (1:2 Drug:βCD:SOLO at 10% S.E.) significantly increased the rate of dissolution and saturation solubility. Hence, it can be concluded that ternary inclusion systems were more effective than binary formulations in improving the solubility and dissolution of the hydrophobic model drug rivaroxaban, which in turn opens new horizons about ternary inclusion systems [68]. Although acetaminophen-induced liver damage is a well-known issue, there are few ways to prevent it. Despite luteolin's hepatoprotective qualities, its limited bioavailability and poor solubility make it difficult to utilize. Because of their large internal voids and three-dimensional network structures, cyclodextrin metal-organic frameworks (CD-MOFs) are perfect for transporting poorly soluble medications. CD-MOFs were employed as carriers in a study by Dan Yang et al. to improve luteolin's solubility and assess its hepatoprotective, bioavailability, and antioxidant properties. After loading luteolin into β-CD-MOF, the results demonstrated that luteolin-β-CD-MOF was more stable, that its solubility increased by 4.50 times, that its antioxidant activity was enhanced in vitro, The bioavailability of luteolin was increased in normal and acetaminophen-induced liver injury mice [69].

Table 5. *Pharmaceutical products with native and chemically modified cyclodextrins.*

Cyclodextrin	Pharmaceutical Dosage Forms				
	Oral	**Nasal**	**Ocular**	**Dermal**	**Parenteral**
α-CD	_	_	_	_	✓
β-CD	✓	_	✓	✓	Not allowed
γ-CD	✓	_	_	✓	_
HPβCD	✓	_	✓	✓	✓
RAMEB	Not allowed	✓	✓		Not allowed

The check sign (✓) denotes known cases of dosage forms containing CDs for a particular delivery route; adapted

2.3.2. Medical bandages.

Using acryloyl chloride and an extra copolymer with N-isopropylacrylamide (NIPAM) and acrylic acid (AA), Juanli Shen et al. modified β-CD to create PNIPAM-co-β-CD-AC. According to the results, the hydrophobic medication contained in this hydrogel can be continually released for over six days at pH values between 5.5 and 8, which may be in line with the time needed for wound healing. Its quick gel formation, reversibility, and shear-thinning ability as a hydrogel dressing shield the wound from further harm. The β-CD-based hydrogel is a great option for wound dressings because of its outstanding biocompatibility and antioxidant qualities, particularly for wounds that are exposed in the winter [70]. Diabetic wounds are typically challenging to heal due to high blood sugar levels, excessive reactive oxygen species (ROS), compromised immune responses, and delayed angiogenesis. Yuting Zhang et al developed a multi-bond crosslinked hydrogel that possesses drug release regulation, antibacterial, angiogenic, and ROS scavenging properties to effectively promote diabetic wound healing. This hydrogel was synthesized through a one-pot crosslinking process of bamboo parenchymal cellulose and modified β-cyclodextrin, forming multiple bonds including hydrogen and ester bonds. The resulting composite hydrogel features a significantly large pore structure, enabling effective absorption of wound exudate when used as a dressing. Due to its unique network, the hydrogel's internal drug release is regulated by varying responses to the physiological environment's pH. Moreover, the cyclodextrin's cavity structure allows for continuous drug release over 96 hours. With the synergistic design of pore and cavity structures, the composite hydrogel demonstrates superior drug loading and release capabilities. In vitro bacteriostasis tests confirmed that the hydrogel dressing (BPCAH-C) exhibits significant bacteriostatic effects against E. coli and S. aureus, with a bacteriostasis area increase of up to 230%. The hydrogel dressing has shown to achieve a 90% healing rate within 14 days and a 75% free radical clearance rate. This type of hydrogel dressing, which adapts to and enhances the microenvironment, holds great potential for clinical application in the healing of diabetic wounds [71].

2.3.3. Dentistry.

Although techniques for adhesion of dental materials to tooth surfaces have greatly advanced over the past decades, removal of tightly adhered restorative materials remains a challenge, as it is usually performed by mechanical separation or destruction, which threatens to damage the enamel layers [72].

Nobuhiko et al. suggested using photodegradable polyrotaxanes (PRXs) to address the issue of dental materials being removed from tooth surfaces. They used a clinically approved adhesive, to successfully adhere poly(methyl methacrylate) (PMMA) blocks to bovine dentin utilizing an α-CD chiral material that contained a mononitrobenzyl ester as a cross-linker. After only five minutes of UV exposure, the α-CD chiral polymer gradually breaks down into its constituent parts, methacryloyl and modified butyl carbamate α-CD, with up to 60% breakdown occurring. However, when exposed to UV light, the polymer without α-CD (control material) did not exhibit any discernible alterations. This makes it a great option for enabling the use of UV radiation to remove dental materials from tooth surfaces [73]. In another approach, B.S. Inoue et al synthesized a β-CD inclusion complex with the bactericidal chlorhexidine (CHX) and loaded it into bacterial cellulose membranes to study its effect in treating periodontal diseases. NaIO4 was used as an oxidizing agent to modify the release of (CHX). Membranes containing the inclusion complex (DABC+CHX:βCD) showed superior antimicrobial activity (C. albicans, E. coli and S. aureus) in vitro when compared to those loaded with pure drug only [74]. Trajano et al assessed the impact of a β-CD-enhanced gel on doxycycline's effectiveness in treating periodontitis through a randomized clinical trial involving 33 patients. The antibiotic was administered topically to the periodontal pocket as a hydrogel, with a 10% concentration, both with and without β-CD. The study found that the gel with 10% doxycycline and β-CD significantly improved clinical periodontal parameters, evidenced by increased attachment levels and reduced bleeding, and also decreased plaque formation [75].

