Chapter 1
Cyclodextrin-Based Carriers for Delivery of Dietary Phytochemicals

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Abstract The food and pharmaceutical industry is searching for innovative solutions to enhance the bioavailability and clinical efficacy of dietary phytochemicals. In this regard, cyclodextrins have gained widespread attention as functional excipients. Numerous studies have demonstrated that cyclodextrin inclusion complexes enhance apparent water solubility, physico-chemical stability and improve the bioavailability of the dietary phytochemicals. In addition, dual encapsulation, that is the complexation of dietary molecules with cyclodextrins followed by encapsulation into nanomaterials such as liposomes, nanoparticles, conjugates, has also been investigated. Here, we review the applications of natural and chemically modified cyclodextrins for the delivery of dietary phytochemicals. We focus mainly on outcomes of inclusion complexes for enhancing solubility, bioavailability and efficacy of the delivered phytochemicals. We also discuss recent trends in dual-encapsulation.

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1.1 Introduction

A number of epidemiological and experimental investigations suggests that a regular consumption of fruits, whole grains, vegetables and other plant foods is related with reduced risks of developing chronic diseases such as cancer and cardiovascular diseases (Manach et al. 2009; Liu 2013; Arora and Jaglan 2016). This association has been partly ascribed to the presence of dietary phytochemicals which are bioactive compounds commonly found in plant-based foods. These dietary phytochemicals are generally classified into several categories as polyphenols, terpenoids, alkaloids and other nitrogen compounds, carbohydrates, lipids, phytosterols, and carotenoids (Fig. 1.1) (Manach et al. 2009; Liu 2013; Arora and Jaglan 2016). However, despite having good pharmacological activities of these phytochemicals, most of them are often associated with poor water solubility, poor stability due to 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). Depending on the number of glucopyranose units, the natural occurrence of cyclodextrins can be classified in to 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 (due to chair conformation of the glucopyranose units) with tapered cavity of 0.79 nm in depth, while both the top and bottom diameters are increased with the number of glucose units (Li and Purdy 1992; Jambhekar and Breen 2016). 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 (Mellet et al. 2011; Jambhekar and Breen 2016). 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 unique ability to trap a guest molecule inside its cavity and has been extensively exploited by the pharmaceutical industry to improve bioavailability of poorly aqueous soluble or biodegradable drugs, 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 et al. 2005; Loftsson and Duchêne 2007; Zhang and Ma 2013).

In recent years, cyclodextrins have been used in food industry due to various reasons: (i) to protect lipophilic dietary photochemicals that are sensitive towards degradation due to oxygen, light or heat; (ii) to solubilise food colourings and

