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REVIEW

Cyclodextrin-based delivery systems for dietary pharmaceuticals

Divya Arora[1,2] · **Ankit Saneja**[3] · **Sundeep Jaglan**[1,2]

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Abstract
The food industry is increasingly seeking innovative solutions for enhancing the bioavailability and clinical efficacy of phytochemicals. In this regard, cyclodextrins have gained widespread attention as functional excipients. Numerous studies have demonstrated that cyclodextrin inclusion complexes enhance the apparent water solubility, physical chemical stability, and improve the bioavailability of dietary phytochemicals. Recently, the dual-encapsulation approach has been developed, which involves the complexation of dietary molecules with cyclodextrins, followed by encapsulation into nanomaterials such as liposomes, nanoparticles and conjugates. Here, we review the current applications of natural and chemically modified cyclodextrins for the delivery of dietary phytochemicals. The main emphasis is given on inclusion complexes for enhancing the solubility, bioavailability and efficacy of dietary phytochemicals. We also discuss dual-encapsulation-based approaches developed for improved efficacy of dietary phytochemicals.

Keywords Cyclodextrins · Hydroxypropyl-β-cyclodextrin · Drug delivery · Nanoparticles

Introduction

A number of epidemiological and experimental investigations suggest that a regular consumption of fruits, whole grains, vegetables and other plant foods is associated with reduced risks of emerging chronic diseases such as cancer and cardiovascular diseases (Arora and Jaglan 2016; Liu 2013; Manach et al. 2009). This association has been partly attributed to the presence of dietary phytochemicals which are bioactive compounds commonly found in plant-based foods. These dietary phytochemicals are generally classified into various categories as polyphenols, terpenoids, alkaloids and other nitrogen compounds, carbohydrates, lipids, phytosterols and carotenoids (Arora and Jaglan 2016; Liu 2013; Manach et al. 2009). However, despite having good pharmacological activities of these phytochemicals, most of them are often associated with poor water solubility, poor stability because of gastric and colonic pH, metabolism by gut microflora, absorption across the intestinal wall, active efflux mechanism and first-pass metabolic effects which ultimately leads to poor bioavailability in humans (Aqil et al. 2013; McClements et al. 2015). Therefore, in order to tackle these challenges, food industry has shifted its considerable attention towards making inclusion complexes of these dietary phytochemicals with cyclodextrins (Astray et al. 2009).

Cyclodextrins are a series of natural cyclic oligosaccharides synthesized from the union of glucose monomers (glucopyranose) linked by α-1,4 glycosidic bonds (de Oliveira Makson et al. 2015). Based on the number of glucopyranose units, the natural occurrence of cyclodextrins can be classified into α- , β- and γ-cyclodextrins, which are composed of 6, 7 and 8 glucose units, respectively (Zhang and Ma 2013). Cyclodextrins are shaped like a truncated cone instead of perfect cylinders (because of chair conformation of the glucopyranose units) with tapered cavity of 0.79 nm in depth, whereas both the top and bottom diameters are increased with the number of glucose units (Jambhekar and Breen 2016; Li and Purdy 1992). The hydroxyl groups are oriented to the outer space flanking the upper and lower rims, with the primary hydroxyl groups of the sugar residues towards the narrow edge of the cone and the secondary hydroxyl groups towards the wider edge (Jambhekar and

✉ Sundeep Jaglan
sundeepjaglan@iiim.ac.in

[1] Microbial Biotechnology Division, CSIR-Indian Institute of Integrative Medicine, Canal Road, Jammu 180001, India

[2] Academy of Scientific and Innovative Research (AcSIR), Jammu Campus, Jammu 180001, India

[3] Product Development Cell-II, National Institute of Immunology, Aruna Asaf Ali Marg, New Delhi 110067, India

Breen 2016; Mellet et al. 2011). The central cavity of the cone is lined with the skeletal carbons and ethereal oxygen of the glucose residues, which impart a hydrophobic character (Jambhekar and Breen 2016). The hydrophobic cavity of cyclodextrins exhibits the exceptional ability to trap a guest molecule inside its cavity and has been extensively exploited by the pharmaceutical industry to enhance bioavailability of poorly aqueous soluble or biodegradable therapeutic agents, to prevent adverse effects or to enhance permeability of biological membranes (Mellet et al. 2011). It is noteworthy to emphasize that currently there are more than 30 marketed products based on cyclodextrin complexes (Loftsson and Duchêne 2007; Loftsson et al. 2005; Zhang and Ma 2013).

