Environmental Chemistry Letters (2021) 19:4297–4310
https://doi.org/10.1007/s10311-021-01275-y

REVIEW

Cyclodextrin-based nanoparticles for pharmaceutical applications: a review

Abhishek Pandey[1]

Received: 14 May 2021 / Accepted: 9 July 2021 / Published online: 22 July 2021

Abstract
The development of effective drug delivery systems is very challenging due to poor solubility, low membrane permeability, instability, and short biological half-life of active substances. Conventional drug delivery systems lack the features of extended drug release and targeted drug delivery. These issues can be solved by cyclodextrins and derivatives. Benefits include higher bioavailability, targeted drug delivery, non-toxicity, inclusion complex ability, and higher aqueous solubility. Cyclodextrin-conjugated nanoparticles combine the advantages of cyclodextrins and nanoparticles: enhanced water solubility and drug loading, targeted drug delivery with minimum toxicity to normal cells, greater surface area, improved drug loading and higher stability than other nanocarriers such as microparticles and liposomes. Here, I review cyclodextrin-containing nanoparticles and their applications in advanced drug delivery such as anticancer drugs, gene delivery, protein, and peptide drug delivery. Furthermore, this review also describes cyclodextrins applications using polymeric, gold, silver, magnetic, and lipid-based nanoparticles. Additionally, I present potential pharmaceutical applications of amphiphilic cyclodextrin-based nanoparticles in anticancer, antimicrobial, gene delivery, and miscellaneous administration routes of cyclodextrin-based nanoparticles such as nasal and transdermal.

Keywords Cyclodextrin · Nanoparticles · Gene delivery · Drug delivery · Protein · Peptides

Abbreviations

MCF-7	Michigan cancer foundation-7
MDR1	Multidrug resistance protein 1
mRNA	Messenger ribonucleic acid
siRNA	Small interfering ribonucleic acid

Introduction

Cyclodextrins are cyclic oligomers obtained from starch by enzymatic degradation and were discovered in 1891 by the French pharmacist Villiers (Crini et al. 2021). Cyclodextrins have remarkable capability to establish supramolecular host–guest interactions because of their toroidal shape and non-polar inside (Morin-Crini et al. 2021; Petitjean et al. 2021). Cyclodextrin molecules contribute distinguished advantages due to their novel architectural features to form inclusion complexes with several kinds of molecules like ions, protein, and oligonucleotides (Lysik and Wu-Pong 2003). Inclusion complexes are formed when the "guest" molecule, usually a drug, is partially or fully included inside the "host's cavity" (Szente and Szejtli 1999). Owing to the hydrophobic cavity, cyclodextrins as ghosts offer the guest a suitable environment for interaction (Fig. 1). The outer hydrophilic surface of cyclodextrins is compatible with water, which allows hydrogen bonding cohesive interactions (Challa et al. 2005). Cyclodextrin-conjugated nanoparticles offer numerous advantages such as enhanced drug solubility, improved encapsulation efficiency, and drug loading and serve as drug carriers to a specific target site such as cancer cells with minimum toxicity to normal cells, greater surface area over microparticles, and higher stability over liposomes.

This review discusses cyclodextrin-based nanoparticles to explain their versatility and high potential for advanced drug delivery, protein and peptide delivery, and gene delivery. It also highlights the role of cyclodextrins in specific types of nanoparticles such as gold, silver, and magnetic, polymeric, and lipid-based nanoparticles. Additionally, pharmaceutical applications of amphiphilic cyclodextrin nanoparticles and miscellaneous administration routes of cyclodextrin-based nanoparticles are also discussed. This article is an abridged

✉ Abhishek Pandey
pandey_pharma@yahoo.co.in

[1] School of Studies in Pharmaceutical Sciences, Jiwaji University, Gwalior, Madhya Pradesh 474011, India

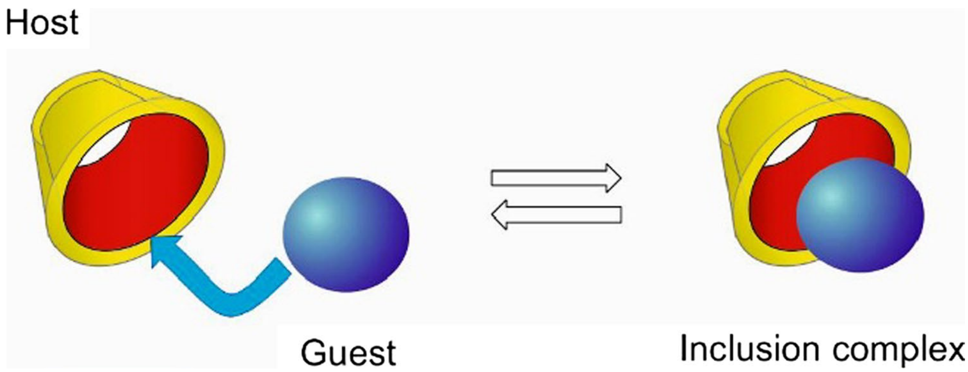

Fig. 1 Inclusion complex of cyclodextrins. A complex is formed when the "guest" molecule, such as a drug, is partially or fully included inside the host's cavity. Cyclodextrins have various practical applications in different fields such as pharmaceuticals, food, cosmetics, hygiene and toiletries, agrochemistry, catalysis, chromatography, biotechnology, nanotechnology, medical imaging, textile industry, and soil and water treatment

version of the chapter published by Pandey (2020) in the series Environmental Chemistry for a Sustainable World.

Cyclodextrin nanoparticles as drug delivery system

The cyclodextrins have the exceptional ability to trap a guest molecule inside of their hydrophobic cavity and have been significantly exploited by pharmaceutical researchers to enhance the bioavailability, aqueous solubility, and stability of several therapeutic agents (Arora et al. 2019). Cyclodextrin-based nanoparticles can improve bioavailability, modify drug metabolism, reduce toxicity, and increase the biological half-life of drugs after systemic administration (Bilensoy 2011; Crini et al. 2018). Cyclodextrins act as true carriers by dissolving and delivering hydrophobic drug molecules through the aqueous exterior of lipophilic biological membrane barriers, e.g., mucosa. In general, only dissolved drug molecules can partition into the barrier and then penetrate through the mucosa. In addition, cyclodextrins are known to self-assemble to form nanosized aggregates in aqueous solutions and thus have the potential of being developed into novel drug delivery systems (Messner et al. 2010). This characteristic is promising for a broad range of nanotechnology domains such as drug delivery, cancer therapy, gene delivery, and biosensing. Cyclodextrin-based nanoparticles facilitate a novel drug delivery system with the advantages of both components: The cyclodextrin molecules offer enhanced water solubility and drug loading, while the nanoparticles afford targeted drug delivery.

Anticancer drugs

Nanotechnology-based drug delivery system provides an exceptional platform for the delivery of anticancer agents to enhance their targeting ability and bioavailability. Oral administration of paclitaxel is still considered one of the most suitable and safe modes of delivery. Hamada et al. (2006) studied the aqueous solubility behavior of anticancer agent paclitaxel employing 11 kinds of cyclodextrins and the bioactivity of the paclitaxel–cyclodextrin inclusion complex. They have reported that 2,6-dimethyl-*β*-cyclodextrin was most effective, and paclitaxel showed significant solubility in 2,6-dimethyl-*β*-cyclodextrin aqueous solution. Moreover, this inclusion complex revealed a 1.23-fold polymerization activity as paclitaxel in a tubulin assay. One of the main advantages of loading anticancer drugs into nanoparticles is to enhance their cellular uptakes by bypassing the different multidrug-resistant mechanisms. For example, paclitaxel isolated from *Taxus brevifolia* is a potent anticancer agent approved for the treatment of a large number of solid tumors. But hydrophobic nature of paclitaxel results in low bioavailability. Therefore, to overcome the issue of hydrophobicity, Bilensoy et al. (2008a, b) have developed amphiphilic cyclodextrin as a nanoparticulate carrier system for paclitaxel drug delivery. This yielded nanospheres via nanoprecipitation technique with good cytotoxicity against L929 cells, high encapsulation efficiency, prolonged drug release, and a threefold increase in the loading capacity of nanoparticles when formed directly from the inclusion complex. In another approach, Agüeros et al. (2009) investigated the concept of utilizing cyclodextrin–polyanhydride nanoparticles for oral delivery of paclitaxel. The addition of cyclodextrin increases the solubility of paclitaxel by developing an inclusion complex, and the use of polyanhydride enhances intestinal permeability. In conclusion, cyclodextrin-based nanoparticles improve solubility and increase the targeting ability and bioavailability of anticancer drugs.