2.3.4. Ophthalmology.

One medication that is frequently recommended to treat dry eyes is fluorometholone (FMT). It is typically administered as an ocular suspension, which has a limited bioavailability and makes it challenging to determine the exact dosage, because of its poor solubility in water. For visual purposes, the ophthalmic suspension's opaque look is undesirable. Without the use of organic solvents, Tian-zuo et al. used cyclodextrin (CD) nanoparticle technology to create a transparent nanoformulation of FMT (FMT-CD NPs). According to studies, FMT is encapsulated in a non-crystalline state, which enhances corneal penetration effectiveness and speeds up release. Several tests confirmed that FMT-CD NPs are biocompatible. Most importantly, FMT-CD NPs were more effective than store-bought eye drops at reducing the symptoms of dry eyes [76]. With demonstrated benefits over conventional topical NSAIDs, napafenac is a useful NSAID for managing postoperative ocular inflammation and pain after cataract surgery. However, because of its sticky, uneven consistency, discomfort, obscured vision, and foreign body sensation, Nevanac®, a suspension eye drop, frequently results in poor patient compliance. Sodium hyaluronate and hydroxypropyl-β-cyclodextrin was added to nepafenac eye drops by Anna Vincze et al. to promote mucoadhesion, appropriate viscosity and total dissolution. Viscosity, mucoadhesion, drug release, and corneal permeability were evaluated in vitro for 11 formulations, including two references, using an experimental approach. Eleven formulations, including two references, were evaluated in vitro using an experimental methodology to determine their viscosity, mucoadhesion, drug release, and corneal permeability. Two formulas seemed promising.The results showed that one formulation had a higher ex vivo bioavailability than Nevanac® 0.1% suspension, while another formulation matched Nevanac® in ex vivo efficacy with just 60% of the original dose, indicating a potential for nepafenac eye drops with better patient compliance [77]. The central nervous system-specific enzyme CYP46A1 helps control the amount of cholesterol in the brain and retina by removing cholesterol from these organs by converting it to 24-hydroxycholesterol. 2-hydroxypropyl-β-cyclodextrin (HPCD) synthetic substance licensed by the FDA, it is presently being researched for a number of medicinal applications, including conditions affecting the retina. Although studies have demonstrated that HPCD lowers cholesterol levels in mice's retinas, its potential as a treatment has not yet been assessed. The impact of HPCD on mice given a high-fat, high-cholesterol diet for 14 months was investigated by Nicole et al. According to the findings, HPCD treatment improved the retina's cholesterol homeostasis and had an impact on the quantity of six distinct protein groups: vesicular transport, endocytosis and lysosomal processing, genetic information transfer, cytoskeleton organization, removal of misfolded proteins, homeostatic lipid stasis, and Wnt signaling. This result encourages more investigation into HPCD as a possible therapy for diabetic retinopathy, which is brought on by an imbalance in retinal cholesterol,

and age-related macular degeneration [78]. **(Table. 6).** presents a selection of cyclodextrin-based embedding complexes in ophthalmology [79].

Table 6. *Examples of CD-based formulations for different drug delivery systems that incorporate antifungal drugs[79].*

CD	Drug	Routeof Administration	Experimental Findings	R ef.
βCD	Itraconazole	Ocular	Excellent stability, safety, mucoadhesion, and penetration into a rabbit's cornea, along with decreased anterior chamber clinical symptoms, white lesions, and corneal opacity	[123]
	Econazole	Dermal	Increased goatskin permeation in vitro and the capacity to stop fungal growth in both in vitro and in vivo investigations	[124]
	Natamycin	Vaginal	High mucoadhesion and prolonged drug release	[125]
γCD	Amphotericin B	Ocular	Better stability than traditional nanoemulsion, prolonged in vitro drug release, reduced amphotericin B aggregation and hemolytic characteristics compared to commercial products, and active against Candida albicans	[126]
SBEβCD	Econazole	Oral	enhanced medication solubility and rate of dissolution; showed antifungal and mucoadhesive effectiveness and controlled-release characteristics	[127]
	Ketoconazole	Ocular	Excellent mucoadhesive properties, controlled release, and antifungal effectiveness	[128]
			Increased ex vivo increased corneal retention time, corneal permeation and biocompatibility	[129]
HPβCD	Miconazole	Oral	Demonstrated high drug release and enhanced antifungal activity	[130]
	Fluconazole	Ocular	Excellent stability, safety, mucoadhesion, and penetration into a rabbit's cornea, along with decreased anterior chamber clinical symptoms, white lesions, and corneal opacity	[131]
	Itraconazole	Dermal	Both active antifungal action against Candida albicans and superior permeability to the epidermal layer compared to traditional liposomes	[132]