In recent years, cyclodextrins have been used in food industry due to various reasons: (1) to protect lipophilic dietary photochemicals that are sensitive towards degradation due to oxygen, light or heat; (2) to solubilise food colourings and vitamins; (3) to stabilize fragrances, flavours, vitamins and essential oils against undesirable changes; (4) to mask unpleasant odours or tastes; (5) to achieve a controlled release of dietary components; and (6) to enhance the bioavailability of dietary molecules (Fig. 1) (Astray et al. 2009; Loftsson et al. 2005; Pinho et al. 2014). However, the regulatory status of cyclodextrins in foods varies from country to country. For example, α- , β- and γ-cyclodextrins have obtained the generally recognized as safe (GRAS) status as per United States Food and Drug Administration (USFDA) and can be commercialized as such. However, in Japan these cyclodextrins are recognized as natural products and their commercialization in the food sector is restricted subject to their purity. While in Australia and New Zealand γ- and α-cyclodextrins are classified as Novel Foods from 2003 and 2004, respectively (Cravotto et al. 2006; Martina et al. 2013). Several reviews have been published describing the mechanism of cyclodextrins complexation and methods to improve the complexation efficiency (Challa et al. 2005; Hirayama and Uekama 1999; Jambhekar and Breen 2016; Loftsson et al. 2005; Zhang and Ma 2013). In this review, we mainly focus on the recent advances in cyclodextrin-based delivery of dietary molecules for enhancing the solubility and therapeutic efficacy of these molecules. In addition, the drug delivery systems consisting of dual systems of cyclodextrins and functional materials such as liposomes and nanoparticles have also been described.

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Chemically modified cyclodextrins

Natural cyclodextrins, in particular β-cyclodextrin, are of limited aqueous solubility resulting into precipitation of the complexes in water and aqueous systems after their inclusion with hydrophobic molecules. Further, their use is limited to oral and topical formulations due to nephrotoxicity which results from the accumulation of cyclodextrins crystals or cyclodextrin-cholesterol complexes due to their low aqueous solubility (Zhang and Ma 2013). Therefore to circumvent these problems, native cyclodextrins can be modified by hydroxyalkylation, alkylation or sulfoalkylation. The ultimate goal of these modifications is to enhance the aqueous solubility of parent cyclodextrins. For example, the addition of the hydroxyl propyl group to β-cyclodextrin (HP-β-CD) enhanced its solubility by more than 27-folds (Al-Rawashdeh et al. 2010; Gould and Scott 2005). Similarly, sulfobutylether-β-cyclodextrin

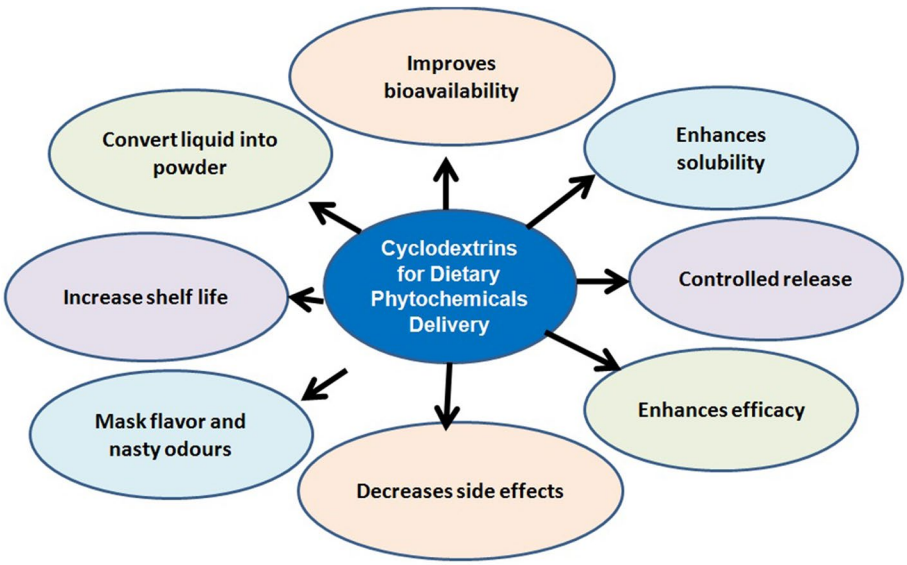

Fig. 1 Advantages of cyclodextrin-based carriers for delivery of nutraceuticals. Cyclodextrins have been used for the delivery of dietary photochemical with a variety of aims such as enhancing solubility, bioavailability, shelf-life and efficacy