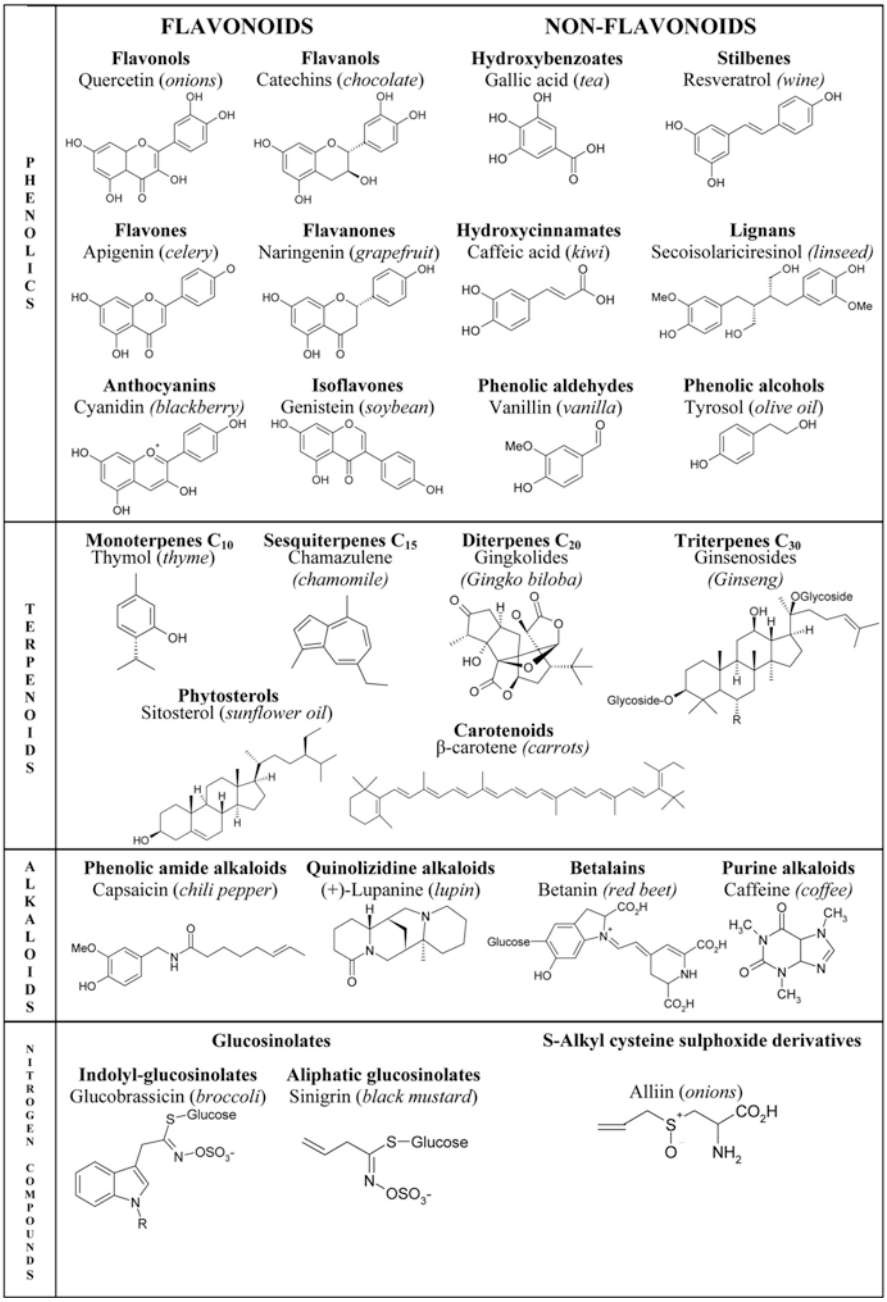

Fig. 1.1 Major classes of phytochemicals in food. Reproduced from Ref. (Manach et al. 2009) with permission from Wiley

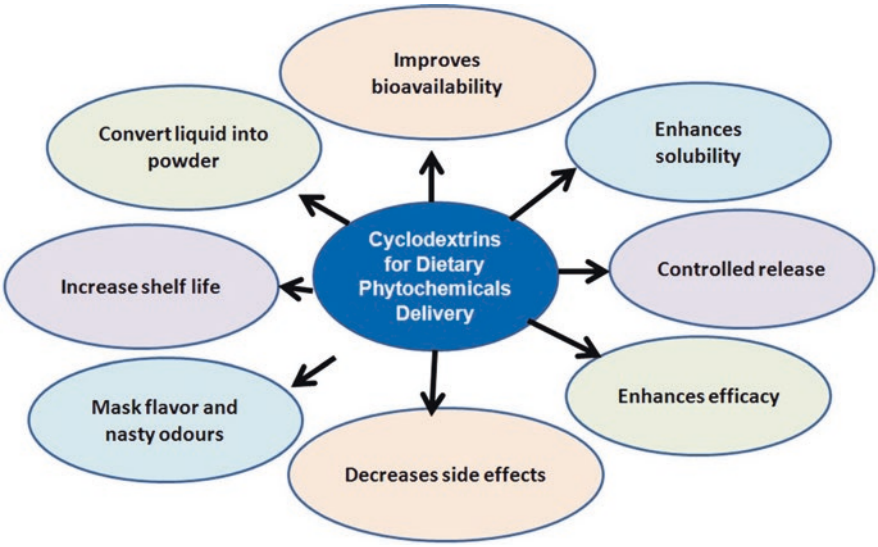

Fig. 1.2 Advantages of cyclodextrin based carriers for delivery of nutraceuticals. Cyclodextrins have been used for delivery of dietary photochemical with a variety of aims like enhancing solubility, bioavailability, shelf-life and efficacy

