Role of Cyclodextrins in Nanoparticle Based Drug Delivery Systems

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Abstract

Cyclodextrins (CDs) are cyclic oligosaccharides with unique hydrophobic interior surface. Three parent CDs, α-CD, β-CD, and γ-CD, are further chemically modified primarily to make them suited for parenteral administration and these are used for many pharmaceutical applications. CDs offer distinctive advantages due to their unique ability to form inclusion complexes with a variety of organic and inorganic lipophilic molecules. This attribute is promising for a wide range of fields such as drug delivery, cancer therapy, gene delivery, and biosensing. In recent years, CDs have become more commonly used as functional materials in nanoparticle (NP) based drug delivery. The properties of NPs can be advantageously modified by the inclusion of CDs or their derivatives. CD conjugated NPs (CD-NPs) have many benefits such as improved drug solubility, serve as drug carriers to specific locations such as cancer cells, which reduces toxicity to normal cells. Additionally, CDs can overcome the limitations of NPs such as low encapsulation efficiency and drug loading. This review will discuss the various uses of CDs as it applies to nanoparticle based drug carriers. Specifically how CDs enhance the characteristics of polymeric, magnetic, lipid, metallic and mesoporous NPs are discussed.

Keywords:
cyclodextrin, nanotechnology, biomedical, nanoparticles, inclusion complexes, solubilizing agents
Introduction

Cyclodextrins (CDs) are a group of unique compounds composed of rings of sugar molecules, α-1, 4-linked α-D-glucopyranose, making them cyclic oligosaccharides (Figure 1). French scientist Villiers first discovered CDs in 1891 when he noticed that starch produces a crystalline substance after the digestion by Bacillus amylobacter. Amylases and glycosyl transferase, successfully break a turn in the starch helix and fuse the two ends of the fragment, thereby creating a cyclic molecule, the non-reducing CD. The three natural parent CDs produced from the starch digestion are α-CD, β-CD, and γ-CD, consisting of 6, 7, and 8 glycopyranose units, respectively. The CD interior is lined with carbons and ethereal oxygen of the glucose residues, while the exterior is lined with hydroxyl groups. Therefore, the parent CD molecules are amphiphilic structures containing a hydrophobic core and a hydrophilic shell. Additionally, the parent CDs have a homogenous crystalline structure and are non-hygroscopic. However, the parent CDs have limited aqueous solubility; therefore, a plethora of derivatives have been developed. The hydroxyl groups of the parent CD are functionalized to obtain more hydrophilic, hydrophobic, or ionizable derivatives. Common processes used to synthesize CD derivatives are amination, etherification, and esterification of the primary face and secondary face hydroxyl groups. Cyclodextrin derivatives and their applications have been extensively published in the recent years.

Cyclodextrins offer distinctive advantages due to their unique ability to form inclusion complexes with a variety of organic and inorganic lipophilic molecules. This attribute is promising for a wide range of nanotechnology fields such as drug delivery, cancer therapy, gene delivery, and biosensing. CDs are beneficial in drug delivery because the bucket shaped cavity protects the drug from degredation and irritation is reduced at the administration site. The weak bonds of the inclusion complex allow the drug to become temporarily lodged in the CD cavity, yielding improved solubility and bioavailability.

Cyclodextrins have also been useful for oral drug delivery due to the sweet taste and taste masking properties. Additionally, the inclusion complex prevents drug-drug or drug-excipient interactions.
Cyclodextrins are useful in cancer therapy because they increase the loading capacity and encapsulation efficiency of tumor-targeting NP delivery systems. Gene delivery uses CDs to assist in the destabilization of biological membranes, because CDs bind and remove the cholesterol in the membrane making the cell membranes more permeable. Additionally, CDs can stabilize a biological molecule for delivery by protecting them from non-specific interactions. For biosensing applications, CDs help immobilize the target molecule onto the electrode by increasing sensitivity and selectivity. Table 1 lists US Food and Drug Administration (FDA) approved CDs and their individual uses in dosage forms for various routes of administration.

The inclusion process between CD and the ‘guest’ molecule occurs when the CD expels enthalpy rich water molecules from its hydrophobic core due to competition from the lipophilic guest molecule. Chemical bonds are neither created nor destroyed during the complexation. The inclusion complex occurs via electrostatic and non-covalent interactions such as hydrogen bonding, van der Waals forces as well as release of ring strain, especially in α-CD. The physicochemical properties of the complex differ from that of the host and guest molecule alone. Potential guest molecules can be small molecular weight drugs (usually less than 500 Daltons), hydrophobic amino acid structures, enzymes and siRNA. The guest molecules are caged and protected from oxygen, water, heat, and radiation; thereby preventing degradation of the guest molecule.

Cyclodextrins are generally considered safe for oral administration because they are not absorbed across gastrointestinal tract and are eliminated in feces. The few CDs that do get absorbed are rapidly eliminated from the body and are excreted in the urine unmetabolized. A study revealed that after intravenous administration, 100% of a given dose of CD was recovered in the human urine after 6-12 hours. Natural CDs are toxic when administered intravenously. For instance, α-CD causes aggregates and β-CD causes nephrotoxicity when given via parenteral route; therefore, these CDs are not used for injections. Additionally, if the kidneys are already damaged, large amounts of CDs accumulate leading
to vacuolation of the proximal tubular epithelium. The vacuolation will reverse itself once the CD treatment is removed. Furthermore, some CDs (β-CD and HP-β-CD) form insoluble complexes with cholesterol in the blood and collect in the kidneys leading to nephrotoxicity. Therefore, for specific biological applications care must be taken when deciding which CDs to use.

In recent years, CDs have become more commonly used as functional materials in NP based drug delivery. Nanoparticles (NPs) have many benefits such as targeting drug carriers to specific locations, such as cancer cells, which reduces toxicity to normal cells. Additionally, CDs can overcome the limitations of NPs such as low encapsulation efficiency and drug loading. Nanoparticles aided by CDs yield a novel drug delivery system with the benefits of both components: the CDs offer improved water solubility and drug loading while the NPs provide targeted drug delivery. Furthermore, some of the complexes created in CD-assisted NPs are considered non-conventional complexes because the CDs will act as surfactants or result in aggregation. Together these aforementioned elements have resulted in a large variety of CD-linked NPs such as lipid, magnetic, gold, and polymeric NPs.