(SBE-β-CD) enhanced the aqueous solubility of the parent β-cyclodextrin and considered safe at relatively high doses for the parenteral route (Irie and Uekama 1997; Stella and He 2008). The detailed reviews on chemically modified cyclodextrins have already been presented in the literature (Brewster and Loftsson 2007; Hirayama and Uekama 1999; Jambhekar and Breen 2016; Loftsson and Brewster 2012; Loftsson and Duchêne 2007; Loftsson et al. 2005).

Cyclodextrin in dietary phytochemicals delivery

Cyclodextrins can be considered as empty capsules which act as "host" in which bioactive molecules "guest" molecules can be totally or partially incorporated. There are several methods for the formation of inclusion complexes between cyclodextrins and dietary molecules, and the selection of suitable method is based on physicochemical properties of the guest molecule, the facilities available and the cost involved. The commonly employed methods are neutralization, co-precipitation, kneading, spray drying, freeze drying, melting and solid dispersion (Fig. 2) (Hedges 1998; Marques 2010; Pinho et al. 2014). The detailed reviews on approaches for cyclodextrin complexation, mechanisms for formation of inclusion complexes and methods to enhance complexation efficiency are already been present in the literature (di Cagno 2016; Loftsson and Brewster 2012). The applications of cyclodextrin for phytochemicals delivery are described in following sections.

Fig. 2 Methods used for cyclodextrin complexation with dietary phytochemicals. The most common methods for these are neutralization, kneading, precipitation, spray drying, freeze drying and melting

Cyclodextrin complexation with dietary phytochemicals

The complexation of dietary molecules with cyclodextrins has emerged as promising delivery systems for overcoming the solubility and pharmacokinetic limitations of dietary phytochemicals. In recent years, a wide array of cyclodextrins inclusion complexes with dietary molecules has been prepared in order to improve their solubility and efficacy (Table 1). As discussed earlier, most of the dietary phytochemicals are poor aqueous soluble which leads to their incomplete absorption. For example, Apigenin (Api, 5,7,4'-trihydroxyflavone) which is consumed in the human diet from the main sources German chamomile (*Matricaria chamomilla* L.) (Avallone et al. 2000), celery (*Apium graveolens* L.) (Popović et al. 2006) and parsley (*Petroselinum crispum L.*) (Meyer et al. 2006) is having poor aqueous solubility (1.35 µg/mL). Therefore, in order to enhance the solubility of apigenin different complexes with cyclodextrin and its derivates were developed (Pápay et al. 2016). The solubility studies demonstrated RM-β-cyclodextrin (random methyl β-cyclodextrin) enhanced much solubility as compared to other cyclodextrin derivates and solubility was found to be in order of RM-β-CD > SBE-β-CD (sulfobutyl ether-β-cyclodextrin) > γ-CD > HP-β-CD (hydroxypropyl-β-cyclodextrin) > β-CD > α-CD.

In another study, betulinic acid, a pentacyclic triterpene found to be an antimelanoma agent was complexed with octakis-[6-deoxy-6-(2-sulfanyl ethanesulfonic acid)]-γ-cyclodextrin (GCDG) in order to enhance its solubility and efficacy (Soica et al. 2014). The complex formed demonstrated reduction in tumor volume and weight in vivo in C57BL/6 J mice. Xu et al. (2014) prepared β-cyclodextrin (β-CD) complex of naringenin and enhanced aqueous solubility by more than tenfold. Further, the prepared complex also significantly reduced choroidal neovascularization (CNV) area than native naringen in laser-induced CNV model in rats.

