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REVIEW ARTICLE

Cyclodextrins and their potential applications for delivering vitamins, iron, and iodine for improving micronutrient status

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Abstract

Cyclodextrins (CDs) have been investigated as potential biopolymeric carriers that can form inclusion complexes with numerous bioactive ingredients. The inclusion of micronutrients (e.g. vitamins or minerals) into cyclodextrins can enhance their solubility and provide oxidative or thermal stability. It also enables the formulation of products with extended shelf-life. The designed delivery systems with CDs and their inclusion complexes including electrospun nanofibers, emulsions, liposomes, and hydrogels, show potential in enhancing the solubility and oxidative stability of micronutrients while enabling their controlled and sustained release in applications including food packaging, fortified foods and dietary supplements. Nano or micrometer-sized delivery systems capable of controlling burst release and permeation, or moderating skin hydration have been reported, which can facilitate the formulation of several personal and skin care products for topical or transdermal delivery of micronutrients. This review highlights recent developments in the application of CDs for the delivery of micronutrients, i.e. vitamins, iron, and iodine, which play key roles in the human body, emphasizing their existing and potential applications in the food, pharmaceuticals, and cosmeceuticals industries.

Keywords Cyclodextrin (CD) inclusion complex · Micronutrients · Enhanced solubility · Improved stability · Controlled release · Health-promoting applications

Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides consisting of macrocyclic glucose rings produced from enzymatic conversion of starch [1–3]. During recent years, there has been a burgeoning interest in their applications in the *pharmaceuticals*, *food and beverage*, *environmental*, *chemical*, and *agricultural* industries [4–6]. The global market of CDs surpassed USD 260 million in 2020 and was projected to grow at a compound annual growth rate (CAGR) of 5.5% from 2021 to 2027 [7]. CDs have been used mainly in the pharmaceuticals and food industries as complexing agents for enhancing the solubility of poorly water-soluble drugs and nutraceuticals or for improving their stability [8, 9]. The reduced hydrophobicity of drug compounds or nutraceutical ingredients as a result of their inclusion complexation with CDs can facilitate their absorption and uptake by the body and enhance their bioavailability [9, 10]. CDs can simultaneously improve the chemical, physical, and thermal stability of active pharmaceutical ingredients (APIs) and nutraceutical compounds and protect them from oxidation, or decomposition when exposed to radiation or elevated temperatures [11–14]. Encapsulation and inclusion of drugs inside CDs can reduce their irritancy while protecting them from interaction with other incompatible drug components [8, 15]. The unpleasant taste of drugs or other flavor-active compounds can also be masked using CDs [16–18]. With the potential of CDs as carriers of therapeutics and bioactive ingredients, they have found their applications in the development of drugs [19, 20], vaccines [21–23], cosmeceutical and personal care products [24, 25], dietary supplements [26, 27], and fortified or functional foods [28, 29]. In the food industry, their application has been tested at an industrial scale for the production of reduced-cholesterol dairy products [6, 30]. As another example of their application in the

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pharmaceuticals industry, they have been recently used for the formulation of the antiviral drug, Remdesivir and used as an adjuvant for formulating vaccines for the therapy of COVID-19 [31–33]. In the Food industry, CDs can deliver antioxidants in foods such as meat products and prevent lipid oxidation while simultaneously finding their applications in food packaging and preservation [34–37].