2.3.5. Heart disease.

Thrombotic diseases pose a significant hazard to global public health, resulting in elevated death and disability rates. The majority of thrombolytic medicines, particularly protein-based medications, possess a brief half-life in circulation, hence diminishing their thrombolytic effectiveness. For effective clot analysis, an intelligent drug delivery system that accurately delivers and releases the medication at proximal clot locations under regulated conditions must be developed. A novel drug delivery system (MCRUA) was introduced by Caijie Yuan et al. It targets platelets specifically and releases the medication in reaction to the clot's surroundings. The MCRUA system is made up of cross-linked CaCO3/cyclodextrin structures of organometallic acid (MC) that are loaded with the urokinase-type plasminogen activator (uPA) and the anti-inflammatory medication aspirin (acetylsalicylic acid, ASA). Furthermore, MCRUA dissociates in the acidic clot site environment, releasing uPA to break down the clot and aid in revascularization. Additionally, Cyclodextrin-encapsulated ASA can also address the inflammatory environment within the clot, enhancing the anti-platelet aggregation effects and improving the treatment of cooperative thrombolysis. When used in the treatment of thrombotic disorders, the MCRUA drug delivery system improves clot resolution, reduces coagulation, and enhances biosafety while reducing hemorrhagic side effects [90]. Carvedilol, a beta-blocker used to treat chronic heart failure, has low bioavailability and rapid first-pass metabolism upon oral administration. The development of tip microarray patches (MAPs) made of triplet cyclodextrin (CD) complexes of carvedilol for transdermal distribution has been advanced by Q.K. Anjani et al. The ternary combination containing poly(vinylpyrrolidone) (PVP) and hydroxypropyl γ-cyclodextrin (HPγCD) decreased the crystallization of carvedilol, according to analyses. The ternary compound was used as the needle layer in a two-step procedure to create MAPs.Ex vivo, the produced MAPs could reach a depth of about 600 micrometers through the skin of newborn pigs. The needle dissolves after two hours after implantation, enabling carvedilol to be delivered transdermally. In cell experiments, MAPs have demonstrated adequate biocompatibility and low toxicity. With a delay in Tmax and consistent plasma levels over a few days, it produced noticeably larger AUC levels in rats than oral carvedilol. These findings imply that limb microarray patches (MAPs) infused with carvedilol may revolutionize the

treatment of chronic heart failure [91]. One of the manifestations of cardiotoxicity resulting from doxorubicin (Dox) is cardiac arrhythmia. while cardiotoxicity is an effects resulting of anticancer therapies, therapeutic options for its management remain limited. Aimée Obolari et al. studied the cardioprotective effect of hydroxypropyl-β-cyclodextrin (HβDL) and d-limonene (DL) during Dox treatment, by inducing cardiotoxicity in Swiss mice with 20 mg/kg Dox, and administering 10 mg/kg HβDL 30 min before Dox. The results suggest that HβDL provides cardioprotection against Dox-induced cardiac arrhythmias, which is thought to be due to its effects in inhibiting CaMKII overactivation [92].

Current study is looking into the use of medications like statins and cyclodextrin, which control fat metabolism and lower cholesterol, as possible treatments for neurological conditions like Alzheimer's disease and Niemann-Pick disease type C. fluvastatin belongs to a class of statins that are frequently used to prevent heart disease, Because it lowers cholesterol and other fat levels. Derivatives of β-cyclodextrin can also scavenge cholesterol by encouraging its efflux from cells to external receptors. This connection inspired M. Nicolosi and colleagues to create and describe new CD-fluvastatin conjugates by combining fluvastatin with β-cyclodextrin functionalizations 3 and 6 positions through an amide link. They investigated these novel compounds' cytotoxicity, stability, and cell-protective properties. They discovered that fluvastatin derivatives are well tolerated by cultured neurons and that fluvastatin-cyclodextrin conjugates are stable in animal brain and plasma homogenates, offering total protection against cell death brought on by Aβ oligomers. Overall, fluvastatin derivatives show potential as treatments in heart-related diseases [93]. (FAR) Farnesol is a sesquiterpene alcohol compound that has a range of biological effects, including antioxidant, cardioprotective, and antiarrhythmic effects. Due to its volatility, Eric Ayan et al. have proposed the use of drug delivery systems such as cyclodextrin to enhance its pharmacological properties. The aim of this study was to characterize and evaluate the effect of farnesol in combination with β-cyclodextrin on blood pressure reduction in rats. Mean blood pressure (MAP) and heart rate (HR) were measured in hypertensive rats before and after oral administration of FAR/βCD and farnesol alone. FAR/βCD produced better blood pressure-lowering results than farnesol alone, which may be relevant for improving current cardiovascular therapy using natural ingredients [84]. D-Limonene (D-LIM) is a monoterpene compound found mainly in the essential oils of citrus compounds, and its cardiovascular effects have been widely investigated. Although it has valuable pharmacological effects, its chemical properties prevent its clinical use. Yandra et al. developed and described a D-LIM inclusion compound with hydroxypropyl-β-cyclodextrin (HP-β-CD), and evaluated its cardiovascular effects for Bay K 8644-induced arrhythmia in an animal system. This compound showed significant efficacy in reducing arrhythmia. Regulated cardiac arrhythmia, reduced severity and duration, and prevented tachycardia compared to D-LIM alone [95].

2.3.6. Polyp lexes - Nucleic acid vectors.

Gene therapy has become a promising approach for treating or preventing hereditary and acquired diseases. Currently, viral and nonviral vectors are used in gene therapy as the main methods of gene transfer. Viral vectors are effective in gene transfer but suffer from several drawbacks, including inducing host inflammatory and immune responses. These issues can be overcome by using nonviral vectors such as cationic liposomes or polymers [96] . In particular, cationic polymers such as polyethylenimine (PEI), polyamidoamine (PAMAM) dendrimer, poly(lysine), chitosan, and cyclodextrin derivatives, where positive charges interact electrostatically with negative charges of siRNA to form polymeric nanoparticles [97]. The complexes are known as lipoplexes or polyplexes, and are a promising alternative to viral vectors in gene therapy [96]. On this approach, Chotima et al synthesized and analyzed a complex comprising cationic β-cyclodextrins with adamantane (Ad) conjugated to poly(vinyl alcohol) (PVA), and a poly(ethylene glycol) (PEG) copolymer as a carrier for siRNA demonstrated cytotoxicity assay. siRNA-loaded nanoparticles have results similar to those achieved using Lipofectamine® 2000. Therefore, cationic β-CD self-assembling with Ad-PVA-PEG bound to siRNA is a safe and effective siRNA delivery system [98]. Chemotherapy, a prevalent cancer treatment modality, offers limited benefits to HCC patients due to its inefficient delivery and intrinsic chemoresistance of the hepatoma. Bioinformatics analysis revealed the therapeutic potential of liver-specific microRNA (miR-122) in enhancing the