Borghetti et al. (2009) prepared β-cyclodextrin solid complex of quercetin (3,3′,4′,5,7-pentahydroxy flavone), which is a frequent component of major dietary constituents, such as onions, apples, red wine and green tea (Borghetti et al. 2009). The developed complex demonstrated enhancement of aqueous solubility by 4.6-fold. Oommen et al. (1999) prepared inclusion complex of plumbagin with β-cyclodextrin and then encapsulated it into niosomes using a lipid layer hydration method. The developed niosomes demonstrated enhanced anticancer activity as compared to native plumbagin when administered subcutaneously to C57BL/6 J mice-bearing melanoma (B16F1).

Resveratrol (3,4′,5-trihydroxystilbene) which is found in variety of dietary components (such as mulberries, peanuts and grapes) is sparingly aqueous soluble, which ultimately

Table 1 Various cyclodextrin-based inclusions developed for nutraceutical delivery along with their major outcomes

Nutraceutical	Outcome	References
Apigenin	Apigenin inclusion complexes demonstrated higher solubility and increased antioxidant activity	Pápay et al. (2016)
Betulinic acid	Betulinic acid inclusion into the octakis-[6-deoxy-6-(2-sulfanyl ethanesulfonic acid)]-γ-cyclodextrin enhanced solubility as well as efficacy compared to native betulinic acid	Soica et al. (2014)
Carvacrol	Encapsulation of carvacrol in β-cyclodextrin enhanced antinociceptive effect as compared to carvacrol without producing motor deficit to orofacial pain rodent models	Silva et al. (2016)
Chrysin	Inclusion of chrysin in β-CD increased the solubility of chrysin as well as its therapeutic efficacy	Zhu et al. (2016)
Curcumin	Curcumin-β-cyclodextrin-loaded sponge demonstrated comparable wound healing rate as compared to that of marketed formulation	Kaur et al. (2016)
	Curcumin-β cyclodextrin complex enhanced the solubility of free curcumin and improved its antitumor activity	Zhang et al. (2016)
	Curcumin-β-cyclodextrin complex demonstrated improved color stability against sunlight, pH, storage and isothermal heating as compared to native colorant	Mangolim et al. (2014)
Dentatin	Complexation of dentatin in hydroxypropyl-β-cyclodextrin enhanced aqueous solubility by > 300 fold as compared to dentatin alone	Ashwaq et al. (2017)
Fisetin	Complexation of fisetin with sulfobutylether-β-cyclodextrin enhanced the aqueous solubility of fisetin	Mohtar et al. (2017)
Gallic acid	Inclusion complex of gallic acid with hydroxypropyl-β-cyclodextrin had better antibacterial efficiency and also exhibited higher stability	Pinho et al. (2015)
Hinokitiol	Hinokitiol cyclodextrin inclusion complexes enhanced 4 times more antimicrobial activity than hinokitiol crystals	Suzuki et al. (2015)
	Pharmacokinetic study demonstrated honokiol-in-HP-β-CD-in-liposome prolonged the circulation time hinokitiol	Wang et al. (2011)
Naringenin	β-cyclodextrin inclusion complexes demonstrated enhanced water solubility and thermal stability of naringenin	Yang et al. (2013)
	Hydroxypropyl-β-cyclodextrin inclusion complexes enhanced the solubility of naringenin and its transport across a Caco-2 model by 400 and 11-fold respectively. Further, the pharmacokinetic studies in rats demonstrated the developed inclusion complex enhanced the AUC by 7.4-fold and Cmax by 14.6-fold	Shulman et al. (2011)
	Naringenin β-cyclodextrin complex enhanced water solubility and improved biological activity leading to more potent inhibitory effect on CNV formation in rats	Xu et al. (2014)
Resveratrol	Resveratrol hydroxypropyl-β-cyclodextrin complex demonstrated improved antioxidant efficacy as compared to resveratrol β-cyclodextrin complex	Lu et al. (2009)
	Pharmacokinetic studies after oral administration in BALB-c mice demonstrated hydroxypropyl-β-cyclodextrin complexation enhanced AUC0-120 and Cmax by 2 and fourfold respectively as compared with resveratrol nanosuspension	Yang et al. (2016)
	Resveratrol complexation with methylated-β-cyclodextrin enhanced its aqueous solubility while retaining its biological properties	Duarte et al. (2015)
Silibinin	Silibinin hydroxypropyl-β-cyclodextrin demonstrated enhanced solubility and cytotoxicity as compared to native silibinin	Kellici et al. (2015)
Simvastatin	Simvastatin hydroxypropyl-β-cyclodextrin inclusion complex demonstrated superior efficacy than simvastatin in reducing total cholesterol and TG levels due to improved solubility and dissolution	Jun et al. (2007)
Sulforaphane	Inclusion complex of sulforaphane with hydroxypropyl-β-cyclodextrin enhanced the heat and chemical stability of sulforaphane	Wu et al. (2010)
Thymoquinone	In vitro cytotoxicity on MCF7 cells demonstrated higher cytotoxicity of thymoquinone-cyclodextrin nanoparticles as compared to native thymoquinone	Abu-Dahab et al. (2013)
Ursolic acid	In vitro anti-proliferative activity of ursolic acid hydroxypropyl-γ-cyclodextrin complex demonstrated higher activity as compared to the native ursolic acid	Oprean et al. (2016)
Quercetin	β-cyclodextrin quercetin complex enhanced aqueous solubility of quercetin	Borghetti et al. (2009)

