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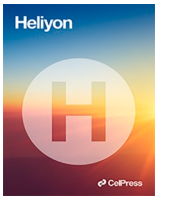

Review article

Advancements in cyclodextrin-based controlled drug delivery: Insights into pharmacokinetic and pharmacodynamic profiles

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ABSTRACT

This article discusses and summarizes some fascinating outcomes and applications of cyclodextrins (CDs) and their derivatives in drug delivery. These applications include the administration of protein, peptide medications, and gene delivery. Several innovative drug delivery systems, including NPs, microspheres, microcapsules, and liposomes, are designed with the help of CD, which is highlighted in this article. The use of these compounds as excipients in medicine formulation is reviewed, in addition to their well-known effects on drug solubility and dissolution, as well as their bioavailability, safety, and stability. Furthermore, the article focuses on many factors that influence the development of inclusion complexes, as having this information is necessary to manage these diverse materials effectively. An overview of the commercial availability, regulatory status, and patent status of CDs for pharmaceutical formulation is also presented. Due to the fact that CDs can discover new uses in drug delivery consistently, it is predicted that they will solve a wide range of issues related to the distribution of a variety of unique medications through various delivery channels.

1. Introduction

Cyclodextrins (CDs), which have hydrophilic exterior surfaces and lipophilic inner cavities, can form noncovalent inclusion complexes with various guest molecules (Fig. 1). There are at least six D-(+) glucopyranosyl units joined by α-(1, 4) glycosidic connections in CDs, and they are categorized as cyclic oligosaccharides from a chemical perspective. The CDs, their derivatives, and their acronyms are presented in Table 1. Each of the three natural CDs, namely α-, β-, and γ-CDs, which contain 6, 7, or 8 glucose units respectively, exhibits distinct differences in their ring size and solubility, as seen in Table 2. There is a restriction on the formation of CDs with fewer than six glucose units because of the steric hindrance. Furthermore, higher homologs that contain nine or more glucose units are highly challenging to purify. A comparatively significant quantity of δ-CD (Cyclomaltonose) with 9 glucose units was produced by Endo et al. [1]. This approach isolates and purifies different types of big ring CDs [2–4].

The α-CD is inadequate for many medications because of its small cavity size and relatively expensive. Generally, the ability of δ-CD to form complexes is lower than that of conventional CDs. For drugs like digitoxin and spiranolactone, δ-CD had a stronger solubilizing effect than α-CD. On the other hand, δ-CD has a lower effect compared to both α- and β-CDs. As a result of its availability and cavity size that is ideally suited for the widest possible variety of pharmaceuticals, β-CD has been extensively utilized in the first stages of pharmaceutical applications. Nevertheless, the low water solubility and nephrotoxicity of β-CD limits its use, particularly in parenteral

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drug administration processes [5].

Chemically modified CD derivatives have enabled the expansion of the progenitor CD's physicochemical properties and inclusion potential. Chemical changes to CDs have led to synthesizing several amorphous, noncrystallizable CD derivatives with greater physical and microbiological durability, lower parenteral toxicity, and better water solubility [6,7]. A very negative log $P_{o/w}$ value, the logarithmic value of the octanol/water partition coefficient is the consequence of CDs' hydrophilic outer surface and their abundance of hydrogen bond donors and acceptors. Acid hydrolysis of CDs in water at low pH opens their rings, producing glucose units and multiple linear oligosaccharides. Nevertheless, they maintain their stability when exposed to an acidic environment.

Deprotonation of CDs begins at a pH of about 12 due to the hydroxyl groups connected to the edge of the structure. Their core hollow size and water solubility are the main differentiating factors among the three natural CDs. While β-CD's solubility is the lowest, its cavity size is suitable for building complexes with a wide range of medications [9,10]. Molecular inflexibility and the impact of intermolecular hydrogen bonding in the crystalline form are the probable causes of the low solubility of CD (Antlsperger & Schmid, 1996; G., 1992).A complete secondary belt is formed when hydrogen bonds are established between the neighboring C2-OH and C3-OH groups in the β-CD molecule. This results in a rigid structure and reduces the ability of the β-CD molecule to form intermolecular hydrogen bonds with water molecules in its immediate vicinity [11]. Molecular dynamic simulations have shown that the β-CD molecule has a high-water density and a strong ordering of water molecules [10,12,13]. This indicates that the water molecules around the dissolved β-CD molecules undergo an unfavorable shift in heat content and a reduction in disorder, which would explain why β-CD is not as good at dissolving in water as other CDs seen in nature. In contrast, γ-CD has a non-coplanar structure, and α-CD has an imperfect arrangement of hydrogen bonds. Consequently, both α-CDs and γ-CDs are more soluble in water.

2. Absorption, distribution, metabolism, excretion toxicity (ADMET) analysis of CDs

β-amylases, which break down starch at the nonreducing end of a carbohydrate chain, can resist CDs. However, α-amylases, which break down starch from inside the chain, gradually hydrolyze it. Various physiological fluids, such as tear fluid, saliva, and bile, include human α-amylase, which easily facilitates the hydrolysis of linear dextrins. However, the cyclic structure and substituents of CD molecules prevent the enzyme from catalyzing their hydrolysis. The only type of CD highly susceptible to hydrolysis by α-amylase is unsubstituted γ-CD [13–16]. When an inclusion complex forms, it hinders the hydrolysis of CDs by α-amylase and considerably slows down the hydrolysis of substituted γ-CDs. Bacterial digestion occurs in the gastrointestinal tract's lower parts for CDs that cannot be broken down by human α-amylase [10]. γ-CD is totally broken down by the gastrointestinal tract when supplied orally. Microorganisms in the colon are responsible for digesting CD derivatives, such as γ-CD and β-CD. α-CD is absorbed at a slower rate than β-CD. After being delivered intravenously, glomerular filtration accounts for approximately 90 % of the CDs' subsequent unchanged removal in urine. The remaining quantity is removed by other excretion mechanisms, such as biliary excretion and hepatic metabolism [17,18].

Human studies indicates that sugammadex, HP-β-CD, and SBE-β-CD are primarily eliminated by the glomerular filtration system at unchanged dosages [20–22]. Table 3 shows that sugammadex, HP-CD, and SBE-CD have very comparable pharmacokinetic characteristics. The elimination phase (t½) is scheduled to last between 1.6 and 1.9 h. According to pharmacokinetic studies, the bulk of CD

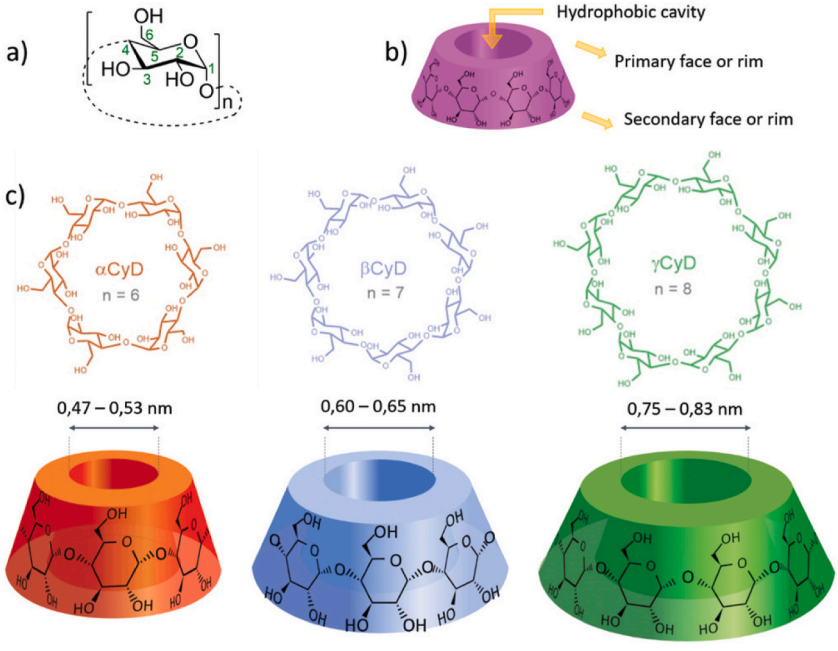

Fig. 1. a) The glucose unit, b) the toroidal shape, and c) the chemical structure of all three CD molecules [8].

(more than 90 %) is eliminated from the body after 6 h of parenteral administration and more than 99.9 % within 24 h. Thus, CD accumulation will not be noticed in patients with normal renal function, even at high doses [21]. The converse is true for those with severe renal impairment, who will display indications of CD accumulation if their renal creatinine clearance (ClCr) is less than 10 ml/min. Oligosaccharides, monosaccharides, and gases such as hydrogen, carbon dioxide, and methane are produced during metabolism in the gastrointestinal tract, which is mostly carried out by bacteria [23]. CD does not accumulate in those with normal excretion levels but can accumulate in individuals with kidney disease. HPCD's oral bioavailability varies from 0.5 to 3.3 %, with the majority of the remaining dose being digested by bacteria in the colon and 50–65 % being removed intact in the feces [16]. Almost all water-soluble, very hydrophilic CDs and CD compounds have similar pharmacokinetic properties [16]. The only notable differences are CD's small intestine digestion efficiency and the slightly higher oral bioavailability (up to 12 %) of RMCD. The longer $t_{1/2}$ of RMCD up to 7 h is a result of its higher affinity.

The safety and toxicity of CDs used in medicinal products have been investigated in details in several studies [9,24–27]. CDs are hydrophilic oligosaccharides with a low octanol-water partition coefficient and many hydrogen bond donors and acceptors. Molecules with these properties cannot passively diffuse through membranes in living beings [28–31]. There is limited evidence that CDs can penetrate biological membranes via transporter-mediated permeation, and the oral bioavailability of CDs is exceedingly poor. In rats, RM-β-CD has an oral bioavailability of roughly 12 % (log $K_{o/w}$ approximately 6) [32]. α-CD, β-CD, and γ-CD, aLoftsson effect of nd their hydrophilic derivatives, are minimally hazardous when given orally due to their low bioavailability [28,33,34].

3. The role of CDs in pharmaceutical formulation

3.1. The effect of CDs on drugs' solubility

CDs have been instrumental in the development of drugs that are poorly soluble in water. They accomplish this by increasing the drugs' apparent dissolution and/or dissolution via inclusion association or solid dispersion, acting as hydrophilic recipients for drugs lacking the necessary molecular properties for complexation, or improving the tablet dissolution of high-dose drugs such paracetamol, which makes using a drug/CD complex difficult [24]. Within the range of 0–100,000, the apparent stability constant, K in M^{-1}, may be found for complexes involving numerous drugs and CDs. Table 4 summarizes eight different uses of CD as a solubilizing agent. The most efficient solubilizers amongst commercially available CDs are methylated CDs with a relatively low molar substitution. Another factor contributing to the drug's higher apparent solubility and dissolving rate is the decrease of drug crystallization during association or solid distribution with CDs. Drug solubility can be improved without solid-state complexation using CDs to create in situ inclusion complexes in the dissolving media [30].

The SBE-β-CD is an excellent solubilizer for various pharmaceuticals, surpassing the performance of β-CD but falling short of the capabilities of DM-β-CD solubilizer. There are 93 CDs that can operate as release facilitators. For example, β-CD has been shown to improve the rate of dispensing weakly soluble naproxen and ketoprofen from neutral acrylic polymers and hydrophilic swellable (high-viscosity hydroxy propyl methyl cellulose [HPMC]) tableted matrices. By increasing the medication's purported permeability and rate of dissolution, β-CD contributed to the enhancement of the dissolution of theophylline from the HPMC matrix [82] One of the most essential characteristics of medication absorption is its water solubility, which has the potential to boost the drug's bioavailability when administered orally. It is possible to optimize the bioavailability of drugs classified as BCS Class II or IV by increasing their dissolution and solubility rates. CD complexes can solubilize therapeutic compounds by generating noncovalent complexes in solution by forming chemical complexes.

3.2. Role of CDs on inflammation

Inflammation can be regulated directly by CDs' ability to bind to complex molecules (Fig. 2), as seen in neurological illnesses and NPCs [49,51]. Atherosclerosis is one example of cholesterol (chol) buildup in the arteries triggering macrophage recruitment and an inflammatory response [51].

HP-β-CD effectively treats atherosclerosis by reprogramming macrophages through the Liver X Receptor (LXR) signaling pathway [53] and increasing chol efflux [52]. Specifically, overexpression of ATP-Binding Cassette Transporter A1 (ABCA1) and ATP-Binding Cassette Transporter G1 (ABCG1) contributed to the increase of chol efflux, further supported by a recent study indicating that this CD

Table 1
Physicochemical properties of major CD.

CD	α	β	γ
Glucopyranose units	6	7	8
Formulae	$C_{36}H_{60}O_{30}$	$C_{42}H_{70}O_{35}$	$C_{48}H_{80}O_{40}$
Molecular weight (g/mol)	972.9	1135.0	1297.1
Central cavity diameter: external/internal (Å)	5.3/4.7	6.5/6.0	8.3/7.5
Height of torus (Å)	7.9	7.9	7.9
Approximate volume of cavity (Å)	174	262	427
Water solubility at 25 °C (g/L)	145	18.5	232
Number of water molecules within cavity	6–8	11–12	13–17
pKa	12.3	12.2	12.1

Table 2
The cavity size and some essential physicochemical properties of natural CDs and some of their derivatives [7].

Types	Substituent	Inner Cavity Diameter (Å)	Hydrogen Donors	Hydrogen Acceptors	Solubility (mg/mL, 25 °C)	Log $P_{o/w}$	Surface Tension (mN/m)
Natural CDs							
α-CD	H	4.7–5.3	18	30	145	−13	71
β-CD	H	6.0–6.5	21	35	18.5	−14	71
γ-CD	H	7.5–8.3	24	40	232	−17	71
Modified CDs							
HP-α-CD	$-CH_2-CHOH-CH_3$	4.5–5.3	18	36	–	–	–
CM-β-CD	$-CH_2-CO_2H$	–	21	49	50	−4.9	–
DM-β-CD	$-CH_3$	5.8–6.5	7	35	570	–	62
RM-β-CD	$-CH_3$	–	9	35	>500	−6	57.5–54.1
TM-β-CD	$-CH_3$	4–7	0	35	310	–	56
HE-β-CD	$-CH_2-CH_2OH$	–	21	42	>2000	–	–
HP-β-CD	$-CH_2-CHOH-CH_3$	6.0	25	39	>1200	−11	54.8–57.5
SBE-β-CD	$(CH_2)_4-SO_3Na$	–	21	35	>1200	<−10	71
HP-γ-CD	$-CH_2-CHOH-CH_3$	8.0	24	45	800	−13	–
SBE-γ-CD	$(CH_2)_4-SO_3Na$	–	–	–	–	–	–
SUG	$-SCH_2CH_2CO_2Na$	7.5–8.3	24	48	Very soluble	−16	72.2
Branched CDs							
G_1-β-CD	glucosyl	6.0–6.5	24	40	970	−9	71
G_2-β-CD	maltosyl	–	27	45	>1500	−9	72
GUG-β-CD	glucoronylglucosyl	–	–	–	>2000	–	73

Table 3
Physiochemical and biological characteristics of CDs present in commercially available pharmaceuticals [19].

Types of CDs	Molar degree of substitution MS[a]	Mol. Wt. (g/mol)[b]	log $P_{oct/water}$[c]	S_{water} (mg/ml)[d]	F_{oral}[e]	t½ (h) f	$f_{unchanged\ with\ urine}$g
α-CD	Not any	972.8	−13	130	0.02	Not any	Not any
β-CD	Not any	1135	−14	18.5	0.006	Not any	Not any
HPβCD	0.65	1400	−11	More than 600	0.03	1.9	0.95
SBE-β-CD sodium salt	0.9	2163	Less than −10	More than 500	0.02	1.6	0.95
Randomly methylated β-CD (RM-β-CD)	1.8	1312	−6	More than 600	0.1	Not any	Not any
γ-CD	Not any	1297	−17	249	<0.001	Not any	Not any
HP-γ-CD	0.6	1576	−13	More than 500	<0.001	Not any	Not any
Sugammadex sodium salt	1.0	2178	−16	Highly water soluble	Unavailable	1.7	1.0

[a] log $P_{oct/water}$ = the logarithm of the calculated octanol/water partition coefficient.
[b] S_{water} = CD solubility in water at 25 °C.
[c] F_{oral} = fraction of the CD dose that is absorbed intact after oral administration to rats.
[d] $t_{½}$ = the terminal half-life of CD after parenteral administration to humans.
[e] Fraction of CD excreted unchanged with the urine after parenteral administration to humans.

Table 4
Drugs solubility and dissolution enhanced by CD.

Types of CD	Drugs	Ref.
β-CD	Glimepiride, Isradipine, Praziquantel, Nimesulide, Griseofulvin, Chlorthalidon, Exodolac, Piroxicam, Itraconazole, Ibuprofen, Eslicarbazepine acetate, Polylactic acid, Catechin, α-tocopherol, Nootkatone	[35–56]
α-CD	Praziquantel, 13-cis-retinoic acid, and prostaglandin E1 respectively	[57–59]
γ-CD	Digoxin, Praziquantel, and Omeprazole	[60–62]
DM-β-CD	Naproxen, Camptothesin	[63,64]
SBE-β-CD	Fluasterone, Spiranolactone, Danazol, Nateglinide, and DY-9760e	[65–69]
RM-β-CD	ETH-615, Tacrolimus	[70,71]
HP-β-CD	Nootkatone, Glimepiride, Astaxanthin, Phenytoin, and Rutin, Levemopamil HCl, Sulfomethiazole, Albendazole, DY-9760e, Itraconazole, Carbamazepine, Griseofulvin, ETH-615, Ketoprofen, Zolpidem are some of the medications that are currently being used	[66,70, 72–80]
Randomly acetylated amorphous-β-CD	Naproxen	[81]

reduced plasma levels of inflammatory cytokines and triglycerides while increasing plasma HDL chol. HP-β-CD interacts with chol crystals, reducing IgG accumulation and inducing complement activation, as measured by endpoint activation. Furthermore, it has been shown to suppress the expression of specific receptors on monocytes [54]. Injection of HP-β-CD reduced inflammation-promoting cytokines such as IL-1α, TNF, and IL-6. An alternative deposition, such as monosodium urate crystal, was utilized to test this effect, but it was ineffective. This discovery indicates that this activity is limited to chol crystals [55,56]. observed that HP-β-CD can inhibit chol crystal-induced complement-mediated inflammation.

3.3. Role of CD complexation in enhancing drug stability

Pharmaceutical stability is a fundamental quality requirement. In addition to influencing pharmaceutical effectiveness and safety, it also serves as the foundation for choices in manufacturing methods, formulations, packaging materials, and storage and transit circumstances [83]The term "pharmaceutical product stability" refers to the capacity of pharmaceuticals to keep their originality, efficacy, and purity throughout time [84]. Pharmaceutical compounds having flexible groups in their molecular structure may be chemically broken down in certain conditions. A drug may degrade by a number of mechanisms, the most frequent of which are hydrolysis, dehydration, isomerization, racemization, oxidation, and photodegradation. It might deteriorate physically rather than chemically, resulting in a range of changes to the medication's physical properties (Table 5).

Physical instability may arise during phase transition [85]. Many active pharmaceutical ingredients (API) that are effective in therapeutic applications may have severe restrictions in clinical usage due to poor chemical or physical stability properties. Within the context of this unique setting, the use of pharmacological science to medical stability is both intriguing and challenging. Complex building between medicines and excipients is often used to alter medication stability. Complexation is the process by which molecules from a substrate reversibly attach to a receptor, resulting in the formation of a complex with specified stoichiometry and physical-chemical characteristics that may change significantly from the substances that were originally there. CD complexation

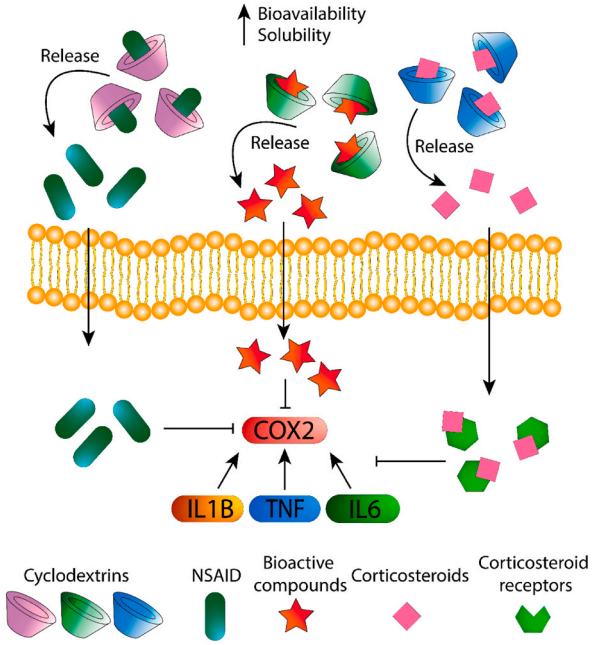

Fig. 2. A schematic illustration of the complexes formed between CD/corticosteroids and some CD/bioactive chemicals to combat inflammation. The specific pathway may vary depending on the molecule involved [51].

involves the molecular encapsulation of labile pharmacological molecules. This is achieved by developing a molecular barrier that protects the molecules from many degradation processes. SBE-β-CD significantly increased the stability of chemically unstable drugs compared to other CDs [85].