There has been an increasing interest in CD applications for the delivery of micronutrients [38–41]. The inclusion complexes formed between CDs and micronutrients including *vitamins* [42–44], *iron* [41, 45, 46], or *iodine* [40, 47, 48] not only enhance the solubility of micronutrients but also improve their bioavailability and uptake when delivered orally in foods or dietary supplements [49, 50]. They have a similar effect when delivered topically or transdermally and utilized in the formulation of pharmaceutics, cosmetics, or skin care products [43, 51]. Inclusion complexation with CDs improves the stability of micronutrients, by preserving them from oxidation or degradation when exposed to oxygen, light or heat and facilitates the formulation of products with extended shelf-life and durability [52–54]. Additionally, some iron compounds such as ferrous sulphate are metallic in taste and result in rusty color when oxidized to ferric forms [41, 55, 56]. Another iron source, ferrous fumarate, can also darken under highly oxidizing conditions [57] and when interacting with iodine [58, 59]. Some vitamins such as vitamin B_1 (thiamine) or vitamin B_6 (pyridoxine) are identified as bitter [60, 61]. CDs have found their applications for masking bitter or undesired tastes [1, 62] and show potential to be used for masking the metallic or bitter tastes of micronutrients [60]. The deficiency of micronutrients can cause several autoimmune [63, 64], chronic [65, 66], or neurological diseases [67]. Therefore, to prevent micronutrient-deficiency diseases, the nutritional profile of foods should be improved through fortification with micronutrients. Specific attention is devoted to the application of CDs and their inclusion complexes with hydrophilic [43, 51, 68, 69] or lipophilic vitamins [34, 42, 44, 70–72]. *Vitamins* are vital micronutrients, lack of which can lead to deficiency diseases such as scurvy, rickets, beriberi, anaemia, or xeropthalmia and blindness [73, 74]. *Iron* is another key micronutrient in the human body playing an indispensable role in the formation of myoglobin and hemoglobin and transport of oxygen [75]. Low intake and bioavailability of iron can cause diseases such as iron deficiency anaemia, which affects mostly young children and women of low-income and developing countries [76, 77]. Compared with vitamins, the number of publications on the application of CDs for iron delivery is scarce in the literature as most iron sources are hydrophilic and have a reduced tendency to form inclusion complexes with CDs with a hydrophobic cavity [41]. *Iodine* is another essential micronutrient necessary for the synthesis of thyroid hormones and cell metabolism. Deficiency of iodine and the subsequent lack of thyroid hormones can cause endemic goiter [78]. Inclusion complexes formed between iodine and CDs show potential for regulating thyroid hormones [47, 79].

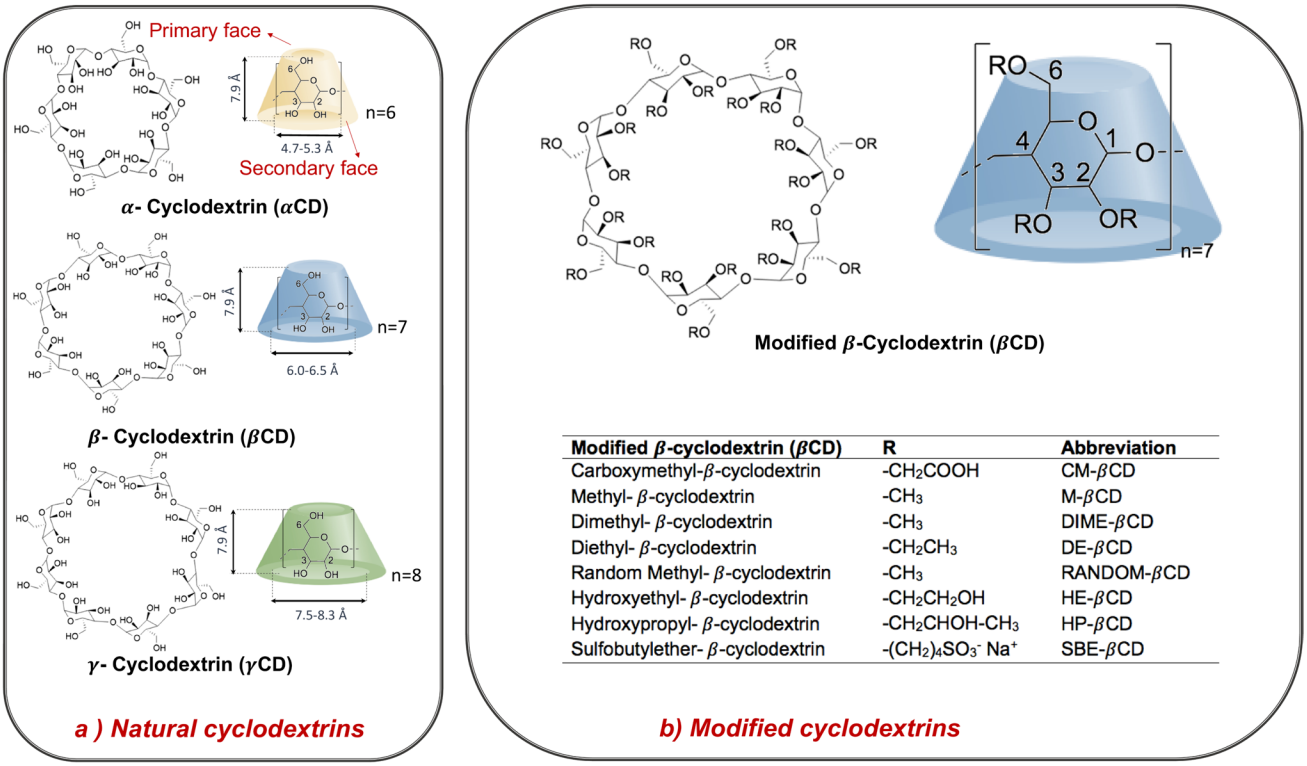
Considering the importance of vitamins, iron, and iodine for the human body and the emergence of CDs as delivery carriers of micronutrients, this review aims to highlight recent advancements in delivery systems designed with CDs and their inclusion complexes with vitamins, iron, or iodine and discuss their health-promoting applications in food packaging, formulating fortified foods, dietary supplements, or developing pharmaceutical, cosmeceutical, or personal care products.