A literature search on “cyclodextrins” and “nanoparticles” resulted in over 1000 articles using the PubMed database, which included various types of NPs in the gene or drug delivery and biosensing. Among the many are a few recent review articles that discuss CDs and their applications, specifically on the formulation of NPs. The scope of this article is to expand the focus of CD linked NPs and their applications in chemotherapeutics, drug delivery, gene delivery, and biosensing. This article will also focus on reviewing the role of CDs in designing the specific types of NPs such as magnetic, polymeric, lipid-based NPs. In addition, this article will also explore newer types of CD NPs such as mesoporous, gold and silver NP. Table 2 lists general types of nonionic, anionic, and cationic CDs and their applications in various types of NPs.
Application of CDs in Magnetic Nanoparticles

Magnetic nanoparticles (MNPs) have become more common in biomedical applications due to advantageous properties such as: narrow size distribution, high colloidal stability, low toxicity, and high specific surface area. Magnetic NPs also exhibit superparamagnetism: they are easily magnetized when an external magnetic field is applied and they revert back to a demagnetized nature once the magnetic field is removed. This valuable property makes these NPs easy for magnetic separation, removal and recovery. Such magnetic property enables the NPs to localize at the targeted site within the human body in response to the externally applied magnetic field. However, MNPs tend to agglomerate due to small size and high surface free energy, leading to lack of tissue distribution and intracellular targeting upon administration. Additionally, bare magnetic NPs are easily oxidized leading to demagnetization. Therefore, silica is generally added to the surface of the NP to maintain the stability of magnetic NPs. Cyclodextrins are commonly linked to the silica-coated surface of the MNP via linkers, such as 3-aminopropyltriethoxysilane (APTS). This conjugation allows the CD to function as a carrier for drugs, proteins, and cell targeting ligands on the surface of the MNPs. Furthermore, to prevent premature drug release into non-target regions, such as blood and extracellular space, some magnetic nanoparticles are equipped with stimuli-sensitive drug release. Stimuli responsive factors include pH, light, enzymes, temperature, competitive binding and redox. For instance, certain linkers are cleavable once the MNPs are in the cancer cell microenvironment. The most common use of functionalized magnetic CD NPs is for hydrophobic anti-cancer drug delivery. However, MNPs have been applied to other applications such as solid-phase extraction and biosensing materials.

Magnetic NPs have been developed for the delivery of 5-fluorouracil (5-FU), which is used to treat different cancers (breast, stomach, colon, and lung) and has detrimental effects on normal cells, as it is not targeted specifically for the tumor cells. Anirudhan et al. produced magnetic hydrogels by the chemical precipitation method for the controlled delivery of 5-FU. β-CD was grafted with maleic
anhydride to create a new CD derivative, maleated CD (MACD), which consisted of unique properties: increased water solubility, pH sensitivity, and lowered toxicity. This system was tested on breast cancer cells and the results suggested that the cytotoxicity was significantly higher as compared to 5-FU alone (control). The CD-MNP delivery system also displayed lower toxic side effects to normal cells. Lv et al.26 fabricated a pH-dependent 5-FU delivery system consisting of magnetic colloidal nanocrystals decorated with β-CD polymer brushes (polymers tethered to a surface). The β-CD magnetic nanocrystals, averaging 230 nm in diameter, yielded a 32% higher 5-FU adsorption capacity as compared to CD-free magnetic nanocrystals. Similarly, Ding et al.13 created a MNP (Fe$_3$O$_4$) hydrogel for the delivery of 5-FU by crosslinking carboxymethyl-β-CD (CM-β-CD) with chitosan via emulsion chemical crosslinking-method. The anionic CM-β-CD has a high aqueous solubility and low toxicity, while the cationic chitosan provides the MNP with mucoadhesive properties. The hydrogel yielded 97.6% encapsulation efficiency due to the negative charged CM-β-CD having strong electrostatic interactions with the positively charged 5-FU. Furthermore, unlike previous examples, Ding’s tumor-targeting drug delivery system provided dual mechanisms of drug release: diffusion of drug molecules and degradation of polymer chitosan matrix, giving a desirable controlled released mechanism.

Recently, all-trans retinoic acid (ATRA) has been studied in the treatment of various types of cancers27. Banerjee et al. 28 devised Fe$_3$O$_4$ MNPs coated with gum arabic grafted with HP-β-CD for the delivery of ATRA. The resultant NPs had a mean diameter of 17 nm, and exhibited a significantly higher capability for ATRA loading than those without HP-β-CD. Badruddoza et al.29 constructed a silica coated Fe$_3$O$_4$ MNP cross-linked with CM-β-CD for the delivery of ATRA. These MNPs had mean diameter of 11 nm and contained two functionalities that Banerjee’s MNPs lacked: fluorescence labeling by FITC and a common cancer-targeting ligand, folic acid (Figure 2).29. Where APTS was used to conjugate the CM-β-CD, folic acid, and FITC to the MNP surface. The amount of ATRA absorbed to Banerjee’s MNPs as well as the release profiles were comparable to dual-functionalized MNPs developed by Badruddoza; however,
the latter MNPs offer the advantage of targetability to cancer cells. Cytotoxicity studies showed that the
drug-loaded functionalized MNPs increased cellular uptake and successfully targeted tumor cells due to
folic acid receptor binding.

Cyclodextrin-MNPs are also used for solid-phase extraction techniques, because the target molecule can
complex with the CD and the MNPs can be removed using a magnet and reused with the same
efficiency. One specific example is the solid-phase extraction of a common cancer biomarker 5-
hydroxyindole-3-acetic acid (5-HIAA) from urine using Fe₃O₄-APTS-CD complex. 5-HIAA forms a strong
complex with mono-6-deoxy-6(p-tolylsufonyl)-β-CD (Ts-β-CD) allowing for easy identification and
extraction. Similarly, Shamekhi grafted β-CD on 3-mercaptopropyltrimethoxy silane modified Fe₃O₄
nanoparticle for the sorption and extraction of sertraline hydrochloride, Zoloft, from human biological
fluids. Abdolmohammad-Zadeh et al. achieved an extremely high recovery of gemfibrozil from
pharmaceutical wastewater and human serum, by grafting β-CD onto a graphene oxide/Fe₃O₄ nano-
hybrid.