4. CDs- natural product inclusion complex

CD has medical and scientific uses involving bioactive substances originating from natural sources, such as polyphenols, alkaloids, terpenoids, flavonoids, and essential oils. The succeeding study focuses mostly on how complexation with CDs improves the in vitro activities of bioactive compounds with strong pharmacological features, such as anticancer, anti-inflammatory, and neuroprotective activity. Ursolic acid, a triterpenoid found in therapeutic plants as well as the human diet, is one example. Compared to the pure molecule, ursolic acid's antiproliferative action on melanoma cell lines was greatly increased in vitro by complexation with HP-β-CD [127]. Furthermore, inclusion complexes were effective in improving the anticancer activities of two other terpenoids, namely saikosaponin-d and betulinic acid. HP-β-CD improved saikosaponin-d's solubility and anticancer activity against human skin squamous cell carcinoma in a cell line [16,128]. Betulinic acid microencapsulation in β-CD reduced the growth of human breast cancer cells [129]. Fucoxanthin, a marine-derived carotenoid, has been shown to have anticancer effects in vitro employing human colorectal carcinoma cells and HP-β-CD [130]. The anticancer activities of camptothecin and its natural counterpart, luotonin A, alkaloids produced from Camptotheca acuminata, are being studied scientifically. Combining β-CD and HP-β-CD improved the stability of these two alkaloids. Furthermore, the anticancer activity of camptothecin and luotonin A against a variety of cancer cell lines was increased by the latter inclusion complexes when compared to their free forms [131]. Another study used the well-known flavonoid dihydroquercetin (taxifolin) to build a combination with β-CD. This compound demonstrated enhanced in vitro antioxidant and anticancer activity against a hepatocellular carcinoma [131]. Similarly, β-CD increased the cytotoxic action of the naphthoquinone mansonone G on lung cancer cells [201]. The compound's increased biological activity may be attributed to the complexation it forms with CDs. Bioactive chemicals are protected against degradation by inclusion complex formation, extending their activity. Furthermore, their increased solubility makes them more easily absorbed by human cells (Table 6).

Curcumin, a well-known curcuminoid, has had its solubility increased via encapsulation in a variety of CD-based systems employed in cancer research. and, by implication, its anti-tumor effects. Curcumin's cytotoxic effects on osteosarcoma and breast cancer cell lines were improved when HPCD liposomes were added [135]. A different type of curcumin, coupled with chitosan microspheres and HPCD, improved the therapeutic index in a cell line derived from human colorectal cancer [142]. It is vital to recognize that studying the anticancer and antitumor effects of encapsulated natural bioactive chemicals on CDs and related systems is very challenging. The bulk of research report their results in vitro, casting doubt on the possible usefulness of these biological activities when used in vivo. However, the current results are optimistic regarding the ability of CD-based systems to enhance the anticancer activities of the bioactive chemicals being studied. As a result, greater study is needed in this area.

Table 5
Comparative evaluation of medicinal stability through complexation with various CDs.

Active Pharmaceutical Ingredients	CDs	Effect Observed	References
Clostridium difficile Toxoid A	α-CD	inhibits protein accumulation	[86]
V antigen	β-CD		
Fibroblast growth factor 10	HP-β-CD		
	SBE-β-CD		
	γ-CD		
Human growth hormone	α-CD,	inhibits protein accumulation	[87]
	HP-β-CD,		
	SBE-β-CD,		
	Sulfated -β-CD,		
	Monoglycosyl-β-CD,		
	Monomaltosyl-β-CD,		
	Monoacetyl-β-CD,		
	γ-CD		
IgG	β-CD,HP-β-CD	inhibits protein accumulation	[88]
Glucagon	γ-CD	Enhanced physical and chemical stability	[89]
Insulin glargine	SBE-β-CD	a decrease in the amount of degradation caused by enzymes at the injection location	[90]
Z-ligustilide	HP-β-CD	increase in photostability	[91]
Resveratrol	SBE-β-CD	degradation kinetics in biological matrices inhibited	[92]
	HP-β-CD	stability improved	[93]
	multicomponent: HP-β-CD and hyaluronic acid	increases stability dependent on the polysaccharide concentration	
Oxyresveratrol	HP-β-CD	elevated levels of thermal stability	[93]
Quercetin	α-CD, β-CD	improve photostability	[94]
	multicomponent: HP-β-CD and hyaluronic acid	improve stability depended on polysaccharide concentration	
	HP-β-CD	improve stability	[95]
Rutin	β-CD, HP-β-CD	Rutin	[96]
Ethanol extract of Cannabis sativa	DM-β-CD	elevated levels of thermal stability	[97]
UV filters (oxybenzone, octocrylene, and ethylhexyl-methoxycinnamate)	β-CD	inhibits protein accumulation	[98]
Phenylbenzimidazole sulfonic acid	HP-β-CD	Decrease hydrolysis and cyclization	[99]
Tretinoin	β-CD	decrease hydrolysis	[98]
Tetra-1,2-diethylamino substituted zinc (II) phthalocyanine	α-CD,	significantly increase stability after Gamma irradiation	[100]
	β-CD,		
	γ-CD		
Enalapril	β-CD	–	[101,102]
Hydrocortisone	HP-β-CD	–	[103]
	β-CD	–	[104]
		faster decomposition under alkaline conditions	[104]
Famotidine	HP-β-CD,	degradation reduced under acidic conditions	[105]
	CM-β-CD	improve physical stability	[106]
Lansoprazole	HP-β-CD	stabilization effects under light, heat, and humidity exposition	[107]
	β-CD		
Camptothecin	RDM-β-CD	decrease hydrolysis	[108]
Nintedanib	SBE-β-CD	stability in simulated intestinal fluid enhanced	[109]
Posaconazole	β-CD	deterioration via oxidation decrease	[110]
Nicardipine	βCD, HP-α-CD, 2-hydroxyethyl-β-CD	protective effect against light	[111]
	α-CD	degradation due to light	[112]
Doxycycline hyclate	β-CD	photoprotective effect	[112]
Oxytetracycline hydrochloride	β-CD	drop in the degradation rate	[113]
Doxorubicin	HP-β-CD	increase photostability	[114]
Furosemide	multicomponent: β-CD and triethanolamine	decrease chemical degradation	[115]
Ascorbic acid	HP-β-CD	pH-dependent stabilizing effect in solution	[116]
	multicomponent: HP-β-CD and triethanolamine	improve aqueous solubility is	[117]
	multicomponent: γ-CD and polyvinyl alcohol	reduce photodegradation	[118]
Dihydroartemisinin	multicomponent: HP-β-CD and soybean lecithin	improve stability in aqueous solutions	[119]
Benzylpenicillin	HP-β-CD,	decrease hydrolysis in acidic conditions	[120]
	RM-β-CD		[120]
	HP-β-CD	accelerate hydrolysis under neutral and basic conditions	[120]
	RM-β-CD	decrease catalytic activity in basic solution	[120]
	γ-CD	catalytic effect of hydrolysis	[120]

(*continued on next page*)

Table 5 (*continued*)

Active Pharmaceutical Ingredients	CDs	Effect Observed	References
	randomly methylated γ-CD,	reduce catalytic effect of hydrolysis	[121]
	octakis(2,3,6-triO-methyl)-γ-CD	Decrease degradation by no catalytic effect	[121]
	heptakis(2,3,6-tri-O-methyl) β-CD	reduce catalytic effect	[121]
β-lactam antibiotics	β-CD	destabilizing effect	[122]
Cefixime	β-CD	destabilizing effect	[123]
Rifampicin	γ-CD	destabilizing effect	[124]
	multicomponent: γ-CD and arginine	stabilizing effect	[124]
Norfloxacin	β-CD	increase photostability of form C	[125]
Omeprazole	β-CD, DM-β-CD, HP-β-CD, Ma-β-CD	accelerate hydrolysis	[126]

Table 6
CD-natural product inclusion complex.

CD Type	Bioactive Compound	Improved Characteristics	Biological Study	In Vitro/In Vivo Study	Reference
HP-β-CD	Ursolic acid	Stability	Antitumor activities	Melanoma cell lines (A375, B16 4A5 and SK-Mel 2)	[127]
HP-β-CD	Saikosaponin-d	Solubility	Antitumor activities	Squamous carcinoma cell line (HSC-1)	[16]
β-CD	Betulinic acid	–	Antitumor activities	Breast cancer cell line (MCF7)	[129]
HP-β-CD	Fucoxanthin	Solubility and stability	Antitumor activities	Colorectal carcinoma (CRC) cells (HCT116 and Caco-2)	[130]
β-CD	Dihydroquercetin	Solubility	Antioxidant and antitumor activities	Hepatocarcinoma cell line (HepG2)	[131]
β-CD	Mansonone G	Solubility	Antitumor activities	Lung cancer cells (A549)	[132]
β-CD: CDI 1:4	Oxyresveratrol	Dissolution	Antitumor activities	Prostate (PC-3), colon (HT-29 and HCT-116) cell lines	[133]
CD-NSs	Ferulic acid (FA)	Stability	Antitumor activities	Breast cancer cell lines (MCF7 and 4T1)	[134]
γ-CD liposomal NPs	Curcumin	Solubility	Antitumor activities	Osteosarcoma (KHOS) and breast cancer (MCF-7) cell lines	[135]
HP-β-CD	Thymoquinone	Solubility	Antiallergic effects	Rat basophilic leukemia cell line (RBL-2H3)	[136]
γ-CD	Green propolis supercritical extract (GPSE)	–	Anti-inflammatory activities	Female C57BL/6NRj wild-type mice (liver)	[137]
HP-β-CD	Silybin (silibinin)	Solubility	Restored the gut microbiota and intestinal integrity	Hamsters	[138]
β-CD	(−)-linalool	Solubility and stability	Gastroprotective effect	Mice	[139]
β-CD, γ-CD	Epigallocatechin gallate	Stability	Antiviral effect	Influenza virus and hCoV-229E	[140]
α-CD	Moringin (MOR)	–	Neuro protection	Neuroblastoma cells (SH-SY5Y) exposed to amyloid beta peptide	[141]

5. CDs mediated drug delivery

CDs are used in the pharmaceutical sector to improve the water solubility, stability, and bioavailability of poorly soluble pharmaceuticals in water and are prone to instability [140]. CDs can form hydrophilic inclusion complexes containing lipophilic active components. Drug molecules in aqueous solutions develop an inclusion complex with CD, creating a dynamic equilibrium between bound and free drug molecules. CDs boost the solubility of drugs in water while retaining their natural capacity to travel through lipid membranes [141]. Because of their tiny size and affinity for water, CDs and drug/CD complexes can only infiltrate hydrophobic bio membranes like intact skin in trace amounts. CDs promote drug transport across biomembranes by making the drug more accessible on the membrane's surface. When the drug molecules reach the surface, they detach from the CD pocket and penetrate the lipid-rich membrane [143]. As a result, a well-designed CD formulation will enhance the concentration gradient of the drug across the membrane, improving the pace at which the drug travels through it. Because of limited permeability across biomembranes, excessive CD in pharmaceutical formulations may reduce drug bioavailability. CDs are used in almost all drug delivery systems, the role of CDS in various major delivery methods is discussed in the following sections.

5.1. Oral drug delivery

CDs are used in oral drug delivery to increase drug solubility, reduce drug-induced discomfort and taste masking, and improve the rate and extent of dissolution and the drug's durability within the absorbing site, such as the gastrointestinal tract (GIT) or in the formulation. It was revealed that CDs complexation lowers local medication irritation and alters drug release timing during GI transit. CDs promote mucosal drug permeability largely by increasing free drug availability on the absorption site's surface [82,83]. Their complexation may improve and uniformly absorb low-soluble drugs with poor and unpredictable absorption [136] while also increasing the drug's activity when delivered orally. It also boosted albendazole's anthelmintic activity, resulting in a high plasma concentration of the active metabolite.

The FDA Biopharmaceutics classification system categorizes medications based on their ability to dissolve in water and their permeability to the gut mucosa. Hydrophilic CDs often lack the potential to increase the bioavailability of class I medicines. Nonetheless, their objective is to improve medication absorption while reducing localized drug discomfort. Because Class II medicines have low solubility, oral absorption is limited; hence, water solubility slows dissolution rate. Adding water-soluble CD complexes to these medications will improve transepithelial diffusion, enhancing oral bioavailability. Despite being water soluble, Class III medicines have difficulties entering biological membranes due to their big size and high hydration level. As a consequence, rather than increasing the bioavailability of hydrophilic pharmaceuticals in the mouth, the formation of CD complexes reduces the ability of dispersed drug molecules to disperse from the hydrophilic surface into the gastrointestinal system lining. This is because CD complexes form when hydrophilic medicines dissolve in water. Class IV medicines are water soluble and have limited ability to penetrate through lipophilic biological membranes. They are designated as drug class IV. However, hydrophilic compounds that are insoluble in water, such as

Table 7
CD mediated oral drug delivery.

Drugs	CDs	References
Acyclovir	β-CD	[143]
Albendazole	HP-β-CD	[144]
Amobarbital (amylobarbitone)	β-CD, γ-CD	[145]
Artemisinin	β-CD, γ-CD	[146]
Benzaldehyde semicarbazone	β-CD	[147]
4-Biphenylacetic acid	β-CD, DM-β-CD, TM-β-CD,	[148,149]
para-Boronophenylalanine	Glu-α-CD, Mal-α-CD, Dmal-α-CD Complex	[150]
Carbamazepine	DM-β-CD	[151,152]
Chloramphenicol palmitate	HP-β-CD	[153]
Cinnarizine	β-CD, SBE-β-CD, HP-β-CD	[154]
Clomipramine	HP-β-CD	[155]
Cyclosporin A	DM-β-CD	[79,156]
Diphenhydramine	DM-β-CD, HP-β-CD	[157]
Dipyridamole	β-CD	[158,159]
Entacapone	HP-β-CD	[160]
17- β- Estradiol	HP-β-CD	[161]
Fenbufen	α- CD, γ- CD	[41]
Fluoxetine HCl	γ-CD	[162]
Flutamide	HP-β-CD	[163]
Glibenclamide	β-CD, SBE-β-CD	[164]
Gliclazide	β-CD	[165]
Gliquidone	HP-β-CD	[166]
Indomethacin	E-α-CD, β-CD, HE-β-CD, HP-β-CD	[167,168]
Itraconazole	HP-β-CD	[20,169]
Ketoprofen	β-CD, HP-β-CD	[170]
Miconazole	HP-β-CD	[171]
Naproxen	β-CD	[81]
Nicardipine	HP-β-CD	[172]
Nifedipine	β-CD, HP-β-CD	[173,174]
Phenytoin	E-β-CD, Glu-β-CD, Mal-β-CD, SBE-β-CD, HP-β-CD	[44,175,176]
Piroxicam	β-CD	[177–179]
Renin inhibitors	β-CD	[179]
all-trans-Retinoic acid	HP-β-CD	[180]
Rofecoxib	β-CD	[181]
Rutin	HP-β-CD, β-CD	[182]
Silibinin	β -CD	[183]
Spironolactone	β-CD, γ-CD, DM-β-CD, SB–-β-CD, HP-β-CD	[69,184]
Tacrolimus	DM-β-CD, SBE-β-CD, HP-β-CD	[71]
Testosterone	HP-β-CD	[185]
Tiaprofenic acid	DE-β-CD	[186]
Tolbutamide	β-CD, HP-β-CD	[187]
α-Tocopheryl nicotinate	DM-β-CD	[188]
Ursodeoxycholic acid	HP-β-CD	[189–191]
Zidovudine	HP-β-CD, DM-β-CD	[192,193]

zwitter ions, do not readily form CD complexes. As a consequence, these drugs' oral bioavailability does not rise. CDs, on the other hand, can increase the water solubility of certain large lipophilic compounds. This, in turn, increases medication availability at the mucosal surface, resulting in greater oral bioavailability. Table 7 shows CD formulations for oral, sublingual, and buccal usage, along with clinical and bioavailability studies [143–193].

α-CD = α-CD; β-CD = β-CD; γ-CD = γ-CD; DE-β-CD = heptakis(2,6-di-O-ethyl)-β-CD; dMal-α-CD = dimaltosyl-α-CD; DM-β-CD = dimethyl-β-CD; E-α-CD = α-CD epichlorohydrin polymer; E-β-CD = β-CD epichlorohydrin polymer; Glu-α-CD = glucosyl-α-CD; Glu-β-CD = glucosyl-β-CD; HE-β-CD = hydroxyethyl-β-CD; HP-β-CD = 2-hydroxypropyl-β- CD; Mal-α-CD = maltosyl-α-CD; Mal-β-CD = maltosyl-β-CD; SBE-β-CD = sulfobutylether-β-CD sodium salt; TM-β-CD = trimethyl-β-CD.

However, there is a lack of evidence on the oral safety of methylated CDs, despite the fact that HP-β-CDs are superior to β-CD and other parent CDs. Oral delivery is virtually safe because the gastrointestinal system does not absorb CDs. As a consequence, CDs' slightly favorable safety properties provide a challenge for drug dosages used in drug/CD complexes, as well as the LD50 of CD. The most cost-effective CD molecule is β-CD, whereas HP-β-CD and SBE-β-CD are more expensive. The β-CD monograph has already been included in many pharmacopoeias and national formularies (NF). β-CD is most effective for drug complexation when taken orally. Modified CDs such as HP-β, SBE-β-CD, and DM-β-CDs are used when their specific features are required in the formulation. SBE-β-CD was used to produce osmotic pump tablets due to its osmotic properties [90,91]. CD derivatives, such amorphous HP-β-CD and SBE-β-CDs, have been extensively studied for parenteral delivery. This is because of their significant water solubility and low toxicity. HP-β-CD's excellent water solubility allows for safe parenteral delivery of various medicines. Consequently, it is used more often in formulations for parenteral delivery. A parenteral injectable has been commercially available in both the United States and Europe. This injection comprises itraconazole and HP-β-CD at a 40 % concentration by weight per volume [93].