Proteins and peptides

Cyclodextrin complexation represents an effective strategy for improving protein therapy by stabilizing them against aggregation, thermal denaturation, and degradation. Proteins are mostly hydrophilic and too bulky to be wholly included in the cavity of cyclodextrins. Nevertheless, the hydrophobic side chains in the peptides may penetrate into the cavity of the oligosaccharide, leading to the formation of non-covalent inclusion complexes, which improves the stability of proteins. Da Silveira et al. (1998) have prepared and evaluated nanoparticulate systems of progesterone composed of poly(isobutyl cyanoacrylate) and cyclodextrins for enhancing the loading of the particles with substances. The authors have demonstrated that an increase in hydroxypropyl-β-cyclodextrin concentration resulted in small nanoparticles of size less than 50 nm and a 50-fold increase in progesterone loading compared to nanoparticles prepared without cyclodextrins. Cyclodextrins are believed to enhance nasal absorption of peptides by opening tight junctions and/or solubilizing membrane components (Merkus et al. 1999). In light of these facts, Zhang et al. (2011) fabricated a novel nanoparticle system based on the coupling of cyclodextrin and hyperbranched polyglycerols to enhance the nasal transport of insulin. The in vitro release study showed significant release rate of insulin under acidic conditions than physiological conditions. In vitro cytotoxic evaluation against Caco-2 cells exhibited that hyperbranched polyglycerol-β-cyclodextrin had significant biocompatibility. Moreover, the capacity of hyperbranched polyglycerol-β-cyclodextrin nanoparticles to penetrate the nasal mucosal epithelia was proved by confocal laser scanning microscopy. Glutathione is the main thiolated small peptide in mammalian cells used to treat drug poisoning and protection against cytotoxic chemotherapy and radiation trauma. However, glutathione inclusion and preservation into conventional pharmaceutical dosage forms are challenging tasks due to low and variable oral bioavailability, non-enzymatic pH-dependent oxidation, chemical and enzymatic degradation of glutathione in the jejunum (Langie et al. 2007). Therefore, to resolve these issues, Trapani et al. (2010) have developed new nanoparticles containing chitosan or cyclodextrin and demonstrated that chitosan nanoparticles containing the anionic cyclodextrin sulfobutylether 7 m-β-cyclodextrin seem to be significant potential oral glutathione carriers, as they combine enhanced glutathione loading along with the ability to improve glutathione permeabilization through the intestine, as observed in a frog intestinal sac model. More recently, He et al. (2019) reported a novel oral protein delivery system of ovalbumin with improved intestinal permeability and enhanced antigen stability. Results of the in vivo study of nanoparticles revealed that ovalbumin-loaded cyclodextrin/chitosan nanoparticles possess the capacity to induce an intestinal mucosal immune response and could serve as a potential antigen-delivery system for oral vaccination. The above examples reveal that cyclodextrin-containing nanoparticles significantly increase drug-loading capacity and enhance stability and intestinal permeability of protein and peptide molecules.

Cyclodextrin nanoparticles as gene delivery systems

Gene therapy offers advantages over conventional protein therapy such as improved bioavailability and reduced systemic toxicity. Therefore, to avoid the toxicity issue of viral vectors, researchers have developed cyclodextrin-based nanoparticles as non-viral vectors. Teijeiro-Osorio et al. (2009) first investigated a new generation of hybrid polysaccharide nanocarriers composed of chitosan and anionic cyclodextrins, to evaluate their ability to penetrate epithelial cells and improve gene expression in the Calu-3 cell culture model. Furthermore, hybrid chitosan and anionic cyclodextrins nanoparticles were developed and loaded with plasmid deoxyribonucleic model that encodes the expression of secreted alkaline phosphatase. Results of cellular uptake studies revealed that the nanoparticles were efficiently internalized by the cells and confirm their potential as gene vectors. The application of small interfering ribonucleic acid (siRNAs) is a promising approach to restrict the mutation of protein. The major hindrance in siRNA-based strategies is the lack of efficient and non-toxic transportation vectors to ensure target delivery to the nervous system. This stimulated Godinho et al. (2013) to develop modified amphiphilic β-cyclodextrins as novel siRNA neuronal carriers. The results showed that the cyclodextrin formed nanosize particles significantly reduced the expression of the *huntingtin* gene in rat striatal cells and human Huntington's disease primary fibroblasts. These findings firmly support the utility of modified β-cyclodextrins as safe and effective siRNA delivery vectors. In another study to facilitate the delivery of siRNA, cationic cyclodextrin conjugated with polyethylene glycol chain to expedite the attachment of targeting group anisamide. Parenteral administration of anisamide-tagged PEGylated (polyethylene glycol chain conjugated) cyclodextrin nanoparticles presented notable tumor inactivation with diminished toxicity when investigated preclinically in a rodent prostate tumor model, hence serving as an excellent drug delivery system of siRNA delivery for prostate cancer therapy (Guo et al. 2012). The siRNAs generally exhibit weak cell penetration with limited stability; the inclusion of cyclodextrins as a key excipient can aid in the delivery of oligonucleotides. Zokaei et al. (2019) recently developed chitosan β-cyclodextrin complexes as a tropical agent. These polymer cyclodextrin complexes loaded with the messenger ribonucleic acid (mRNA) cleaving DNAzyme that targets the mRNA of the multidrug resistance protein 1 (MDR1) gene in the doxorubicin-resistant breast cancer cell line (MCF-7/DR). Results proved the downregulation of MDR1 mRNAs in MCF-7/DR/DNZ by a real-time polymer chain reaction, compared to the MCF-7/DR as control. To sum up, results substantiate chitosan β-cyclodextrin complexes in association with chemotherapy drug for cancer therapy and notably valuable at the delivery of DNAzyme in reviving chemosensitivity. These findings reveal that cyclodextrin-based nanoparticles are promising non-toxic transportation vectors that facilitate safe, effective, and targeted gene delivery.

Role of cyclodextrin in magnetic nanoparticles

The magnetic nanoparticles offer several advantages over other types of nanomaterials, such as narrow size distribution, high colloidal stability, low toxicity, and high specific surface area to render them suitable for biomedical applications (Ahmed et al. 2014). Additionally, magnetic nanoparticles displayed the phenomenon of superparamagnetism: They are promptly magnetized under the influence of the external magnetic field and vice versa. This unique characteristic allows the nanoparticles to localize at the targeted site in vivo in response to the externally applied magnetic field. Silica is generally added to the surface of the nanoparticles to prevent their oxidation that leads to demagnetization, which subsequently maintains the stability of magnetic nanoparticles. Wang et al. (2003) first proved the role of cyclodextrin to enhance the stability of magnetic nanoparticles in an aqueous medium. They have modified the surface properties of these magnetic nanoparticles through the formation of an inclusion complex between surface-bound surfactant molecules and α-cyclodextrin, thus improving oleic acid stabilized nanoparticles dispersion for a prolonged period in water. Banerjee and Chen (2007) have developed cyclodextrin-citrate-gum Arabic modified magnetic nanoparticles for hydrophobic drug delivery. The results showed that cyclodextrin-citrate-gum Arabic-modified magnetic nanoparticles exhibited a considerable adsorption capability for ketoprofen as compared to gum Arabic-modified magnetic nanoparticles. Therefore, this system seems to be a very promising vehicle for the administration of hydrophobic drugs. A decade later, Chen et al. (2017) have amalgamated double-layer polymer-coated magnetic targeted nanoparticles (coated with β-cyclodextrin and polymer chitosan) to ensure stability and biocompatibility of the nanoparticles and effective drug delivery of ibuprofen, a hydrophobic drug delivery. They noted that nanocarriers exhibited sufficient magnetic properties, high drug-loading capacity, and significant in vitro drug release. Recently, the same authors have developed β-cyclodextrin-based magnetic nanocarriers via a molecular docking technique. Herein, the introduction of the molecular docking technique establishes a method to fast select an effective β-cyclodextrin-based surface coating for the development of high-performance magnetic nanoparticles (Chen et al. 2019). In another study, Ding et al. (2015) developed a novel hydrogel of poorly soluble drug 5-fluorouracil, based on chitosan crosslinked carboxymethyl-β-cyclodextrin polymer-modified Fe_3O_4 magnetic nanoparticles. Experimental results showed that the nanocarriers displayed a high loading efficiency and pH-dependent swelling and diffusion-controlled drug release. This report tentatively proposed the mechanism of 5-fluorouracil encapsulated into the magnetic chitosan nanoparticles. Camptothecin, a hydrophobic anticancer agent, acts by inhibiting the enzyme topoisomerase I. The primary mechanism of action of camptothecin involves cell death at the S-phase of the cell cycle (Behera and Padhi 2020). The bioactive lactone form of camptothecin rapidly hydrolyzes to the inactive carboxylate form under physiological conditions, thus limiting the delivery and therapeutic application of camptothecin in cancer therapy (Pandey 2021). Therefore, to overcome these limitations, Enoch et al. (2018) synthesized β-cyclodextrin-based magnetic nanoparticles of camptothecin. The fabricated nanoparticles showed superparamagnetic behavior. Further research showed that coating the magnetic nanoparticles with the cyclodextrin–tethered polymer improves the drug-loading capacity, sustained drug release, and enhanced cytotoxicity. Wang et al. (2018) fabricated a magnetic and pH-sensitive composite nanoparticulate system prepared by double emulsion technique and incorporating acetylated β-cyclodextrin as a key ingredient to recognize the pH response and Fe_3O_4 as a component to realize magnetic response. Results showed irreversible pH response property and reversible magnetic responsive properties at different pH environments for the composite nanoparticle. Moreover, drug release behavior exhibited pH-dependent property through preliminary in vitro evaluation. In conclusion, cyclodextrin-containing magnetic nanoparticles significantly improve the solubility of hydrophobic drugs, increase stability, modify drug release, and enhance the cytotoxicity of anticancer drugs.