vitamins; (iii) to stabilize fragrances, flavours, vitamins, and essential oils against undesirable changes; (iv) to mask unpleasant odours or tastes; (v) to achieve a controlled release of dietary components and (vi) to enhance the bioavailability of dietary molecules (Fig. 1.2) (Loftsson et al. 2005; Astray et al. 2009; 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 (Hirayama and Uekama 1999; Challa et al. 2005; Loftsson et al. 2005; Zhang and Ma 2013; Jambhekar and Breen 2016). In this chapter, we mainly focus on the recent advances in cyclodextrins based delivery of dietary molecules in order to enhance the solubility and efficacy of these molecules. In addition, the drug delivery systems consisting of dual systems of cyclodextrins and functional materials such as liposomes, nanoparticles have also been described.

Table. 1.1 Physicochemical properties of cyclodextrins and their derivatives for delivery of nutraceuticals. Reproduced from Ref. (Brewster and Loftsson 2007) with permission from Elsevier

Cyclodextrin	Substitution[a]	MW[b] (Da)	Solubility in water (mg/mL)[c]
α-Cyclodextrin	0	972	145
β-Cyclodextrin	0	1135	18.5
2-Hydroxypropyl-β-cyclodextrin	0.65	1400	>600
Sulfobutylether β-cyclodextrin sodium salt	0.9	2163	>500
Randomly methylated β-cyclodextrin	1.8	1312	>500
6-O-Maltosyl-β-cyclodextrin	0	1459	>1500
γ-Cyclodextrin	0	1297	232
2-Hydroxypropyl-γ-cyclodextrin	0.6	1576	>500

[a]Average number of substituents per glucose repeat unit
[b]MW: Molecular weight
[c]Solubility in pure water at approx. 25 °C

1.2 Chemically Modified Cyclodextrins

The natural cyclodextrins, in particular β-cyclodextrin, are of limited aqueous solubility which results in 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 (Table 1.1). 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 (Gould and Scott 2005; Al-Rawashdeh et al. 2010). Similarly, sulfobutylether-β-cyclodextrin (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 literature (Hirayama and Uekama 1999; Loftsson et al. 2005; Brewster and Loftsson 2007; Loftsson and Duchêne 2007; Loftsson and Brewster 2012; Jambhekar and Breen 2016).

1.3 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

Fig. 1.3 Various methods used for cyclodextrin complexation with dietary phytochemicals. The most common used methods for these are neutralization, kneading, precipitation, spray drying, freeze drying and melting

cyclodextrins and dietary molecules, and the selection of the process is clearly based on physicochemical properties of the guest molecule, the facilities available and the cost involved. The most common methods are neutralization, co-precipitation, kneading, spray drying, freeze drying, melting and solid dispersion (Fig. 1.3) (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 literature (Loftsson and Brewster 2012; di Cagno 2016). The applications of cyclodextrin for phytochemicals delivery are described in following sections.

1.3.1 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 1.2). 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 a 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 that RM-β-cyclodextrin (random methyl β-Cyclodextrin) enhanced much solubility as compare 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.