5.2. Ocular drug delivery

After administering eye drops to the eyes, the liquid solutions and suspensions will mix with the natural tear fluid and distribute uniformly throughout the surface of the eye (Fig. 3). Nonetheless, certain elements positioned in front of the cornea will limit medicine

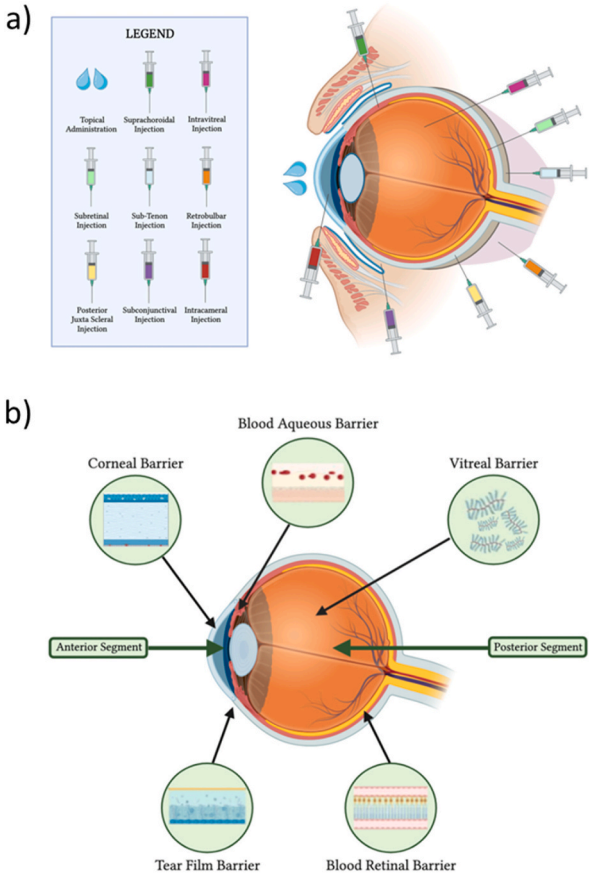

Fig. 3. a) Two primary obstacles of topical ocular medication delivery. Tear film barrier: a mucus layer resembling gel and a high tear turnover rate. Corneal barrier: a five-layer structure with alternating polarity and tight connections in the corneal epithelial cells. b) A schematic representation of drug loading, vector synthesis, and the benefits of Novel Drug Delivery System (NDDS) for topical ocular delivery [188].

absorption into the eye by minimizing the time the drugs spend in touch with the cornea [194]. The most important characteristics are effective evacuation of the supplied fluid, absorption via tissues other than the cornea, and stimulation of tear formation [195]. The corneal barrier and these factors will limit the penetration of an ophthalmic drug administered topically. As a result, just a tiny amount of the injected dosage is delivered to the tissues inside the eye. Between 50 % and 100 % of the specified dosage will be absorbed into systemic drug circulation, which may result in undesirable consequences [196,197]. Applying an irritating medicine or vehicle directly to the eye causes the drug to be lost more rapidly from the front of the eye due to increased tear flow [198]. Non-corneal absorption, predominantly via the conjunctiva, is another important route for drug loss from the pre-corneal region. The described structure has a much bigger surface area than the cornea and a permeability that is 2–30 times higher (depending on the medication) [199]. In contrast to the cornea, the conjunctiva has an abundant blood supply. The cornea is widely recognized as the principal route for drugs administered topically into the eye, albeit it is not the only route [199]. The conjunctiva and sclera have more permeability than the cornea [199,200]. However, the bloodstream quickly removes the substance before it reaches the inner ocular tissues. The ocular epithelium is comparatively impermeable compared to other epithelial tissues (such as the intestinal, nasal, bronchial, and tracheal). However, the stratum corneum is more porous than the skin's outermost layer [196,201]. The most common method of giving medicine in ocular illnesses and diagnostics is the topical administration of eye drops, suspensions, or ointments into the lower cul-de-sac. Typically, ophthalmic drugs work inside the eye. Unfortunately, after administering an eyedrop, less than 5 % of the prescribed dosage often reaches the intraocular tissues [194,198]. This ocular medication's low efficacy is due to the drug's inability to penetrate the cornea barrier and the rapid depletion of the administered solution in the region in front of the cornea.

The delivery of possible pilocarpine prodrugs via eye drops caused substantial ocular discomfort, which worsened as the lipophilicity of the prodrug increased [202]. Combining HP-β-CD, SBE4-β-CD (with an average degree of substitution of 4), or SBE7-β-CD (with an average degree of substitution of 7) significantly reduced ocular irritation induced by pilocarpine prodrug. The viscous solution's ocular absorption was increased because it was held in the precorneal region for a longer amount of time. SBE7-β-CD caused the bulk of prodrug molecules to become complex, leaving just a small amount unbound. Topical administration of the prodrug/SBE7-β-CD carrier results in fast absorption of the unbound drug into the cornea [203]. Cetirizine, an antiallergic medication, produces considerable discomfort when administered to the eyes [234]. To minimize irritation, inject α-CD, β-CD, and γ-CD simultaneously. However, β-CD lowered the efficiency of the supplied dose. 3,4-Dihydro-2,8-diisopropyl-3-thioxo-2H-1,4-benzoxazine-4--acetic acid is a useful therapeutic drug for preventing and treating diabetic complications, particularly retinopathy and keratopathy [204]. When applied as aqueous eye drops, the chemical causes significant ocular discomfort. The simultaneous administration of β-CD decreased ocular irritation, but α-CD and γ-CD did not show this effect.

Dipivefrine, commonly known as dipivalyl epinephrine, is a prodrug of epinephrine that activates and produces adrenaline when absorbed by the cornea [205]. Dipivefrine has a 17-fold greater permeability to the human cornea than epinephrine [205]. The negatively charged SBE7-β-CD improved the stability of the positively charged dipivefrine in water, increasing it by 15–30 times at pH 5.0 and 20–300 times at pH 7.4. However, neutral HP-β-CD (9.2 mM) only increased dipivefrine stability by 4–5 times. CDs enhance drug permeability by increasing drug availability. At the outside of the eye. HP-β-CD enhanced ocular permeability, inhibiting the conversion of dexamethasone acetate and salt acetate to less permeable dexamethasone. Only unbound substances penetrate biological membranes [205].

Complexation with HP-β-CD significantly reduces the transfer of hydrocortisone (HC) from the aqueous to organic phases. The drug partition coefficient and the relative drug concentration magnitude establish the inclusion complex's stability constant. Different

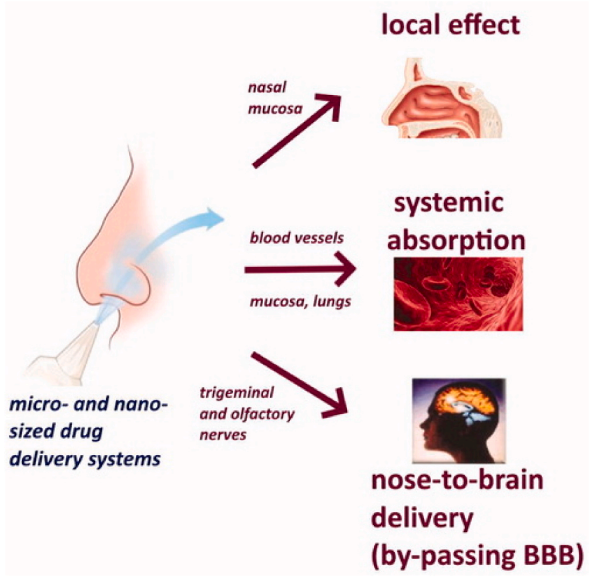

Fig. 4. Nasal drug delivery [211].

release and solubility characteristics of HC and its inclusion complex from cellulose in polyvinyl alcohol (PVA) and high molecular weight PVA polymeric films for ocular delivery [104]. Formulations with HP-β-CD and no HPMC showed higher maximum concentration and bioavailability. Furthermore, HP-β-CD increased miotic responsiveness and permeability without affecting the rabbi's healthy ocular tissue [104].

5.3. Nasal drug delivery

CDs are an efficient excipient for medication administration via the nose. They improve nasal medication absorption by increasing aqueous drug solubility and/or nasal drug permeability (Fig. 4). However, significant interspecies variances have been discovered. CD improves nasal medication absorption. Animal and human studies have been undertaken to investigate the effects of giving the female steroid hormones estradiol and progesterone via the nasal route [206,207]. Compared to oral administration, administering estradiol via the nasal route provides a lower dose. This approach prevents high amounts of the metabolite estrone in the circulation, resulting in a more balanced estrone/estradiol ratio consistent with physiological values [206–209]. Rats and rabbits received estradiol and dimethyl-β-CD. This resulted in average absolute bioavailabilities of 94.6 % and 67.2 %, respectively. A pharmaceutical excipient, dimethyl-β-CD, was used as a solubilizer [32]. Estradiol and dimethyl-β-CD were administered nasally to women with oophorectomy, resulting in rapid absorption of estradiol [207]. In a 6-month study, estrogen replacement therapy was effectively delivered to postmenopausal women who had undergone oophorectomy, with no side effects [243]. In rats and humans, combining progesterone and estradiol with dimethyl-β-CD resulted in nasal absorption comparable to individual steroids [207,208]. Humans received pirodavir, a lipophilic antiviral drug, intranasally with 10 % hydroxypropyl-β-CD as a solubilizer [210]. Regular use of intranasal sprays (six times per day) was found to be effective in minimizing the frequency of symptomatic colds following purposeful rhinovirus infection. Dimethyl-β-CD accelerated morphine absorption via the nasal route and into the cerebrospinal fluid. In contrast, 2-hydroxypropyl-γ-CD sustained morphine levels in plasma and cerebral fluid throughout time (Table 8).

5.4. Transdermal drug delivery

Transdermal medicine delivery systems have become becoming increasingly prevalent. This approach has successfully delivered several medications for both local and systemic effects [219]. However, the permeability of the stratum corneum CD (G-β-CD) limits transdermal transportation of drugs, leading to poor absorption for medical reasons [219,220]. Several attempts have been undertaken to improve the topical absorption of these medications. Drug delivery through the skin can be improved in four ways: (i) improved drug release from transdermal pharmaceutical preparations, (ii) increased drug flux through the skin or prolonged drug retention in the skin, (iii) enhanced drug delivery to specific areas of the skin or targeted tissues, or (iv) a combination of (i), (ii), and (iii) [220]. The CD derivatives' greater stabilizing effects have been established compared to the original CDs. Uekama et al. [221] found that CME-β-CD improved the stability of prostaglandin E (PGE) in both FAPG ointment and aqueous solution. However, the original β-CD accelerated the breakdown of PGE in neutral and alkaline solutions (Table 9).

5.5. Rectal drug delivery

CDs have also been used to improve the rectal delivery of systemic drugs (Fig. 5). Table 10 summarizes the primary parent CDs and CD descendants [281–291]. Several studies have found that the impact of CDs on pharmaceutical rectal administration is significantly influenced by the type of vehicle (hydrophilic or oleaginous), the physicochemical properties of the complexes, and the presence of tertiary excipients such as viscous polymers, among other factors [47,211,253–255]. CDs boost lipophilic medication absorption through the rectum principally by increasing drug release from carriers and improving dissolution rates in rectal fluids [256]. CDs, on the other hand, make it easier to transport medications that cannot be absorbed, such as antibiotics, peptides, and proteins, via the rectal epithelial cells. Conversely, the prolonged effect of CDs on drug concentrations in circulation is attributed to continued release from carriers, slower breakdown rates in the rectal fluid, or the inhibition of drug absorption in the rectum due to the formation of non-absorbable complexes [253]. As a result, the effect of CDs on medication delivery via the rectum appears to be related to a wide range of physiological and physicochemical characteristics.

When used as a base for rectal suppositories, CDs may improve the chemical stability of drugs. AD-1590, an acidic NSAID, exhibited enhanced autooxidation when complexed with β-CD [256]. Hydroquinone, a comparable antioxidant, failed to suppress

Table 8
CD mediated nasal drug delivery.

Drugs	Type of CDs	References
Leuprolide	α-CD	[212]
ACTH (4–9) analogue	α-CD, Dimethyl-β-CD, 2-Hydroxypropyl-β-CD	[213]
Buserelin	α-CD, β-CD, Γ-CD, G2-β-CD, Dimethyl- A-CD, Dimethyl-β-CD, 2-Hydroxypropyl-α-CD, 2-Hydroxypropyl-β-CD, Carboxymethyl- α-CD, Carboxymethyl β-CD, Sulfobutylether β-CD	[214]
Calcitonin	Dimethyl-β-CD, 2,3,6-Tri-O-methyl-β-CD	[215]
Glucagon	Dimethyl-β-CD	[216]
rhG-CSF	α-CD, β-CD, γ-CD, Dimethyl-β-CD	[217,218]

Table 9
CD mediated transdermal drug delivery.

Drugs	Type of CDs	References
Miconazole	α-CD, 2-Hydroxypropyl-β-CD	[222]
Tixoxortol 17-butyrate 21-propionate	β-CD	[223]
Betamethasone	β-CD	[224]
4-biphenylacetic acid	β-CD, Dimethyl-β-CD, 2-Hydroxypropyl-β-CD	[47,225]
Chloramphenicol	β-CD	[226]
Ciprofloxacin	β-CD	[226]
Ethyl 4-biphenylyl acetate	β-CD, Dimethyl-β-CD, 2-Hydroxypropyl-β-CD	[227,228]
Flurbiprofen	β-CD	[229,230]
Hydrocortisone	β-CD, Randomly methylated β-CD, 2-Hydroxypropyl-β-CD, Maltosyl-β-CD	[231,232]
Indomethacin	β-CD, Dimethyl-β-CD	[233,234]
Nitroglycerin	β-CD	[235]
Norfloxacin	β-CD	[236]
Piroxicam	β-CD	[237,238]
Prednisolone	β-CD, Dimethyl-β-CD	[239]
Prostaglandin	β-CD	[240–243]
Chlorpromazine hydrochloride	β-CD, Dimethyl-β-CD	[244]
Tretinoin	β-CD	[245,246]
Beclomethazone dipropionate	γ-CD	[247]
Betamethasone	γ-CD	[224]
Predonisolone	γ-CD	[239]
Sulfanilic Acid	Dimethyl-β-CD	[234]
Acitretin	Randomly methylated β-CD	[248]
Piribedil	Randomly methylated β-CD	[249]
S-9977	Randomly methylated β-CD	[249]
Dexamethasone	2-Hydroxypropyl-β-CD	[250]
17-β- Estradiol	2-Hydroxypropyl-β-CD	[251]
Liarozole	2-Hydroxypropyl-β-CD	[252]

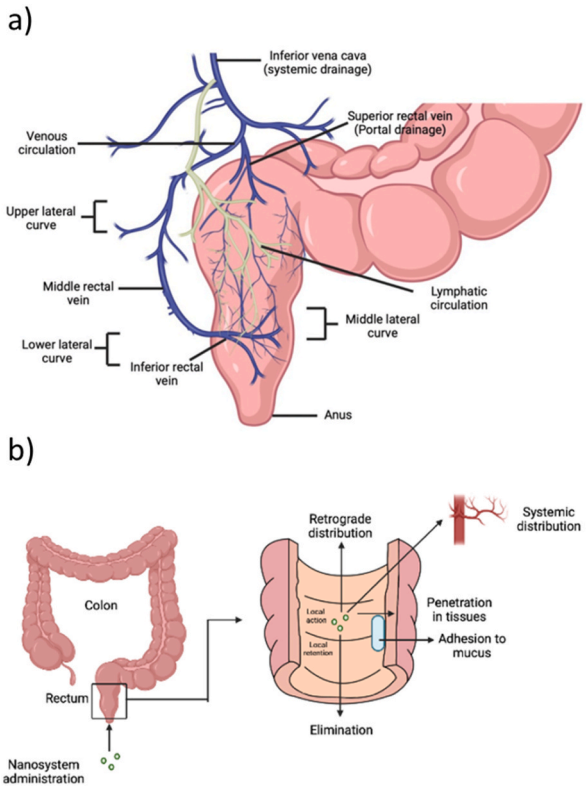

Fig. 5. Rectal drug delivery system [256].

Table 10
CD mediated rectal drug delivery.

Drugs	Type of CDs	References
Morphine hydrochloride	α-CD	[257]
Cefmetazole	α-CD	[258]
rhG-CSF	α-CD	[259]
AD1590	β-CD	[253,260]
Carmofur	β-CD, Dimethyl-β-CD	[253]
Ethyl 4-biphenylyl acetate	β-CD, Dimethyl-β-CD, 2-Hydroxypropyl-β-CD	[261]
4-biphenylacetic acid	β-CD, Dimethyl-β-CD, 2-Hydroxypropyl-β-CD	[148,262]
Naproxen	β-CD	[263]
Phenobarbital	β-CD	[264]
Piroxicam	β-CD	[237]
Diazepam	γ-CD, Dimethyl-β-CD, TM-β-CD, 2-Hydroxypropyl-β-CD	[283]
Flurbiprofen	γ-CD, Dimethyl-β-CD, TM-β-CD	[283]
Insulin	Dimethyl-β-CD	[265]
Carmofur	β-CD	[253]

autooxidation. Carmofu retained its increased stability in DM-β-CD and TM-β-CD complexes, which hydrolyze to 5-FU, in oleaginous suppository base rath. The stabilizing effects of β-CD and DM-β-CD can be attributed to the insoluble nature of these medicines. Using in-situ recirculation, drugs containing β-CD, DM-β-CD [217], and HP-β-CD significantly slowed EBA conversion in rats' rectal lumens. These inhibitory characteristics may assist to reduce the rectal discomfort caused by the medications. According to Ref. [46], complexation improved the solubility of lipophilic medicines at the interface between the molten base and the surrounding fluid. It also blocked the drug from re-diffusing into the vehicle itself. The study found that HP-β-CD enhanced EBA absorption in the rat rectum more than β-CD and DM-β-CD complexes. The most efficient chemicals tested for enhancing rectal absorption include salycilates, medium-chain glycerides, enamines, lipid/nonionic surfactant mixed micelles, and lipid/bile salt mixed micelles [26,254,255]. When placed to the rectum, CDs may increase absorption. According to research, CDs may increase medicine permeability via rectal epithelial cells. Watanabe et al. [266] found that rectal suppositories containing morphine hydrochloride increased morphine absorption when coupled with α-CD and β-CD. The researchers developed Caco-2 cells, a kind of human colorectal cancer cell line, to analyze the effects of DM-β-CD as absorption enhancer. Watanabe et al. [266] found that CDs increased the permeability of various proteins, including rabbit epithelial cells, recombinant human granulocyte insulin [266], and insulin [267]. CDs may improve the efficiency of absorption enhancers in rabbit rectums, as shown in Ref. [211]. In a study [267], acetaminophen was extracted from hydrogels and aqueous solutions using a combination of β-CD and hydroxypropylmethylcellulose. When administered orally, CDs alleviate NSAID-induced stomach mucosal irritation [268].

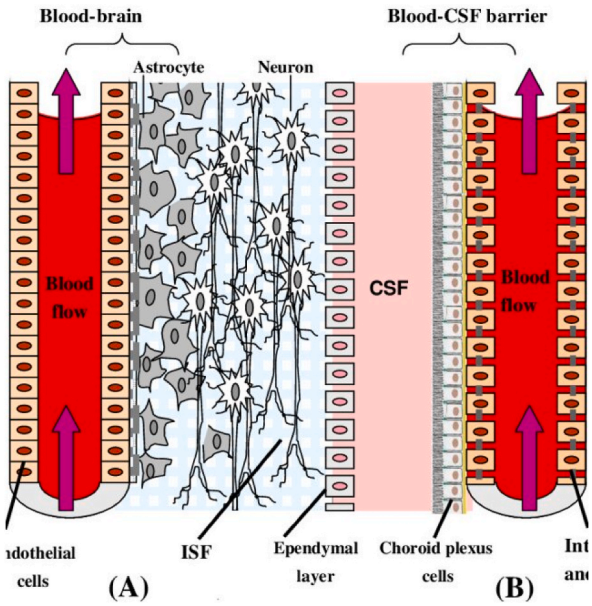

Fig. 6. Drug delivery to brain [316].

5.6. Brain-delivered drugs

Active pharmacological substances might be especially challenging to transfer to the brain (Fig. 6). A variety of potential therapeutic drugs are prevented from entering the brain by its inherent defense systems, which also protect it from external toxins. Despite the brain's massive blood flow, two physiological barriers prohibit it from obtaining its blood supply. These barriers regulate the flow of substances into and out of the brain, both naturally occurring and artificially created. Their distinct physiological requirements determine individuals' capacity to cross the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB) [269]. The BBB must be passed before active chemicals may enter the brain from the bloodstream. Microglia (perivascular macrophages), astrocytes, endothelial cells, and pericytes all congregate near the BBB in the brain's capillaries. The BBB separates the blood moving through the body from the brain's interstitial fluid (ISF). The cerebral microvessel endothelial cells (BMEC) that comprise the BBB have certain physical properties such as limited fluid intake, the lack of microscopic holes, and tight cell connections. Taken together, these characteristics limit the movement of substances from the circulation to the brain's surrounding tissues. Lactoferrin (Lf) is a cationic iron-binding glycoprotein found in mammals [270]. It is a transferrin (Tf) family member with around 690 amino acids and one polypeptide chain in length. This chain's two globular lobes each contain an iron-binding site. The lactoferrin conjugated β-CD derivative (Lf-CD) was generated when thiolated Lf interacted with the maleimide (MAL) group of the difunctional polyethyleneglycol (PEG) linker, NHS-PEG-MAL. Lf, a ligand targeting the brain, was chemically linked to β-CD via the NHS-PEG-MAL linker, a heterobifunctional polyethyleneglycol. As a result, Lf-CD, or lactoferrin conjugated β-CD, was produced [270]. The results of tissue distribution experiments revealed that Lf-CD/IR therapy significantly increased blood-brain barrier transfer. Furthermore, compared to IR alone, the area under the curve of ischemic stroke in the brain after Lf-CD/IR therapy was seven times greater, indicating that using Lf-CD nano-carriers greatly boosted the AUC in brain tissue. To be sure, CDS prodrugs are not highly water-soluble due to their lipophilic component. HP-β-CD can dissolve medications and improve the chemical stability of dihydro nicotinic acid in water, addressing CDS solubility issues [271–273]. CDS development, particularly for brain targeting, is primarily reliant on formulation.