efficacy of chemotherapy for hepatic tumor. , Qingqing et al established a cyclic core-shell star nanoparticle (sCDP/DOX/miR-122) system to co-deliver miR-122 with doxorubicin (DOX) for the treatment of HCC. The nanosystem can selectively release miR-122, which increases sensitivity to chemotherapy and synergistically enhances cell growth inhibition effects. sCDP/DOX/miR-122 also showed clearly improved antitumor activity in in vitro and in vivo experiments compared with sCDP/DOX-3. The study presents an influential strategy for improving chemotherapy for liver tumors [99]. A study using multilayered gold nanoparticles (AuNPs) as non-viral gene carriers was reported by Bogdan et al, For the targeted delivery of nucleic acids to MCF-7 cancer cells, these vectors exhibit low cytotoxicity and high transfection efficiency. The nonviral vector is created using an adamantyl moiety of polyethylene glycol decapeptide, overlayers of polyethylenimine, and supramolecular "host-guest" inclusion complexes of β-cyclodextrin on the surface of AuNPs.The resultant tiny AuNPs include a cationic coating that is known to efficiently condense genetic material, and β-CD helps the targeting moieties bind by creating a "host–guest" inclusion complex. Because of the special affinity of nanoparticles with aptamer activity for breast cancer cells, in vitro tests validate the system's capacity to efficiently and selectively target cancer cells. The results indicate that this modular system could be a very promising platform for AuNP-based non-viral vectors [100]. It has been shown that combination therapy, which uses a nano-assembled structure to deliver genes and anti-cancer medications simultaneously, is an effective treatment for breast cancer. In order to treat cancer, Hanieh et al. developed redox-sensitive folate-appended-polyethylenimine-β-cyclodextrin (roFPC) host-guest supramolecular nanoparticles (HGSNPs) as a targeted co-delivery system for doxorubicin (Dox) and human telomerase reverse transcriptase-small interfering RNA (hTERT siRNA). The synthesis of the nanotherapeutic system involved the electrostatic self-assembly of hTERT siRNA with roFPC/Ad-Dox after adamantane-conjugated doxorubicin (Ad-Dox) was incorporated into roFPC via supramolecular assembly. The host-guest architectures of the roFPC allow for simultaneous, effective gene transfection and pH-dependent intracellular drug release in a regulated way. This co-delivery vector targets folate receptor-positive cells at low N/P ratios, causing effective cell apoptosis for cancer treatment. It also demonstrates excellent water solubility and biocompatibility, significantly improved hemocompatibility, and combined anti-tumor effects from Dox-enhanced gene transfection [101]. A novel FCT (folate and carboxymethyl-β-cyclodextrin grafted trimethyl chitosan) polymer was successfully created by Y. Zhang et al. using TMC as the core structure in a one-step non-polymerization reaction. Then, using the ionic gelation procedure, nanoparticles (FCT NPs) were created, and their potential as siRNA and doxorubicin co-carriers was assessed. As anticipated, the spherical-shaped FCT NPs had a suitable size distribution, good blood compatibility, and stability in serum. They had a steady surface potential of about +21 mv and a uniform particle size of about 200 nm. It is expected that FCT nanoparticles will respond to the acidic pH of drug concentration in tumor tissues and reduce side effects in healthy tissues. The co-nanocarrier demonstrated exceptional encapsulation capacities and optimal controlled release qualities of loaded drugs. The MTT test findings demonstrated that the drug-loaded FCT NPs considerably increased the anticancer drug's capacity to eradicate cancer cells [102].

2.3.7. Drugs Delivery

One possible method for treating intestinal disorders is the creation of novel oral phytochemical delivery techniques. These tactics, however, have a number of drawbacks, such as low bioavailability, inadequate biocompatibility, and restricted therapeutic efficacy. In a study by Tao Chen et al., resveratrol (Res) was encapsulated in cross-linked cyclodextrin metal-organic framework (CDF) to create Res-CDF. This Res-CDF was then added to natural polysaccharide hydrogel microspheres (Res-CDF in MPs) for targeted oral delivery to treat ulcerative colitis. (UC). Molecular dynamics simulations were used to demonstrate the fundamental adsorption process of Res by γ-CD. More significantly, the Res-CDF formulation in MPs preserves the bioactivity of Res while guarding against degradation by stomach acid. The development of novel oral therapies that use natural phytochemicals to treat intestinal illnesses is made possible by this creative oral delivery method, which increases the bioavailability of phytochemicals by utilizing the advantageous qualities of polysaccharide hydrogel and CDF [103]. Due to the clearance caused by nasal cilia and the nasal mucosal barrier, traditional nasal drug delivery techniques targeting the brain are limited. Shuiyao and others