Table 1.2 Various cyclodextrin-based inclusions developed for nutraceutical delivery along with their major outcomes

Nutraceutical	Outcome	Ref.
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 antioxidant potential, antimicrobial activity and anti-tumor activity.	(Zhu et al. 2016)
Curcumin	Curcumin-β-cyclodextrin-loaded sponge demonstrated comparable wound healing rate as compared to that of marketed formulation with no sign of adverse consequence.	(Kaur et al. 2016)
	Curcumin- β cyclodextrin complex enhance the solubility of free curcumin and improve its antitumor activity.	(Zhang et al. 2016)
	Curcumin–β- cyclodextrin complex demonstrated improved color stability against sunlight, pH, storage and isothermal heating as that of the pure 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 without altering its *in vitro* antioxidant activity.	(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 significantly retarded the elimination of honokiol and prolonged the residence time in circulating system.	(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 by over 400-fold, and its transport across a Caco-2 model of the gut epithelium by 11-fold. Further, the pharmacokinetic studies in rats demonstrated the developed inclusion complex enhanced the AUC by 7.4-fold and C_{max} 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)

(continued)

Table 1.2 (continued)

Nutraceutical	Outcome	Ref.
Resveratrol	Resveratrol hydroxypropyl-β-cyclodextrin complex demonstrated a higher antioxidant efficacy both in terms of capacity and rate of scavenging DPPH radical as compare to resveratrol β- cyclodextrin complex.	(Lu et al. 2009)
	Pharmacokinetic studies after oral administration in BALB-c mice demonstrated hydroxypropyl-β-cyclodextrin complexation enhanced $AUC_{0–120}$ and C_{max} by two and four-fold respectively as compared with resveratrol nanosuspension.	(Yang et al. 2016)
	Resveratrol complexation with methylated-β-cyclodextrin enhanced its aqueous solubility while retaining resveratrol's 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 thermal stability and the chemical stability of sulforaphane.	(Wu et al. 2010)
Thymoquinone	*In vitro* cytotoxicity on MCF7 cells demonstrated higher cytotoxicity of thymoquinone - cyclodextrin nanoparticles as compare 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)

Table Abbreviations: *AUC* Area under curve; C_{max} Concentration maximum; *DPPH* 2,2-diphenyl-1-picrylhydrazyl

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 caused a reduction in tumor volume and weight *in vivo* in C57BL/6 J mice. Silva *et al.* developed β-cyclodextrin complex with carvacrol (5-isopropyl-2-methylphenol), an isoprenoid present in the essential oils of genera *Origanum* and *Thymus* belongs to Lamiaceae family (Silva et al. 2016). The developed complex was evaluated in formalin, capsaicin, and glutamate induced orofacial nociception in mice. The study demonstrated the developed complex showed superior efficacy than native carvacrol. The carvacrol-β-cyclodextrin complex (20 mg/kg, p.o.) produced 49.3% behavior pain while native carvacrol produced 28.7% analgesic inhibition at same dose in the second phase of formalin test. Zhu *et al.* prepared chrysin (5,7-dihydroxyflavone)-β-cyclodextrin inclusion complex in order to improve its solubility as well as efficacy (Zhu et al. 2016). The study demonstrated the solubility of chrysin and inclusion complex were 1.93 mmol/L

and 7.32 mmol/L, respectively at pH 7.5. The antioxidant activity determined using scavenging oxygen free radicals, scavenging 2,2-diphenyl-1-picrylhydrazyl (DPPH) and scavenging hydroxyl free radical showed much stronger antioxidant activity of inclusion complex than in native chrysin. *In vitro* cytotoxicity in H22 mouse liver tumor cells after 72 h demonstrated the inclusion complex demonstrated almost equal cytotoxicity as compare to native chrysin.

Zhang *et al.* developed curcumin-β-cyclodextrin complex in order to enhance the solubility of curcumin and improve its antitumor activity (Zhang et al. 2016). *In vitro* cytotoxicity in lung cancer cells (A549, NCI-H446 and NCI-H520) demonstrated higher cytotoxicity of the complex as compare with native curcumin. Further, *in vivo* efficacy in H22 tumor cells induced Kunming mice demonstrated higher tumor inhibition rate of the complex 34.64% as compare with native curcumin 9.52%. In another study, curcumin was complexed with β-cyclodextrin using co-precipitation, freeze-drying and solvent evaporation methods (Mangolim et al. 2014). The inclusion complex increased the solubility of curcumin by 31-folds and exhibited a sunlight stability 18% higher than native curcumin. Kaur *et al.* developed curcumin-β-cyclodextrin complex and then loaded into gelatin sponge (Kaur et al. 2016). The curcumin-β-cyclodextrin-loaded sponge treated wound was found to heal in rate as compare to marketed formulation silver sulfadiazine with no sign of adverse consequence.