Cloned bovine brain endothelial cells (BCECs) are co-cultured with rat astrocytes. The model displays high transendothelial electrical resistance and low permeability values. The study studied all three types of CDs in their native, methylated, and hydroxypropylated forms using a well-known and strictly regulated BBB culture model [274,275]. The cytotoxicity of CDs was determined by evaluating the permeability of sucrose, an indication of paracellular flow, across co-cultured bovine brain endothelial cell monolayers and rat glial cells. Native CDs (1e20 mM) enhanced endothelial cell permeability in the order of αCD, β-CD, and γ-CD. Methylation decreased α-CD's detrimental influence on cell layers, but hydroxypropylation did not. However, only hydroxypropylation (not methylation) of β-CD and γ-CD reduced toxicity. CDs were shown to be particularly efficient in dissolving chol, phosphatidylcholine, and sphingomyelin in brain endothelial cells [269,276,277]. CDs with the highest permeability were natural β-CD, α-CDs, and HP γ-CD. However, their permeability remains relatively low when compared to minuscule molecules that may cross the BBB. There is little evidence that brain endothelial cells absorb or move these CDs. The transport rate of HP-β-CD and Me-β-CD via brain endothelial cells was the lowest and equivalent to that of efflux pump ligands. In vivo studies confirmed the limited flow of HP-β-CD across the blood-brain barrier seen in culture models [278,279]. Culture models of the BBB show that CDs may increase the transendothelial permeability of lipophilic medications that are actively carried out of the BBB (Table 11).

RAMEB and CRYSMEB significantly promote doxorubicin transport through cow brain endothelial cell monolayers, but β-CD does not [294]. It's likely that doxorubicin's capacity to efficiently mobilize chol from cerebral endothelial cells accounts for its enhanced

Table 11
CD mediated brain drug delivery.

Drugs	Type of CDs	References
Doxorubicin	β-CD (1 mM)	[278]
Doxorubicin	RM-β-CD (1 mM)	[280,281]
Doxorubicin	Partially secondary rim methylated β-CD (2.5 mM)	[114]
Doxorubicin	γ-CD (1 mM)	[282]
Doxorubicin	HP-γ-CD (1 mM)	[282]
Doxorubicin	Quaternary ammonium β-CD NP	[277]
Doxorubicin	α-CD galanin-like peptide	[283]
Ribavirin	α-CD	[284]
Ribavirin	β-CD	[285]
Galanin-like peptide	2,6-Dimethyl β- CD	[283]
Lactoferrin	Ethylenediamine-β-CD	[286]
Transferrin	Ethylenediamine-β-CD transferrin	[287]
Estradiol	HP-β-CD	[288]
Testosterone	HP-β-CD	[185]
Cholesterol	HP-β-CD	[289]
Dexamethasone	HP-β-CD	[250,290]
Cyclic Opioid Peptides	HP-β-CD	[290]
Chloralose	HP-β-CD	[290]
Melarsoprol	HP-β-CD	[291]
Melarsoprol	RM- β-CD	[291]
Carbamazepine	SBE-β-CD carbamazepine	[292]
Crocetin	γ-CD	[293]

transportation. Simultaneous treatment of the efflux pump's ligand vincristine with CRYSMEB improves transportation, suggesting that a reduction in P-glycoprotein activity facilitates the effect. In vitro, γ-CD and HP-γ-CD do not enhance doxorubicin transport, despite their lower efficacy in removing chol from the plasma membrane [295,296]. CRYSMEB reduces the function of P-glycoprotein in brain endothelial cells by eliminating chol and disrupting the lipid raft associated with transporters [281]. NP carriers containing quaternary ammonium β-CD (QA-β-CD) increased doxorubicin transport across cultured brain endothelial cells [296]. The same team of researchers produced a novel doxorubicin-transporting polymeric NP [297] that comprised β-CD and poly (b-amino ester). It was shown that this NP could pass through brain endothelial monolayers undamaged.

6. Role of CDs on controlled drug delivery

There are two primary changes in plasma drug levels over time: rate-controlled and time-controlled (late release). The rate-controlled sort has three subtypes: quick release, extended discharge, and modified release (Table 12). Hydrophobic and hydrophilic CDs are ideal for compositions that require immediate and long-term release [273]. Using O-carboxymethyl-O-ethyl-β-CD can result in the development of delayed release systems. CDs and other carrier materials can help increase the effectiveness of medication release [298].

6.1. Immediate drug release

Analgesics, antipyretics, cardiac vasodilators, and other medications in instant release formulations are extremely useful in emergencies. A variety of hydrophilic components are used to create an instant-release formulation. This is because the dissolution rate of poorly water-soluble medications greatly influences the rate and degree of bioavailability in the mouth of pharmaceuticals. Many medications, including steroids, cardiac glycosides, barbiturates, antiepileptics, benzodiazepines, antidiabetics, vasodilators, and others, use hydrophilic CDs to improve oral bioavailability. Recently, researchers employed water-loving CD derivatives including 2-HP-β-CD [299], maltosyl-β-CD [300,301], and SBE-β-CDs [302,303] to produce a fast-dissolving solution in the gut. This formulation improves the oral delivery of poorly soluble drugs in water. HP-β-CD alters the physical features of solid-state medicines, including particle size and polymorphic transition. Hydrophilic CD-based drug complexes dissolve fast and are best administered sublingually or buccally. This drug entry strategy rapidly increases medicine levels throughout the body and prevents the drug from breaking down in the liver and intestines.

6.2. Delayed drug release

As the delayed-release dosage form passes through the gastrointestinal system and enters the upper region of the small intestine, which has a higher pH, the drug release is regulated by pH dependence. The drug-CD combination may be selectively dissolved, which has pH-dependent solubility [304–306]. Molsidomine absorption was much slower when stomach acidity was high compared to low. Fasting enhanced the impact of high stomach acidity on delayed absorption [307,308].

6.3. Prolonged drug release

Most slow-release formulations aim for zero-order or pH-independent drug release to maintain a steady blood level over time. Several advantages of this formulation include a reduction in dosing frequency, an extension of the drug's efficacy, and the absence of toxicity that can be linked to ingesting a plain tablet [309–311]. Hydrophobic CDs, such as alkylated and acylated derivatives, can gently release water-soluble drugs into circulation [312–315].

Modified Drug Release.

The usual formulation of nifedipine, a typical calcium-channel blocker, must be used twice or three times daily due to its short elimination half-life caused by considerable first-pass metabolism. It also poses certain pharmacological issues, such as reduced absorption when given orally due to its low solubility in water, and a decrease in its rate of dissolution over time during storage. As a result, the rate at which nifedipine is delivered must be adjusted in order to promote more equal oral bioavailability and long-term therapeutic efficacy. Researchers at [322,323] developed a dual-layer tablet by mixing HP-CD with pharmaceutical excipients. They then assessed the table's capacity to release the drug. This study used a spray-dried amorphous nifedipine powder, which was synthesized using HP-CD and HCO-60, as a fast-release component. Its goal was to ensure fast dissolution at the start and prevent crystal formation during storage. Various viscosity classes [174,175,184,316,317]of hydroxypropyl celluloses were utilized as a slow-release component to produce a sufficient quantity of sustained release of nifedipine from viscous matrices, which has limited

Table 12
Temporal profiles of plasma drug levels.

Release patterns	CDs
Immediate-release	HP-β-CD, Dimethyl-β-CD, SBE-β-CD, Branched β-CDs
Prolonged-release	Ethylated β-CDs, Acylated β-CDs
Modified-release	Simultaneous use of different CDs and/or other excipients
Delayed-release	Carboxymethyl β-CD, Drug–CD conjugate

water solubility.

7. Role of CDs on Peptide and protein delivery

Regarding the actual use of therapeutic Peptides and proteins make up a cell's biochemical and enzymatic components. Unpredictable, with little biological membrane penetration, rapid plasma clearance, unpredictable dose response patterns, and immunogenicity.

Inclusion phenomena, in which the CD's cavity functions as a small pocket, have historically been the focus of CDs-peptides/protein chemistry. Because of the size disparity, the tiny pocket cannot accommodate complete biomolecules [318]. Small hydrophobic components such as aromatic rings (tryptophan, tyrosine, or phenylalanine) or alkyl chains (leucine, glutamic acid, or lysine) may be present, but [319,320]. This method may alter numerous features, including dissolution, heat stability, folding, conformations, and biological barrier penetration. CDs, which play a role in folding, are also known as small-chaperone mimics [318,321,322]. The main purpose of biomolecule CD attachment is to use a covalent bonding-based conjugation approach [327]. Various substances are conjugated to CDs, including proteins, peptides, nucleotides, carbohydrates, steroids, and low molecular weight pharmaceuticals. LHRH is a kind of gonadotropin-releasing hormone (GnRH) that binds to a synthetic nonapeptide known as leuprolide. Gonadotropins govern gamete and steroid sex hormone synthesis, and GnRHs release them into the circulation [323–326]. Because of its amino acid makeup, leuprolide is a peptide that may be degraded by proteolysis. Its enhanced proteolytic sensitivity is due to its poor intestinal absorption and bioavailability, which is less than 1 % [323,325]. Kordopati et al. [327]synthesized a novel conjugate that is less sensitive to proteolysis. The conjugate (pGlu-His-Trp-Ser-Tyr-dLeu-Leu-Arg-Pro-Gly""Ahx-OH) was produced by mixing a 3-monoamino-β-CD with an LHRH analogue, Leuprolide. The Huisgen reaction, commonly known as azide-alkyne cycloaddition (AAC), is a very effective mechanism for binding biomolecules to other compounds.

CDs have the potential to build polymeric structures by covalent bonding. These molecules have several functional active sites. The Poly CD family of CD polymers has extremely large molecular weights and can dissolve or remain insoluble in water, depending on the formulation [27,328–330] The three primary forms of Poly CD that exist now are cross-linked, grafted, and poly(pseudo)rotaxanes. These systems have many reactive groups, making them suitable for peptide use. Cancer cells rapidly multiplying include fibroblast growth factor receptors (FGFRs), a subtype of receptor tyrosine kinases. Because of their importance in cancer cell proliferation, FGFRs are a prospective pharmacological or gene target for treating various malignancies [330–332]. Maruta et al. [333] discovered that FHF2 receptors may bind to a 7-mer bioactive peptide called MQLPLAT. Ping and colleagues used high-molecular-weight PEI to produce an 11-mer peptide (MQLPLATGGGC, MC11). There is a definite preference for Hep G2 cells with this method [334].

Surprisingly, β-CDs can connect with "poly("-lysine), serving as a regulated channel for material entrance into cells [335]. Jiang et al. synthesized conjugates by attaching β-CD amino analogues to poly(ε-lysine) through a succinic anhydride ring. Three amino derivatives of β-CD were synthesized in two stages: monoamino-β-CD, diethylenediamino-β-CD, and diethylenetriamino-β-CD. Step two involved investigating how succinic anhydride interacted with the "poly("-lysine") amino group. As a result, succinic acid, which had one free carboxylic group, formed a side chain with the peptide. The carboxyl group was employed to react with amino derivatives of β-CD, which were then linked to the "oly ("-lysine). Additionally, N-hydroxysuccinimide (NHS) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI) were used to help in the synthesis step [330].

Cell piercing peptides (CPP) are short peptides that exhibit amphipathic and/or cationic characteristics. Cationic cell-penetrating peptides (CPPs) are a kind of peptide that may efficiently transport bioactive chemicals into cells, often by conjugation. These peptides generally contain 7 to 30 amino acids. Low cytotoxicity and high transduction efficacy, namely plasma membrane translocation, are required [336–338]. The therapeutic efficiency of biomacromolecules is limited by their low enzymatic stability and poor mucosal permeability [339]. To address this issue, Kamei and colleagues produced insulin-penetrating (PEN) compounds that form by electrostatic contact [340]. Although chemical conjugation was not required for the non-covalent electrostatic contact approach, the complexes might have been unstable due to their relatively high ionic strength.

Alzheimer's disease (AD) is the most frequent kind of dementia in the aged, causing severe difficulties with global health and a significant financial burden [341–343]. Amyloid β-protein (Aβ) buildup in brain tissue causes senile plaques, a hallmark of Alzheimer's disease. This accumulation causes impaired brain activity and impacts cell membrane function [344]. The enzymes α- and β-secretases break down the transmembrane APP sequentially to create Aβ peptides [341]. The use of small molecule inhibitors, particularly peptides or peptide mimetics, has demonstrated promise in delaying the progression of Alzheimer's disease. These compounds are useful due to their extensive distribution in biological systems and manufacturing simplicity [345–347]. Zhang et al. synthesized a blend of β-CD and a hydrophobic heptapeptide to improve the peptide's solubility and inhibitory efficacy against Aβ aggregation in treating Alzheimer's disease. The heptapeptide was synthesized based on the Aβ16-21 sequence. The peptide's sequence was Ac-LVFFARK-NH2(LK7). The conjugate was synthesized using a LK7-NH_2-CD reaction. To form an amide bond, the carboxyl group of lysine in LK7 came into contact with the amino group of CD.

Cell attachment is based on artificial biomaterials, which may be changed with extracellular matrix (ECM) proteins or combined with specific peptide sequences to create unique ECM architectures. As a result, innovative pretreatment procedures focusing on chemical changes are becoming increasingly widespread. These processes include amination, esterification, click chemistry, and others. Li et al. developed a compound using β-CD and peptide to improve cell adherence to biomaterial surfaces. When mixed with adamantane (Ada) on poly (ethylene oxide) (PEO) and polystyrene (PS), an inclusion complex was formed. A linker named sulfo-succinimidyl 4-[N-maleimidomethyl] [348,349]. The compound was synthesized using cyclohexane-1-carboxylate (Sulfo-SMCC) by combining monoamino-β-CD with CRGDS or CGIKVAV peptides. In peptides, the thiol group of terminal cysteine is linked with the linker's maleimide group, whereas the carboxylate group of Sulfo-SMCC establishes an amide connection with the amino group CD.

The CD and adamantane lock-and-key mechanism formed a strong connection between the CD's cavity and the biomaterials.

The pancreatic islets' β cells develop insulin, a peptide hormone. It is well recognized as a key anabolic hormone. Insulin modulates glucose absorption by cells, which regulates blood sugar levels. It aids the liver, adipose tissue, and skeletal muscle cells in absorbing glucose from the blood and regulates lipid and carbohydrate metabolism in particular. Hirotsu et al. synthesized a new chemical by combining CD and insulin. GUG-CD's inhibitory properties were used to treat familial amyloid polyneuropathy [265].

Following that, GUG-CD was esterified with NHS, which included the carboxyl group interacting with a nitrogen-linked hydroxyl group. Aminolysis was employed to chemically bond the NHS-GUG-CD molecule to insulin. An amide bond was established with the protein's amino group, resulting in the opening of the NHS ring. When denatured insulin interacts with hydrophobic surfaces, it adsorbs onto such surfaces [265]. An intra-CD inclusion complex containing a hydrophobic insulin amino acid might potentially interfere with the interaction. The enzymatic stability of the sample was determined using trypsin and other proteases, while its thermal stability was determined by aggregation following incubation. In contrast to insulin's 20–40 % effect retention rate, the conjugation technique obtained a retention rate of around 100 %, according to the enzymatic investigation. These findings suggest that insulin conjugated with B29-lysine may have a protective effect. The heat experiment revealed that the conjugate did not clump and remained totally intact after 7 days, most likely because the hydrophilic regions of the protein came into contact with the cavity of the CD. An NHS linker was employed to synthesize GUG-CD-insulin, a conjugation that exhibits superior characteristics to insulin alone [141].

A nasal spray containing liquid and powder glucagon formulations and DM-β-CD increased medication bioavailability by 98 % compared to subcutaneous administration. More than 100 % of insulin delivered nasally to mice with a solution containing 3 %–5 % DM-γ-CD was absorbed into the bloodstream [350]. To reduce the severe nasal toxicity caused by sodium deoxycholate, a kind of bile salt, β-CD or DM-β-CD reduced leucine aminopeptidase synthesis in the nasal mucosa. Despite its reduced toxicity, the bile salt retained its ability to increase insulin absorption [265].

One well-established method that allows for enhanced peptide absorption in the nasal cavity is the interaction of proteins and lipids in the nasal epithelium's membrane, which diminishes the efficiency of the membrane barrier. Inhibiting proteolytic enzyme activity in the nasal mucosa and acting directly on protein or peptide molecules to prevent aggregation improves absorption. CDs are safer than other regularly used enhancers since they have reversible absorption-enhancing properties. For example, it was discovered that CDs had a moderate, reversible, and less dangerous influence on the frequency of nasal ciliary beats. However, the amount to which CD solutions improved the absorption-enhancing peptides of different species differed greatly. DM-β-CD was shown to be the only nasal absorption enhancer that improved insulin and adrenocorticotropic hormone (ACTH) assimilation in rat solutions among all CDs tested [213]. These chemicals provide a 100 % increase in bioavailability. Nonetheless, there was no noticeable increase in nasal absorption when the same CD/insulin solution was tested in rabbits and healthy human volunteers. Nasal administration of powdered formulations, including DM-β-CD resulted in a 13 % improvement in insulin bioavailability compared to the reference formulation using lactose. Protein and peptide drugs can be physically and chemically stabilized by including CDs, with the greatest impact occurring at higher CD levels [351]. Water-soluble β-CD sulfate reduced proteolytic degradation of the basic fibroblast growth factor (FGF)0.1-Alginate microspheres were created utilizing an emulsion-based method, and insulin incorporation was improved by adding CD. This method may assist an oral insulin medicine delivery system, as it has been demonstrated that optimized microsphere-derived insulin travels through the GI tract [332,333].

8. Role of CDs on oligonucleotide and gene delivery

Nonviral vectors were developed for gene delivery since viral vectors are toxic and immunogenic. In addition to plasmid- or virus-based vector systems, researchers investigated numerous delivery techniques, including nucleotide derivatives as a viable therapeutic agent. Co-delivery systems, which include the simultaneous injection of medications and/or nucleic acids (genes), are a revolutionary approach to cancer treatment. Current approaches rely on self-assembled NPs, which may encapsulate a variety of compounds and perform several activities. Molecules can coexist and interact simultaneously [352,353]. Ma and colleagues studied the prospect of employing CD coupled with poly(L-lysine) dendrons in combination cancer therapies by examining their biological features. CuAAC was combined with propargyl focal point poly(L-lysine) dendron and per-6-azido-β-CD to synthesize the whole conjugate. The third generation dendron was developed by successively adding the t-butyloxycarbonyl group on poly(L-lysine) and then selectively protecting and deprotecting it [334]. Furthermore, the conjugate was demonstrated to form complexes with plasmid DNA (pDNA), and this self-assembled system (CD-PLLD) has been studied for gene transfection. Researchers investigated MCF-7 cells as a model for real breast cancer. The cells were examined under a fluorescence microscope to see if they produced any green fluorescent proteins. The CD-PLLD has excellent gene transfection effectiveness, making it a promising gene therapy tool for breast cancer. Lipophilic methotrexate, a cancer treatment, further boosted the novel approach. The efficacy of preventing cancer formation by assessing the survival rate of MCF-7 cells is established. Even while greater dosages of the loaded pharmaceuticals had a lower impact than pure treatments, the hypothesis was that the complexed methotrexate retained its anticancer potency. The new CD-poly(L-lysine) conjugate may attach to pDNA and show potential for co-delivery in cancer treatment, according to Refs. [352,353]. In addition to decreasing undesired side effects such as immunological activation, CDs have been shown to improve the stability of oligonucleotides (Ons) against endonucleases. Niven and Freemann discovered that adding β-CD (1 %) to the original DNA: lipid formulations boosted gene expression in the rat lung by sixfold [37]. This was caused by the issue's ability to increase CD-membrane penetration [354]. When compared to the impact of other additions (such as sodium glycholate, which generated a 125-fold rise in formulations), the observed increase is insignificant. Nonetheless, no detectable injury was observed in live organisms when exposed to formulations containing β-CD. Roessler et al. began research on the links between polymer-based transfection methods and CDs. Adding CDs to the formulations did

not directly affect the cell membrane's permeability; rather, it resulted in smaller, more stable, and equally dispersed particles. CDs' stabilizing impact on gene delivery systems has also been seen to extend to viral vectors [355]. Croyle and colleagues tested cationic and neutral CD derivatives and found that adenoviruses promote gene expression [355,356]. The cationic CD derivatives attach to the negatively charged surface of adenoviruses inhibit non-specific interactions and promote their entrance into cells with high transfection resistance, such as intestinal epithelial cells. A sophisticated gene delivery strategy developed by Ref. [356] combines transfective DNA complexes with a cationic CD called heptakis(6-deoxy-6-pyridylamino). Multilayered films, such as PLL/HA, include this CD embedded within. These systems delivered the CD-DNA complex to the designated cells more successfully than the identical structure without CD. This technology will most certainly influence the development of tailored gene treatments for tissue engineering [357,358]. Gene delivery by CD-based polymeric structures has been the subject of extensive research and development. To simplify this study, the data will be divided into two parts based on the location of the CD components inside the polymer network. First, there are polymeric molecules known as CD-embedding polymers, which have CDs embedded inside their structure. The second form of gene delivery polymers is CD-dependent polymers, which have been modified by linking CD derivatives to them. The discovery of the therapeutic potential of CD-based polymers and the non-viral gene vector potential of polycationic species sparked the development of a new class of cationic polymers dedicated to delivering macromolecular therapies. Their synthesis approach involved polycondensation of difunctionalized CD monomers with cationic difunctionalized co-monomers, in which two hydroxyl groups were selectively substituted with cysteaminyl segments. This technique resulted in a polymeric chain with CD and cationic units alternating linearly. To improve DNA poly-CD-plexes with targeting ligands, researchers used the molecular encapsulating properties of CD-grafted PEI polymers. Pack and colleagues chemically engineered human insulin to fit into the CD cavity [358]. The CD-PEI ternary composition, which incorporated DNA and a targeting ligand, resulted in nearly harmless particles. When compared to PEI, these particles' gene transport effectiveness was about tenfold more. Various CD-modified polymers have been developed by combining commercially available polymers with certain amounts of mono-6-O-tosyl-bCD. The CD grafting approach lowered toxicity but decreased transfection efficacy as compared to bare PEI. However, including Ad-PEG conjugates significantly increased the formulation's stability under culture conditions, significantly restoring the NPs' effectiveness. Research on live mice demonstrated that PEG-shielded CD-PEI-DNA polyCDplexes effectively delivered genes throughout the body. The molecular inclusion capabilities have been improved by utilizing CD units from CD-grafted PEI polymers. The goal of this alteration is to include specific ligands into DNA polyCDplexes. Pack and colleagues synthesized the fatty acid alkyl group to improve human insulin's compatibility with the CD compartment [359,360]. The gene transport effectiveness of the almost non-toxic particles produced by the CD-PEI ternary formulation (DNA plus a targeting ligand) was more than 10 times greater than that of PEI. The CD-grafting of the PEI method can help to increase the immobilization of PEI-DNA NPs on solid surfaces. Pun et al. [358] employed adamantane-modified surfaces and polyplexes of β-CD-grafted PEI-DNA to control the discharge of transfective particles.