Molecular structure of cyclodextrins (CDs)

Natural CDs

CDs are a group of products obtained from the degradation of carbohydrates [3, 80, 81]. These bucket or truncated cone-shaped cyclic oligosaccharides are comprised of D-glucopyranose units linked in α (1-4), bonds and have a hydrophobic interior cavity and a hydrophilic exterior surface [82, 83]. Due to the chair-like conformation of glucopyranose units, they form a truncated cone and not a cylindrical shape. The naturally occurring CDs are α-cyclodextrin (αCD), β-cyclodextrin (βCD), and γ-cyclodextrin (γCD) with 6, 7, or 8 glucopyranose units respectively [3, 83, 84]. CDs have two flat hydroxylated surfaces of primary and secondary (see Fig. 1a). While primary hydroxyl (C6-OH) groups are positioned at the primary face, the secondary (C2/C3-OH) groups are arranged at the secondary face of the CD molecule [3, 85]. Skeletal carbons and ethereal oxygens of the glucose units are lined in the central cavity of CDs imparting a hydrophobic nature to the CD interior [82, 83]. The hydrophobic nature of the CD cavity facilitates the inclusion of several lipophilic guest molecules inside CDs and the formation of inclusion complexes. These can be formed through the displacement of water from the cavity and its replacement by the guest molecules (here micronutrients). The size of the micronutrient molecule, which should fit inside the CD cavity, the electrostatic and Van der Waals forces and hydrophobic interactions are the major driving forces for the formation of an inclusion complex [86–88].

The structural characteristics of natural CDs, including their cavity size and volume, together with their degree of solubility shown by the *log P* value (partition coefficient in octanol/water solution) and *log S* (the intrinsic solubility) are presented in Table 1.



Modified β-cyclodextrin (βCD)	R	Abbreviation
Carboxymethyl-β-cyclodextrin	-CH_2COOH	CM-βCD
Methyl- β-cyclodextrin	-CH_3	M-βCD
Dimethyl- β-cyclodextrin	-CH_3	DIME-βCD
Diethyl- β-cyclodextrin	-CH_2CH_3	DE-βCD
Random Methyl- β-cyclodextrin	-CH_3	RANDOM-βCD
Hydroxyethyl- β-cyclodextrin	-CH_2CH_2OH	HE-βCD
Hydroxypropyl- β-cyclodextrin	-$CH_2CHOH-CH_3$	HP-βCD
Sulfobutylether- β-cyclodextrin	-$(CH_2)_4SO_3^-$ Na^+	SBE-βCD

Fig. 1 Molecular structure of **a** Natural cyclodextrins (CDs) **b** Modified cyclodextrins (CDs) [89]