Role of cyclodextrin in polymeric nanoparticles

The inclusion property of cyclodextrin renders polymeric nanoparticles to conveniently deliver hydrophobic molecules to the targeted site by encapsulating the drugs in the hydrophobic cyclodextrin cavity. The polymeric nanoparticles have cyclodextrin casting outer shells, while the core of the polymeric nanoparticles is composed of natural or synthetic polymer. Thus, the drugs can be loaded in the core of the polymeric nanoparticles, or they can be conjugated with the cyclodextrin in the outer shell. Nanoparticulate systems can be prepared either by dispersion of preformed polymers or polymerization. Among the polymers used in nanoparticle preparation are poly(cyanoacrylates) which are particularly interesting because of their biodegradability and very simple polymerization process. One of the major drawbacks of this type of nanoparticle is related to the difficulty of entrapping in hydrophobic drugs. Da Silveira et al. (1998) first proposed cyclodextrin to overcome this problem. The authors proposed the possibility of preparing nanoparticles of poly-(isobutyl cyanoacrylate) in the presence of hydroxypropyl-*β*-cyclodextrin by anionic polymerization of isobutyl cyanoacrylate. Later, Ren et al. (2009) dissolved adamantane-end-capped poly(*ε*-caprolactone) and poly(vinylpyrrolidone)-cyclodextrin in *N*-methyl-2-pyrrolidone, a common solvent for both polymers. Further addition of this mixed polymer solution in solvent results in self-assembled polymeric nanoparticles. The summary of various major cyclodextrin-based polymeric nanoparticles loaded with pharmaceuticals including natural compounds and techniques of drug inclusion is illustrated in Table 1.

Cyclodextrin-based lipid nanoparticles

Lipids generally obtained from the natural origin are nontoxic, biodegradable, and biocompatible. These properties make lipids superior to polymers. Hence, the lipid-based nanoparticulate system provides a better platform for safe and effective drug delivery (Chaudhari et al. 2020). The association of cyclodextrin into lipid nanoparticle formulations not only promotes the hydrophobic drug loading within the aqueous components of the lipid cyclodextrin nanoparticles but also maintains the targetability of nanoparticles. To ensure stable encapsulation, McCormack and Gregoriadis (1994) suggested an approach wherein cyclodextrin/drug inclusion complexes are embedded into liposomes. This strategy is designated as drug-in-cyclodextrin-in-liposome. Arima et al. (2006) developed PEGylated (polyethylene glycol chain conjugated) liposomes entrapping the doxorubicin complex with *γ*-cyclodextrin and evaluated the antitumor effect of doxorubicin in rodents bearing colon-26 tumor cells. The findings of the study displayed retardation in tumor growth and an increase in drug retention. Curcumin, a well-known bioactive compound, possesses antibacterial, anti-inflammatory, antioxidant, and antitumor activity. But, curcumin exhibits instability and poor solubility. Therefore, to resolve these issues, Dhule et al. (2012) fabricated curcumin-loaded cyclodextrin-based liposomal nanoparticles and studied them to treat osteosarcoma. The resulting 2-hydroxypropyl-*γ*-cyclodextrin/curcumin–liposome complex exhibits promising cytotoxic potential. Ji et al. (2016) practiced the use of cyclodextrin to enhance the tumor-targeting ability of the lipid nanoparticles on the outside of the liposomal wall. The surface of the liposome consisted of pirfenidone-loaded *β*-cyclodextrin linked with a cleavable peptide, along with arginyl–glycyl–aspartic acid peptide to target pancreatic tumor cells, while the interior of the liposome carried the chemotherapeutic agent gemcitabine. Results showed this integrated nanomedicine effectively targets and kills pancreatic tumor cells, moreover, facilitating a promising strategy for the improvement of pancreatic cancer therapy. Solid lipid nanoparticles represent an alternative carrier system to conventional colloidal carriers due to their specific features such as the use of natural fabrication components, size and related narrow distribution, enhanced stability, and increased permeation through biological barriers. Skiba et al. (1993) first described the development and application of a novel cyclodextrin-based dispersible colloidal system in the form of spherical particles of matrix type with size ranging from 90 to 900 nm (nanospheres), which might contain an active pharmaceutical ingredient. This nanoparticulate system was used as a carrier for numerous pharmaceuticals and cosmetic agents. Nanostructured lipid carriers represent an upgraded generation of lipid nanoparticles, which overcome the major drawback of solid lipid nanoparticles, particularly the tendency of discharge of the drug during storage as an outcome of their highly ordered crystalline composition. A summary of recently developed cyclodextrin-based solid lipid nanoparticles, lipid nanoparticles, and their therapeutic applications is illustrated in Table 2.

Role of cyclodextrins in gold and silver nanoparticles

In recent years, gold and silver nanoparticles have been widely investigated for nanomedicine due to their superior optical, chemical, and biological properties. Gold and silver cyclodextrin nanoparticles are commonly produced by connecting cyclodextrin to the metallic core using a linker, such as adamantane, which forms a strong stable complex with the cyclodextrins. Liu et al. (1998) first developed a novel technique for the surface derivatization of gold colloidal particles to prepare gold colloidal particles of diameter higher than 10 nm. They demonstrated aqueous solubilization of aliphatic thiols by α-cyclodextrin, which effectively binds to the aliphatic chains and carries the hydrophobic thiol molecules to the surface of the gold particles. Wang et al. (2016a, b) described an easy method to produce the host–guest assembly of gold nanoparticles induced by intracellular glutathione. Results showed that the synthesized aggregates retained for a long time in

Table 1 Formulation of various cyclodextrin-based polymeric nanoparticles loaded with pharmaceuticals including natural compounds and techniques of drug inclusion to facilitate the improved drug stability, sustained, controlled, and targeted drug delivery including encapsulation of hydrophilic and hydrophobic compound

Polymer	Cyclodextrin	Pharmaceuticals	Technique	Outcomes offered by cyclodextrin-based polymeric nanoparticles	Reference
Chitosan	Cationic β-cyclodextrin	Insulin	–	Facilitates slow-release oral delivery of insulin and protection from gastric environment	Zhang et al. (2010)
Chitosan	Carboxymethyl-β-cyclodextrin	Sulindac	Ionotropic gelation technique	Encapsulation of sulindac and continuous release of the drug throughput 24 h	Ammar et al.(2012)
Chitosan	Sulfobutylether-β-cyclodextrin	Econazole nitrate	Ionotropic gelation technique	Controlled delivery of drug to the eye	Mahmoud et al. (2011)
Chitosan	Carboxymethyl-β-cyclodextrin	Indomethacin	–	Controlled drug release and biodegradability	Anirudhan et al. (2013)
Chitosan	Sulfobutylether-β- cyclodextrin	Quercetin	Ionotropic gelation technique	Anti-quorum sensing or anti-bacterial activities	Nguyen and Goycoolea (2017)
N-maleoyl chitosan	β-Cyclodextrin	Ketoprofen	Ionic gelation method	Sustained release of poorly water-soluble drugs	Hou et al. (2017)
Chitosan	β-Cyclodextrin	Carvacrol and linalool	Kneading method	A promising carrier for botanical pesticides	Campos et al. (2018)
Polyethylene glycol and polyethylenimine	β-Cyclodextrin	5-Fluorouracil	–	Anticancer drug delivery in tumor therapy	Prabha and Raj (2016)
Polyethylene glycol	Amphiphilic cyclodextrins	Short interfering ribonucleic acid	–	Improved stability and reduced clearance	Godinho et al. (2014)
Polyethylene glycol	Modified β-cyclodextrin and derivatives	Short interfering ribonucleic acid	–	Efficient cellular uptake, gene-knockdown ability	Gooding et al. (2015)
Poly lactic acid	Hydroxypropyl-β-cyclodextrin	Doxorubicin	Double-emulsion method and nanoprecipitation method	Significant anticancer activity	Wang et al. (2011)
Poly (lactic acid and glycolic acid)	β-Cyclodextrin	Docetaxel	Double-emulsification method	Targeted delivery of docetaxel to cancer cells	Bu et al. (2015)
Poly (lactic acid and glycolic acid)	Hydroxypropyl-β-cyclodextrin	Puerarin	Emulsion solvent evaporation technique	Targeted delivery of puerarin nanoparticles to brain injury induced by ischemic-reperfusion	Tao et al. (2013)
Poly (lactic acid and glycolic acid)	Hydroxypropyl-β-cyclodextrin	Fisetin	Simple coacervation technique	Improved anticancer activity and oral bioavailability	Kadari et al. (2017)
Poly (lactic acid and glycolic acid)	Cyclodextrin	Erlotinib	Multiple emulsion solvent evaporation	Improved therapeutic efficacy against non-small cell lung cancer cells	Vaidya et al. (2019)
Poly (lactic acid and glycolic acid)	Hydroxypropyl-β-cyclodextrin	Methotrexate	Double emulsion method	Controlled drug release	Gorjikhah et al. (2017)

Table 1 (continued)