created dissolvable micro-needles with nano-carriers to improve drug delivery from the nose to the brain to overcome this problem. A toothbrush-like micro-pattern has been created, with tiny hyaluronic acid and gelatin needles interwoven with tannic acid as a basis. The needles dissolve entirely in the nasal mucosa in a matter of seconds, leaving just the base behind. then releases the cyclodextrin-loaded metal-organic frameworks (CD-MOFs) without influencing the nasal microbial communities or cilia. These metal-organic structures, which are loaded with high concentrations of Huperzine A and augmented with lactoferrin and stigmasterol, are nanocarriers that have superior biocompatibility and material durability, enabling efficient drug transport to the brain. The damage caused by scopolamine and H2O2 to nerve cells has significantly reduced thanks to this system. By inhibiting acetylcholinesterase activity, reducing brain damage caused by oxidative stress, enhancing learning abilities, and stimulating brain-derived neurotrophic factor and the extracellular signal-regulated kinase pathway, Huperzine A also improved the effectiveness of treating memory impairment in mice induced by scopolamine, D-galactose, AlCl3 and The cyclic AMP response element is kinases. Regardless of everything, this innovative approach offers a new way to effectively deliver drugs to the brain and highlights the potential therapeutic use of Huperzine A in managing Alzheimer's disease [104]. γ-Cyclodextrin metal-organic frameworks (CD-MOFs) are biocompatible, ecologically benign materials that have a lot of promise for drug delivery. Compressed MOFs exhibit distinct aerosol properties, and accordingly, Yongpeng et al. developed these frameworks using a vapor diffusion method and a combination of modifiers to improve transpulmonary delivery of cyclosporine A (CsA). In contrast to oral administration of Neoral®, inhalation of CsA-loaded CDs considerably increases bioavailability, according to in vivo pharmacokinetic studies. The great biocompatibility of CD MOFs as a transpulmonary drug delivery system has also been validated by repeated inhalation toxicity tests. Therefore, the findings show that tiny CD-MOFs, a potential carrier, can be employed to deliver drugs to the lungs in an efficient manner [105]. In recent years, microneedles (MNs) have received increasing interest in drug formulation thanks to their non-invasive and convenient nature for patients. The technology of dissolving MNs emerges as a promising method to improve transdermal drug delivery painlessly, without producing sharp waste, and with the possibility of self-administration. Silvana et al reported the development and characterization of soluble MNs made from cyclodextrin for intradermal delivery of nanovaccines. Different types of cyclodextrin have been tried and promising MNs have been fabricated using micromolding technology. The efficiency of MNs in penetrating the skin and transporting the drug outside the body was examined. In addition, in vivo studies were performed to evaluate skin tolerance to cyclodextrin-based MNs. The results showed that MNs were well tolerated and effective. This opens new horizons for the potential of cyclodextrin-based soluble MNs as a versatile platform for intradermal vaccine delivery, providing a favorable environment for nanoparticle formulations to enhance the immune response [106]. Bose Allben Akash et al studied the hydrothermal synthesis of copper nanoparticles coated with β-cyclodextrin. More than 94% of the medicinal chemical substance 5-fluorouracil was successfully loaded onto nanoparticles. Drug release that was time-dependent and lasted longer than 12 hours was investigated. The drug-loaded and empty nanocarriers were used in in vitro cytotoxicity tests on MDA-MB-231 breast cancer cell lines. Cytotoxicity is shown to be dose dependent, and IC50 values were recorded for both empty and drug-loaded nanocarriers. The effects of both the empty and 5-fluorouracil-loaded nanocarriers on distinct stages of the cell cycle were further demonstrated by flow cytometry and cell cycle arrest studies. The results confirmed the validity of using copper nanoparticles coated with β-cyclodextrin-citrate as a nanocarrier for 5-fluorouracil [107].

2.3.8. Anticancer.

Many people agree that photodynamic therapy (PDT) is a novel way to treat cancer. PDT eliminates cancers that exhibit minimal resistance to medication therapy by converting oxygen into reactive oxygen species (ROS) through the activation of photosensitizers (PSs) by light radiation. The primary disadvantage of conventional PDT is the limited depth to which external light can penetrate tissues because it depends on activation by an external light source. Furthermore, PDT effects are inhibited by the tumor's hypoxia and the cells' reductive microenvironment. Wenbin et al. created a multifunctional photosensitizer by attaching nitric oxide donor S-nitroso-acetyl-penicilamine (SNAP), luminol, and chlorine e6 (Ce6) to β-cyclodextrin (β-CD-NH2) in