Ashwaq *et al.* developed dentatin-hydroxypropyl-β-cyclodextrin (HPβCD) complex for enhancing the solubility of dentatin (Ashwaq et al. 2017). The solubility of dentatin was enhanced more than 300-fold after complexation as compare to dentatin alone. Moreover, the complexation of dentatin did not reduce cytotoxicity on prostate cancer (LNCaP), human adenocarcinoma breast cancer (MDA-MB-231) and human gastric adenocarcinoma cell line (HDT). Mohtar *et al.* prepared complexation of fisetin with sulfobutylether-β-cyclodextrin with the aim of increasing the solubility of fisetin (Mohtar et al. 2017). Further, the developed complex was spray dried into dry powder inhaler (DPI) formulation with optimized aerodynamic properties and tested against the human lung adenocarcinoma cell line (A549). The study revealed fisetin-SBE-β-cyclodextrin complex improved the solubility of fisetin and was capable of delivering high amount of fisetin to the deep lung region for therapeutic applications.

Pinho *et al.* developed inclusion complex of gallic acid with β-cyclodextrin, (2-hydroxy) propyl-β-cyclodextrin and methyl-β-cyclodextrin (Pinho et al. 2015). The inclusion complex of gallic acid with HP-β-cyclodextrin had better antibacterial efficiency and also exhibited higher stability than other complexes. Suzuki *et al.* developed solid dispersion on mixtures of hinokitiol (HT) and γ-cyclodextrin (c-CD) and of hinokitiol and (2-hydroxypropyl)-γ-cyclodextrin (HP-γ-CD) (Suzuki et al. 2015). The developed ground mixtures enhanced the antimicrobial activity 4 times than the HT crystals which is due to increase in the solubility of HT as a result of the formation of HT/cyclodextrin inclusion complexes. In another study Wang *et al.*prepared honokiol with hydroxypropyl-β-cyclodextrin and encapsulated it into liposome (Wang et al. 2011). The pharmacokinetic study demonstrated that honokiol-in-HP-β-cyclodextrin-in-liposome significantly retarded the elimination

and prolonged the residence time in circulating system as compare with native honokiol which was quickly removed from the circulating system after intravenous injection. Further, the *in vitro* cytotoxicity in A549 and HepG2 cells demonstrated the bioactivity of honokiol-in-HP-β-cyclodextrin-in-liposome was relatively a little weak as compare with free honokiol which maybe, due to the reason that honokiol was not completely released from honokiol-in-HP-β-cyclodextrin-liposome in 48 h.

Yang *et al.* developed β-cyclodextrin and its derivatives, heptakis-(2,6-di-O-methyl)-β-cyclodextrin (DMβCD) and heptakis (2,3,6-tri-O-methyl)-β-cyclodextrin (TMβCD) complexes of naringenin which is one of the most abundant flavonoids in grapefruits and citrus fruits in order to enhance its solubility (Yang et al. 2013). The solubility studies demonstrated that the water solubility of naringenin was increased after their inclusion with cyclodextrins. The native naringenin demonstrated solubility 4.38 μg/mL which was remarkably enhanced to approximately 1.34, 1.60 and 1.52 mg/mL by the solubilizing effects of β-cyclodextrin, DM-β-cyclodextrin and TM-β-cyclodextrin, respectively. Shulman *et al.* developed hydroxypropoyl-β-cyclodextrin (HPβCD) complex of naringenin and demonstrated its enhanced solubility by 400-fold, and transport across a Caco-2 model of the gut epithelium by 11-fold (Shulman et al. 2011). Further, the pharmacokinetic studies in rats demonstrated enhanced AUC values by 7.4-fold and C_{max} by 14.6-fold as compare to native naringenin. Xu *et al.* prepared β-cyclodextrin (β-CD) complex of naringenin and demonstrated its solubility was increased by more than ten-fold (Xu et al. 2014). Further, the prepared complex also significantly reduced choroidal neovascularization (CNV) area than native naringen in laser-induced CNV model in rats.