AUC area under curve; *Cmax* concentration maximum; *DPPH* 2,2-diphenyl-1-picrylhydrazyl

results in its limited absorption upon oral administration (Alarcon De La Lastra and Villegas 2005; Arora and Jaglan 2017; Frémont 2000). Therefore, in order to enhance its efficacy its inclusion with β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD) was prepared (Lu et al. 2009). The inclusion ability of HP-β-cyclodextrin is larger than that of β-cyclodextrin. Further, the antioxidant activity also demonstrated a higher scavenging capacity of HP-β-cyclodextrin as compared to β-cyclodextrin. Yang et al. (2016) compared the pharmacokinetics of resveratrol

2-hydroxypropyl-β-cyclodextrin (HP-β-CD) complex and resveratrol nanosupension (obtained by diluting a resveratrol ethanol solution with phosphate buffer saline, added of 0.05% hydroxyethylcellulose). The pharmacokinetic studies after oral administration in BALB-c mice demonstrated HP-β-cyclodextrin complexation enhanced twofold augment of RVT AUC0-120 and ~ fourfold increment in Cmax as compared with resveratrol nanosuspension. Duarte et al. (2015) developed inclusion complexes of resveratrol with methylated-β-cyclodextrin in order to enhance its aqueous solubility. The resveratrol complexation enhanced 400-fold improvements in its aqueous dissolution.

Yee et al. (2017) prepared phenoxodiol-β-cyclodextrin complex via a modified co-evaporation method and demonstrated enhancement in aqueous solubility by ~ ninefolds. Lee et al. (2007) prepared inclusion complexes of soy isoflavone extract (IFE) with β-cyclodextrin in order to improve its solubility and bioavailability. The study demonstrated the complexes of isoflavone extract with β-CD enhanced the aqueous solubility by 26-folds than that of native isoflavone extract. Further, the pharmacokinetic studies in Sprague–Dawley rats demonstrated the bioavailablity of major components of isoflavone extract, i.e. daidzein, genistein and glycitin increased to 126%, 180% and 170%, respectively, as compared to that of native IFE. Wu et al. (2010) prepared the inclusion complex of sulforaphane (SF) with hydroxypropyl-β cyclodextrin (HP-β-CD) using co-precipitation method in order to enhance its stability. The study demonstrated that inclusion complex of sulforaphane with HP-β-cyclodextrin enhanced the thermal stability and the chemical stability of SF. Oprean et al. (2016) developed ursolic acid complexes of 2-hydroxypropyl-β-cyclodextrin and 2-hydroxypropil-γ-cyclodextrin and demonstrated higher in vitro anti-proliferative activity of ursolic acid HP-γ-cyclodextrin complex as compared to the native ursolic acid.

Dual encapsulation of cyclodextrin with nanocarriers

In recent years, there have been considerable trends towards dual-nano-encapsulation approach, i.e. initially forming the inclusion complexes with cyclodextrins and then encapsulating it into nanocarrier. As in inclusion complexes, there was no covalent association between host and guest molecules and the dissociation of nutraceuticals occurs rapidly because of displacement by blood components or dilution by blood plasma/extracellular fluid (Chen et al. 2014). Further, these inclusion complexes do not provide any tumor-targeting benefit and thus limit their use less favorable for cancer treatment. Thus considering these aspects, Soo et al. developed 2-hydroxypropyl-β-cyclodextrin complex of resveratrol and then encapsulated it into liposomes. In vitro cytotoxicity studies in HT-29 colon cancer cell lines showed the developed liposomes exert dose dependent and enhanced cytotoxicity as compared to native resveratrol.