Polymer	Cyclodextrin	Pharmaceuticals	Technique	Outcomes offered by cyclodextrin-based polymeric nanoparticles	Reference
Poly (lactic acid and glycolic acid)	Hydroxypropyl-*β*-cyclodextrin	Formononetin	Neutralization agitation method	Promising carrier for poor lipophilic and poor hydrophilic drugs	Guo et al. (2017)
Poly (lactic acid and glycolic acid)	*β*-Cyclodextrin	–	Emulsion evaporation process	Enhanced internalization of nanoparticles into the Caco-2 cells	García-González et al. (2016)
Poly (ethylene glycol)-poly (*ε*-caprolactone)	Hydroxypropyl-*β*-cyclodextrin	Zinc (II) phthalocyanine as drug carrier	Melting/sonication procedure	Novel vehicle for the skin delivery of highly lipophilic compounds	Conte et al. (2015)

cancer cells and provoke apoptosis of cells when exposed to near-infrared irradiation. *β*-cyclodextrin-functionalized gold nanoparticles are more efficient in anticancer therapy when incorporated with anticancer agents. For example, Bakar et al. (2015) reported decreased breast cancer cell (MCF-7) proliferation by complexing various ligands (pinoresinol, lariciresinol, and secoisolariciresinol), with thiolated-*β*-cyclodextrin and decorating them on the exterior of gold nanoparticles. Conventional anticancer molecules such as doxorubicin, paclitaxel, and docetaxel were incorporated into the *β*-cyclodextrin-functionalized gold nanoparticles and targeted to cancer cells. The findings of cell line studies showed that the doxorubicin-loaded *β*-cyclodextrin gold nanoparticles enhanced the cellular uptake and exerted a significant antiproliferative effect. Similarly, Wang et al. (2016a, b) constructed a twofold nanoparticulate delivery system based on host–guest nanoplatforms loaded with anticancer agent docetaxel and genetic material siRNA using gold nanorods coated with polyethylenimine-grafted *β*-cyclodextrin. The developed gold nanoparticles upon exposure to near-infrared laser irradiation generate a significant hyperthermia effect to trigger siRNA and docetaxel release from the cyclodextrin and remarkably inhibit lung metastasis of 4T1 breast tumors. In another study, Gannimani et al. (2016) coupled the antibacterial properties of silver nanoparticles and hydrophobic drug carrier characteristic of cyclodextrin to fabricate supramolecules to provide cutting-edge for antibacterial efficacy of chloramphenicol. Likewise, Gaurav et al. (2015) utilized *β*-cyclodextrin to solubilize clotrimazole, an antifungal agent, and then attach to albumin-stabilized silver nanoparticles. These hybrid nanoparticles exerted a synergistic effect when evaluated for antifungal activity against candida yeast cells. Zhai et al. (2017) investigated the uptake of biocompatible nanoparticles into viable cells in a microfluidic chip by utilizing surface-enhanced Raman spectroscopy, which modified the surface of *β*-cyclodextrin-capped silver nanoparticles using para-amino thiophenol and folic acid. The para-amino thiophenol molecules serve as the Raman reporter, while the folic acid fragments have a high proclivity for folate receptors that are over-expressed on the surface cancerous cells so that the nanoparticles can penetrate the cells and be observed by the Raman reporter. The above findings delineate that surface functionalization of gold and silver nanoparticles by cyclodextrins improves solubility, enhances permeability, and modifies drug release with retaining safety and efficacy.

Pharmaceutical applications of amphiphilic cyclodextrin nanoparticles

The potential use of cyclodextrin in a biological system needs amphiphilic properties because natural cyclodextrin has relatively low solubility both in water and in organic solvents, thus limiting their uses in pharmaceutical

Table 2 Formulations of cyclodextrin-based solid lipid nanoparticles and lipid nanoparticles loaded with various drugs, utilizing the advantages of both cyclodextrin and nanolipid carriers by incorporating the drug–cyclodextrin inclusion complex into the lipid nanoparticles

Type of lipid nanoparticle	Cyclodextrin	Active ingredients	Therapeutic use	Reference
Solid lipid nanoparticles	2-Hydroxypropyl-β-cyclodextrin	Diclofenac sodium	Colon-specific drug delivery	Spada et al. (2012)
Solid lipid nanoparticles	2-Hydroxypropyl-β-cyclodextrin	Paclitaxel	Anticancer agent	Baek et al. (2015)
Solid lipid nanoparticles	Hydroxypropyl-beta-cyclodextrin and sulfobutyl-ether-beta-cyclodextrin	Hydrochlorothiazide	Antihypertensive and diuretic	Cirri et al. (2017)
Solid lipid nanoparticles	Carboxymethyl-β-cyclodextrin	Famotidine	H_2 receptor (antagonistic effects on gastric secretion)	Mady et al. (2010)
Solid lipid nanoparticles	β-Cyclodextrin	Simvastatin	Antihyperlipidemic	Vakhariya et al. (2017)
Solid lipid nanoparticles	Tetradecyl-γ-cyclodextrin	Resveratrol	Antioxidant activity	Carlotti et al. (2012)
Solid lipid nanoparticles	Hydroxypropyl-β-cyclodextrin	Indomethacin	Nonsteroidal anti-inflammatory drug	Hippalgaonkar et al. (2013)
Nanostructured lipid carriers	Methylated-β-cyclodextrin	Oxaprozin	Nonsteroidal anti-inflammatory drug	Mennini et al. (2016)
Nanostructured lipid carriers	Hydroxypropyl-β-cyclodextrin and sulfobutyl-ether-β-cyclodextrin	Hydrochlorothiazide	Antihypertensive and diuretic	Cirri et al. (2018)
Nanostructured lipid carriers	Hydroxypropyl-β-cyclodextrin	*Lippia origanoides* (essential oil)	Follicular accumulation and controlled delivery	Pires et al. (2019)
Nanostructured lipid carriers	β-Cyclodextrin-epichlorohydrin polymer	Ketoprofen	Nonsteroidal anti-inflammatory drug	Cirri et al. (2012)
Nanostructured lipid carriers	Cyclodextrin and derivatives	Vinpocetine	Protective and anti-aging agent	Lin et al. (2014)

formulations. Amphiphilic or ionizable cyclodextrins can modify the rate or time of drug release and bind to the surface membrane of cells that may be used for the enhancement of drug absorption across biological barriers (Bilensoy and Hincal 2009). According to the chemical structure of the amphiphilic cyclodextrin, different carrier systems could be obtained such as solid lipid nanoparticles, bilayer vesicles, liposomes, and nanoparticles (Donohue et al. 2002). Their unique properties can improve the drug-loading capacity, cellular interaction and tumoral penetration, drug release profiles, and cytotoxicity of drug delivery systems. Table 3 summarizes the various potential pharmaceutical applications of amphiphilic cyclodextrin-based nanoparticles such as anticancer, cholesterol-targeted, folate-targeted, and amphiphilic cyclodextrin nanoparticles for gene delivery.

Miscellaneous

As per the biopharmaceutical classification system of drugs, poor drug solubility or poor mucosa permeability attributes of drugs limit their pharmaceutical applications. These cyclodextrin-based polymeric nanoparticles represent a more reliable drug delivery system when compared with control nanoparticles; they displayed homogeneous bioadhesive interactions with the gastrointestinal mucosa due to the presence of several hydroxyl groups in cyclodextrin nanoparticles, which would promote hydrogen bonding with the gut, subsequently enhancing the bioadhesive potential (Agüeros et al. 2011). Furthermore, Luppi et al. (2011) examined the potential of different cyclodextrins in nasal drug delivery using albumin nanoparticles for the treatment of the most common neurodegenerative disorder Alzheimer's disease to validate their effect on the drug release, mucoadhesiveness of nanoparticles, and permeability of model drug tacrine. Maestrelli et al. (2006) synthesized chitosan nanoparticles in the presence of cyclodextrin as a nanocarrier system for transdermal drug delivery of the triclosan (an antifungal agent) and furosemide (a diuretic). This nanocarrier system exhibited fast release followed by a delayed release of drug. It confirms the inclusion of the drug inside the cyclodextrin cavity and later encapsulation inside the chitosan polymer. Similarly, Khalil et al. (2012) formulated nanoparticles of warfarin, an anticoagulant drug, by loading it in chitosan–cyclodextrin-complexed nanoparticle systems for transdermal drug delivery. The results of in vitro release studies and ex vivo permeation studies of nanoparticles paved the new way for the delivery of hydrophobic drugs. Datz et al. (2018) have synthesized a new β-cyclodextrin-based biocompatible and multifunctional substance that cross-linked with rigid organic linker molecules to yield thermostable, readily water-dispersible

Table 3 The historical landmarks of amphiphilic cyclodextrins-based nanoparticles containing anticancer, antimicrobial drugs including gene delivery to facilitate improved drug-loading capacity, significant cytotoxicity, and vectorized gene delivery