order to get over the significant drawbacks of traditional PDT. The findings demonstrated that endogenous hydrogen peroxide (H2O2), which initiates the energy conversion interaction between luminol and Ce6, can accomplish self-excited photodynamic treatment (PDT) without the use of external light sources. The photodynamic impact can only be strengthened inside cancer cells because of their high H2O2 and iron (Fe3+) content. This allows for the selective removal of cancer cells with minimal adverse consequences. In order to increase PDT's effectiveness, the generated nitric oxide (NO) is also anticipated to lessen tumor hypoxia and lower intracellular glutathione (GSH) levels. It is anticipated that self-excited PDT will increase the practical applications for treating deep-seated and metastatic cancers and overcome the challenges related to classical PDT [108]. Many studies have been conducted on ultrasound-guided therapy (SDT), a revolutionary non-surgical therapeutic option for breast cancer. However, the effectiveness of sonodynamic therapy during SDT is limited by the sonosensitizers' weak water solubility and imperfect biocompatibility. As a result, using the host-guest interaction of β-CD-TPP and FC-COS, Yongyan et al. created a nanoplatform to effectively enhance SDT against breast cancer. Furthermore, electrostatic adsorption was used to load glucose oxidase (GOx), which effectively limits the energy supply in tumor tissue to improve SDT's effectiveness. The findings demonstrated that porphyrin sensors used in photochemotherapy might have their water solubility and biocompatibility significantly increased by the proposed nanoplatform. As a result, there were little adverse effects in vivo and efficient tumor suppression. This study may improve the design and development of SDT methods by offering fresh perspectives on the application of natural oligosaccharides in the creation of multifunctional nanocarrier systems [109]. A new targeted carrier, M-Lactose@ZIF-8-β-CD, was created by Hassan et al. using magnetic lactose-modified ZIF-8 metal-organic frameworks (MOFs) cross-linked with β-cyclodextrin. for the pH-responsive and regulated release of anticancer medications, such as hydrophobic curcumin (CUR) and water-soluble doxorubicin (DOX), to treat MCF-7 breast cancer cells. M-Lactose@ZIF-8-β-CD was shown to have an encapsulation effectiveness of 65.01% for CUR and 95.16% for DOX. The effectiveness of the produced carrier under cancer-like conditions was confirmed by in vitro release tests that showed exact and pH-responsive release of each DOX and CUR from M-Lactose@ZIF-8-β-CD at pH 5. Because of the natural sugars they contain, the synthesized M-Lactose@ZIF-8-β-CD carriers have great antioxidant activity, high blood compatibility, and outstanding biocompatibility, according to in vitro cytotoxicity, hemolysis, and antioxidant investigations. M-Lactose@ZIF-8-β-CD can therefore be utilized as a successful carrier for targeted co-drug delivery in cancer treatment [110]. Combination therapy has shown promising potential in tumor therapy, with opportunities for development. A study by Hao et al. examines a unique approach to improving the therapeutic result of prostate cancer by combining ferroptosis, apoptosis induction, and DNA damage. created a supramolecular oxidative stress nanoamplifier using poly(ethylene glycol) ferrocene, paclitaxel, and β-cyclodextrin. Paclitaxel caused apoptosis and G2/M phase arrest via altering the system's microtubule dynamics. Simultaneously, ferrocene increased the number of reactive oxygen species, reduced glutathione levels, lipid peroxidation, and iron chelation by using hydrogen peroxide to create harmful hydroxyl radicals in cells through the Fenton reaction. DNA damage in cancer cells was exacerbated as a result of the elevated hydroxyl radical count and THZ531's suppression of DNA repair processes. The results revealed the outstanding efficacy of the supramolecular nanoparticles in delivering the drug to cancer cells or tissues, while demonstrating good in vivo biological safety and enhanced lethal effect on prostate cancer [111]. Because of its strong bioactivity, star anise essential oil (SAEO) has garnered a lot of attention. However, its application in the food and pharmaceutical industries is restricted by issues including instability and poor water solubility. In order to overcome these obstacles and improve bioavailability, Qiang et al. encapsulated SAEO in β-cyclodextrin (β-CD) using a saturated aqueous solution technique. According to in vitro research, SAEO-IC remains stable in the stomach while the active components are expelled in the intestine. SAEO-IC is a promising contender as a natural antimicrobial and anticancer agent because the encapsulating technique also improved SAEO's antimicrobial and antitumor activity while maintaining its antioxidant qualities [112]. The field of cancer therapy has shown a great deal of interest in stimuli-responsive nanomaterials, particularly those with targeting capabilities. However, there is still uncertainty regarding these innovative materials'

biological safety in vivo, which makes their clinical application difficult. Shouhui et al. have developed a dual-responsive and pH- and H2O2-targeted nanocarrier system. Using MSN@Fe3O4 as the core structure, scutellarin (SCU) as the anticancer therapeutic, and polymeric cyclodextrin (PCD) as the molecular switch, the composite is referred to as PCD@SCU@MSN@Fe3O4, abbreviated as NCS. In vitro results under pH and H2O2 conditions indicated that the drug-carrying nanosystem (NCS) exhibited excellent performance in pH and H2O2-responsive release drug SCU . Due to its dual reactivity to pH and H2O2, the system also demonstrated great cytotoxicity against cancer cells (Huh7 and HCT116) with no discernible adverse effects. In addition to improving SCU's bioavailability, NCS uses magnetic targeting technology to deliver SCU precisely to tumor locations, indicating its exciting potential for clinical use [113]. Supramolecular nanomedicines have attracted wide interest in the field of cancer therapy, however, potential immunotoxicity limits their use in clinical applications. In this regard, Jin et al. used a chemical click approach between the host (CD-N3) and the guest (Annexin-ATS) to successfully build a supramolecular nanomedicine system (CD-ATS). According to the study, supramolecular nanomedicine system is 30 times more soluble in water than free ATS. Furthermore, when CD-ATS was tested against HCT116 cancer cells, it demonstrated better antitumor activity than the common medication Taxol. The increased production of reactive oxygen species (ROS), which eventually causes apoptosis, is thought to be the cause of this amplified impact [104].

3. Cyclodextrin-based 1,2,3,-triazole compounds via click chemistry.

1,2,3-Triazole is an unsaturated, aromatic, five-membered ring containing three nitrogen atoms and two carbon atoms with two double bonds. Among the three nitrogen atoms, one is of the pyrrole type, and the other two are of the pyridine type. The interest of the unique structural features of the 1,2,3-triazoles nucleus concerning the nature of nitrogen atom ring structure and size and arrangement of the nitrogen atoms makes the classification the 1,2,3-triazole nucleus of interest. Accordingly they are primarily categorized into three types: (1) monocyclic 1,2,3-triazoles, (2) benzotriazoles, and (3) 1,2,3-triazolium salts. Based on the location of the NH proton, monocyclic 1,2,3-triazoles are further classified into three subclasses. The 1H- and 2H-1,2,3-triazoles exist in equilibrium both in solution and in the gas phase and are aromatic, whereas the 4H-1,2,3-triazole is non-aromatic [115]. **(Figure. 10).**

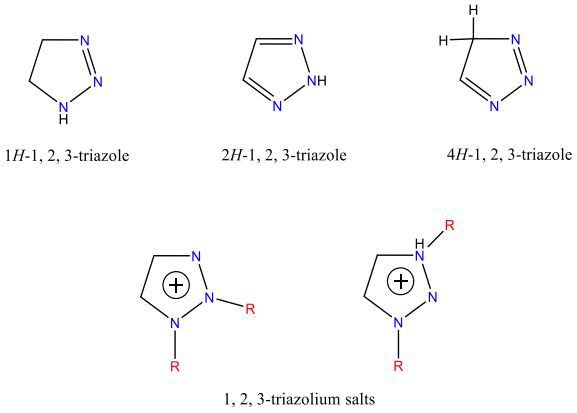


Figure 10. Subclasses of monocyclic 1,2,3-triazole compounds based on the position of the NH proton.