In another study, Popat et al. (2014) developed curcumin (CUR)-γ-hydroxypropyl cyclodextrin (CUR-CD) hollow spheres using spray drying method and then encapsulating it into positively charged biodegradable chitosan (CUR-CD-CS) nanoparticles. The developed CUR-cyclodextrin-CS nanoparticles were found to be more effective than the native CUR and CUR-CS in human skin cancer SCC25 cell lines and induce cell cycle arrest of S phase and G2/M phase followed by complete apoptosis (~ 99.9%). Kellici et al. (2015) prepared inclusion complexes of silibinin (SLB) with 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) in different molar ratios. The silibinin solubility increased upto 10–100-folds upon interaction with HP-β-cyclodextrin as compared to native silibinin. Further, in vitro cytotoxicity studies in MCF7 cell line demonstrated enhanced cytotoxicity of SLB HP-β-cyclodextrin as compared to native SLB.

Serri et al. (2017) developed curcumin complex with (2-hydroxypropyl)-β-cyclodextrin and then encapsulated the complex in the poly(D,L-lactic-co-glycolic acid) nanoparticles using nanoprecipitation method. The purpose of formation of inclusion complex was to improve the loading efficiency due to more encapsulation of the inclusion complex in the internal aqueous phase of the emulsion used to produce the nanoparticles. More interestingly, the increase in the encapsulation did not cause significant alterations in nanoparticle dimension, polydispersity index, zeta potential and yield.

Ji et al. (2017) developed a biodegradable nanocomplex from β-cyclodextrin-grafted hyaluronic acid (HA) and phenylalanine-based poly(ester amide) for gambogic acid (GA) delivery in order to treat multidrug-resistant tumor. In vitro cytotoxicity results demonstrated the nanocomplex enhanced the therapeutic potency of GA in MDA-MB-435/MDR multidrug-resistant melanoma cells and leads to induction of apoptosis and mitochondrial depolarization.

In another study, Baek and Cho (2017) developed combinatorial lipid nanoparticle for co-delivery of curcumin and paclitaxel for multidrug-resistant breast cancer (MCF-7/ADR) cells. Initially, curcumin was encapsulated in 2-hydroxypropyl-β-cyclodextrin (HPCD) in order to improve its stability, aqueous solubility and for providing quicker release compared to that of paclitaxel. The faster release of curcumin will lead to the sufficient p-gp inhibition for improving intracellular accumulation of paclitaxel against MCF-7/ADR cells. The developed nanoparticles were attached to folic acid for achieviving targeted delivery. The results demonstrated that folate-conjugated combinatorial nanoparticles exhibited enhanced uptake of paclitaxel and curcumin into MCF-7/ADR cells *via* folate receptor-mediated internalization.

Aadinath et al. co-encapsulated curcumin-β-cyclodextrin inclusion complex (IC) and iron oxide nanoparticles (IONPs) in liposomes in order to achieve the combinatorial antioxidant potential of curcumin and IONPs. The developed curcumin-in-β-cyclodextrin-innanomagnet liposomes demonstrated the highest DPPH radical scavenging activity (IC50 value, 64.7791 µg/mL) as compared to IONPs and curcumin liposome and thus demonstrating synergistically improvement in radical scavenging property.

Conclusion

The use of dietary phytochemicals has received great interest during the last decade. However, their pharmaceutical applications are hampered because of their poor aqueous solubility and bioavailability. The uses of cyclodextrin have demonstrated the capability of improving the aqueous solubility as well as bioavailability. Further, they have also demonstrated their potential in protecting these dietary phytochemicals from higher temperatures, pH values or moisture-induced degradation. Recent advances in dual-drug delivery, i.e. combination of cyclodextrins and other drug delivery systems assemblies such as nanoparticles, liposomes, have also demonstrated promising results. Nevertheless, most of these studies are in the preclinical stage and require much effort for successful translation of these laboratory innovations to clinical reality.

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