Drug/mechanism	Amphiphilic cyclodextrin	Indication	Outcomes offered by amphiphilic cyclodextrin nanoparticles	Historical landmarks	References
Amphiphilic β-cyclodextrin nanosphere	β-Cyclodextrin	In vivo tissue distribution	No particular sign of toxicity	First report of in vivo behavior of amphiphilic cyclodextrin nanoparticles	Gèze et al. (2007)
Paclitaxel	Cyclodextrin derivatives	Anticancer	No effect on cell proliferation and no hemolysis of red blood cells		Bilensoy et al. (2008a,b)
Camptothecin	β-Cyclodextrin	Anticancer	Improved release profiles and significant antitumor efficacy	First comparison of amphiphilic cyclodextrin nanoparticles with polymeric analogues	Çirpanli et al. (2009)
Camptothecin	Cyclodextrin	Anticancer	Significant anticancer efficacy		Çirpanli et al. (2011)
Docetaxel	Cyclodextrin heptakis	Anticancer	Prolonged cell arrest in mitosis		Quaglia et al. (2009)
Acyclovir	Fluorinated alpha-cyclodextrin hexakis	Antiviral	Improved encapsulation efficiency, sustained release of acyclovir	First report on antiviral drug nanoparticles based on amphiphilic cyclodextrin	Ghera et al. (2009)
Plasmid deoxyribonucleic acid	Polycationic cyclodextrin	Transfection capability	Vectorized gene delivery		Díaz-Moscoso et al. (2011)
Nucleic acid	Polycationic cyclodextrin	Gene therapy	Efficiently mediated serum-resistant transfection in HeLa and HepG2 cells		Méndez-Ardoy et al. (2011)
Plasmid deoxyribonucleic acid	Polycationic amphiphilic cyclodextrin	Gene therapy	Efficiently mediated transfection	First performing self-assembled nanocomplexes from a polycationic amphiphilic cyclodextrin and plasmid deoxyribonucleic acid	Aranda et al. (2013)
Doxorubicin	Star-like polymers composed of a β-cyclodextrin	Anticancer	pH-responsive sustainable drug release	A new generation of drug delivery systems	Xu et al. (2015)
small interfering ribonucleic acid	Cyclodextrins	Brain cancer	Enhanced gene silencing efficiency		Gooding et al. (2015)
Cholesterol targeted	Nonionic or cationic β-cyclodextrin	Cholesterol-targeted anticancer effects	Apoptosis of cancer cells via cholesterol extraction		Varan et al. (2016)
Paclitaxel (folate-targeted)	β-Cyclodextrin	Anticancer	Reduced cell proliferation		Erdogar et al. (2017)
Doxorubicin	β-Cyclodextrin	Anticancer	Inhibit the growth of MDA-MB-231 cancer cells	First report on nanoparticles equipped with multivalent mannose target units	Ye et al. (2016)
small interfering ribonucleic acid	Cationic cyclodextrin	Prostate cancer	Transfect prostate cancer cells in a 3D model of bone metastasis	First report of targeted cyclodextrin to transfect prostate cancer cells in a 3D model of bone metastasis	Evans et al. (2017)
Iodinin	β-Cyclodextrin	Anti-leukemic activity	Significant cytotoxicity and improved water solubility	First report on iodinin amphiphilic β-cyclodextrin nanoparticles	Prandina et al. (2018)

Table 3 (continued)

Drug/mechanism	Amphiphilic cyclodextrin	Indication	Outcomes offered by amphiphilic cyclodextrin nanoparticles	Historical landmarks	References
Paclitaxel	β-Cyclodextrin	Anticancer	Stronger anti-tumoral activity in the 3D multicellular tumor mode	First report on the 3D multicellular tumor mode	Varan et al. (2018)

particles having a nanosize range approximately 150 nm. In the next step, these nanoparticles covalently linked with dye molecules to enable effective tracking of them during in vitro cell experiments. Results showed the successful nuclei staining with Hoechst 33,342 dye, including effective cell killing with the doxorubicin cargo molecules and , therefore, representing a promising approach for the development of novel theranostic systems. The above examples confirm that cyclodextrin-based nanoparticles significantly enhance the bioadhesive potential and permeability of drug molecules and, thus, act as a promising carrier for nasal and transdermal drug delivery.

Conclusion

There is a significant discussion about the potential advantages, characteristics, and therapeutic applications of cyclodextrin-based nanoparticles reported in previous years. Cyclodextrin-based polymeric nanoparticles, including new generation nanoparticles such as magnetic, gold, and silver nanoparticles, have emerged as an effective nanocarrier system for advanced drug delivery such as anticancer drugs, peptides, proteins, deoxyribonucleic acid, and other genetic material. They facilitate improved drug-loading capacity, inclusion complex ability, increased aqueous solubility, targeted drug delivery, and significant cytotoxicity against different cancer cell lines. Cyclodextrin-containing nanoparticles have shown their potential to improve the loading capacity of liposomes, solid lipid nanoparticles, and nanostructured lipid carriers. The chemical modification of cyclodextrin polymers is a unique strategy to explore their potential pharmaceutical applications. Some cyclodextrin-containing nanoparticles, such as CRLX101, a tumor-targeted nanopharmaceuticals, and CALAA-01 for siRNA delivery, are among the most promising nanotherapeutics in clinical phase II trials for cancer diseases (Weiss et al. 2011; Zuckerman et al. 2014). Apart from these promising research findings, safety, efficacy, pharmacokinetic evaluation for cyclodextrin-based nanoparticles in the body, and mechanism of elimination of nanoparticles need to be further investigated.

Funding None.

Declarations

Conflict of interest The author declares that he has no conflict of interest.

Consent for publication I hereby give my consent for the publication of manuscript.

References

Agüeros M, Ruiz-Gatón L, Vauthier C, Bouchemal K, Espuelas S, Ponchel G, Irache JM (2009) Combined hydroxypropyl-β-cyclodextrin and poly(anhydride) nanoparticles improve the oral permeability of paclitaxel. Eur J Pharm Sci 38:405–413. https://doi.org/10.1016/j.ejps.2009.09.010

Agüeros M, Espuelas S, Esparza I, Calleja P, Peñuelas I, Ponchel G, Irache JM (2011) Cyclodextrin-poly(anhydride) nanoparticles as new vehicles for oral drug delivery. Expert Opin Drug Deliv 8:721–734. https://doi.org/10.1517/17425247.2011.572069

Ahmed GHG, Laíño RB, Calzón JAG, García MED (2014) Magnetic nanoparticles grafted with *β*-cyclodextrin for solid-phase extraction of 5-hydroxy-3-indole acetic acid. Microchim Acta 181:941–948. https://doi.org/10.1007/s00604-014-1192-y

Ammar H, El-Nahhas S, Ghorab M, Salama A (2012) Chitosan/Cyclodextrin nanoparticles as drug delivery system. J Incl Phenom Macrocycl Chem 72:9950–9955. https://doi.org/10.1007/s10847-011

Anirudhan TS, Dilu D, Sandeep S (2013) Synthesis and characterisation of chitosan crosslinked-*β*-cyclodextrin grafted silylated magnetic nanoparticles for controlled release of Indomethacin. J Magn Magn Mater 343:149–156. https://doi.org/10.1016/j.jmmm.2013.04.007

Aranda C, Urbiola K, Méndez Ardoy A, García Fernández JM, Ortiz Mellet C, de Ilarduya CT (2013) Targeted gene delivery by new folate-polycationic amphiphilic cyclodextrin-DNA nanocomplexes in vitro and in vivo. Eur J Pharm Biopharm 85:390–397. https://doi.org/10.1016/j.ejpb.2013.06.011

Arima H, Hagiwara Y, Hirayama F, Uekama K (2006) Enhancement of antitumor effect of doxorubicin by its complexation with *γ*-cyclodextrin in pegylated liposomes. J Drug Target 14:225–232. https://doi.org/10.1080/10611860600711136

Arora D, Saneja A, Jaglan S (2019) Cyclodextrin-based delivery systems for dietary pharmaceuticals. Environ Chem Lett 17:1263–1270. https://doi.org/10.1007/s10311-019-00878-w

Baek JS, Kim JH, Park JS, Cho CW (2015) Modification of paclitaxel-loaded solid lipid nanoparticles with 2-hydroxypropyl-*β*-cyclodextrin enhances absorption and reduces nephrotoxicity associated with intravenous injection. Int J Nanomed 10:5397–5405. https://doi.org/10.2147/IJN.S86474

Bakar F, Caglayan M, Onur F, Nebioglu S, Palabiyik I (2015) Gold nanoparticle-lignan complexes inhibited MCF-7 cell proliferation in vitro: a novel conjugation for cancer therapy. anticancer agents. Med Chem 15:336–344. https://doi.org/10.2174/1871520614666141202144152

Banerjee SS, Chen DH (2007) Magnetic nanoparticles grafted with cyclodextrin for hydrophobi drug delivery. Chem Mater 19:6345–6349. https://doi.org/10.1021/cm702278u

Behera A, Padhi S (2020) Passive and active targeting strategies for the delivery of the camptothecin anticancer drug: a review. Environ Chem Lett 18:1557–1567. https://doi.org/10.1007/s10311-020-01022-9

Bilensoy E (2011) Cyclodextrins in pharmaceutics, cosmetics and biomedicine. Current and future industrial applications. Wiley, Hoboken. https://doi.org/10.1002/9780470926819

Bilensoy E, Hincal AA (2009) Recent advances and future directions in amphiphilic cyclodextrin nanoparticles. Expert Opin Drug Deliv 6:1161–1173. https://doi.org/10.1517/17425240903222218

Bilensoy E, Gürkaynak O, Doğan AL, Hincal AA (2008a) Safety and efficacy of amphiphilic ß-cyclodextrin nanoparticles for paclitaxel delivery. Int J Pharm 347:163–170. https://doi.org/10.1016/j.ijpharm.2007.06.051

Bilensoy E, Gürkaynak O, Ertan M, Şen M, Hincal AA (2008b) Development of nonsurfactant cyclodextrin nanoparticles loaded with anticancer drug paclitaxel. J Pharm Sci 97:1519–1529. https://doi.org/10.1002/jps.21111