Borghetti *et al.* 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 enhancement of aqueous solubility of quercetin to 4.6-fold in the presence of 15 mM of β-cyclodextrin. Oommen *et al.* prepared inclusion complex of plumbagin with β-cyclodextrin and then encapsulated it into niosomes using a lipid layer hydration method (Oommen et al. 1999). The niosome entrapped drug complex had improved anticancer activity as compare to native plumbagin when administered subcutaneously to C57BL/6 J mice bearing melanoma B16F1 at a dose of 5 mg kg^{-1}, the as evidenced by the enhanced volume doubling time and growth delay.

Resveratrol (3,4′,5-trihydroxystilbene) which is found in a number of which are dietary components, such as mulberries, peanuts, and grapes is sparingly soluble in water, which may be responsible for its limited absorption upon oral administration (Frémont 2000; Alarcon De La Lastra and Villegas 2005; Arora and Jaglan 2017). Therefore, in order to enhance its efficacy its inclusion with β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD) were 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 compare to β-cyclodextrin. Yang *et al.* 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) (Yang et al. 2016).

The pharmacokinetic studies after oral administration in BALB-c mice demonstrated HP-β-cyclodextrin complexation enhanced two-fold augment of RVT AUC_{0-120} and ~ four-fold increment in C_{max} as compare with resveratrol nanosuspension. Duarte *et al.* developed inclusion complexes of resveratrol with methylated-β-cyclodextrin in order to enhance its aqueous solubility (Duarte et al. 2015). The resveratrol complexation enhanced 400-fold improvements in its aqueous dissolution. Further, the developed inclusion complex also preserved the potential of resveratrol in decreasing the cell viability of Caco-2 cells, as well as the very strong antioxidant activity of resveratrol.

Yee *et al.* prepared phenoxodiol- β-cyclodextrin complex *via* a modified co-evaporation method and demonstrated enhancement in aqueous solubility by ~nine-folds (Yee et al. 2017). Further the developed, complex demonstrated enhanced *in vitro* anti-proliferative activity against three different cancer cell lines, namely the neuroblastoma cells SKN-BE(2)C, the triple negative breast cancercells MDA-MB-231 and the glioblastoma cells U87.

Jun *et al.* prepared inclusion complex of simvastatin (SV) with hydroxypropyl β-cyclodextrin (HP-β-CD) using supercritical antisolvent (SAS) process in order to improve its efficacy (Jun et al. 2007). The study demonstrated that SV/HP-β-CD inclusion complex showed superior efficacy than SV in reducing total cholesterol and TG levels which was attributed to improved solubility and dissolution associated with inclusion complex between simvastatin and HP-β-CD.

Lee *et al.* prepared inclusion complexes of soy isoflavone extract (IFE) with β-cyclodextrin in order to improve its solubility and bioavailability (Lee et al. 2007). The study demonstrated the complexes of isoflavone extract with β-CD enhance 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 compare to that of native IFE. Wu *et al.* prepared the inclusion complex of sulforaphane (SF) with hydroxypropyl-β cyclodextrin (HP-β-CD) using co-precipitation method in order to enhance its stability (Wu et al. 2010). 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.* 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 (Oprean et al. 2016).