Ma and colleagues designed a CD-based polymeric assembly capable of transporting medications and genes. Inclusion-driven supramolecular assembly was used to generate core-shell NPs by grafting β-CD onto PEI and covering it with poly (b-benzyl-L-aspartate). A cationic shell is intended to compress DNA, and these NPs contain a hydrophobic core that can hold hydrophobic medicines. The authors examined transfection effectiveness on osteoblast cells with unadulterated and drug-loaded (dexamethasone, DMS) granules. Even while gene delivery wasn't as good as with regular PEI-based polyplexes, it's nevertheless worth highlighting that drug loading did assist cells survive and convey genes to some extent.

The CD-polyrotaxane architecture is appropriate for developing gene vectors that can activate in a cell-dependent way and release oligonucleotide payload into the intracellular environment [358]. Yui and colleagues successfully designed a CD-based nanosystem with controlled pDNA release capabilities by combining CD mobility with polyrotaxane dissociation. This was in response to the critical importance of proper transfecting complex dissociation in increasing overall gene delivery effectiveness [361]. The researchers used disulfide connections to yield biocleavable polyrotaxane. They threaded cationic α-CD derivatives (DMAEC-α-CD) on PEG chains (4 kDa) capped with benzyloxycarbonyl tyrosine. Polyrotaxanes successfully reduced the size of pDNA to NPs less than 200 nm in diameter. The premise behind their invention was that having a larger internal reducing potential would make disulfide bonds simpler to break, hence speeding up CD detachment and plasmid DNA (pDNA) release [362].

DNA can wrap around dendrimers to shield the plasmid from its surroundings, causing DNA to condense into dendriplexes, which are denser supramolecular structures. Dendriplexes, formed at the nanoscale by combining DNA with inexpensive PAMAM dendrimers, have an [363]extraordinary ability to carry genetic material into many types of cells [364]. According to one study, selectively breaking down PAMAM dendrimers improved gene transfer success. This is the underlying idea of the SuperFectt gene vector available from Quiagen [365].

A more adaptable and effective technique has been proven by adding CDs to PAMAM, which increases pDNA binding and allows for control over the transfection capabilities of the resultant dendriCDplexes [366]. Li and colleagues used biodegradable carbamate connections to construct a number of tiny oligoethyleneimine (OEI)-grafted α-CDs. Multiple factors, including DNA complex formation, NP size, cytotoxicity, and gene transport, were investigated to determine the impact of oligoethyleneimine (OEI) size and branching, as well as the degree of carboxylic acid (CD) grafting [296]. Compared to commercial PEI (25 kDa), OEI-α-CD combinations chemically attached to branched 14-mer OEI had a more favorable cytotoxicity profile.

An extension of the initial notion was to make a succession of cationic dendripolymers centering around β-CD in the shape of a star. Radical polymerization was used sequentially using dimethylaminoethyl metacrylate (DMAEMA) and oligoethyleneglycol metacrylate [364]. Current cationic polymer molecules or dendrimers can benefit from CDs' transfection-enhancing properties. Their ability to modify chol distribution and so permeate cell membranes is mostly responsible for this. However, further ways are now being explored. Because of their inherent features, CDs can be utilized to modify the structural properties of polymer chains by rotaxanation, enhancing their interactions with polynucleotides. Surfaces can be coated with polyCDplexes via supramolecular interactions because

their nanometric cavity is easily accessible. Many functional components, such as those involved in self-assembly, DNA binding, targeting, or visualization, are made feasible by the molecule's anisotropy, which is an important discovery [367]. Despite being among the best, existing CD-based gene delivery technologies fall well short of the success rates of viral and other nonviral gene vectors. However, combining covalent and supramolecular approaches offers new avenues for developing personalized viral mimics. Improved chol-containing gene delivery formulations are another advantage of CD use. Chol modulates cellular absorption because it regulates the pliability of cell membranes.

9. Immune responses to gene delivery/therapy

Various nonviral and viral gene delivery methods have been developed to alter human cells and tissues affected by different diseases. Among these methods, the nonpathogenic, efficient, and relatively safe recombinant adeno-associated viral (rAAV) vectors are favored for gene delivery in treating human disorders. The challenge of clinical gene therapy lies in developing effective and safe gene transfer carriers that can achieve the right levels of therapeutic gene expression in a specific target. However, their clinical use is still limited by obstacles such as host immune responses and physiological barriers that slow down the process [368].

The immune responses of the host, which consist of T lymphocytes mediated and humoral immune responses, pose significant challenges in gene therapy. Gene delivery systems contain potential immunostimulants, such as viral and non-viral vectors. When foreign genes are transferred into the targeted tissues, viral gene products, transgene products, viral proteins derived from viral particles required by dead-end infection, and CpG DNA in plasmid may all play crucial roles in eliciting the host immune responses [369].

Gene therapy can lead to various issues with the immune system, including short-term expression of the therapeutic gene, difficulty in re-administering the same vectors, and severe side effects during clinical trials. While RNA interference (RNAi) could be used to suppress specific gene expression, not enough attention has been given to the potential non-specific effects it might cause. Studies have shown that small interfering RNAs (siRNAs) may trigger the host interferon response when introduced into mammalian cells. Several research efforts have focused on finding solutions to these challenges, such as using immunosuppression, selecting different administration routes and vector doses, employing tissue-specific promoters, and modifying the vectors.

10. Applications of CDs in the designing of certain innovative delivery systems

Liposomes.

A liposome is a small vesicle with a membrane that encloses a whole water-filled compartment. The aqueous core could include hydrophilic molecules, whereas the membrane can hold lipophilic molecules [370]. Amphiphilic molecules are more likely to be found at the lipid-water interface. Liposomes typically include organic, biodegradable, non-toxic, and non-immunogenic lipid molecules [371]. They have been used to transport active substances to living organisms and to create synthetic model membranes. One proposed solution to the problem of inconsistent drug encapsulation is to include CD/drug inclusion complexes in liposomes [372]. This approach combines the two carriers to generate a drug-in-CD-in-liposome (DCL) system. Water-soluble CD/drug inclusion complexes can be captured within liposomes, allowing insoluble drugs to be integrated into the watery component of the vesicles. Capturing CD-drug combinations within liposomes is a unique technique to drug administration that combines the benefits of CDs (e.g., drug solubility increase) and liposomes (e.g., drug targeting) into a single system, reducing their respective shortcomings [373]. Liposomes can retain medicines as they travel to their destination by entrapping hydrophobic drugs within lipid bilayers and attracting hydrophilic molecules in the aqueous phase. Liposomes can only store a limited number of critical pharmaceuticals since some lipophilic substances can interfere with bilayer formation and stability. CDs' ability to form water-soluble complexes with insoluble drugs would open up several drug delivery possibilities, including increased drug-to-lipid mass ratio, the ability to encapsulate a broader range of insoluble drugs (such as membrane-destabilizing agents), drug targeting, and reduced drug toxicity [374,375]. CD complexes are encapsulated in liposomes, inhibiting their rapid excretion through urine and kidney injury, both associated with intravenous administration [376].

Table 13
CD/drug-loaded liposomes.

Drugs	Type of CDs	References
Betamethasone	HP-γ-CD, β-CD, partially methylated β-CD, 2,6-Dimethyl β- CD, RM-β-CD, Heptakis-(2,3,6-tri-O-methyl)-β-CD	[379]
Benzocaine Butamben	HP-β-CD	[376]
Celecoxib	B-CD	[380]
Curcumin	HP-γ-CD	[381]
Doxorubicin	Γ- CD	[382]
Indomethacin	β-CD, HP-β-CD	[282]
Ketoprofen	β-CD, HP-β-CD	[383]
β- Lapachone	HP-β-CD	[378]
Nifedipine	HP-β-CD	[384]
Prednisolone	β-CD, HP-β-CD	[382]
Prilocaine	HP-β-CD	[385]
Tretinoin	2,6-Dimethyl β- CD	[246]

When HP-β-CD molecules of dexamethasone, dehydroepiandrosterone, retinal, and retinoic acid were entrapped into liposomes, the production of dehydration-rehydration vesicles (DRV liposomes) was maintained even in the presence of blood plasma [377].

Encapsulating inclusion complexes within lipid bilayers changes their method of action. After liposomal breakdown in tissues, the complexes' long-term stability influenced the drug metabolism rates, leading to increased absorption by the liver and spleen and a considerable decrease in urine clearance of HP-β-CD/drug complexes [374,375]. CD complexation can decrease the release of lipophilic medicines from liposomal carriers, enhancing liposomal entrapment. In addition to increasing liposomal stability in plasma, complexation with CDs improved nifedipine's liposomal entrapment by decreasing its association with lipid bilayers [378]. To pack a lot of lipophilic drugs into liposomes, you'll need to choose a CD monomer that generates an incorporation complex with a ton of drugs to CD. Prednisolone was better trapped in lipid bilayers when coupled with HP-β-CD than when it was free. CD selection may significantly influence the amount of medication bound to vesicles. HP-β-CD retains more medication in its vesicles than β-CD due to its lipophilic core and high-water solubility (Table 13).

Studies show that CD inhibits drug release from liposomes in a controlled environment with a pH of 7.4 and an average temperature of 37 °C [374]. Chen and colleagues (2007) showed that Indomethacin is rapidly and directly released from lipid bilayers [386]. This happened because the lipid bilayers enveloped the bulk of the hydrophobic medicine. Nonetheless, two separate methods exist for releasing pharmaceuticals from drug-CD complexes (DCLs): CD/drug complexes with inclusions can be transported to lipid bilayers via the inner aqueous phase and subsequently released into the medium in their intact state. Water, which is in equilibrium with the inclusion complex, enables the release of free medicine. The results reported in Refs. [370,371] were conflicting; the former showed that the DCL method released pharmaceuticals faster than drug-loaded liposomes.

A study [381] shows that incorporating the HP-CD/curcumin inclusion complex into liposomes had significant positive effects against breast cancer cells in both laboratory and animal settings. According to Refs. [387,388], the HP-CD/CLEFMA inclusion complex contained in liposomes demonstrated anti-proliferative activity against xenograft lung tumors while having no adverse effects on normal fibroblasts. The analgesic properties of benzocaine [372], prilocaine [389], and butamben were also studied.

10.1. Drug- β-CD- liposome interaction

The stability of liposomes during incubation in the presence of CDs has been investigated. Various formulations of drug-encapsulating liposomes, including dried-rehydrated vesicles (DRV), multilamellar vesicles (MLV), and small unilamellar vesicles (SUV) composed of different lipid types, were prepared. The retention of calcein was monitored over a 24-h period during incubation with hydroxypropyl-β-CD (HP-β-CD) or methyl-β-CD (Me-β-CD). This methodology has led to developing an innovative drug delivery system that integrates liposomes with CD complexes of lipophilic drugs, resulting in drug-in-CD-in-liposome (DCL) formulations. Nevertheless, it has been noted in recent studies [335,362] that the release of lipophilic drugs from these DCL systems occurs rapidly. This phenomenon is attributed to the capacity of CDs to form inclusion complexes with lipid components of cell membranes, thereby extracting them [385,390,391]. Consequently, membrane lipids may enter the CD cavity, displacing the drug from the complex, which results in the drug being released from the vesicles at a rate comparable to that of a plain drug encapsulated in liposomes. It has been shown that the release rate of prednisolone from liposomes, when the drug is encapsulated as a CD–drug complex is equivalent to that of plain drug encapsulation, particularly with the use of the β-CD complex [384]. Differential scanning calorimetry demonstrated that dimethyl-β-CD (DOM-β-CD) induced a decrease in the enthalpy of transition of lipid vesicles made from dipalmitoylglycero-PC (DPPC), which was attributed to the CD's ability to extract DPPC molecules from the vesicles [391].

HP-β-CD did not induce any changes in the thermotropic parameters of vesicles. In a separate investigation conducted [391], it was observed that the influence of CD molecules on the enthalpy of transition in DPPC dispersions followed the order of effectiveness: DOM-β-CD > x-CD > TOM-β-CD (trimethyl-β-CD). Additionally, it was determined that the interactions between CDs and phospholipids are influenced by the length of the fatty acid chain in the lipids, as well as the hydrophobicity and cavity size of the CD, as noted [390]. A more recent study proposed that methyl-β-CD molecules facilitate the solubilization of liposomes, converting liposome dispersions into micelles through the formation of complexes with the lipids. The impact of liposome type and lipid composition was assessed by examining various liposome types, including small unilamellar vesicles (SUV), multilamellar vesicles (MLV), and dried-rehydrated vesicles (DRV), alongside different lipid compositions. Three distinct lipids were utilized for liposome preparation: phosphatidylcholine (PC) or egg lecithin, hydrogenated phosphatidylcholine (H-PC), and distearoylphosphatidylcholine (DSPC). These lipids were selected due to their ability to form different membrane types; PC, a natural phospholipid (egg lecithin), creates liquid-type membranes that are significantly more permeable than the other lipids, while H-PC, a hydrogenated variant of egg lecithin, forms gel-type membranes that are more rigid and less permeable. Lastly, DSPC, a synthetic phospholipid, produces very rigid membranes compared to the other two lipids.

Various types of liposomes, differing in size, lamellarity, and lipid composition, were examined in this study. The findings may prove beneficial for formulating stable liposomal preparations for lipophilic drugs, mainly through encapsulating drug–CD complexes within the aqueous compartments of lipid vesicles [135,282,303,373–375,379,380] The experimental data indicate that certain CDs can destabilize liposomes, reducing their structural integrity [148]. Notably, this study reveals that the liposome type and lipid composition influence the destabilization of liposomes induced by CDs. Additionally, the specific type of CD plays a significant role in determining the extent of vesicle destabilization and the underlying mechanism of this process.

Regarding the type of CD, Me-β-CD induced a greater degree of liposome destabilization compared to HP-β-CD and HP-β-CD. HP-β-CD and HP-β-CD exhibited similar effects on the integrity of the vesicle membranes across all tested liposomes. This finding suggests that the lipophilicity of the CD, rather than its size, is the critical factor influencing liposome destabilization. This implies that the ability of CDs to penetrate the vesicles is essential for a significant reduction in liposome membrane integrity and the eventual

"solubilization" of the vesicles. Me-β-CD destabilizes liposomes through a surfactant-like mechanism, where CD molecules form mixed micelles with lipids, akin to the action of surfactants. The observed decrease in turbidity is likely attributed to the extraction of lipid components from the vesicle bilayers and the subsequent reorganization of the remaining lipids into smaller vesicles or micelles. When the relative turbidity of the vesicle dispersions approaches zero, it suggests that a substantial number, if not all, of the liposomes have been affected [392,393].

As the relative turbidity of vesicle dispersions approaches zero, likely, a significant proportion, if not all, of the lipid molecules within the vesicles exist as CD-complexes or micelles. Measurements of vesicle size and visual assessments of the samples support this conclusion. The observation that Me-β-CD, the most lipophilic CD, is the sole type capable of completely dissolving liposomes under the conditions employed in the studies of membrane integrity and turbidity indicates that the internalization of CD molecules into lipid membranes may be essential for the complete disruption of vesicles, particularly when CD concentrations are below 100 mg/mL. The type of liposome appears to significantly influence the degree of membrane integrity loss induced by the various CD molecules examined [374,386,393–396].

SUV liposomes, the only unilamellar type among the three studied, exhibited the highest stability. A plausible rationale for the superior stability of SUV liposomes, primarily affected by Me-β-CD, is that the curvature of the vesicle surface may hinder initial interactions between the membrane components and the CD molecules, allowing for interaction only through surface contact. In contrast, Me-β-CD, which can traverse the bilayer into the liposomes, as suggested by previous research [148], also engages with the lipids on the inner side of the membrane bilayer. Nonetheless, SUV liposomes demonstrate greater stability than DRV, even in the presence of Me-β-CD, as evidenced by turbidity results indicating that higher concentrations of Me-β-CD are required to initiate and complete vesicle solubilization.

The initial interaction of CD with the liposome membrane appears to be crucial for the interaction between Me-β-CD and the membrane and the internalization of vesicles. The stability of DSPC small unilamellar vesicles (SUVs) in the presence of Me-β-CD suggests that the rigidity of the lipid membrane is a significant factor influencing the interaction between CD molecules and liposomes. This rigidity may affect the capacity of Me-β-CD to penetrate the vesicles or its initial engagement with the membrane components [303,388].

In DRV, stability is maintained in the presence of all CDs examined except H-PC/Chol. The specific association constant between the drug and CD is also a critical factor when utilizing drug-CD-liposome systems. Suppose a drug is strongly associated with a particular CD molecule and cannot be displaced by chol or other lipid components of the liposome membranes. In that case, employing CD molecules that promote membrane solubilization may be feasible, provided that the specific CD offers additional benefits for the drug formulation, such as high entrapment efficiency. This was recently illustrated with betamethasone [395].

10.2. Experimental data for CDs to enhance the stability and encapsulation efficiency

DCL was introduced by McCormack and Gregoriadis [375] as a method to enhance the loading efficiency of hydrophobic compounds and to facilitate their sustained release in comparison to traditional liposomes and CD/drug inclusion complexes. In DCL system, hydrophobic pharmaceuticals are incorporated into the aqueous phase of the liposome as CD/drug inclusion complexes.

CDs enhance drug delivery by interacting with membrane components [291,299,397]. Such interactions can lead to alterations in the lipid bilayer, impacting membrane characteristics such as fluidity [387,398] and permeability [297,399,400]. A comprehensive understanding of the interactions between CDs, biomimetic (liposomal), and biological membranes is vital in pharmacology to effectively manage CD-mediated drug delivery and release.