Bu X, Zhu T, Ma Y, Shen Q (2015) Co-administration with cell penetrating peptide enhances the oral bioavailability of docetaxel-loaded nanoparticles. Drug Dev Ind Pharm 41:764–771. https://doi.org/10.3109/03639045.2014.902465

Campos EVR, Proença PLF, Oliveira JL, Melville CC, Vechia JFD, De Andrade DJ, Fraceto LF (2018) Chitosan nanoparticles functionalized with *β*-cyclodextrin: a promising carrier for botanical pesticides. Sci Rep. https://doi.org/10.1038/s41598-018-20602-y

Carlotti M, Sapino S, Ugazio E, Gallarate M, Morel S (2012) Resveratrol in solid lipid nanoparticles. J Disper Sci Tech 33:465–471. https://doi.org/10.1080/01932691.2010.548274

Challa R, Ahuja A, Ali J, Khar RK (2005) Cyclodextrins in drug delivery: an updated review. AAPS Pharm SciTech 6:2. https://doi.org/10.1208/pt060243

Chaudhari VS, Murty US, Banerjee S (2020) Lipidic nanomaterials to deliver natural compounds against cancer: a review. Environ Chem Lett 18:1803–1812. https://doi.org/10.1007/s10311-020-01042-5

Chen P, Song H, Yao S, Tu X, Su M, Zhou L (2017) Magnetic targeted nanoparticles based on *β*-cyclodextrin and chitosan for hydrophobic drug delivery and a study of their mechanism. RSC Adv 7:29025–29034. https://doi.org/10.1039/C7RA02398G

Chen P, Yao S, Chen X, Huang Y, Song H (2019) A new strategy for the construction of *β*-cyclodextrin-based magnetic nanocarriers: a molecular docking technique. New J Chem 43:4282–4290. https://doi.org/10.1039/c8nj06131a

Çirpanli Y, Bilensoy E, Lale Doğan A, Çaliş S (2009) Comparative evaluation of polymeric and amphiphilic cyclodextrin nanoparticles for effective camptothecin delivery. Eur J Pharm Biopharm 73:82–89. https://doi.org/10.1016/j.ejpb.2009.04.013

Çirpanli Y, Allard E, Passirani C, Bilensoy E, Lemaire L, Caliş S, Benoit JP (2011) Antitumoral activity of camptothecin-loaded nanoparticles in 9L rat glioma model. Int J Pharm 17:201–206. https://doi.org/10.1016/j.ijpharm.2010.10.015

Cirri M, Bragagni M, Mennini N, Mura P (2012) Development of a new delivery system consisting in "drug - In cyclodextrin - In nanostructured lipid carriers" for ketoprofen topical delivery. Eur J Pharm Biopharm 80:46–53. https://doi.org/10.1016/j.ejpb.2011.07.015

Cirri M, Mennini N, Maestrelli F, Mura P, Mannelli GCC, L, (2017) Development and in vivo evaluation of an innovative "hydrochlorothiazide-in cyclodextrins-in solid lipid nanoparticles" formulation with sustained release and enhanced oral bioavailability for potential hypertension treatment in pediatrics. Int J Pharm 521:73–83. https://doi.org/10.1016/j.ijpharm.2017.02.022

Cirri M, Maestrelli F, Mura P, Ghelardini C, Mannelli LDC (2018) Combined approach of cyclodextrin complexation and nanostructured lipid carriers for the development of a pediatric liquid oral dosage form of hydrochlorothiazide. Pharmaceutics 10:287. https://doi.org/10.3390/pharmaceutics10040287

Conte C, Costabile G, d'Angelo I, Pannico M, Musto P, Grassia G, Ialenti A, Tirino P, Miro A, Ungaro F, Quaglia F (2015) Skin transport of PEGylated poly(*ε*-caprolactone) nanoparticles assisted by (2-hydroxypropyl)-*β*-cyclodextrin. J Colloid Interface Sci 454:112–120. https://doi.org/10.1016/j.jcis.2015.05.010

Crini G, Fourmentin S, Fenyvesi É, Torri G, Fourmentin M, Morin-Crini N (2018) Cyclodextrins, from molecules to applications. Environ Chem Lett 16:1361–1375. https://doi.org/10.1007/s10311-018-0763-2

Crini G, Fenyvesi É, Szente L (2021) Outstanding contribution of Professor József Szejtli to cyclodextrin applications in foods, cosmetics, drugs, chromatography and biotechnology: a review. Environ Chem Lett 19:2619–2641. https://doi.org/10.1007/s10311-020-01170-y

Da Silveira AM, Ponchel G, Puisieux F, Duchêne D (1998) Combined poly (isobutylcyanoacrylate) and cyclodextrins nanoparticles for enhancing the encapsulation of lipophilic drugs. Pharm Res 15:1051–1055. https://doi.org/10.1023/A:1011982211632

Datz S, Illes B, Gößl D, Schirnding CV, Engelke H, Bein T (2018) Biocompatible crosslinked β-cyclodextrin nanoparticles as multifunctional carriers for cellular delivery. Nanoscale 10:16284–16292. https://doi.org/10.1039/c8nr02462f

Dhule SS, Penfornis P, Frazier T, Walker R, Feldman J, Tan G, He J, Alb A, John V, Pochampally R (2012) Curcumin-loaded γ-cyclodextrin liposomal nanoparticles as delivery vehicles for osteosarcoma. Nanomedicine 8:440–451. https://doi.org/10.1016/j.nano.2011.07.011

Díaz-Moscoso A, Guilloteau N, Bienvenu C, Méndez-Ardoy A, Jiménez Blanco J, Benito J, Gourriérec L, Di Giorgio C, Vierling P, Defaye J, Mellet C, García Fernández J (2011) Mannosyl-coated nanocomplexes from amphiphilic cyclodextrins and pDNA for site-specific gene delivery. Biomaterials 32:7263–7273. https://doi.org/10.1016/j.biomaterials.2011.06.025

Ding Y, Shen SZ, Sun H, Sun K, Liu F, Qi Y, Yan J (2015) Design and construction of polymerized-chitosan coated Fe_3O_4 magnetic nanoparticles and its application for hydrophobic drug delivery. Mater Sci Eng C 48:487–498. https://doi.org/10.1016/j.msec.2014.12.036

Donohue R, Mazzaglia A, Ravoo BJ, Darcy R (2002) Cationic β-cyclodextrin bilayer vesicles. Chem Commun 2:2864–2865. https://doi.org/10.1039/b207238f

Enoch IVMV, Ramasamy S, Gopinath MSP (2018) Cyclodextrin-PEG conjugate-wrapped magnetic ferrite nanoparticles for enhanced drug loading and release. Appl Nanosci 8:273–284. https://doi.org/10.1007/s13204-018-0798-5

Erdogar N, Varan G, Bilensoy E (2017) Amphiphilic cyclodextrin derivatives for targeted drug delivery to tumors. Curr Top Med Chem 17:1521–1528. https://doi.org/10.2174/1568026616666161222101104

Evans J, Malhotra M, Fitzgerald K, Guo J, Cronin M, Curtin C, O'Brien F, Darcy R, O' Driscoll K (2017) Formulation and evaluation of anisamide-targeted amphiphilic cyclodextrin nanoparticles to promote therapeutic gene silencing in a 3d prostate cancer bone metastases model. Mol Pharm 3:42–52. https://doi.org/10.1021/acs.molpharmaceut.6b00646

Gannimani R, Ramesh M, Mtambo S, Pillay K, Soliman ME, Govender P (2016) γ-Cyclodextrin capped silver nanoparticles for molecular recognition and enhancement of antibacterial activity of chloramphenicol. J Inorg Biochem 157:15–24. https://doi.org/10.1016/j.jinorgbio.2016.01.008

García-González L, Yépez-Mulía L, Ganem A (2016) Effect of β-cyclodextrin on the internalization of nanoparticles into intestine epithelial cells. Eur J Pharm Sci 81:113–118. https://doi.org/10.1016/j.ejps.2015.10.012

Gaurav C, Nikhil G, Deepti S, Kalra S, Goutam R, Amit GK (2015) Albumin stabilized silver nanoparticles-clotrimazole β-cyclodextrin hybrid nanocomposite for enriched anti-fungal activity in normal and drug resistant Candida cells. RSC Adv 5:71190–71202. https://doi.org/10.1039/c5ra08274a

Gèze A, Chau LT, Choisnard L, Mathieu JP, Marti-Batlle D, Riou L, Putaux JL, Wouessidjewe D (2007) Biodistribution of intravenously administered amphiphilic β-cyclodextrin nanospheres. Int J Pharm 344:135–142. https://doi.org/10.1016/j.ijpharm.2007.06.050

Ghera BB, Perret F, Chevalier Y, Parrot-Lopez H (2009) Novel nanoparticles made from amphiphilic perfluoroalkyl alpha-cyclodextrin derivatives: preparation, characterization and application to the transport of acyclovir. Int J Pharm 22:155–162. https://doi.org/10.1016/j.ijpharm.2009.04.004

Godinho BMDC, Ogier JR, Darcy R, O'Driscoll CM, Cryan JF (2013) Self-assembling modified β-cyclodextrin nanoparticles as neuronal siRNA delivery vectors: focus on huntington's disease. Mol Pharm 10:640–649. https://doi.org/10.1021/mp3003946