A unique solid-phase extraction technique using CM-β-CD conjugated MNPs to prevent glycation of
proteins was reported. CM-β-CD was conjugated to Fe₃O₄ NPs using tetraethyl orthosilicate. The
particle size of CM-β-CD-MNPs was about 20 nm, which is slightly bigger than that of bare MNPs.
Thioflavin was used to measure the amount of amyloid formation in the presence and absence of CM-β-
CD with the MNP. The amount of thioflavin was significantly lower in the presence of CM-β-CD proving
that CD protects the proteins and prevents amyloid formation. Therefore, the strong complexation
capabilities of CDs make them optimal for extraction of a plethora of compounds in a variety of
environments.

MNPs combined with CDs have also been utilized for biosensing applications, since they are capable of
capturing the target molecule more effectively while exhibiting the same amount of
superparamagnetism. A variety of methods have been used to create CD-MNPs for biosensing, some more complex than others. A biosensor based on mono-6-formyl-β-CD coated MNPs to detect catechol and xanthine was reported\textsuperscript{12}. In this case, the magnetic core (Fe\textsubscript{3}O\textsubscript{4}) was coated with APTS and then mono-6-formyl-β-CD was attached. NaBH\textsubscript{3}CN was introduced to the system to reduce the CDs to CD-substituted secondary derivatives. These MNPs are then attached to an electrode. Next, the CDs form complexes with two adamantane-modified enzymes, tyrosine and xanthine oxidase, which are used to detect catechol and xanthine. These CD-MNP electrodes showed 10 and 6 times higher sensitivity and a lower detection limit when compared to the original tyrosine and xanthine biosensors. Similarly, Xie et al.\textsuperscript{32} designed an electrochemical biosensing electrode to detect prostate specific antigens with high sensitivity and good conductivity. The MNPs contained the β-CD-ferrocene complex, which were used to transduce peptide cleavage events into electrochemical signals.

Sinniah et al.\textsuperscript{18} constructed MNPs coated with β-CD functionalized-ionic liquid (Fe\textsubscript{3}O\textsubscript{4}-β-CD-IL) attached to glass carbon electrodes for the detection of Bisphenol A (BPA). The ionic liquids decreased aggregation and provided a stabilized protective shell for the MNPs. Finally, Duan et al.\textsuperscript{33} avoided using conventional electrodes and instead they fabricated surface molecular imprint polymers from the polymerization of β-CD, chitosan, and graphene oxide to capture bovine serum albumin. This chemiluminescence biosensor provided high sensitivity and near perfect recovery.

**Application of CDs in Polymeric CD Nanoparticles**

Polymeric NPs (PNPs) are highly versatile, as various functionalities decorated on the NP surface can determine when and where the NP disassembles in the body. For instance, functionalities can be added to control the response of the PNPs to pH, temperature, light, magnetic fields, and oxidative, reductive, and enzymatic conditions\textsuperscript{34}. Polymeric NPs are both biocompatible and biodegradable, so the fate of the PNPs in biological system is not a concern. Examples of natural and synthetic polymers used in the
PNPs are: chitosan, polyethylene glycol (PEG), poly(lactic acid) (PLA), and poly(lactic-co-glycolic acid) (PLGA)\textsuperscript{35-37}. By varying the polymer composition, the particle size, surface charge, the drug release can be altered.

Conjugation of CDs with PNPs allow the PNPs to successfully deliver poorly soluble drugs by encapsulating the drugs in the hydrophobic cyclodextrin core. The PNPs have CDs forming the outer shell, while the core of the PNP is a synthetic or natural polymer. Therefore, the drugs can be loaded in the core of the PNP or it can be complexed with the CD in the outer shell. Other PNPs simply have a cross linked matrix consisting of polymers and CDs\textsuperscript{36}. The CD loaded PNPs are used for intravenous dual-drug delivery or siRNA delivery to the tumor sites.

**Chitosan-CD Nanoparticles**

Chitosan is a common polysaccharide obtained from shrimp shells. This polymer is cationic in nature and can be conjugated with CDs to provide NPs with high drug loading, mucoadhesive properties and targeting capabilities. Zhang et al.\textsuperscript{38} designed acid-resistant PNPs containing cationic-β-CD (CP-β-CD) and chitosan for the slow-release oral delivery of insulin. Three variations of CP-β-CDs were formulated with the following ratios of β-CD/epichlorohydrin/choline chloride: 1/15/4, 1/15/6, and 1/15/10, with particle sizes of 146, 338, 165 nm, respectively. The cationic charge of the CP-β-CD protected the insulin from degradation within the stomach's gastric fluids, which in turn allowed for a higher release of insulin (40%) compared to insulin alone (18%) in the intestinal fluids. In a similar study this formulation was altered by using a chitosan derivative, trimethyl chitosan (TMC), because TMC is soluble at higher pH values and penetrates enterocytes, which produced a particle size of 150.82 ± 21 nm\textsuperscript{39}. In both scenarios, the cationic β-CD was modified using a quaternary ammonium group; yielding better drug-CD complexation and leaving the CD unable to bind to cholesterol. Additionally, alginates were added to both formulations to create a gel-like matrix when the formulation comes in contact with Ca\textsuperscript{2+} ions as
well in an acidic pH; therefore, the drug molecule can be carried through the stomach protected from acid degradation and then can be released later in the intestine. The cumulative intestinal release of insulin showed that TMC NPs had a 38% lower release than the chitosan CP-β-CD-NPs. Caco2 cell permeability studies performed showed higher permeability by TMC NPs, most likely due to the positive charge of the NPs. Release studies in simulated gastric and intestinal medium revealed that the chitosan derivative had a 27% higher release in the intestine compared to the original chitosan/β-CD mixture, making the TMC β-CD NPs more acceptable for oral insulin delivery. In another study, a low molecular weight chitosan was used to increase the water solubility of hydrocortisone. Ionotropic gelation technique was used to prepare a PNP matrix consisting of SBE-β-CD (anionic) cross-linked with chitosan (cationic), which had approximately 3-times higher release rate when compared to hydrocortisone alone.