The freeze-drying process of liposomes is critical for prolonging their shelf life [387]. Additionally, sperm cryopreservation has been widely utilized in artificial insemination programs [401]. However, the freezing process can lead to membrane damage [402], necessitating the addition of appropriate cryoprotectants. CDs can form hydrogen bonds with the polar groups of membrane lipids, thus stabilizing the structured conformation of liposomes and spermatozoa during freeze-drying. Moreover, CD/chol inclusion complexes act as chol donors, facilitating the incorporation of chol into membranes for stabilization. As a result, free CDs [387,403] and chol-loaded CDs [404] effectively preserve membrane integrity during freeze-drying, thereby providing protection. The influence of CDs on membrane fluidity is noteworthy.

The impact of CDs on the fluidity and stability of liposome membranes, as well as biological systems such as the stratum corneum and colon carcinoma cells, was assessed through differential scanning calorimetry (DSC), fluorescence anisotropy, and electron spin resonance (ESR) methodologies.

In lipid membrane studies, DSC is employed to analyze the thermal characteristics of lipid bilayers in the presence of active compounds, specifically CDs. This technique allows for the determination of thermodynamic parameters, including pre-transition temperature (T_p), main transition temperature (T_m), main transition enthalpy (ΔH_m), and the temperature width at half peak height ($\Delta T_{1/2}$) [405].

A flat endothermic peak indicates the Tp, and its absence signifies the interaction of the drug with the polar head groups of phospholipids (PLs). Conversely, Tm is characterized by a sharp endotherm, represented by the peak's apex [394,405]. ΔH_m denotes the heat necessary for the complete transition and is derived from the area beneath the main transition peak. A reduction in ΔH_m indicates enhanced membrane fluidity and disorder, attributed to an increase in the number of acyl chains adopting the gauche conformation, while an increase in ΔH_m suggests a drug interaction with the upper glycerol head group region of the lipid bilayer. Additionally, $\Delta T_{1/2}$ reflects the cooperativity of the transition, being inversely related to it and highly sensitive to the presence of additives [387].

Most existing literature has focused on the effects of CDs on DPPC liposome membranes. Without CDs, these membranes exhibit a

pre-transition at approximately 35 °C and a main transition around 41 °C [387]. The interaction of CDs with liposomal membranes leads to modifications in the calorimetric parameters of the membranes. The DSC results for CD-loaded liposomes, detailing the liposomal membrane composition, type and concentration of CDs, as well as the lipid: CD molar ratio.

Numerous studies have indicated that integrating a drug into liposomes as a CD/drug inclusion complex enhances encapsulation efficiency (EE) and/or loading rate values while prolonging drug release compared to traditional liposomes. For instance, the loading rate for eugenol-loaded phospholipon 90 H: Chol liposomes was measured at 31.5 ± 4.2 %, which increased to 63.54 ± 2.28 % when utilizing HP-β-CD/eugenol-loaded phospholipon 90 H: Chol liposomes [406]. In a similar vein, the loading rate for anethole was found to be twice as high in phospholipon 90 H: Chol DCLs (0.83 ± 0.15 %) compared to conventional phospholipon 90 H: Chol liposomes (0.48 ± 0.07 %). Additionally, DCLs exhibited a slower drug release profile, retaining 38 % of the initial anethole content within the vesicles, in contrast to the 22 % retention observed in conventional liposomes [239]. Furthermore, the EE values for flurbiprofen-loaded DCL systems prepared with SBE-β-CD or HP-β-CD were lower than those of flurbiprofen-loaded liposomes; however, DCLs were effective in delaying the release of flurbiprofen [230]. Moreover, nerolidol was successfully incorporated into both lipoid E80 conventional liposomes and DCLs, achieving high EE and loading rate values exceeding 90 %, with DCLs demonstrating superior efficacy in prolonging the release of nerolidol compared to conventional liposomes [407]. DCLs also showed enhanced cholestetrol EE and a slower release rate than conventional liposomes, although both formulations exhibited a significant drug release extent of 80 % after 6 h [408,409]. In contrast, the EE of HP-β-CD/risperidone-loaded SPC: Chol liposomes was lower than that of risperidone-loaded SPC: Chol liposomes, and risperidone was released more rapidly from DCLs than from conventional liposomes [399].

Challenges for Practical Application of HP-β-CD.

Liossi et al. [410] demonstrated that HP-β-CD has a reducing effect on the ΔH_m of the DPPC membrane. The presence of α-CD, dimeb [390,410], or HP-β-CD [410] resulted in a significant decrease in the ΔHm of the DPPC membrane, indicating an enhancement in membrane fluidity and disorder. In contrast, Gharib et al. [387] reported an increase in the ΔH_m of DPPC liposomes at lower molar fractions of HP-β-CD (1.81 and 4.54), suggesting an interaction of HP-β-CD with the upper chain, glycerol, and head group regions of the lipid bilayer. However, at higher molar fractions (9.09 and 13.63), HP-β-CD was found to decrease the ΔH_m, indicating its interaction with the hydrophobic core of the lipid bilayer, which disrupts the packing order of DPPC. Additionally, the presence of Chol appears to influence the effects of CDs on DPPC membranes. Specifically, β-CD and trimeb consistently increased the ΔH_m of the DPPC Chol ration (90:10) membrane across all tested lipid to CD molar ratios. In contrast, the impact of dimeb varied with its molar fraction; the ΔH_m reached its peak value (4.94 ± 0.18 kcal/mol) at a lipid: CD molar ratio of 1:7, but further increases in molar fraction (1:32) resulted in a decrease in ΔH_m (2.88 ± 0.31 kcal/mol). The authors noted that dimeb can extract both DPPC and Chol at elevated CD molar fractions [394]. It is established that the anisotropy value is inversely related to membrane fluidity. Gharib et al. [387] were the only researchers to utilize fluorescence anisotropy to assess the impact of CDs on membrane fluidity.

The researchers assessed the DPH anisotropy values of both blank and HP-β-CD-loaded DPPC liposomes, which were formulated at various molar ratios of DPPC to HP-β-CD (100:181, 100:454, 100:909, and 100:1363) at temperatures of 28, 41, and 50 °C. The findings indicated that HP-β-CD decreased the DPH anisotropy of the DPPC membrane across all temperatures examined, dependent on concentration. This suggests that the presence of HP-β-CD enhances the fluidity of DPPC liposomes' membranes [387].

Limited research has explored the influence of CDs on the cooperativity of phase transitions. The addition of dimeb, trimeb [394], or HP-β-CD [388] increased the $\Delta T_{1/2}$ of DPPC vesicles. This phenomenon may be attributed to the interaction between CDs and the hydrophobic regions of the DPPC bilayer, leading to membrane disruption [387,411].

10.3. The impact of DCL on compound pharmacokinetics

The ability of drugs to permeate biological barriers and their solubility in biological environments are critical considerations in drug development, as these factors can significantly hinder or completely obstruct the molecules' access to their intended targets. Utilizing DCL for drug transport presents a method to enhance the pharmacokinetics of these compounds. A diverse range of drugs has been encapsulated within DCL to augment their water solubility and permeability. The use of DCL systems can modify the absorption of drugs across various biological barriers, thereby facilitating access to target sites. Additionally, DCL may influence the quantity of drug that can be loaded into the system. Numerous studies concerning DCL formation have indicated that these parameters can be optimized using such nanocarriers. It is noteworthy that the DCL system has the potential to address several limitations associated with both CDs and liposomes, making it a viable strategy for a variety of drugs with different mechanisms of action, target locations, and routes of administration.

10.4. Enhancement of the bioavailability of a bioactive compound

Recent advancements in drug discovery methodologies have led to the development of numerous molecules with effective pharmacological properties. However, despite these efforts, many compounds exhibit poor water solubility, resulting in inadequate oral absorption. This is particularly concerning as patients, for its convenience and adherence, often favor oral administration. To address this challenge, formulating poorly soluble molecules presents a significant obstacle in the development process. Among the various nano formulation strategies explored, liposomes have emerged as a highly suitable option due to their histocompatibility, cellular affinity, and targeting capabilities. DCLs offer a promising approach to enhance the water solubility of bioactive compounds. Furthermore, DCL systems have proven effective in improving the pharmacokinetic profiles of drugs administered through alternative routes. Numerous studies have investigated the extent of lipid extraction facilitated by CDs. Generally, CDs are capable of rapidly

extracting membrane lipids, with alpha-CDs primarily targeting phospholipids, while β-CDs, particularly methylated variants, preferentially extract chol. In contrast, γ-CDs exhibit less selectivity for lipids compared to their counterparts. Various studies have also assessed the capacity of CDs to induce lipid extraction from both liposomal and biological membranes, with extraction kinetics evaluated by monitoring the process over time and determining release rate constants or half-lives.

Chol release from liposomes and biological membranes typically exhibits rapid exponential kinetics, as noted by Iborra et al. [411] and Milles et al. [412]. In contrast, Yancey et al. [413] found that the release of Chol mediated by HP-β-CD from mouse L-cell fibroblasts, human fibroblasts, and rat hepatoma cells followed a bi-exponential pattern. This study identified a fast pool with half-lives of 19–23 s and a slow pool with half-lives between 15 and 35 min. Kilsdonk et al. [289] showed that HP-β-CD facilitated a rapid release of Chol from mouse L-cell fibroblasts during the initial phase (approximately 2 h) until equilibrium was established between the Chol in the external medium and within the membrane compartment. Furthermore, the kinetics of phospholipid extraction from liposomes by Me-α-CD and Me-β-CD were also described by a bi-exponential equation, as reported by Denz et al. [414].

11. Optimization parameters for different drug types

11.1. CD type and concentration

The interactions of methylated CDs, specifically Me-α-CD, Me-β-CD, and Me-γ-CD, with liposome membranes containing NBD-labeled phospholipids were investigated through the detection of Förster resonance energy transfer (FRET) between NBD and Rh-PE, as previously outlined [414]. Both Me-α-CD and Me-β-CD demonstrated comparable efficacy in promoting a significant efflux of fluorescently labeled phospholipids from the membrane, while Me-γ-CD exhibited no observable effect. Additionally, the interactions of various CDs (α-CD, β-CD, HP-β-CD, Me-β-CD, and γ-CD) with NBD and BODIPY-labeled chol were characterized [412]. The findings indicated that Me-β-CD facilitated the highest chol extraction, whereas α-CD showed no significant impact.

Furthermore, numerous studies have explored the effects of CDs on erythrocyte membranes. β-CD induced a greater chol extraction from human erythrocytes than other native CDs. Conversely, α-CD was more effective in promoting phospholipid extraction [415]. The effects of various CD derivatives on rabbit erythrocyte membranes were also examined, revealing that both α-CD and DM-α-CD were capable of extracting phospholipids, while HP-α-CD had no significant effect [416]. Additionally, methylated β-CD derivatives were shown to induce greater chol efflux from the erythrocyte membrane than β-CD [416].

The presence of β-CD and its derivatives, including HP-β-CD and Me-β-CD, did not alter the PL content in the membranes of mouse L-cell fibroblasts; however, they did decrease Chol levels in the following order: Me-β-CD > β-CD > HP-β-CD [289]. Furthermore, a blood-brain barrier model illustrated the influence of different CD types on lipid release. Specifically, α-CD was found to preferentially enhance PL extraction, β-CD selectively extracted Chol, while both types of CD facilitated sphingomyelin (SM) release [278]. Research utilizing various β-CD derivatives indicated that these compounds promoted Chol efflux from human umbilical vein endothelial cells, with rameb demonstrating the most significant effect [417]. Additionally, several β-CD derivatives, including HP2-SBE3-β-CD, HP3-SBE2-β-CD, SBE-β-CD, Me-β-CD, and dimeb, were shown to extract Chol from human embryonic kidney cells, with dimeb exhibiting the strongest effect [399]. The effects of three native CDs and G2-α-CD and G2-β-CD on Caco-2 cell membranes were also examined [418]. The findings revealed that β-CD and G2-β-CD did not influence the PL content, while α-CD extracted the majority of PLs from the cell membrane, and γ-CD had no effect. According to Szente et al. [419], the size of the cavity and the substituent groups of CDs affected their capacity to extract chol from biological membranes and induce cellular damage. Methylated CDs, such as dimeb and rameb, were more effective in solubilizing Chol than HP-β-CD and SBE-β-CD, whereas HP-γ-CD did not extract Chol.

11.2. Types of PLs

The literature has addressed the influence of PL acyl chain length, saturation, and head group type on the efficacy of CD-mediated PL extraction [414,420]. It has been observed that short-chain lipids are extracted more efficiently than their long-chain counterparts from liposome membranes when various methylated CDs are utilized. Furthermore, phosphatidylcholine (PC) was found to be removed from liposome membranes more effectively than phosphatidylethanolamine (PE) and phosphatidylserine (PS) [414]. Additionally, β-CD demonstrated the ability to extract PC from monolayers without affecting phosphatidylglycerol (PG) monolayers [420].

Regarding the saturation of acyl chains, an unsaturated acyl chain has been shown to enhance the desorption of PLs induced by β-CD from monolayers [420]. A double bond introduces a kink in the carbon chain, resulting in a less densely packed structure. Moreover, the lipid backbone plays a significant role in extraction; sphingomyelin (SM), which has a sphingosine backbone, is extracted more readily from biomimetic membranes than PLs with a glycerol backbone [420]. This disparity can be attributed to the fact that SM can function as a hydrogen bond donor and acceptor, whereas PC serves solely as a hydrogen bond acceptor. The hydrogen bonds formed between lipids and CDs stabilize the lipid-CD complex, thereby facilitating lipid extraction [421].

11.3. The composition of membrane lipids

Different composition of membrane lipids was examined in relation to the desorption of chol mediated by CDs from pure Chol monolayers, as well as those containing Chol mixed with PLs or SM. The findings indicated that CDs prompted a significantly lower Chol efflux from mixed monolayers than pure Chol monolayers [422,423]. Furthermore, it was observed that SM had a more pronounced effect in reducing the Chol desorption rate than PLs [423]. The extraction rate of sterols mediated by HP-β-CD was found to be

greater from POPC: sterol vesicles than from SM: sterol vesicles [441]. Additionally, Ohvo et al. [440] noted that incorporating SM into dioleoyl-phosphatidylcholine: Chol (DOPC: Chol) vesicles decelerated Me-β-CD-mediated Chol extraction.

11.4. Types of cells

The influence of CDs on chol extraction rates was examined across three distinct cell types: mouse L-cell fibroblasts, human skin fibroblasts, and rat hepatoma cells [410,431]. In the study conducted by Kilsdonk et al. [415], β-CD, HP-β-CD, and Me-β-CD were utilized at concentrations ranging from 0 to 10 mM, while Yancey et al. [410] employed HP-β-CD at concentrations between 0 and 200 mM. The findings from the former study indicated that chol release rates were consistent across the different cell types. Conversely, Yancey et al. [410] reported variability in chol release rates among the cell types, with the following order observed: rat hepatoma cells exhibited the highest release, followed by mouse L-cell fibroblasts, and finally, human skin fibroblasts. This discrepancy may be attributed to the varying concentrations of CDs used; at elevated concentrations, such as 200 mM, HP-β-CD may exhibit differing capacities for chol efflux across the various cell types.

12. Long-term biocompatibility of CD encapsulation and off target effects

To our understanding, CDs do not engage with specific membrane receptors. Instead, they operate via a non-traditional mechanism that involves the extraction of various membrane constituents, such as chol, PL, lipid metabolites, and proteins, as well as the disruption of lipid raft domains [424]. This process can lead to modifications in signaling pathways. For instance, the removal of Chol by CDs induces several effects, including.

- the activation of the phosphatidylinositol-3-kinase/protein kinase B/Bcl-2-associated death promoter (PI3K/Akt/Bad) signaling cascade [425];
- the promotion of extracellular signal-regulated kinase (ERK) phosphorylation while simultaneously inhibiting PI3K/Akt phosphorylation, which results in decreased expression of the transcription factor c-Jun in colon carcinoma cells [426];
- the inhibition of resveratrol-induced activation of kinase-dependent signaling pathways (c-Jun NH_2-terminal kinase/ERK/Akt) and caspase-dependent apoptosis in colon cancer cells [427];
- The activation of protein kinase A and tyrosine kinase leads to protein phosphorylation and sperm capacitation [428];
- there is an enhancement of antigen receptor-mediated intracellular calcium release in Ramos B cells [429], while this process is inhibited in Jurkat T cells [424];
- signaling pathways linked to β1-adrenergic receptors are enhanced, resulting in a compartmentalized cyclic adenosine monophosphate (cAMP) response in cardiac monocytes [424];
- cAMP-dependent protein kinase (PKA) modulation of voltage-gated potassium channel (K_v) current is suppressed in rat mesenteric artery smooth muscle cells [274];
- signaling pathways associated with the chemokine receptor (CCR5) are suppressed, which inhibits calcium release and negates the inhibition of forskolin-stimulated cAMP accumulation in Chinese hamster ovary cells and human embryonic kidney cells [430];
- insulin-stimulated Akt phosphorylation is suppressed in mouse hepatocytes [431];

Furthermore, extracting various membrane components, such as PLs or proteins, induced by CDs may influence multiple signal transduction pathways. For example, DM-α-CD has been shown to inhibit the production of nitric oxide and tumor necrosis factor-α (TNF-α), as well as the activation of nuclear factor-KB (NF-KB) in stimulated macrophages, a phenomenon attributed to the efflux of PLs and a cluster of differentiation 14 from lipid rafts [425].

13. Some limitations of CD- liposome system

In general, liposome-based vectors face numerous challenges that must be addressed. Their stability, encapsulation efficiency, and the release rate of encapsulated molecules necessitate precise control. Several parameters are susceptible to the incorporation of hydrophobic molecules within liposomes. While hydrophobic molecules tend to be solubilized preferentially in the lipid bilayer, the volume of this bilayer in liposomes is relatively limited. Consequently, achieving the desired molecules concentration may require a high concentration within the bilayer. Under these circumstances, incorporating hydrophobic molecules can destabilize the lipid bilayer, potentially resulting in either an excessively rapid release of the encapsulated molecules or complicating the control of the release process [372]. Similarly, the release of hydrophilic molecules within the aqueous core of liposomes, which is dependent on the stability of the lipid bilayer, can also be challenging to regulate. Using CDs and their derivatives presents a compelling strategy to mitigate these challenges. CDs can convert hydrophobic molecules into hydrophilic CD complexes, thereby enabling the exploitation of the more substantial volume of the inner aqueous core of liposomes in contrast to the lipid bilayer's volume. Additionally, CDs can influence both the stability and size of liposomes.

14. Alternative strategies for enhancing liposomal stability

Solutions of water-soluble CD complexes containing insoluble drugs can be effectively encapsulated within the aqueous phase of stable multilamellar liposomes, hrough dehydratiorehydration. Optimal enion of these complexes and unbound CDs is achieved when

the liposomes are formulated with high melting phospholipids or when equimolar chol is included, irrespective of the specific phospholipid utilized. It has been observed that during the entrapment of complex solutions, the drugs included are partially displaced from the CD cavity by the liposomal lipids, with the extent of displacement being contingent upon the specific drug, likely reflecting the stability constant of the complex. Displaced drugs tend to be released rapidly from liposomes in the presence of plasma or phosphate-buffered saline (PBS). Ongoing research aims to determine the optimal conditions for entrapment that minimize drug displacement and to identify water-insoluble drugs that exhibit resistance to significant displacement by liposomal lipids. It is acknowledged that the drugs selected for this study may not necessarily fulfill the criteria that would favor this method over direct incorporation into lipid bilayers. Nevertheless, it is expected that the entrapment of a diverse array of water-insoluble or soluble drugs as CD inclusion complexes within the aqueous phase of liposomes will address the challenges associated with their direct application.

Upon exposure of entrapped complexes to plasma, a certain degree of dissociation was observed, resulting in varying levels of leakage for each of the three drugs into the surrounding media. PLs can displace drugs from the cavity of CDs [432], with the extent of displacement appearing to correlate with the stability constant of the drug: CD complex. Displaced drugs can integrate into the lipid bilayers, enhancing their fluidity [405] and permeability [400]. It has been proposed [374] that these displaced drugs tend to localize at or near the surface of the vesicles, facilitating their association with plasma proteins. In the case of the entrapped complexed Dihydroepiandosterone, 30 % was detected in the media after 2 min, which increased to 56 % after 60 min. The release of RET was lower initially at 10 %, but this figure more than doubled to over 60 min. Conversely, only 2.8 % of DEX was released at the 2-min mark, with a slight increase to 11 % by the 60-min interval. Notably, minimal amounts of HP-β-CD (up to 1.5 %) were detected in the media after 60 min, suggesting no destabilization of the vesicles. This finding aligns with previous research [374] involving co-entrapped carboxyfluorescein, a known marker for liposomal stability [433], indicating negligible release.