Godinho BMDC, Ogier JR, Quinlan A, Darcy R, Griffin BT, Cryan JF, Caitriona MOD (2014) PEGylated cyclodextrins as novel siRNA nanosystems: correlations between polyethylene glycol length and nanoparticle stability. Int J Pharm 473:105–112. https://doi.org/10.1016/j.ijpharm.2014.06.054

Gooding M, Malhotra M, McCarthy DJ, Godinho BMDC, Cryan JF, Darcy R, O'Driscoll CM (2015) Synthesis and characterization of rabies virus glycoprotein-tagged amphiphilic cyclodextrins for siRNA delivery in human glioblastoma cells: In vitro analysis. Eur J Pharm Sci 71:80–92. https://doi.org/10.1016/j.ejps.2015.02.007

Gorjikhah F, Azizi Jalalian F, Salehi R, Panahi Y, Hasanzadeh A, Alizadeh E, Akbarzadeh A, Davaran S (2017) Preparation and characterization of PLGA-β-cyclodextrin polymeric nanoparticles containing methotrexate and evaluation of their effects on T47D cell line. Artif Cells Nanomed Biotechnol 45:432–440. https://doi.org/10.3109/21691401.2016.1160915

Guo J, Ogier JR, Desgranges S, DarcyODriscoll RC (2012) Anisamide-targeted cyclodextrin nanoparticles for siRNA delivery to prostate tumours in mice. Biomaterials 33:7775–7784. https://doi.org/10.1016/j.biomaterials.2012.07.012]

Guo B, Xu D, Liu X, Liao C, Li S, Huang Z, Li X, Yi J (2017) Characterization and cytotoxicity of PLGA nanoparticles loaded with formononetin cyclodextrin complex. J Drug Deliv Sci Technol 41:375–383. https://doi.org/10.1016/j.jddst.2017.08.010

Hamada H, Ishihara K, Masuoka N, Mikuni K, Nakajima N (2006) Enhancement of water-solubility and bioactivity of paclitaxel using modified cyclodextrins. J Biosci Bioeng 102:369–371. https://doi.org/10.1263/jbb.102.369

He M, Zhong C, Hu H, Jin Y, Chen Y, Lou K, Gao F (2019) Cyclodextrin/chitosan nanoparticles for oral ovalbumin delivery: preparation, characterization and intestinal mucosal immunity in mice. Asian J Pharm Sci 14:193–203. https://doi.org/10.1016/j.ajps.2018.04.001

Hippalgaonkar K, Adelli GR, Hippalgaonkar K, Repka MA, Majumdar S (2013) Indomethacin-loaded solid lipid nanoparticles for ocular delivery: development, characterization, and *in vitro* evaluation. J Ocul Pharmacol Ther 29:216–228. https://doi.org/10.1089/jop.2012.006

Hou X, Zhang W, He M, Lu Y, Lou K, Gao F (2017) Preparation and characterization of β-cyclodextrin grafted N-maleoyl chitosan nanoparticles for drug delivery. Asian J Pharm Sci 12:558–568. https://doi.org/10.1016/j.ajps.2017.07.007

Ji T, Li S, Zhang Y, Lang J, Ding Y, Zhao X, Zhao R, Li Y, Shi J, Hao J, Zhao Y, Nie G (2016) An MMP-2 responsive liposome integrating antifibrosis and chemotherapeutic cyclodextrin drugs for enhanced drug perfusion and efficacy in pancreatic cancer. ACS Appl Mater Interfaces 8:3438–3445. https://doi.org/10.1021/acsami.5b11619

Kadari A, Gudem S, Kulhari H, Bhandi MM, Borkar RM, Kolapalli VRM, Sistla R (2017) Enhanced oral bioavailability and anticancer efficacy of fisetin by encapsulating as inclusion complex with HPβCD in polymeric nanoparticles. Drug Deliv 24:224–232. https://doi.org/10.1080/10717544.2016.1245366

Khalil SK, El-Feky GS, El-Banna ST, Khalil WA (2012) Preparation and evaluation of warfarin-β-cyclodextrin loaded chitosan nanoparticles for transdermal delivery. Carbohydr Polym 15:1244–1253. https://doi.org/10.1016/j.carbpol.2012.06.056

Langie SAS, Knaapen AM, Houben JMJ, van Kempen FC, de Hoon JPJ, Gottschalk RWH, Godschalk RWL, van Schooten FJ (2007) The role of glutathione in the regulation of nucleotide excision repair during oxidative stress. Toxicol Lett 168:302–309. https://doi.org/10.1016/j.toxlet.2006.10.027

Lin C, Chen F, Ye T, Zhang L, Zhang W, Liu D, Xiong W, Yang X, Pan W (2014) A novel oral delivery system consisting in “drug-in cyclodextrin-in nanostructured lipid carriers” for poorly water-soluble drug: Vinpocetine. Int J Pharm 465:90–96. https://doi.org/10.1016/j.ijpharm.2014.02.013

Liu J, Xu R, Kaifer AE (1998) In situ modification of the surface of gold colloidal particles. Preparation of cyclodextrin-based rotaxanes supported on gold nanospheres. Langmuir 14:7337–7339. https://doi.org/10.1021/la981385q

Luppi B, Bigucci F, Corace G, Delucca A, Cerchiara T, Sorrenti M, Catenacci L, Di Pietra AM, Zecchi V (2011) Albumin nanoparticles carrying cyclodextrins for nasal delivery of the anti-alzheimer drug tacrine. Eur J Pharm Sci 44:559–65. https://doi.org/10.1016/j.ejps.2011.10.002

Lysik MA, Wu-Pong S (2003) Innovations in oligonucleotide drug delivery. J Pharm Sci 92:1559–1573. https://doi.org/10.1002/jps.10399

Mady FM, Abou-Taleb AE, Khaled KA, Yamasaki K, Iohara D, Taguchi K, Anraku M, Hirayama F, Uekama K, Otagiri M (2010) Evaluation of carboxymethyl-β-cyclodextrin with acid function: Improvement of chemical stability, oral bioavailability and bitter taste of famotidine. Int J Pharm 397:1–8. https://doi.org/10.1016/j.ijpharm.2010.06.018

Maestrelli F, Garcia-Fuentes M, Mura P, Alonso MJ (2006) A new drug nanocarrier consisting of chitosan and hydroxyl propyl cyclodextrin. Eur J Pharm Biopharm 63:79–86. https://doi.org/10.1016/j.ejpb.2005.12.006

Mahmoud AA, El-Feky GS, Kamel R, Awad GEA (2011) Chitosan/sulfobutylether-β-cyclodextrin nanoparticles as a potential approach for ocular drug delivery. Int J Pharm 413:229–236. https://doi.org/10.1016/j.ijpharm.2011.04.031

McCormack B, Gregoriadis G (1994) Drugs-in-cyclodextrins-in liposomes: a novel concept in drug delivery. Int J Pharm 112:249–258. https://doi.org/10.1016/0378-5173(94)90361-1

Méndez-Ardoy A, Guilloteau N, Di Giorgio C, Vierling P, Santoyo-González F, Ortiz Mellet C, García Fernández JM (2011) β-cyclodextrin-based polycationic amphiphilic “click” clusters: effect of structural modifications in their DNA complexing and delivery properties. J Org Chem 76:5882–5894. https://doi.org/10.1021/jo2007785

Mennini N, Cirri M, Maestrelli F, Mura P (2016) Comparison of liposomal and NLC (nanostructured lipid carrier) formulations for improving the transdermal delivery of oxaprozin: effect of cyclodextrin complexation. Int J Pharm 515:684–691. https://doi.org/10.1016/j.ijpharm.2016.11.013

Merkus FWHM, Verhoef JC, Marttin E, Romeijn SG, Van Der Kuy PHM, Hermens WAJJ, Schipper NGM (1999) Cyclodextrins in nasal drug delivery. Adv Drug Deliv Rev 36:41–57. https://doi.org/10.1016/S0169-409X(98)00054-4

Messner M, Kurkov SV, Jansook P, Loftsson T (2010) Self-assembled cyclodextrin aggregates and nanoparticles. Int J Pharm 387:199–208. https://doi.org/10.1016/j.ijpharm.2009.11.035

Morin-Crini N, Fourmentin S, Fenyvesi É, Lichtfouse E, Torri G, Fourmentin M, Crini G (2021) 130 years of cyclodextrin discovery for health, food, agriculture, and the industry: a review. Environ Chem Lett. https://doi.org/10.1007/s10311-020-01156-w

Nguyen HT, Goycoolea FM (2017) Chitosan/Cyclodextrin/TPP nanoparticles loaded with quercetin as novel bacterial quorum sensing inhibitors. Molecules 22:1975. https://doi.org/10.3390/molecules22111975

Pandey A (2020) Role of Cyclodextrins in Nanoparticle-Based Systems for Drug Delivery. In: Crini G, Fourmentin S, Lichtfouse E (eds) The history of cyclodextrins, vol 52. Springer, Cham, pp 305–343

Pandey A (2021) Pharmaceutical and biomedical applications of cellulose nanofibers: a review. Environ Chem Lett 19:2043–2055. https://doi.org/10.1007/s10311-021-01182-2