**PEG-CD Nanoparticles**

NPs are commonly PEGylated to increase circulation time or to enhance permeation across biological membranes. Such properties of PEG could be enhanced when paired with CDs. CDs have immunogenicity and multiple chemical equivalent binding sites for attachment of functional groups, making them ideal for gene delivery. For instance, PEGylated CDs are commonly used for the delivery of siRNA. Godhino et al. determined that an increase in PEG length as well as PEG molecular weight led to an increase in stability of PEGylated CDs used for siRNA delivery. Similarly, PEGylated cyclodextrin (CD) nanoparticles tagged with a CNS-targeting peptide, derived from the rabies virus glycoprotein (RVG), was formulated and characterized. The goal of the formulation was to protect siRNA from degradation, enhance cell uptake and gene silencing efficiency. Various amphiphilic cyclodextrin derivatives such as SC12-CD-click-propylamine (CD1), SC12-CD-click-PEG500 (CD2), SC12-CD-click-PEG500-ethylamine (CD3) and SC12-CD-clickPEG500-RVG (CD4) were synthesized and co-formulated to form nanoparticles containing siRNA. The CD4 siRNA nanoparticles showed enhanced receptor-specific
cellular uptake compared to the untargeted nano-complexes (CD1-CD3) in human glioblastoma cells and achieved gene knockdown. This CD based nano-complex was suitable for systemic delivery of siRNA targeting brain cancer.

**PLA-CD Nanoparticles**

Polylactic acid (PLA) is a safe biodegradable thermoplastic polymer and has been used extensively in NP formulations. A vast amount of research has been conducted on NPs, which consist of a PLA core and a CD shell, for the delivery of hydrophobic anticancer drugs. For instance, Wang et al. formulated NPs containing PLA and 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine (DPPE) along with hydrophilic HP-β-CD to improve the encapsulation efficiency of doxorubicin. These PNPs had improved cytotoxicity and cellular uptake towards A549 cancer cells compared to that of free doxorubicin. Similarly, Miao et al. used a similar system (PLA-DPPE-HP-β-CD) to deliver paclitaxel, but added an integrin-specific targeting peptide. The targeted NPs resulted in high loading capacity as well as a 4-times increase in tumor cell inhibition relative to paclitaxel-loaded NPs. Fagui et al. formulated a PLA core NP with a layered shell of alternating cationic and anionic β-CD (Figure 3) for the controlled intravenous delivery of benzophenone. Increasing the number of alternating β-CD layers resulted in a more sustained release PNP system.

**PLGA-CD Nanoparticles**

Poly(lactic acid and glycolic acid) (PLGA) is another safe biodegradable polymer, in which the lactic acid and glycolic acid content can be varied for degradation at a certain time. PLGA-CD NPs are commonly used for the delivery of poorly water-soluble drugs. Furthermore, like PLA NPs, some PLGA-CD NPs consist of a PLGA core and a CD shell, which allows for the delivery of two different drugs to the targeted site. For instance, Ruiz-Esparza et al. created a sequence-specific dual drug release system for model drugs: rhodamine and Bodipy®, common fluorophores. The nested PNP consists of a PLGA
core that contains rhodamine, while the shell is composed of quaternary ammonium β-cyclodextrin (QA-β-CD) complexed with Bodipy®, with a size of 142 nm. The various forces holding the QA-β-CD shell and PLGA core together are thought to be Van der Waals, ionic and molecular interactions and are responsible for the profound stability of the PNP. The release of Bodipy® was governed by the detachment of the QA-β-CD shell from the polymeric core, once the polymeric core is exposed the rhodamine slowly begins to release from the high viscosity PLGA. As expected and desired, Bodipy® was released at a 2.5 times greater rate when compared to rhodamine, since Bodipy was located in the CD nanoparticle shell and rhodamine was located in the PLGA core. These CD-PNPs showed high internalization rates in breast cancer cells, due to the positive charge of the QA-β-CD shell. In another study, the PLGA-CD NPs containing oxaprozin-methyl-β-CD complex were formulated for enhanced drug penetration in the inflamed tissues. The methyl-β-CD oxaprozin NPs demonstrated 84% higher oxaprozin release than oxaprozin-NPs. Similarly, the HP-β-CD-docetaxel and heptaarginine were loaded in PLGA NPs. The oral bioavailability of docetaxel-CD-heptaarginine NPs increased 9-times as compared to free docetaxel. Tao et al. used PLGA-HP-β-CD NPs to enhance permeation of puerarin across the blood-brain barrier for the treatment of ischemic-reperfusion induced brain injury. The PLGA-HP-β-CD-puerarin NPs significantly reduced the infarction volume as compared to puerarin alone after a three-day period, suggesting that the HP-β-CD aided in transporting puerarin across the blood-brain barrier.

Recently, it has been reported that CDs can prevent drug metabolism by cytochrome P450 3A (CYP3A) and the inhibitory effects of P-glycoprotein (P-gp) when combined with PNPs. Zhang et al. examined poly(methyl vinyl ether-co-maleic anhydride)-graft-HP-β-CD amphiphilic copolymer (CD-PVM/MA) as a PNP oral carrier for tacrolimus, a low bioavailability drug. CD-PVM/MA was prepared by using 1-ethyl-3-(3-(dimethylamino)propyl) carbodiimide (EDC) as a coupling agent to link the PVM/MA to the backbone of the HP-β-CD. The size of the NPs obtained was 273.7 ± 13.3 nm. Fluorescence studies using coumarin-
revealed that the PNPs are taken into the cell by two pathways: clathrin- and caveolae-mediated endocytosis. The former mechanism led the PNPs to blood capillaries via passive diffusion. The latter mechanism led to lymphatic absorption of the PNPs, which bypassed the first-pass effect, thereby increasing the bioavailability of tacrolimus by 20-times. In a similar study, HP-β-CD complexed with fisetin (a plant polyphenol) provided enhanced solubility and loading capacity into PLGA NPs; ~79% loading was achieved with the complexed drug compared to 47% with the native drug. The HP-β-CD also increased oral bioavailability and revealed 4 fold higher cytotoxicity compared to free fisetin, presumably due to the P450/P-gp inhibitory effects.

Also, CDs can be added to PNP formulations to act as a skin permeation enhancer. For example, Conte et al. examined the distribution of Zinc (II) phthalocyanine (ZnPc) in the skin layers after being delivered by an amphiphilic diblock copolymer, polyethylene glycol-b-polycaprolactone (PEG-b-PCL), assisted by HP-β-CD. In this case, HP-β-CD was not attached to the PNPs but it was added to the PNP mixture to assist with transport and enhance skin penetration of the drug (Figure 4). Bare PNPs were only able to deliver the ZnPc to the stratum corneum while the PNPs accompanied by HP-β-CD were able to penetrate deeper into the viable epidermis. Fluorescent imaging revealed that the HP-β-CD PNPs penetrated to deeper layers of skin, proving that HP-β-CD was able to alter the barrier characteristics of the skin layers in order to transport the drug molecules. However, no effects on the lipid composition of the skin could be found, meaning HP-β-CD only alters the skin’s water activity to enhance solute penetration.