1,2,3-Triazoles have wide applications in organic synthesis, drug discovery, chemical biology, polymer chemistry, supramolecular chemistry, bioconjugation, fluorescence imaging, and materials science [116-119]. 1,2,3-Triazoles are essential components of many medical drugs available in the market, such as the anticonvulsant drug rufinamide [120], the anticancer drug carboxyamidotriazole [121], and the antibiotic drug tazobactam, [122] among others. The synthesis of this group of readily available chemicals is desirable. One of the easiest methods to prepare 1,2,3-triazoles is the 1,3-dipolar cycloaddition reaction between azide and alkyne. Also known as click chemistry, it is a revolutionary concept in organic chemistry, first developed in 2001 by Sharpless and his colleagues. This technique involves linking small molecules together to form more complex structures in a manner that mimics biochemical reactions in nature. What makes click chemistry so special is its speed and efficiency, with reactions occurring quickly and with high yields. In 2022, Sharpless and his colleagues were honored with the Nobel Prize in Chemistry for their outstanding contributions to the development of click chemistry, which has revolutionized the way organic and biological molecules are synthesized [123, 124]. **(Figure. 11 and Scheme. 5).**

3.1 Applications

Triazoles have a unique ring structure and the ability to interact with a variety of molecules, making them ideal for applications such as drug design and medical diagnostics, which gives them great biological importance. On the other hand, cyclodextrins are known for their ability to form molecular hosts with cavities capable of accommodating small molecules,

which contributes to enhancing the solubility and biostability of guest compounds

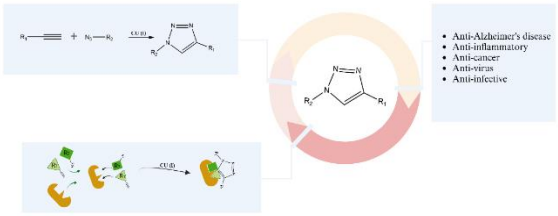
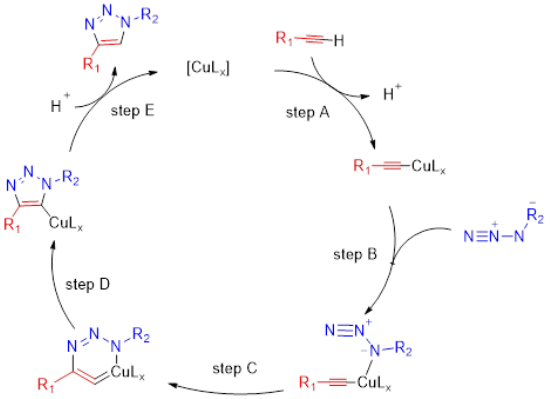
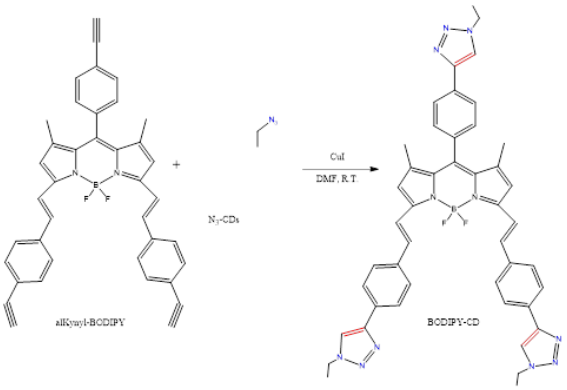


Figure 11. Click interaction of 1,2,3-triazole.



Scheme 5. Schematic Cu(I)-Catalysed Azide-Alkyne Cycliaddition Mechanism.

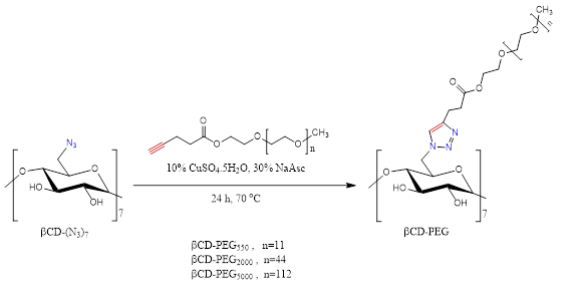
By incorporating these compounds, improvements in drug transport and controlled release can be achieved, in addition to the development of precise and targeted delivery systems. This type of synthesis opens up new avenues in scientific research and medical applications, contributing to the development of more efficient and safer therapies. Several recent studies have shed light on this approach. Bowei et al. created a straightforward and dependable method for photodynamic therapy (PDT), a promising cancer treatment approach that is controllable because of its high therapeutic selectivity and minimal adverse effects. The click reaction between alkynylated BODIPY and azide-modified cyclodextrin was used to create the water-soluble and biocompatible BODIPY-CD. When triazole and cyclodextrin units were added, the fluorescence wavelength was seen to redshift in comparison to alkynylated BODIPY. Furthermore, in the dark, none of the BODIPY-CDs were toxicity to HeLa cells or NIH 3T3 cancer cells. When applied to HeLa cells, BODIPY-β-CD demonstrated exceptional photodynamic treatment efficacy, reducing cell viability to 20% at a dosage of 100 µg/ml after laser irradiation. This study offers the potential for a logical combination of BODIPY and cyclodextrin for photodynamic therapy in the treatment of prostate cancer [125] **(Scheme. 6).**



Scheme 6. Synthesis route of BODIPY-CD complexes.