15. Physicochemical properties that influence the performance of CD- based nanocarriers

CDs can be modified by introducing various functional groups that differ in nature and length, resulting in cationic, anionic, or nonionic amphiphilic characteristics. These modifications are essential for enhancing the interaction between CDs and hydrophobic pharmaceuticals, influencing drug loading and release from NP formulations. The degree of acylation of β-CD plays a crucial role in regulating the mean particle size of NPs, thereby affecting the overall stability of the system. Literature has documented the impact of modifications on both the primary and secondary faces of β-CD on drug loading, particle size, entrapment efficiency, and formulation stability. Furthermore, a correlation exists between the structure of amphiphilic CDs and their capacity to form nanospheres; specifically, compounds with hydrophilic-lipophilic balance (HLB) values exceeding 8.0 exhibit water solubility and the ability to self-assemble into nanospheres in aqueous environments. In contrast, compounds with HLB values below 7.4 are soluble in organic solvents, facilitating NP preparation via nanoprecipitation techniques [434].

15.1. Physicochemical characteristics of drugs

Regarding the physicochemical characteristics of drugs, most are classified as weak acids or weak bases, exhibiting a range of physicochemical properties. Key factors influencing drug loading, entrapment efficiency, and release from CD-based NPs include the association constant between the drug and CD, the octanol-water partition coefficient, molecular weight, solubility, and the size and shape of the drug (guest molecule). A study by Memisoglu-Bilensoy et al. [435] investigated the loading of hydrocortisone, testosterone, and progesterone into CD-based nanocapsules or nanospheres. The findings indicated that progesterone, a lipophilic drug characterized by a higher association constant and partition coefficient, demonstrated superior drug loading compared to the other candidates, irrespective of the drug loading technique employed.

15.2. Properties of Drug-CD complexes

The interaction between drugs and CDs through complexation and electrostatic forces can significantly influence the pharmacokinetic characteristics of the drug. Charman et al. [436]has illustrated the impact of CD on parameters such as maximum concentration (Cmax), volume of distribution, mean residence time, and renal clearance of the drug. The formation of a drug-CD complex can be conceptualized as a form of molecular encapsulation, wherein the CD molecule provides a protective barrier for the drug against potential degradation from the surrounding environment or reactive species [437]. This protective effect may mitigate or entirely prevent the degradation of the drug. Additionally, CDs can mimic the actions of enzyme catalysis or inhibition. The extent to which the drug is stabilized or destabilized following the formation of the inclusion complex is primarily determined by the proportion of the drug encapsulated within the complex and the rate of degradation occurring within it [438].

15.3. Preparation and loading techniques

The techniques employed for preparing and loading drug-CD complexes vary significantly, influencing the overall characteristics of CD-based NPs. A comparative analysis of conventional methods versus emulsification techniques has revealed that these approaches yield distinct colloidal structures, each with unique size distributions and colloidal stability profiles [437]. While the presence of residual organic solvents may help prevent the coalescence of the colloidal system, their physiological implications must not compromise the stability of the formulation [439]. Techniques that utilize preformed steroidal drug-CD complexes, combined with the addition of the drug during the preparation process, have demonstrated enhanced drug-loading capabilities in nanospheres compared

to traditional loading methods [440]. Furthermore, the efficiency of drug loading in nanocapsules appears to be unaffected by the specific techniques employed for loading steroidal drugs.

16. Practical relevance to theoretical discussion

Lopez et al. [441] utilized molecular dynamics (MD) simulations to investigate the mechanism of chol extraction by β-CD. It is established that β-CDs in aqueous solutions tend to form dimers that adhere to the membrane surface, adopting either a tilted or untitled orientation. Only the untitled configuration is effective for chol extraction, facilitating the formation of a membrane-bound CD/chol complex. Although chol is positioned deeply within the channel, the dimethyl end of its hydrophobic tail remains in contact with the monolayer surface until the CD/chol complex rotates by 90°. Ultimately, the complex is desorbed, with each dimer extracting one chol molecule from the membrane.

It is important to note that the CD monomer can interact with the membrane; however, the strength of this interaction is inadequate for the extraction of chol. Yancey et al. [413] suggested that the extraction of chol mediated by CDs occurs through its desorption directly into the hydrophobic core of the CD, bypassing the aqueous phase. Steck et al. [442] proposed that the efflux of chol induced by CDs occurs via an activation-collision mechanism, where the reversible partial projection of chol molecules from the erythrocyte lipid bilayer precedes their capture by CD through collision.

Moreover, Sanchez et al. [443] employed Laurdan generalized polarization to examine the specificity of Me-β-CD (at concentrations of 0.25, 1, and 2 mM) in the removal of chol from the coexisting macro-domains (liquid-ordered and liquid-disordered domains) of GUV membranes composed of DOPC: DMPC: Chol in a 1:1:1 ratio. The authors demonstrated that Me-β-CD selectively extracts chol from the liquid-disordered phase of the liposomal bilayer.

17. Microspheres

If several hydrophilic excipients are very soluble, complexation may not assist the microspheres dissolve the drug more quickly. The dissolution of nifedipine in chitosan microspheres was delayed due to complexation with HP-β-CD, despite higher loading efficiency. The complex must release free material capable of diffusing out of the microspheres, as CD molecules are exceedingly unlikely to do so despite a low stability constant. The observed delay was attributed to the complex's lower drug availability and the resulting longer nifedipine release from the microspheres. A hydrophilic chitosan/CD layer surrounding the lipophilic drug further reduces matrix permeability [103]. Hydrocortisone was continually released from chitosan microspheres containing the HP-β-CD complex, despite no increase in dissolution rate. The delayed release of hydrocortisone was assumed to be caused by the drug's slow breakdown, allowing a layer to form near the interface, making the microsphere surface more hydrophobic [103,444]. An investigation into the in vivo releasing behavior of β-CD during 24 h found that β-CD/polyacrylic acid (PAA) microspheres made using a water/oil solvent extraction approach had a high encapsulating efficiency of 990 percent. These microspheres may potentially bind to the CD covalently. Despite their different solubilities and connection intensities, Rhodamine B, phenolphthalein, and dyes did not exhibit the same in vitro discharge kinetics as β-CD. The unaltered release kinetics could be explained by the following: rapid hydration of the polymer matrix caused by limited crosslinking; disruption of the dye/β-CD complex through oil, solvent-based residues, and/or changes in conformation; and reduction of β-CD complexing capacity upon covalent binding with PAA due to steric hindrance of its cavity [445, 446]. HP-β-CD shown potential as a moderating agent for lysozyme and bovine serum albumin (BSA) in the first emulsification of poly (d, l-lactide-co-glycolide) (PLGA) microspheres. HP-β-CD stabilized proteins by protecting their hydrophobic regions, increasing their hydrophilicity and preventing aggregation at the methylene chloride/water interface. HP-β-CD enhances BSA's conformational stability and facilitates protein recovery from water/oil dispersion by inhibiting binding to PLGA [447]. CDs can limit the rate of peptide release from microspheres. For example, encapsulating HP-β-CD in PLGA microspheres lowered the insulin release rate. The CD's water/oil emulsion was spray-dried to form microspheres, which released insulin constantly for 45 days without an initial surge and maintained peptide stability throughout. According to reports, the peptide's increased size and apparent rise in molecular weight after complexation reduce matrix diffusivity, slowing the overall release rate. The co-encapsulation in the CD lowered the microspheres' apparent particle size [448,449].

Gabexate mesylate (GM) showed great entrapment efficacy in bioadhesive and disposable starch/CD microspheres made by chemically crosslinking an alkaline solution of a starch and CD combination (α-, β-, or γ-CD) with epichlorohydrin. The attraction for CDs and the sequence of their association constants were consistent with the amount of GM present and its proportion in microspheres after storage [448,449]. Drugs such as diclofenac, indomethacin, metronidazole, and propranolol bind well to PVA/CD microspheres created by crosslinking an acidified water solution of PVA and CD (α-, β-, or γ-CD) with gluteraldehyde [450].

Developing controlled release mechanisms for medications insoluble in water is a typical difficulty in microencapsulation. Because of their intrinsic qualities, medications with low water solubility may release slowly. The issue is that their release rate isn't always rapid enough to deliver the drug to an effective concentration. CD inclusion complexes are utilized to improve solubility and create microparticles with release rates independent of the drug's solubility in water [250]. When CDs are present, the release rate of polymeric microparticles can be enhanced or decreased [473]. If the solid medicine, free dissolving medication, CD, and drug/CD combination were balanced, the drug would be released due to its dispersion. Typically, the release rate rises. On the other hand, CDs reduce the amount of free medicine when the concentration of the medication is less than the solubility limit. Drug-CD complexes delay drug release because their diffusion efficiencies in water are lower than those of the unbound drug. Furthermore, CDs can alter the drug's solubility or diffusivity, increase porosity, assist microparticle disintegration, improve hydration and swelling, and alter the medicine release mechanisms that occur in polymeric microparticles [451,452]. CDs were used to synthesize both hydrophilic and

hydrophobic microspheres and microcapsules. The insertion of CDs into poly(L-lactide-co-glycolide) microparticles has been studied for a variety of goals, including enhancing protein stability and refolding [447,449,453,454], improving drug release control [250, 448–450,455], and increasing absorption [484]. Researchers have created permeability small particles of poly(L-lactide-coglycolide) or used HP-β-CD and (SBE)7M-β-CD, two highly soluble CD derivatives, as an alternative osmotic agent in protein microspheres [448, 456].

18. NPs

NPs provide a consistent delivery route for medications not highly soluble in water, potentially increasing bioavailability and efficacy. Unfortunately, when employing standard water emulsion polymerization techniques, NPs have low drug loading and entrapment efficiency. This can lead to the administration of an excessive amount of polymeric material, jeopardizing their safety and effectiveness [173,297].

Some approaches have been demonstrated to be effective in using NPs for medication administration via the mouth or intravenously (Fig. 7). Nanomaterials and CD derivatives can significantly improve the bioavailability of a medicinal formulation. As a result, this approach is becoming increasingly popular for treating various disorders. Many other delivery methods have been investigated, including oral, ocular, intranasal, and intravenous. As previously stated, CD's capacity to increase the medication's solubility and permeability is an important part of its activity. NPs, on the other hand, have a wide range of applications. One conceivable application assists slow and prolonged absorption, whereas another facilitates rapid and thorough absorption. Furthermore, they can improve targeted distribution to particular action sites, increase circulation time, and solubility in aquatic environments. That is why CDs, derivatives, and nanostructures provide fresh hope for treating APIs that are underutilized in traditional formulations due to low bioavailability or drug instability.

These nanosystems enable the development of intelligent drug delivery vehicles for specific illnesses and the execution of personalized treatment (Fig. 8). NP medicine delivery systems give particular advantages due to their tiny size and resilience. NPs have a large surface area, allowing more effective interaction with biological membranes. They may quickly pass through even the smallest blood vessels, entering cells and tissue gaps to reach particular organs [458]. Polymeric NPs have limited applications due to their low drug loading capacity and poor entrapment efficiency. Two key strategies based on CD have been proposed to solve these limitations: i) Amphiphilic CD-based NPs; ii) Polymers or macromolecules coupled to CDs to produce NPs [459]. The CD nanospheres can contain either hydrophilic or lipophilic drugs [498]. Research using C6 and C14 substituents on the primary surface revealed that CDs replaced with C6 aliphatic chains were the most successful in generating nanocapsules by nanoprecipitation, without the need of surfactants [460]. Combining amphiphilic β-CDs with bifonazole and clotrimazole results in 1:1 inclusion complex. These complexes produce densely filled nanospheres with lower hemolytic activity than inclusion complexes containing natural CDs [297]. Hydrocortisone, testosterone, progesterone, tamoxifen, and paclitaxel were successfully integrated into amphiphilic CD NPs.

The NPs, synthesized using free radical polymerization, effectively encapsulate HP-β-CD. They also displayed robust adherence to biological surfaces and efficiently released physiologically active insulin. NPs made of methyl methacrylate and monovinyl-β-CD monomer can modulate the release of the alkaloid camptothecin [461].

To synthesize copolymerized NPs or increase protein stability in acrylate-based NPs, additional γ-CD derivatives have been used. Chiellini et al. [492] used human serum albumin as a protein model and l-O-glycidyl-2,3-O-isopropylidenglycerol-β-CD as a stabilizer to form a polymer called poly(methacryloyl-glycylglycine-Ohx-co-hydroxypropylmethacrylamide). The protein release and

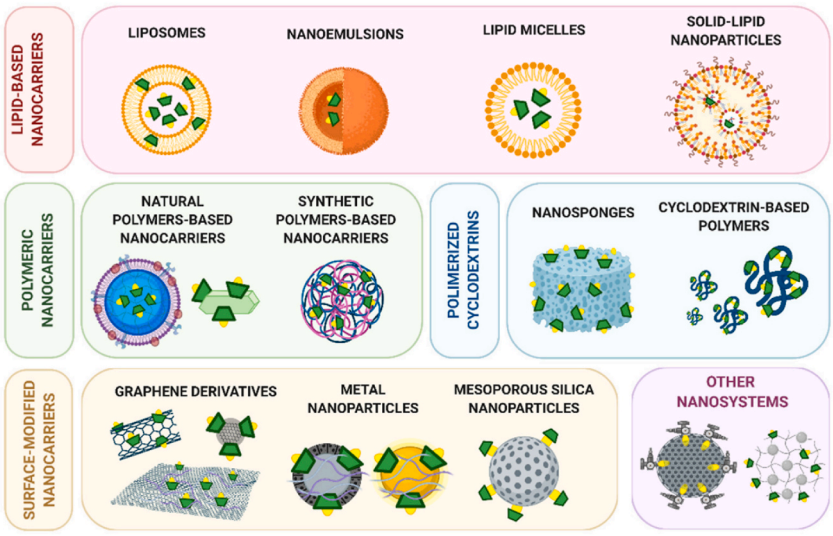

Fig. 7. CD based nanocarriers [457].

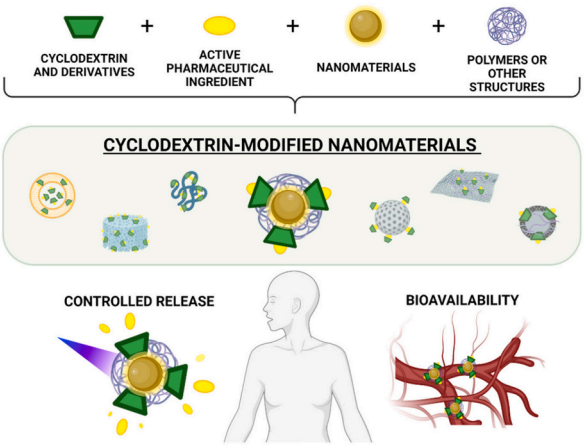

Fig. 8. CD modified nanomaterials [457].

Table 14
The types of nanosystem CD used & polymers [457].

Drug	Type of CD	Type of nanomaterials	Reference
Temoporfin	β-CD	Polymer-based nanosponge	[421]
Sorafenib	β-CD	Polymer-based nanocarrier	[419,464]
DOX	β-CD	Polymer with RGD peptides	[380]
Diclofenac	β-CD	Cationic polymer with fluorescent probe nanocarrier	[303,461]
Ethionamide and BDM-smart420-Booster	β-CD	Polymer-based NP	[465]
Novobiocin Vancomycin	β-CD	Pseudopolyrotaxane-β-CD-based polymer	[317,458]
Paracetamol, Aceclofenac and caffeine	β-CD	A nanosponge made of β-CD polymer	[459]
Nifedipine	β-CD	A nanosponge made of β-CD polymer	[466]
Atorvastatin	β-CD	A nanosponge made of β-CD polymer	[460]
Febuxostat	β-CD	A nanosponge made of β-CD polymer	[467]
Phenylethylamine 2-amino-4-(4-chlorophenyl)-thiazole	β-CD	A nanosponge made of β-CD polymer functionalized with gold NPs	[468]
Curcumin + DOX	β-CD	CD-maleic anhydride-NIsopropylacrylamide-fluoresceinfolic acid multi-walled carbon nanotubes	[469,470]
DOX	β-CD	β-CD graphene oxide-phenylalanine	[471]
DOX & Methotrexate	Mono-6-deoxy-6-ethylenediamino-β-CD	β-CD graphene oxide (Fe_3O_4)	[472]
DOX, Camptothecin Protoporphyrin IX	Aminated- β-CD	β-CD graphene oxide	[473]
5-fluorouracil	α-CD	The supramolecular hydrogel has graphene oxide and mPEG-QPDMAEMA/β-CD as its components	[474]
DOX	Mono-6-deoxy-6-ethylenediamino-β-CD	GO modified with β-CD/Ni NPs and grafted with mitochondrial ion-targeting peptide hyaluronic acid	[475]
Curcumin Gallic acid DOX	6-O-monotosyl-β-CD	Gallic acid @ Chitosan, Curcumin @ CD-oxide graphene	[476]
p-Coumalic acid	Aminated- β-CD	Mesoporous silica NPs modified with β-CD and replaced with tetra-ortho-methoxy azobenzene	[477]
Phenylethylamine and Piperine	β-CD	Modified gold nanostar using electrospun CD/Ag cationic β CD-based polymer	[478]
Ag NPs	2-Hydroxypropyl- β-CD	Electrospun CD/Ag NPs nanofibers	[479]
DOX	6-thio- β-CD	Loaded mono-6-thio-β-CD functionalized Fe_3O_4 magnetic NPs	[480]
Camptothecin	Mono-6-deoxy-6-aminoethylamino-β-CD	NPs of nickel ferrite coated with CD-dextran polymers	[481]
Suberoylanilide hydroxamic acid	β-CD	QDs of ZnSe/ZnS on βCD/chitosan polymer	[482]
DOX	β-CD	NPs of mesoporous silica treated with CDs/2-diazo-1,2-naphthoquinone	[483]
Azidothymidine triphosphate	Phosphated CD	Iron (III) polycarboxylates/CDs functionalized MOF NPs	[484]
DOX	β-CD	Janus gold nanostar-mesoporous silica NP modified with proton-responsive benzoimidazole-β-CD and a thiolated photolabile molecule	[485]
Gentamicin sulfate	β-CD	Fibrous membranes made of polyurethane functionalized with β-CD	[486]

encapsulation efficiency of the NPs containing human serum albumin were satisfactory. Researchers employed NPs containing Eudragit RS 100 and CDs to deliver glutathione transmucosally. They discovered that using CDs affected the medication's release and the durability and ingestion of the peptide [462].

Park et al. [463] developed composite NPs for precise regulation of gene delivery by modifying poly(ethylenimine) with CD. The aim was achieved by connecting β-CD-modified poly(ethylenimine) NPs to adamantine-modified self-assembled monolayers. The intricate architecture of these NPs makes them an attractive choice for efficient and targeted loading onto solid surfaces. CDs can enhance drug loading in solid lipid NPs as an extra advantage (Table 14).

19. Commercialization of CD based NPs

The global presence of numerous CD producers and research teams dedicated to CDs offers a robust foundation for CD investigation and advancement. The global literature is becoming more and more populated with studies on the use of NPs for therapeutic and/or diagnostic purposes, and as a result, these applications are receiving regulatory approval. One example of this is Abraxane, an albumin NP-bound paclitaxel that was approved by the FDA in 2005 [487] to treat metastatic breast cancer. These advancements pave the path for the commercialization and application of CD NPs in treating serious illnesses like cancer.

Drug loading in amphiphilic CD nanospheres/nanocapsules can be achieved through three approaches. In the conventional loading method, an insoluble drug molecule is dissolved in the organic phase along with amphiphilic CD during the nanoprecipitation process. Another method involves pre-loading, where the drug: CD inclusion complex is first prepared, and then the NPs are directly formed from the complex. The high-loading method allows for excess drug loading. To prepare drug-loaded NPs using the high-loading method, the drug: CD inclusion complex is dissolved in an organic solvent with an excess amount of drug, and then the organic phase is added to the aqueous phase using the nanoprecipitation technique [488].

The first background review on the use of CDs as a pharmaceutical excipient was published by the European Medicines Agency in 2014. These advancements have impacted the rate and utilization of CDs in pharmaceutical research, leading to new opportunities for CD formulation. Clinical trials involving products formulated with CDs were also examined in this study. Before the commercialization of a product, the safety and therapeutic effectiveness of the drug must be thoroughly elucidated and evaluated in clinical trials. CRLX101 is a tumor-targeted nanopharmaceutical that consists of a CD-containing polymer conjugated to camphtothecin, which self-assembles into 40 nm diameter NPs and underwent a first-in-human phase 1/2a trial [489].