Furthermore, García-González et al. found that β-CD adsorbed onto PLGA NPs avoids interactions with mucin, thereby increasing internalization into the nucleus and cytoplasm of the intestinal epithelial Caco-2 cells. The interaction between the NPs and Caco-2 cells revealed that NPs with β-CD had greater cell internalization, having higher concentratoins in the cytoplasm and nucleus as compared to those without β-CD. The hydrophilic property and permeation enhancing activity of the β-CD-PLGA-NPs made them an effective drug delivery carrier for oral administration.
**Lipid CD Nanoparticles**

Lipid CD nanoparticles (L-CD-NPs) belong to one of the following categories: colloidal drug carriers, liposomes, nanoemulsions, solid lipid nanoparticles (SLN) or nanostructured lipid carriers (NLC). Liposomes consist of a lipid bilayer enclosing an aqueous core; where the core can store hydrophilic drugs and the shell can hold lipophilic drugs. Additionally, liposomes allow for easier penetration of a cell wall as the lipid bilayer mimics the cell wall; therefore, payloads can either be delivered to the cell membrane or the interior of the cell. Nanoemulsions (typically oil-in-water type) offer ease of preparation and can be delivered through a variety of routes. SLNs are completely solid and consist of a single lipid layer encasing a solid lipid core, whereas NLCs are composed of both liquid and solid lipids yielding a less compact structure allowing for higher drug loading (Figure 5). Additionally, NLCs offer the ability to form micelles with bile salts in the intestine, thereby passing liver metabolism. By introducing CDs into lipid NP systems, an increase in hydrophobic drug loading can be achieved within the aqueous components of the L-CD-NPs, while still maintaining the targetability of L-CD-NPs. The benefits of adding CDs to LNPs are specific for each type of LNPs.

**Nanoemulsions**

Nanoemulsions containing CDs, also known as Pickering nanoemulsions, are most commonly used for pharmaceutical and nutraceutical delivery. The CDs decrease the emulsion droplet size, by reducing the interfacial tension, thereby providing a more stable product compared to traditional nanoemulsions. For instance, a CD-nanoemulsion for the delivery of lutein showed that CD increased the stability, entrapment efficiency and partition coefficient of the lutein into the eye (sclera). Similarly, the poor aqueous solubility and storage stability of Kenaf (Hibiscus Cannabinus L) oil was overcome by a Pickering nanoemulsion using β-CD. In this system, β-CD served as a co-emulsifier with sodium caseinate and Tween 20. Gharibzahedi et al. designed a Pickering nanoemulsion with an optimum ratio of Tween 80:
Span 20: HP-β-CD: sunflower oil, which produced the most stable nanoemulsion. The water insoluble anti-cancer drug, canthaxanthin (Dietzia natronolimnaea), was successfully solubilized by HP-β-CD and the amphiphilic drug complex was incorporated into Pickering nanoemulsion.

**Liposomes**

Traditional liposomes allow lipophilic drugs to be trapped in the lipophilic shell of the liposome; however, these drugs are rapidly released, thus it is more desirable to store the drugs in the aqueous core \(^5^7\). CD-liposomes make this possible since the CDs can encapsulate the lipophilic drug and store it in the aqueous core of the liposome, these systems are termed “drug-in-CD-in-liposome” (DCL) \(^5^8\). For example, a hydrogel consisting of an aceclofenac DCL system for topical skin delivery was prepared (particle size, ~131 nm). Compared to the current marketed formulation, the aceclofenac-CD loaded liposomes had enhanced skin bioavailability, molecule stability and permeation in mice \(^5^9\). Another approach is that the lipophilic drug could be stored in both the core and shell yielding a dual-encapsulation method. Soo et al. \(^6^0\) loaded β-CD-resveratrol complexes into the hydrophilic core and resveratrol alone into the lipophilic shell, which led to a significant improvement in the drug release across a dialysis membrane (100% vs 40-60% for conventional formulation in 24 h), thus more drug was available to inhibit the growth of cancer cells. However, there is some concern as to whether or not the CDs will extract cholesterol from the liposomal wall leading to destabilization of the liposome. For instance, Piel et al. created a betamethasone-in-CD-in-liposome formulation and compared the effects on the liposomal structure by using different CDs such as HP-β-CD, β-CD, γ-CD, HP-γ-CD, Heptakis(2,6-di-O-methyl)-β-CD (Dimeb), heptakis(2,3,6-tri-O-methyl)-β-CD (Trimeb), methylated β-CD (Crysmeb), and randomly methylated β-CD (Rameb) to determine which CDs will remove cholesterol from the liposome causing destabilization of the NP \(^6^1\). The results revealed that the betamethasone (BM) formed stable complexes with HP-β-CD, Crysmeb, HP-γ-CD and Rameb; this is due to the fact that the CD has a higher affinity for the drug compared to the cholesterol. Even though the CD formulations yielded a higher
encapsulation efficiency, the BM-Rameb and BM-HP-γ-CD complex had the same release profile as the CD-free liposomal formulations. Even though CDs improve encapsulation they may not always yield a sufficient drug release depending on the formulation recipe. Joset et al.\textsuperscript{62} performed studies using Rameb inside cholesterol doped dimyristoyl-phosphatidylcholine (DMPC) liposomes and found that Rameb had a high affinity for the cholesterol since no drug was present. Therefore, liposomal stabilization will depend on the type of CD and guest molecule. Finally, Ji et al.\textsuperscript{63} used CDs to enhance the tumor targeting ability of the LNP on the outside of the liposomal wall. The outside of the liposome consisted of pirfenidone-loaded β-CD linked with a cleavable peptide, along with Arg-Gly-Asp peptides to target pancreatic tumor cells while the inside of the liposome contained the chemotherapeutic, gemcitabine\textsuperscript{63}. This effective enzymatic pathway allowed for increased gemcitabine perfusion within pancreatic tumor tissue, 3 and 6 times higher when compared to the free pirfenidone and the control, along with a successful reduction in tumor fibrosis.