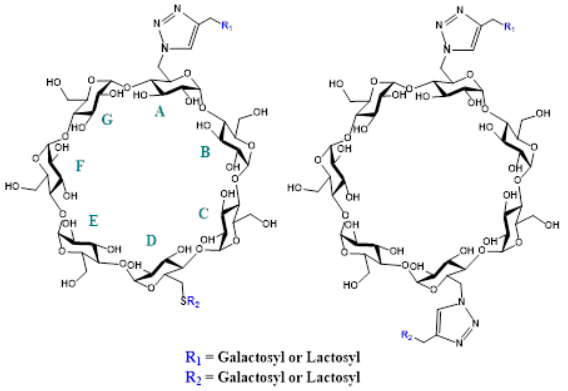
The main ingredient in licorice is Glycyrrhiza glabra, and several of its derivatives have a variety of antiviral properties. To enhance their properties, Shuobin and colleagues created 18 water-soluble β-cyclodextrin (CD)-GA compounds. Through a copper-catalyzed alkyl azide cycloaddition procedure, GA was covalently bonded to the β-CD backbone using a 1,2,3-triazole group and linker chains of different lengths. These compounds were less hydrophobic than the parent chemical GA because of the added β-CD group. These substances were examined utilizing a cytopathic effect assay against the A/WSN/33 (H1N1) virus. Six of these compounds exhibited encouraging antiviral activity, according to preliminary findings, and GA may be utilized as a basic component to create novel, promising anti-influenza drugs [126]. Using click chemistry, Yareli et al. created three star-shaped PEGylated β-cyclodextrin (βCD) derivatives (βCD-PEG5000, βCD-PEG2000, and βCD-PEG550, respectively) by affixing PEG chains of different molecular weights (5000, 2000, and 550 Da) to the principal face of βCD. The purpose of these βCD-PEG systems is to transport bioactive substances. Thus, the effect of chain length of βCD-PEGs on cell viability was investigated. Three cell types were selected for this purpose: human peripheral monocytes, which are progenitors to macrophages; HeLa cells, which are frequently used for preliminary viability assessment; and Vero cells, which have fibroblast-like properties. Among the derivatives, βCD-PEG550 significantly impacted the viability of HeLa cells and human monocytes. Despite the widespread use of PEGylation, their findings highlight the necessity for meticulous and systematic design of PEGylated materials to ensure their

efficacy in future drug delivery systems [1271-30] **(Scheme. 7).**



Scheme 7. General synthetical process for βCD-PEG systems.

Yili et al. successfully designed and synthesized the bifunctional β-cyclodextrin conjugates 6A and 6D galactosyl and lactosyl derivatives as potential HCC drug carriers via SN2 substitution and click reactions in order to enhance the drug's solubility and stability as well as its ability to target HCC. It is thought that the procedures outlined in the article offer a quick and effective way to create the drug's bifunctional complex 6A and 6D [131] **(Scheme. 8)**.



Scheme 8. Structures of triazole based CDs compounds

By imitating the natural receptors of the virus, multivalent N-acetylneuraminic acid (Neu5Ac) derivatives can prevent the virus from entering host cells. The antiviral properties of these unnatural Neu5Ac derivatives, however, have not been thoroughly explored. A study by Xingxing et al. presents a simple and dependable technique for using click chemistry to affix many artificial Neu5Ac molecules to the major face of the β-cyclodextrin (β-CD) core. In hACE2-overexpressing BHK-21 cells, they evaluated the antiviral activity of these conjugates and found that both monovalent and heptavalent artificial Neu5Ac conjugates exhibited variable antiviral effects against SARS-CoV-2 spike pseudovirus, with no discernible cytotoxicity (CC50 > 100 μM). With a half-maximal inhibitory dose of 24.78 μM, conjugate 9c showed the strongest inhibition. suggesting that multivalent unnatural Neu5Ac derivatives may be useful tools for blocking viral entrance [132-134]. Antibiotic resistance and biofilm formation pose significant public health challenges in treating infectious diseases. As an efficient antibacterial treatment, photodynamic therapy not only generates harmful reactive oxygen species (ROS) that kill bacteria but also triggers an immunological response, which lowers the risk of bacterial resistance. Through photodynamic immunotherapy and enhanced antibiotic penetration, Suwen et al. presented a porphyrin (TPP)/ciprofloxacin (CIP) based supramolecular photosensitizer nanoparticle (TPP-CIP NPs) system by click reaction , that can produce ROS, release antibiotics in a cascade, and stimulate an immune response for antibacterial action, biofilm dispersion, and wound healing. In order to eradicate antibiotic-sensitive bacteria that have been weakened by ROS damage to their exterior structures, light irradiation stimulates the porphyrins to create ROS and cleave thioketal linkers, releasing ciprofloxacin. In addition, the ROS trigger strong immunological responses, such as T cells and dendritic cells. According to in vitro research, these nanoparticles efficiently break up biofilms and fight off both Gram-positive and Gram-negative bacteria. TPP-CIP NPs have been shown in in vivo tests to be an effective treatment for methicillin-resistant Staphylococcus aureus infections and to stimulate wound healing. A promising combination strategy to combat bacterial infections resistant to multiple drugs is presented in this study [135].

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