1.3.2 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 is no covalent association between host and guest molecules and the dissociation of nutraceuticals

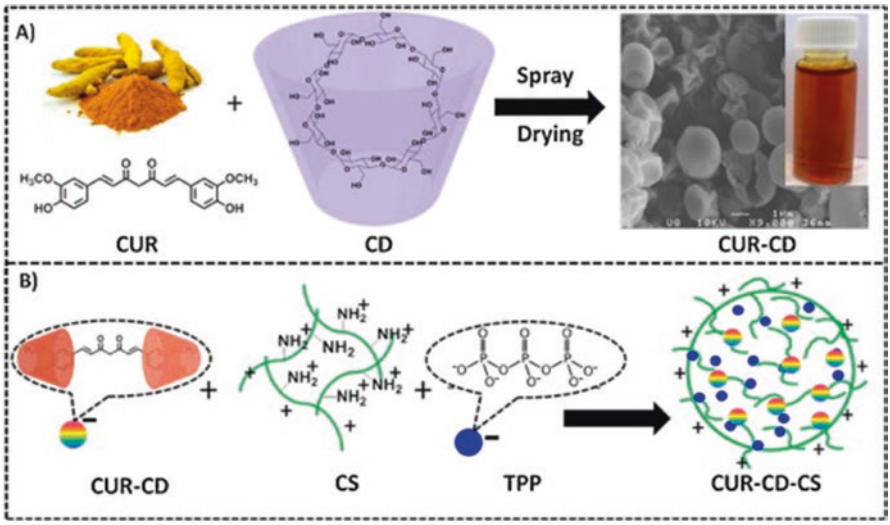

Fig. 1.4 (**A**) The preparation of highly soluble curcumin (CUR)-cyclodextrin (CD) complex by a novel spray drying method. The scanning electron microscopy image represents hollow microspheres after spray drying and inset shows a water solution of curcumin-cyclodextrin; (**B**) the preparation method of curcumin–cyclodextrin-chitosan (CS) nanoparticles. *TPP* triphosphate pentaanion. Reproduced from Ref. (Popat et al. 2014) with permission from Elsevier

occurs rapidly due to 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, thus limits 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 demonstrated that the developed liposomes showed dose dependent and enhanced cytotoxicity as compare to free resveratrol.

In another study, Popat *et al.* 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 (Fig. 1.4) (Popat et al. 2014). The developed CUR-cyclodextrin-CS nanoparticles are 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.* prepared inclusion complexes of silibinin (SLB) with 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) in different molar ratios (Kellici et al. 2015). The silibinin solubility increased upto 10–100-folds upon interaction with HP-β-cyclodextrin as compare to native silibinin. Further, *in vitro* cytotoxicity studies in MCF7 cell line demonstrated enhanced cytotoxicity of SLB HP-β-cyclodextrin as compare to native SLB.

Serri *et al.* 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 (Serri et al. 2017). 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 changes in nanoparticle dimension, polydispersity index, zeta potential and yield.

Ji *et al.* 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 (Ji et al. 2017). *In vitro* cytotoxicity results demonstrated the nanocomplex enhanced the therapeutic potency of GA in MDA-MB-435/MDR multidrug resistant melanoma cells, and induced enhanced level of apoptosis and mitochondrial depolarization.

In another study, Baek *et al.* developed combinatorial lipid nanoparticle for co-delivery of curcumin and paclitaxel for multidrug resistant breast cancer cells (Baek and Cho 2017). Initially, curcumin was encapsulated in 2-hydroxypropyl-β-cyclodextrin (HPCD) in order to improve its stability, aqueous-solubility and for providing faster release relative to the release of paclitaxel. The faster release of curcumin will lead to the sufficient p-gp inhibition for enhanced intracellular accumulation of paclitaxel against MCF-7/ADR cells. The developed nanoparticles were attached to folic acid in order to achieve targeted delivery. The results demonstrated that folate-conjugated curcumin and paclitaxel loaded lipid 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) within liposomes in order to achieve the synergistic antioxidant potential of curcumin and IONPs. The developed curcumin-in-β-cyclodextrin-innanomagnet liposomes demonstrated highest DPPH radical scavenging activity (IC_{50} value, 64.7791 μg/mL) as compared to IONPs and curcumin liposome and thus demonstrating synergistically enhanced radical scavenging property.

1.4 Conclusion

The use of dietary phytochemicals has gained a substantial interest during the last decade. However, their pharmaceutical applications are limited due to 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 elevated 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 much effort is desirable for successful translation of these laboratory innovations to clinical reality.

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