\textbf{Solid Lipid Nanoparticles (SLNs)}

SLNs are more stable in biological fluids compared to nanoemulsions and liposomes, and are typically made from fatty acids, waxes, mono-, di-, triglycerides and surfactants of biological origin, thus they are well tolerated and metabolized by the body\textsuperscript{64}. Cyclodextrins can stabilize SLNs by taking the place of surfactants; however, only a few studies have been reported. Negi et al. prepared γ-CD-stearic acid inclusion complexes for their use in Lopinavir loaded SLNs\textsuperscript{52}. The γ-CD SLNs had higher drug loading and similar NP size (~212.5 nm) when compared to the CD-free drug-loaded SLNs (~180.6 nm). To eliminate the harmful effects of Cremophor EL in commercial paclitaxel formulations, Baek et al. used HP-β-CD to increase the cellular uptake of Cremophor EL-free paclitaxel-loaded SLNs in Caco-2 cells\textsuperscript{64, 65}. The HP-β-CD modified SLNs had a 5 fold higher cytotoxicity, and a 12 fold higher drug concentration in lymph nodes when compared to the solution formulation. In a later study, Baek et al. encapsulated paclitaxel and verapamil, a common p-Gp inhibitor, into CDs to further improve the uptake into MCF-7/ADR.
resistant breast cancer cells. This formulation provided sustained release of both compounds as well as increased cellular uptake, and down-regulated p-Gp expression compared to the solution in MCF-7/ADR resistant breast cancer cells. Recently, Gidwani et al. complexed altretamine with epichlorohydrin-β-CD which was loaded into SLNs, comprising of Poloxamer-188 and soya lecithin. This complexation led to enhanced solubility, resulting in 2.75 times higher oral bioavailability of altretamine compared to the free drug.

**Nanostructured lipid carriers**

When compared to SLNs, the imperfections in the NLC matrix yield higher drug loading, enhanced stability, and decreased chance of drug leakage. Drug-in-CD-in-NLCs are relatively new, but they have been used to improve the solubility of water insoluble drugs. Specifically, Lin et al. used β-CD to solubilize and improve the oral bioavailability of vinpocetine. The CD-NLCs maintained consistently small particle size and high encapsulation efficiency while still providing a higher dissolution rate in varying pH values, compared to the suspension and CD-free NLCs. Similarly, Cirri et al. created CD-NLCs by co-grinding Epichlorohydrin-β-CD and ketoprofen, which provided higher solubilizing action compared to Epichlorohydrin NLCs. The Epichlorohydrin β-CD NLCs had a 1.3-fold higher permeation rate through a lipophilic barrier compared to CD-free NLCs.

**Gold and Silver CD Nanoparticles**

Metallic NPs, such as gold and silver, are easily functionalized with ligands, antibodies and drugs; thus they have a wide variety of biological applications. Gold nanoparticles (AuNPs) and silver nanoparticles (AgNPs) have unique modifiable optical and electronic properties, which make them ideal for molecular imaging, drug/gene delivery, biosensors and therapeutic agents. Furthermore, AgNPs have antibacterial properties that make them desirable for drug delivery systems as they provide additional antimicrobial action. When combined with CDs, these metallic NPs can become more targeted and more
effective. Gold and silver CD NPs are commonly produced by connecting CD to the metallic core using a linker, such as adamantane, which forms a strong stable complex with the CDs. Sometimes the CDs are added by using CD-loaded macromolecules (CD-modified hyaluronic acid)\textsuperscript{11,72-74}. In some instances, the CDs can be capped directly on the surface of the metallic NP without the need for a linker\textsuperscript{75,76}. The CD molecules can then be functionalized or used to carry drugs, siRNA or targeting molecules (Figure 6).

The most common use of CD-AuNPs is for biosensor technology. A single-walled carbon nanotube framework was constructed with β-CD functionalized AuNPs attached to the surface, which encapsulated polymerized adamantane\textsuperscript{11}. The affinity between the polymerized adamantane and the β-CD functionalized AuNPs perfectly mimics the biological interactions of biotin and avidin. The high specific surface of the CD-AuNPs yielded a 3-factor increase in sensitivity and maximum current density with regards to glucose detection. Similarly, Manivannan\textsuperscript{77} mimicked the interactions of biotin and avidin by embedding AuNPs in a sol-gel silicate matrix that was topped with β-CD functionalized reduced graphene oxide nanosheets. The AuNPs increased the interactions between CDs and the reduced graphene oxide as well as improved the durability and electrical communication by behaving as miniature electrodes. Additionally, the CDs-AuNPs led to improved chemical current, which yielded a stronger synergistic electrocatalytic effect in the case of the CD-AuNPs when compared to the electrodes without gold and CDs.

Another common use of CD-AuNPs is for the targeted delivery of cancer therapeutics because the AuNPs can be used to induce radiofrequency ablation leading to destruction of cancer cells\textsuperscript{78,79}. Furthermore, the AuNPs allow for easier imaging of cancer cells. Wang et al.\textsuperscript{80} formulated β-CD AuNPs loaded with ferrocene which formed aggregates once inside the cell, the aggregation was triggered by intracellular glutathione. The aggregates increased in size leading to a proportional rise in AuNPs photothermal properties allowing the aggregates to cause apoptosis when exposed to near-infrared irradiation. Typically, AuNP linked CDs are more effective as anticancer therapeutics when combined
with other anticancer active molecules. For instance, Bakar et al. decreased breast cancer cell (MCF-7) proliferation by complexing various ligands (pinoresinol, lariciresinol, and secoisolariciresinol) with thiolated-β-CD and decorating them on the surface of AuNPs. Common anticancer drugs such as doxorubicin, paclitaxel, and docetaxel were incorporated into the CD-AuNPs and targeted to cancer cells via receptor-mediated endocytosis by a RGD peptide. Cell line studies revealed that the DOX-β-CD-AuNPs increased the uptake and cell cytotoxicity of U87 cancer cells while decreasing the damage done to the COS7 normal cells. Similarly, AuNPs decorated with PEG and poly(N-isopropylacrylamide) attached via complexation between β-CD and adamantane groups. When these AuNPs were exposed to a low temperature, the CD-AuNPs disassemble leading to release of the doxorubicin. These CD-AuNPs can transport the doxorubicin directly to the cancer cell nucleus, providing a unique release mechanism compared to liposomes and polymersomes. Chen et al. delivered paclitaxel to cancer cells by using biotin-modified CD-AuNPs (particle size, ~189 nm) as targeting moieties. The β-CD was linked using adamantane, which was weakened when exposed to acidic environment of the cancer cells, leading to an increase in drug release in cancer cells and a decrease in normal cells. Comparably, Yan et al. constructed AuNPs decorated with sulfhydrylation-modified β-CD and positively-charged PEG for the delivery of paclitaxel. This delivery system can effectively kill cancer cells with P-gp multidrug resistance. Similarly, a dual delivery nanoplatform of docetaxel and siRNA using gold nanorods coated with polyethylenimine-grafted β-CD was reported. When near-infrared laser irradiation (NIR) was applied to the CD-Au nanorod, the siRNA and docetaxel were released from the CD.