Several crucial details in the research on amphiphilic CDs and the NPs made from these molecules still need to be clarified. The literature mostly reported amphiphilic CD NPs lying between 100 and 500 nm in terms of particle size. In this instance, they won't be in the bloodstream long before macrophages identify them and carry them up to the RES organs. Research should concentrate on extending the circulation time for amphiphilic CD NPs to prevent opsonization after injection. These methods can include coating or chemically grafting hydrophilic groups like PEG or PEO into the NPs structure. Alternatively, the particle size can be reduced to less than 100 nm. Significantly reducing the size may cause toxicity problems and a build-up of NPs in the kidneys or lungs, necessitating chemical modification of amphiphilic CDs to change their surface charge. To avoid toxicity concerns and the buildup of NPs material in the kidneys or lungs, chemically modifying amphiphilic CDs to change their surface charge or provide a protein-repellent effect is thought to be more promising. Further clarification is required about the pharmacokinetic characteristics of amphiphilic CDs whether administered via injection or oral administration. Only one study currently provides biodistribution data for β-CDC6 NPs injected into rats [435]; however, further clarification is needed about plasma drug and CD concentrations in various in vivo scenarios.

The addition of β-CD and 2-Hydroxypropyl-β-CD improved the incorporation of hydrocortisone and progesterone into Imwitor 900 and stearic acid-based solid lipid NPs [490]. The rate of drug release may be controlled by altering the chemical composition of a solid NP lipid formulation that contains a combination of free and complexed drugs. Lipophilic α-CD and γ-CD derivatives improved curcumin loading in solid lipid NPs derived from various triglycerides [135,491]. The addition of CD mimics with chain lengths similar to triglycerides increased the drug entrapment efficacy of the NPs.

20. CD polymers as coatings in implants functioning as drug delivery systems

One source for a broad range of different controlled release implants is CD Bioparticles. Physicochemical analysis, in vitro drug transport, and formulation development are among the professional development services that our research team can offer. Implants with controlled release are special devices that provide a long-term, high-bioavailability, low-toxicity medication delivery. In order to offer local or systemic medication release, site-specific implants are made to deliver several active compounds, particularly proteins [492]. This minimizes "poking and prodding" and lowers the frequency of office visits and drug administrations. Enhancing the targeting of medication therapy involves resolving dose-limiting (systemic) toxicity and more effectively delivering pharmaceuticals to the intended therapeutic location. While bigger implants may be removed from the body after usage, smaller implants stay inside. Implants can administer drugs for longer periods of time and provide long-lasting and sustained medication therapy because they have a larger drug loading capacity and a drug release mechanism where the drug progressively diffuses through the polymer matrix and dissolves in the surrounding environment. Promising treatments for cancer, schizophrenia, Alzheimer's disease, contraception, and other illnesses include controlled release implants [8].

In recent years, functionalization or coating of surfaces has grown in importance as a subject in materials science and engineering. In this case, the coating seeks to enhance the material's functionality or better fit it for a particular use [493]. Often, a material's surface determines its qualities more so than its bulk composition. In actuality, surfaces play a key role in technology in a number of fields, including environmental remediation, biomedicine, and catalysis because they play a critical role in the performance and

success of materials' applications [510]. Infections, localised edoema and induration, insufficient healing, and other dangers are part of the intrinsic risks associated with medical implant surgery. These risks increase in immunosuppressed patients due to several illnesses or disorders [494]. Covering the implants with polymeric drug-delivery devices is a highly useful tactic to lower these surgical risks [495]. Applications of CD-based coatings in nonbiomedical applications [496] as well as biomedical applications [497–507] have been documented in a number of research. On the one hand, CD-based coatings have been applied in nonbiomedical applications to clean contaminants or colours and avoid corrosion issues. Conversely, CD-based surface coatings have become more significant for biomedical applications in terms of biocompatibility and drug delivery [298,312,449,497,499–501,503,508–510]. These coatings are primarily meant to be molecular delivery systems, like those used for the administration of pharmaceuticals [491,493,498–500] and antibiotics [507,510,511], among other things.

Using an exponential-type equation, the Korsmeyer–Peppas model provides a straightforward connection that describes drug release from a polymeric system. This model takes into account the geometric properties of the system to analyze both Fickian and non-Fickian release processes [487,512]. It was created by Ritger and Peppas (1987) [512] and Korsmeyer et al. (1983) [513].

The Korsmeyer–Peppas equation is

$$Qt / Q\infty = k\ KP\ tn$$

where $Q(t)$ is the amount of drug released in a time t and $Q\infty$ is the amount of drug released in an infinitely long time; kKP ($h-n$) is the Korsmeyer–Peppas kinetic constant, which characterizes the drug-matrix system and is also considered the release velocity constant; and n is the exponent that indicates the drug-release mechanism.

Table 15 displays the release mechanisms based on the Korsemeyer–Peppas model. Five types of these models may be distinguished [513–515]: The quasi-Fickian model-

(1) shows that drug diffusion predominates, but the matrix is partially swollen;
(2) the Fickian mechanism (called "case I″) indicates that diffusion is the primary phenomenon that is currently occurring;
(3) in anomalous transport, the solvent diffusion velocity and the polymeric relaxation speed have similar magnitudes;
(4) the zero order ("case II") represents the situation in which the drug is released at a constant rate regardless of concentration and the solvent diffusion velocity is less than the polymeric relaxation process;
(5) in the super case transport, the solvent diffusion velocity is significantly higher and accelerates solvent penetration. Tension and polymer breaking result from this (erosion).

Devices called medical implants are made to supplement, replace, or improve biological structures that are lacking [516]. Examples of these include catheter, stents, hip joints, intraocular lenses, and other devices. Since the implant surfaces would touch physiological fluids and tissues directly, biocompatible materials, including silicone, titanium, bioactive glass, and polymers have been used in their design. Furthermore, desirable qualities following the stated application guide the selection of the right biomaterial [517]. The most popular method of integrating medical implants into the body is surgery, which carries dangers of its own, including the potential for bacterial infections, localised induration and edoema, poor healing, immunological reactivity, and other issues [518]. In situations of immunosuppression brought on by specific illnesses or conditions, such as AIDS, cancer, diabetes, malnutrition, and specific genetic abnormalities, the likelihood and severity of these postoperative hazards are increased [403].

The use of CDs as local drug delivery carriers on a range of prosthetic or implant biomaterials was initially investigated [521] in the last ten years. With his original treatment process (polyCDs coating), he was able to improve the drug release profile from poly CDs functionalized biomaterials (polyethylene terephthalate vascular prosthesis [522], polypropylene abdominal wall implant [506], hydroxyapatite orthopaedic implant [500,523], and so forth) for peri-operative infection prevention, pain management, anti-coagulation, etc. with remarkable success.

These achievements serve as excellent proof-of-concept for poly CD as a platform for drug administration on various biomaterials; nonetheless, the steps involved in this notion are unquestionably substrate-dependent. As a result, when the biomaterial to be functionalized changes, the treatment settings must be adjusted to better suit the unique physio-chemical characteristics of each substrate, which is not always simple. Elderly patients with primary coxarthrosis (73 %), dysplasia, osteonecrosis, or post-femoral neck fractures frequently receive hip prosthesis [524–526]. One of the most common surgical procedures carried out worldwide (with 800000 prostheses annually) and in France (with 1,20,000 prostheses annually) is total hip replacement (THR) [525]. In the past, poly (methyl methacrylate) cement, either loaded with or without gentamicin, was used to secure metal prosthesis to reduce the risk of infection. Cement-related issues such as exothermic chemical reactions, deterioration, and other issues led to the gradual replacement of cemented implants with cementless designs that incorporated porous coatings like TiO_2 and hydroxyapatite (HA) to facilitate biologic

Table 15
Release mechanisms following the Korsmeyer–Peppas model for various geometries.

Geometry & n	Release Mechanism
Planer n < 0.5, Cylinder n < 0.45, Sphere n < 0.43	Quasi- Fickian
Planer n = 0.5, Cylinder n = 0.45, Sphere n = 0.43	Fickian diffusion
Planer 1> n > 0.5, Cylinder 1> n > 0.45, Sphere 1 > n > 0.43	Anomalous transport
Planer n = 1, Cylinder n = 0.89, Sphere n = 0.85	Zero order
Planer n > 1, Cylinder n > 0.89, Sphere n > 0.85	Super Case II transport

attachment, also known as osseointegration.

Theoretically, two significant problems of total hip replacement surgery are infection and prosthesis loosening. Cementless hip prostheses are predicted to lower these risks. However, a large body of data [527–530] suggests that they have greater infection rates (0.3–1.7 %) compared to cemented prosthesis [526]. According to Delaunay et al. [525], 11 % of unsuccessful primary hip arthroplasties in France were caused by infection. According to Zilberman and Elsner [531–534], the most common cause of implant-associated infection is bacterial adherence to the implant surface and the subsequent production of a biofilm, which protects the microorganisms from antimicrobial agents and host defence systems [535,536]. High doses of antibiotics are frequently given to patients in order to avoid infection; nevertheless, their effectiveness is restricted because of their relatively poor absorption into the mineral bone matrix [537,538]. Furthermore, certain negative effects, such as systemic toxicity and the development of bacterial strains resistant to antibiotics, are commonly noted. Thus, developing local medicine delivery systems and anti-biofilm strategies is strongly advised.

It is frequently costly and intrusive to repair bone abnormalities caused by trauma, arthritis, cancer therapy, or other skeletal illnesses with bone substitute materials. The potential for bacterial adherence to biomaterials, which results in biomaterial-centered infection (BCI), and the inability of effective tissue integration or compatibility with biomaterial surfaces are the main obstacles to the extensive use of these devices [539]. For hip prostheses, the incidence of BCI is 2 %, and for knee replacements, it is 4 % [524,540]. Due to the fact that bacteria in a biofilm are more resistant to antibiotics than their planktonic counterparts, BCI can result in a number of significant issues and be challenging to cure [507]. It has been demonstrated that using antibiotic prophylaxis during orthopaedic surgery is advantageous [541]. However, inadequate local concentration may hinder the efficiency of intravenous antibiotic therapy [542] and raise the possibility of resistant pneumonia and other systemic bacterial infections [543]. Because systemically delivered medications are not as accessible, local use of drug delivery devices in treating bone infections is advantageous. Antibiotics can be administered locally using suitable drug delivery devices or more traditionally using spacers, impregnated cement beads, or pre-moulded implants [531,534,544–547]. Numerous retrospective studies have supported the use of local antibiotics for patients with open fractures and shown advantages of their administration.

According to Henry et al. [545,548], using an antibiotic bead pouch reduced the likelihood of osteomyelitis and wound infections linked to open fractures. Local antibiotic treatment can also use the blood-bone barrier to successfully shield the body from extremely high local antibiotic concentration. Therefore, it is extremely desired to maintain an effective tissue concentration of antibiotics around the bone prosthetic graft for a considerable amount of time, and new methods of local antibiotic delivery are required. An antimicrobial agent and a delivery vehicle are needed for local antibiotic delivery. Because of their capacity to form reversible inclusion complexes with drugs without changing their physical, chemical, or biological properties once the guest molecule has been gradually released from their cavity, CDs are viable candidates for such a role as antibiotic delivery carriers [273]. A macrocyclic structure is formed by α-1,4 glycosidic linkages connecting six, seven, and eight d-glucopyranose residues in the case of the α-, β-, and γ-CDs, which are the most often utilized native CDs. Since the inside of CD's annulus is hydrophobic, numerous lipophilic substances can form inclusion complexes. The US FDA has authorized CDs as pharmaceutical excipients for several medication compositions since they are thought to be physiologically inert [549]. Surprisingly, a recent work by Liu et al. and Shah et al. [550,551] even showed that certain β-CD derivatives had a strong anabolic impact on bone in vivo. Consequently, CDs may be used as a medicine carrier on bone substitute material to give it antibacterial qualities and promote bone regrowth (Table 16).

21. Conclusion and future prospects

CDs address the need to enhance present drugs' efficacy, stability, and safety. There is evidence that encapsulating CDs is a useful strategy to address these concerns while preserving or increasing the biological activity of the medications under consideration. Their capacity to improve solubility, prevent drug-additive interactions, neutralize unpleasant flavors and odors, and reduce side effects makes them adaptable excipients. Their distinct actions as active medications have the potential to enhance any synergistic benefits. They are available in various medicinal forms, including pills, suppositories, infusions, and sprays.

Furthermore, they have the potential to be developed into complicated drug delivery systems that exceed the constraints of individual CDs. Theoretically, these properties are suitable for developing bioactive chemicals and anti-inflammatory medications. Encapsulation of larger molecules, such as proteins, is also enabled by the invention of new CDs that expand the potential limitations. Given the aforementioned characteristics and the vast amount of study, it is apparent that this topic is now receiving a lot of attention. As a result, more studies on this topic are being conducted.

CD-containing formulations can decompose naturally, exhibit good toxicological qualities, and lessen the pharmaceutical industry's dependency on surfactants and organic solvents. The literature has described a variety of CD assemblies, including NPs, nanoemulsions, nanogels, microspheres, and microcapsules. These structures allow for less invasive medication delivery to specified regions. We are learning more about and making improvements in transmucosal, ophthalmic, and topical drug delivery strategies due to CDs used for medicine administration. Numerous nanomedicines have been successfully turned into drug delivery systems that do not now require invasive procedures. While there is insufficient evidence from human research, the literature discusses the pharmacokinetic features of various formulations. The continuous relevance of CDs in developing and applying drug delivery systems is apparent, considering CDs' promising future in this field.

Parenteral-controlled drug delivery devices, including implants, are becoming more and more useful in real-world applications because they enable optimal treatment outcomes. In orthopaedics and dentistry, titanium implants are regarded as the gold standard of care. Among the most important characteristics of these metallic implants are their low flexibility, corrosion resistance, and biocompatibility. Nonetheless, insufficient osseointegration may result in a long-term clinical failure of implants. Inadequate

Table 16
Types of implants, CD used & formation method.

Drug	Type of CD	Formation	Types of Implants	Reference
Pirfenidone (PFD)	β-CD/citric acid & 2-hydroxypropyl-β-CD/citric acid	Chitosan grafting	Smooth and textured breast implant	[496]
Rose Bengal	β-CD/citric acid & 2-hydroxypropyl-β-CD/citric acid	Chitosan grafting	Smooth and textured breast implant	[496]
KR-12	β-CD/citric acid & 2-hydroxypropyl-β-CD/citric acid	Chitosan grafting	Smooth and textured breast implant	[496]
Tetracycline	Anionic beta CD	Poly (acrylic acid) (PAA) and poly(l-lysine) (PLL) in a ten double layers ($[PAA/PLL]_{10}$) coating onto titanium	Percutaneous implants	[312,508]
Simvastatin	β-CD	stent covered by Simvastatin loaded nanofibers (NFs) produced by electrospinning	Stent coating	[508]
Vancomycin hydrochloride	Hydroxypropyl-β-CD	Microporous hydroxyapatite discs were prepared by sintering and subsequently functionalized with hydroxypropyl-β-CD	Bone implants	[500]
Ciprofloxacin hydrochloride	Hydroxypropyl-β-CD	Microporous hydroxyapatite discs were prepared by sintering and subsequently functionalized with hydroxypropyl-β-CD	Bone implants	[501]
Toluidine blue O Gentamicin	Poly β-CD, Poly Hydroxypropyl-β-CD and Poly Methyl-β-CD	Poly CD functionalized Ti–Hydroxyappatite	Orthopedic implant	[501]
Tobramycin and rifampicin	Poly β-CD, Poly Hydroxypropyl-β-CD and Poly Methyl-β-CD	Poly CD functionalized Ti–Hydroxyappatite	Hip implant	[510]
Resveratrol	α, β & γ-CD	Polymerized CD hydrogel disks were synthesized from lightly crosslinked CD prepolymer	Neural probes implant	[509]
SN-38 (7-Ethyl-10-hydroxycamptothecin)	β-CD	Poly (ethylene glycol) (PEG), poly(ε-caprolactone), and poly(D, L-lactide)	Injectable polymer implants	[503]
Curcumin	2-hydroxypropyl-β-CD	poly (ε-caprolactone) & Curcumin	Polymer implants	[491]
Diclofenac	β-CD	Copolymerization with glycidyl methacrylate (GMA) at various proportions and β-CD	Medicated contact lenses	[519]
Leuprolide acetate	β-CD	Poly (lactic acid-co-glycolic acid) (PLGA) loaded with leuprolide acetate/β-CD (LA/β-CD) complex	In situ forming implants	[497]
Ciprofloxacin	Hydroxypropyl-β-CD	PLLA knit through its functionalization with a CD polymer (polyCD) and activation with ciprofloxacin	Parietal reinforcement implant	[511]
Doxorubicin	β-CD	poly (Sebacic acid-co-ricinoleic-ester anhydride) with β-CD-loaded doxorubicin	Biodegradable polymer implant	[498]
Green tea polyphenols	γ-CD	poly (ε-caprolactone) (PCL)	Polymeric implant	[493]
Tranilast, SU5416, 2-methoxyestradiol, and silibinin	β-CD, γ-CD	CD macromonomers lightly crosslinked with epicholohydrin	Polymeric implant	[520]
Ciprofloxacin	hydroxypropyl-γ-CD (HPγCD)	polypropylene (PP) mesh with citric acid and hydroxypropyl-γ-CD (HPγCD)	Abdominal wall implant	[506]

osseointegration can lead to unpleasant revision operations because it causes inflammation, mobility, increased bone resorption, and osteolysis. It has been demonstrated that topographical changes, increased hydrophilicity, and the creation of controlled-release drug-loading systems enhance cellular adhesion, proliferation, and differentiation. Better osseointegration is clearly demonstrated by surface alterations combined with drug coating, particularly in challenging degenerative disorders, including osteoporosis, osteoarthritis, and osteogenesis imperfecta. Osteointegration is accelerated by anabolic bone-acting medications such as strontium ranelate, vitamin D, prostaglandin-EP4-receptor antagonist, parathyroid hormone peptides, simvastatin, and anti-catabolic bone-acting medications like calcitonin, bisphosphonates, and selective oestrogen receptor modulators. Furthermore, a range of proteins, peptides, and growth factors might be used to complement the concept of localized treatment. Common methods for loading these materials onto modified titanium surfaces include direct coating, adsorption, and incorporating biodegradable polymers. The main strategy for achieving the ideal drug loading involves making a crucial trade-off between elements that hinder a drug's rapid release and those that permit a steady, continuous release. The effectiveness of layer-by-layer coating via electrospinning, hydrogel coating, and adsorption enabled by differential charge on metallic surfaces is now better understood, thanks to recent developments. To promote faster and better osseointegration, this study addresses the current strategies and obstacles for developing reliable and sustained drug delivery systems on titanium implants.

The findings unequivocally show the practicability of functionalizing the CD coating as an implant using the unique poly CD coating technique for a long-lasting local drug administration. Controlled release technology is a compelling and promising approach for delivering antimicrobial agents to specified locations, optimizing their dosage, and ensuring sustainability over the release period. This strategy enables the effective and safe use of existing antibiotics. In recent years, there has been a growing interest in employing

carrier molecules of antimicrobial compounds to create host-guest inclusion complexes with different medications. This strategy, based on biomaterials, aims to prevent infections. The significant medical ramifications and subsequent outcomes of infection linked to percutaneous implant devices highlight the necessity of developing solutions for both prevention and therapy that are resistant to antibiotic resistance. In summary, this successfully demonstrates the proof-of-principle for utilizing current orthopedic implants coated with HA as a medication delivery method to effectively manage peri-implant bone infection.

In conclusion, this review emphasizes the significance of CDs in inflammatory treatment. They have been used to increase access to and enhance the distribution of various licensed pharmaceuticals. However, CDs can influence complement activation and chol-mediated inflammatory processes. Finally, this study suggests that medicine and CDs may work together to combat inflammation. By setting the framework for future advancements, CD adoption will soon enable the development of numerous more complex apps.

CDs are widely used in drug delivery in the pharmaceutical industry because of their versatility and complexity. Notably, these compounds may interact unfavorably with other additives in the formulation, making it critical to detect any such interactions. It is also vital to recognize the many factors that may influence complex formation to develop drug/CD combinations with desirable characteristics that are economically feasible. As CDs find new uses in drug delivery, we may expect these polymers to answer a wide range of challenges connected to the distribution of novel drugs via multiple routes.

CRediT authorship contribution statement

Sharif Neaz: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Md Mahbub Alam:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization. **Abu Bin Imran:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Data availability

The data used to support the findings of this study are included within the article. These data will be available when the researchers request it.

Declaration of competing interest

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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