Petitjean M, García-Zubiri IX, Isasi JR (2021) History of cyclodextrin-based polymers in food and pharmacy: a review. Environ Chem Lett. https://doi.org/10.1007/s10311-021-01244-5

Pires FQ, da Silva JKR, Sa-Barreto LL, Gratieri T, Gelfuso GM, Cunha-Filho M (2019) Lipid nanoparticles as carriers of cyclodextrin inclusion complexes: a promising approach for cutaneous delivery of a volatile essential oil. Colloids Surf B Biointerfaces 182:110382. https://doi.org/10.1016/j.colsurfb.2019.110382

Prabha G, Raj V (2016) Formation and characterization of β-cyclodextrin (β-cyclodextrin)–polyethyleneglycol (PEG)-polyethyleneimine (PEI) coated Fe_3O_4 nanoparticles for loading and releasing 5-fluorouracil drug. Biomed Pharmacother 80:173–182. https://doi.org/10.1016/j.biopha.2016.03.015

Prandina A, Herfindal L, Radix S, Rongved P, Døskeland SO, Le Borgne M, Perret F (2018) Enhancement of iodinin solubility by encapsulation into cyclodextrin nanoparticles. J Enzyme Inhib Med Chem 33:370–375. https://doi.org/10.1080/14756366.2017.1421638

Quaglia F, Ostacolo L, Mazzaglia A, Villari V, Zaccaria D, Sciortino MT (2009) The intracellular effects of non-ionic amphiphilic cyclodextrin nanoparticles in the delivery of anticancer drugs. Biomaterials 30:374–382. https://doi.org/10.1016/j.biomaterials.2008.09.035

Ren S, Chen D, Jiang M (2009) Noncovalently connected micelles based on a β-cyclodextrin-containing polymer and adamantane end-capped poly(ε-caprolactone) *via* host-guest interactions. J Polym Sci Part A Polym Chem 47:4267–4278. https://doi.org/10.1002/pola.23479

Skiba M, Wouessidjewe D, Coleman A, Fessi H, Devissaguet JP, Duchene D, Puisieux F (1993) Preparation and use of novel cyclodextrin-based dispersible colloidal systems in the form of nanospheres. PCT Int Appl 23 pp. PCT Applications FR 93/00594 (Publication No. WO 93/25195)

Spada G, Gavini E, Cossu M, Rassu G, Giunchedi P (2012) Solid lipid nanoparticles with and without hydroxypropyl β-cyclodextrin: a comparative study of nanoparticles designed for colonicyclodextrinrug delivery. Nanotechnology. https://doi.org/10.1088/0957-4484/23/9/095101

Szente L, Szejtli J (1999) Highly soluble cyclodextrin derivatives: chemistry, properties, and trends in development. Adv Drug Deliv Rev. https://doi.org/10.1016/S0169-409X(98)00092-1

Tao HQ, Meng Q, Li MH, Yu H, Liu MF, Du D, Sun SL, Yang HC, Wang YM, Ye W, Yang LZ, Zhu DL, Jiang CL, Peng HS (2013) HP-β-CD-PLGA nanoparticles improve the penetration and bioavailability of puerarin and enhance the therapeutic effects on brain ischemia-reperfusion injury in rats. Naunyn Schmiedebergs Arch Pharmacol 386:61–70. https://doi.org/10.1007/s00210-012-0804-5

Teijeiro-Osorio D, Remuñán-López C, Alonso MJ (2009) Chitosan/cyclodextrin nanoparticles can efficiently transfect the airway epithelium in vitro. Eur J Pharm Biopharm 71:257–263. https://doi.org/10.1016/J.EJPB.2008.09.020

Trapani A, Lopedota A, Franco M, Cioffi N, Ieva E, Garcia-Fuentes M, Alonso MJ (2010) A comparative study of chitosan and chitosan/cyclodextrin nanoparticles as potential carriers for the oral delivery of small peptides. Eur J Pharm Biopharm 75:26–32. https://doi.org/10.1016/j.ejpb.2010.01.010

Vaidya B, Parvathaneni V, Kulkarni NS, Shukla SK, Damon JK, Sarode A, Kanabar D, Garcia JV, Mitragotri S, Muth A, Gupta V (2019) Cyclodextrin modified erlotinib loaded PLGA nanoparticles for improved therapeutic efficacy against non-small cell lung cancer.

Int J Biol Macromol 122:338–347. https://doi.org/10.1016/j.ijbiomac.2018.10.181

Vakhariya RR, Talokar SS, Salunkhe VR, Magdum CS (2017) Formulation development and optimization of simvastatin loaded solid lipid nanoparticles. Asian J Res Pharm Sci 7:49. https://doi.org/10.5958/2231-5659.2017.00008.x

Varan G, Öncül S, Ercan A, Benito JM, Ortiz Mellet C, Bilensoy E (2016) Cholesterol-targeted anticancer and apoptotic effects of anionic and polycationic amphiphilic cyclodextrin nanoparticles. J Pharm Sci 105:3172–3182. https://doi.org/10.1016/j.xphs.2016.06.021

Varan G, Patrulea V, Borchard G, Bilensoy E (2018) Cellular interaction and tumoral penetration properties of cyclodextrin nanoparticles on 3D breast tumor model. Nanomaterials 8:1–18. https://doi.org/10.3390/nano8020067

Wang Y, Wong JF, Teng X, Lin XZ, Yang H (2003) "Pulling" nanoparticles into water: phase transfer of oleic acid stabilized monodisperse nanoparticles into aqueous solutions of α-cyclodextrin. Nano Lett 3:1555–1559. https://doi.org/10.1021/nl034731j

Wang T, Zhang C, Liang XJ, Liang W, Wu Y (2011) Hydroxypropyl-β-cyclodextrin copolymers and their nanoparticles as doxorubicin delivery system. J Pharm Sci 100:1067–1079. https://doi.org/10.1002/jps.22352

Wang D, Wang T, Xu Z, Yu H, Feng B, Zhang J, Guo C, Yin Q, Zhang Z, Li Y (2016a) Cooperative treatment of metastatic breast cancer using host-guest nanoplatform coloaded with docetaxel and siRNA. Small 12:488–498. https://doi.org/10.1002/smll.201502913

Wang Y, Li H, Jin Q, Ji J (2016b) Intracellular host-guest assembly of gold nanoparticles triggered by glutathione. Chem Commun 52:582–585. https://doi.org/10.1039/c5cc07195j

Wang X, Gao Z, Zhang L, Wang H, Hu X (2018) A magnetic and pH-sensitive composite nanoparticle for drug delivery. J Nanomater. https://doi.org/10.1155/2018/1506342

Weiss G, Yen Y, Neidhart J, Young CS, Weiss S, Ryan J (2011) Abstract 1306: A Phase 1b/2a study of CRLX101, a novel nanopharmaceutical of camptothecin, in solid tumor cancer patients who have failed standard therapy. In: Clinical Research. American Association for Cancer Research, pp 1306–1306. https://doi.org/10.1158/1538-7445.AM2011-1306

Xu Z, Liu S, Liu H, Yang C, Kang Y, Wang M (2015) Unimolecular micelles of amphiphilic cyclodextrin-core star-like block copolymers for anticancer drug delivery. Chem Commun 51:15768–15777. https://doi.org/10.1039/c5cc02743h

Ye Z, Zhang Q, Wang S, Bharate P, Varela-Aramburu S, Lu M, Seeberger PH, Yin J (2016) Tumor-targeted drug delivery with mannose-functionalized nanoparticles self-assembled from amphiphilic β-cyclodextrins. Chem Eur J 22:15216–15221. https://doi.org/10.1002/chem.201603294

Zhai Z, Zhang F, Chen X, Zhong J, Liu G, Tian Y, Huang Q (2017) Uptake of silver nanoparticles by DHA-treated cancer cells examined by surface-enhanced Raman spectroscopy in a microfluidic chip. Lab Chip 17:1306–1313. https://doi.org/10.1039/c7lc00053g

Zhang N, Li JJ, Jiang W, Ren C, Li JJ, Xin J, Li K (2010) Effective protection and controlled release of insulin by cationic β-cyclodextrin polymers from alginate/chitosan nanoparticles. Int J Pharm 393:213–219. https://doi.org/10.1016/j.ijpharm.2010.04.006

Zhang X, Zheng X, Wu Z, Gao X, Shu S, Wang Z, Li C (2011) β-Cyclodextrin grafting hyperbranched polyglycerols as carriers for nasal insulin delivery. Carbohydr Polym 84:1419–1425. https://doi.org/10.1016/j.carbpol.2011.01.057

Zokaei E, Badoei-dalfrad A, Ansari M (2019) Therapeutic potential of DNAzyme loaded on chitosan/cyclodextrin nanoparticle to recovery of chemosensitivity in the MCF-7 cell line. Appl Biochem Biotechnol 187:708. https://doi.org/10.1007/s12010-018-2836-x

Zuckerman JE, Gritli I, Tolcher A, Heidel JD, Lim D, Morgan R, Chmielowski B, Ribas A, Davis ME, Yen Y (2014) Correlating animal and human phase Ia/Ib clinical data with CALAA-01, a targeted, polymer-based nanoparticle containing siRNA. Proc Natl Acad Sci USA 111:11449–11454. https://doi.org/10.1073/pnas.1411393111