Like gold NPs, silver NPs display useful properties such as high functionalization and good catalytic activity, which make them ideal for biosensor applications. A sandwich-like α-fetoprotein (AFP) biosensor was designed by Gao et al. using β-CD functionalized silver as the mock enzyme with adamantane modified glucose oxidase attached on the bottom side, while the top side of the sandwich consisted of Fe-CD multiwalled carbon nanotubes (Figure 7). The AFP would become sandwiched
between the two layers, allowing for dual amplification of the electrochemical signals. In this study, β-CD functionalized silver was utilized as a mimic enzyme and a carrier, and β-CD based multiwalled carbon nanotubes were used as a platform.

A guanine and adenine biosensor utilized β-CD as the reducing agent between AgNO$_3$ and graphene oxide$^{86}$. β-CD also served as a stabilizer for the AgNPs-graphene oxide, as a dispersant and provided a microenvironment, which yielded an accelerated absorption of guanine and adenine leading to faster electrocatalysis. Similarly, Qu et al.$^{87}$ produced a more complex nanoparticle: AgNPs-graphene oxide using β-CD as the reducing agent, while CM-β-CD was used to complex and immobilize ferrocenecarboxylic acid for glucose biosensing. This allowed for the creation of a novel dual-path electron transfer mechanism, which lead to a more rapid biosensor. Overall, CD-AgNP biosensors allowed for a wider linear range, 1.7-fold increase in sensitivity, and a 2.8-fold decrease in the detection limit.

Jose et al.$^{88}$ utilized β-CD to increase the antibacterial/antifungal properties of silver without the addition of a drug. Likewise, Gannimani$^{76}$ combined the antibacterial properties of silver NPs with the hydrophobic drug carrier abilities of CD to form supramolecules that improved the antibacterial efficacy of chloramphenicol. A study comparing chloramphenicol with the three different parent CDs showed that γ-CD had the strongest interaction and anti-bacterial activity. Similarly, Gaurav et al. used β-CD to solubilize clotrimazole which was then attached to albumin stabilized AgNPs, while the albumin served to reduce the interaction between the AgNPs and the CD-clotrimazole complex$^{89}$. These hybrid NPs had a synergistic effect against candida yeast cells. Jaiswal et al.$^{90}$ found that in addition to the enhanced biofilm inhibition, the cytotoxicity of AgNPs in human HaCat skin cells was eliminated due to the protective capping of β-CD. To specifically target cancerous cells while continuing to avoid uptake in healthy cells, Zhai et al.$^{91}$ modified the surface of β-CD-capped AgNPs using para-aminothiophenol and folic acid. Therefore, CDs can be used to increase the water solubility of drugs paired with AgNPs as well
as diminish and possibly abolish cytotoxicity of healthy cells and enhance the anti-bacterial activity of AgNPs.

Mesoporous CD Nanoparticles

Mesoporous silica NPs (MSNs) linked with CDs are employed in imaging and cancer therapeutic delivery. MSNs have many advantages such as large surface area, good chemical and mechanical stability, and can be modified for controlled-release by tailoring the pore size of the mesostructure. Additionally, MSNs can be programmed for controlled release by modulating voltage, pH, enzymes, redox reactions and light. MSNs can be combined with CDs to create snap-top nanocarriers. The drug is carried within the MSN pores, which are capped by CDs complexed with a gatekeeper. A cycloreversion allows the CD complex to dissociate from the MSN surface, allowing for the drug to escape.

CD linked MSNs are utilized in the controlled delivery of anti-cancer drugs such as doxorubicin (DOX). Tumor specific enzyme-responsive MSNs were formulated using α-CD as the gatekeeper to release DOX when in contact with the designated tumor enzyme. This allowed for an “off-on” system, which reduced normal cell toxicity in vitro and increased tumor cell apoptosis and growth inhibition. Another internal biological signal release mechanism is acidic pH-activated MSNs, since the microenvironment of the tumor is more acidic than normal tissues. Chen et al. functionalized MSNs with β-CD gatekeepers and used 3-carboxy-5-nitrophenylboronic acid to initiate pH-dependent release of the DOX from the MSNs. In addition, fluorescein was linked to β-CD to allow for molecular imaging, which suggests that MSNs could be administered as probes to track the drug delivery pathway. pH-dependent MSNs were formulated with β-CD and α-CD as gatekeepers and found that β-CD had the better pH-responsive behavior. Wang et al. created monoferrocene-β-CD capped MSN with dual release mechanism, using voltage to release gemcitabine and pH to release the DOX. Similar internally-responsive release MSNs have been created by utilizing CDs and cancer therapeutics.
In contrast to internally controlled MSNs, other researchers have focused on regulating the release of doxorubicin from MSNs via external stimuli such as redox potential\textsuperscript{103, 104}, NIR irradiation\textsuperscript{105} and temperature, although no research has been done using CDs in temperature responsive MSNs to date. For instance, NIR-light-responsive supramolecular valves were lodged in the core of MSNs capped with β-CD for the delivery of doxorubicin was reported\textsuperscript{93}. Similarly, Quin-Lin et al\textsuperscript{106} combined β-CD with copper nanoparticles to serve as both gatekeeper and photothermal agent for the release of DOX. Finally, NIR-light-responsive MSNs with α-CDs as the gatekeepers were prepared and drug release experiments revealed that the α-CD successfully hindered the release of DOX in the absence of NIR (Figure 8)\textsuperscript{107}.

**Summary and Conclusion**

This review has provided all of the unique characteristics of CDs and their role in nanoparticle-based drug delivery systems. The properties of nanocarriers can be advantageously modified by the inclusion of parent CDs and their derivatives. The most important uses of CDs in the NPs are enhanced solubility and stability of drugs, improved targetability of NPs to tumor tissues, and increased drug loading capacity of the NPs. In particular, CDs were very useful for magnetic NPs in improving hydrophobic anti-cancer drug delivery, solid-phase extraction and biosensing materials. CDs were exploited with various polymeric NPs to improve the drug loading and targeting of anti-cancer drugs as well as siRNA delivery. Various lipid-based NPs (especially liposomes, SLNs, and NLCs) increased drug loading, targetability of cancer therapeutics and the NPs physical stability due to the addition of CDs. Gold and silver NPs linked CDs to the metallic surface for stabilized scaffolding of biosensors, targeting of cancer therapeutics, and increased antibacterial/antifungal characteristics of silver NPs. Finally, mesoporous NPs used CDs as gatekeepers over the porous NP core to provide a time-released or stimuli-dependent release drug delivery.
It is unknown if different CD derivatives behave differently when they are associated with the NPs in terms of drug loading, targetability or stability of the given system. Currently, the USFDA has only approved a few parent CDs (γ-CD for intravenous injection, β-CD for oral and topical delivery) and derivative CDs (HP-γ-CD for topical application, SBE-β-CD for injection, HP-β-CD for oral delivery and injection) as listed in Table 1. As more lipophilic drug compounds are discovered, CDs may very well become the next generation excipient to improve solubility of hydrophobic drugs in all routes and types of formulations, as they are safe and relatively non-irritating. Currently, NPs are at the forefront of drug delivery; therefore, it can be expected that newly devised NPs will continue to take advantage of CDs to improve NP characteristics.

Conflict of Interest: Authors declare no personal or financial conflict of interest with any parties

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Figure legends:

Figure 1: Chemical structure and 3D structure of cyclodextrin (CD). The CD interior is lined with carbons and ethereal oxygen of the glucose residues, while the exterior is lined with hydroxyl groups. Therefore, the CD molecules contain a hydrophobic core and a hydrophilic shell. Reproduced with permission from Zafar et al. 1

Figure 2: Structure of CM-\(\beta\)-CD conjugated fluorescein-doped magnetic silica nanoparticles. Fluorescence labeling by FITC and the addition of a common cancer-targeting ligand, folic acid. Reproduced with permission from Badruddoza et al. 29

Figure 3: Schematic for the preparation of PLA core nanoparticles coated with alternating layers of cationic \(\beta\)-CD polymer (light grey, a) and anionic \(\beta\)-CD (dark grey, b) for the controlled intravenous delivery of benzophenone. Reproduced with permission from Fagui et al. 44

Figure 4: Skin transport of PEGylated poly(\(\varepsilon\)-caprolactone) nanoparticles assisted by HP-\(\beta\)-CD, which serves as a permeation enhancer in this study. Reproduced with permission from Conte et al. 35

Figure 5: Solid Lipid Nanoparticles are solid consisting of a solid lipid core encased by a solid lipid core. Nanostructure Lipid Carriers are comprised of both solid and liquid lipids providing a less compact structure for higher drug loading. Reproduced with permission from Kumar et al. 110

Figure 6: Chemical structures and construction of CD-AuNPs loaded with paclitaxel (PTX). AuNPs are targeted and linked with assistance from the host guest interactions of the CDs, and then PTX is loaded in the matrix of the CD-AuNPs. Reproduced with permission from Chen et al. 73

Figure 7: Fabrication of a sandwich-like \(\alpha\)-fetoprotein (AFP) immunosensor using gold nanoparticles and \(\beta\)-CD functionalized silver as the mock enzyme. Adamantine modified glucose oxidase was
attached to the bottom, while the top included Fe-CD multiwalled carbon nanotubes. Reproduced with
permission from Gao et al. 85

Figure 8: Schematic illustration of the mesoporous silica nanoparticles (MSN)-CDs synthesis and the
controlled NIR-light-responsive release of DOX process by the $\alpha$-CD gatekeepers. Reproduced with
permission from Cui et al. 107
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Table 1: List of US-FDA approved CDs in various dosage forms

Table 2: Uses of CDs in various nanoparticle applications
Table 1: List of US-FDA approved CDs in various dosage forms

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<thead>
<tr>
<th>CD type</th>
<th>Route of administration and dosage form</th>
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<tbody>
<tr>
<td>α-CD</td>
<td>Powder for injection as solution</td>
</tr>
<tr>
<td>β-CD</td>
<td>Oral tablet, topical gel</td>
</tr>
<tr>
<td>γ-CD</td>
<td>Intravenous injection as solution</td>
</tr>
<tr>
<td>Sulfobutyl ether Na β-CD</td>
<td>Intravenous/intramuscular/subcutaneous injection as solution</td>
</tr>
<tr>
<td>Hydroxypropyl β-CD</td>
<td>Oral solution; orally disintegrating tablet; lyophilized powder for injection solution; intramuscular/intravenous injection as solution</td>
</tr>
<tr>
<td>Hydroxypropyl γ-CD</td>
<td>Topical Solution</td>
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</tbody>
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Table 2: Uses of CDs in various nanoparticle applications

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<tr>
<th>Type of CD</th>
<th>Types of Nanoparticles</th>
<th>Uses</th>
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<tr>
<td>Nonionic</td>
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<td>Target MDR cancer cells</td>
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<tr>
<td>Nonionic</td>
<td>Fluorescent magnetic silica core-shell NP β-CD$^{29}$</td>
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<tr>
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<td>Nonionic</td>
<td>pH responsive poly(γ-CD- DEAP) derivative$^{113}$</td>
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<tr>
<td>Nonionic</td>
<td>Mono-6-deoxy-6(p-toylsulfonyl)-β-CD$^{20}$</td>
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<tr>
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<td>PEGylated poly(ε-caprolactone) NP assisted by 2-HP-β-CD$^{35}$</td>
<td>Skin transport of drug delivery system</td>
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<tr>
<td>Anionic</td>
<td>Chitosan (CS) cross-linked SBE-β-CD NP loaded with Ciproflaxin $^{114}$</td>
<td>Microbial protection for titanium implants</td>
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<tr>
<td>Anionic</td>
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<tr>
<td>Anionic</td>
<td>Gold- CM-β-CD NP$^{114}$</td>
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<td>Cationic</td>
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<td>Cationic</td>
<td>Heptakis-[2-(ω-amino-oligo-(ethylene glycol))-6-deoxy-6-hexadecylthio]- β-CD$^{115}$</td>
<td>Therapeutic Gene Delivery</td>
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