Modified CDs

CDs can be modified and their structure can be tailored to facilitate host-guest inclusion complex formation. The free hydroxyl groups of the glucopyranose unit of CD positioning at the secondary face (i.e. C2, C3), or at the primary face (i.e. C6) can be modified with various functional groups (shown in Fig. 1b) with different degrees of substitution [89]. The most commonly tested modified CD for the delivery of micronutrients is 2-hydroxypropyl-β-cyclodextrin (HP-βCD), which can be synthesized by substitution of several hydroxyl groups at both extremities of the CD molecule improving its aqueous solubility [91]. The lipophilic nature of the cavity and the hydrophilic exterior with improved aqueous solubility, facilitate the interaction with lipophilic or water-soluble micronutrients [39, 40, 45, 52]. Other modified type CDs with improved aqueous solubility can also facilitate the inclusion of micronutrients considering the structure of the guest molecule and its size. The efficacy of sulfobutylether-β-cyclodextrin (SBE-βCD), known by the commercial name Captisol®, 2,6,dimethyl-O-β-cyclodextrin (DIME-βCD), and 2,3,6, tri-O-methyl-β-cyclodextrin (TRIME-βCD), for solubilizing retinol and protecting it from degradation is reported in some studies [92, 93]. Utilization of methyl-β-cyclodextrin (M-βCD) for inclusion complexation with vitamin C and E is reported to improve the aqueous solubility of the latter and to develop an antioxidant assay while studying the solvent effects [94].

Table 1 Characteristics of natural CDs [83, 84, 90]

Molecule	MWt (g/mol)	Log P[a]	Log S[b]	Cavity diameter (Å)	Cavity height (Å)	Cavity volume ($Å^3$)
αCD	972.8	-10.63	3.75	4.7–5.3	7.9	174
βCD	1135.0	-12.40	5.73	6.0–6.5	7.9	262
γCD	1297.1	-14.17	8.12	7.5–8.3	7.9	427

[a]Log P is the 10-base logarithmic measure of the partition coefficient (P), the ratio of concentrations of an un-ionized compound in the two phases of immiscible solvents (water and *n*-octanol) at equilibrium

[b]Log *S* or intrinsic solubility is the 10-base logarithmic measure of the solubility (mol/L)

Other modified type CDs such as thiolated CDs can be prepared with the attachment of thiol moieties to the oligomeric backbone of CDs. However, their application for micronutrient delivery is not widely explored compared with the other tested modified-type CDs [95]. These modified CDs can be used for mucosal drug delivery as they form disulfide bonds with cysteine-rich glycoproteins of the mucus [96, 97].

Cyclodextrin (CD) inclusion complexes with micronutrients

Stoichiometry

CDs as host molecules can form complexes with micronutrients as guest molecules in different stoichiometric ratios. The most frequent stoichiometry is the ratio of CD: micronutrient of 1:1 with the inclusion of only one guest molecule. However, other stoichiometries of 1:2, 2:1, and 2:2 can also be observed [98]. The depth of the insertion of the guest molecule inside the CD cavity and its positioning close to the primary or secondary face of the CD molecule depends on the molecular structure of the guest molecule and the CD type [99–101]. A schematic view of the most frequent configurations for various stoichiometries of CDs and their inclusion complexes is shown in Fig. 2.

Job's method, or method of continuous variation, is a technique for the determination of CD: guest molecule's stoichiometric ratio. This UV-Vis spectroscopy-based method has been mostly applied for the determination of the stoichiometry for vitamins [102, 103]. Several solutions of the guest molecule and CD can be prepared while varying the mole fraction of the guest molecule. Job's plot can then be generated by plotting $\Delta A \times R$ vs. R, where ΔA is the difference in UV absorbance of the vitamin in the presence or absence of CD and $R = \frac{[Vitamin]}{[Vitamin]+[Cyclodextrin]}$. The value of R measured at the maximum derivation and at 298.15 K shows the stoichiometry of the inclusion complex [102, 103]. The stoichiometry of CD inclusion complexes can also be determined using surface tension or conductivity measurements. With an increase in CD concentration and formation of an inclusion complex with the micronutrient, the surface tension and conductivity decrease and in each curve, a single discernible break can be observed pointing out the formation and the stoichiometry of the inclusion complex [103, 104].

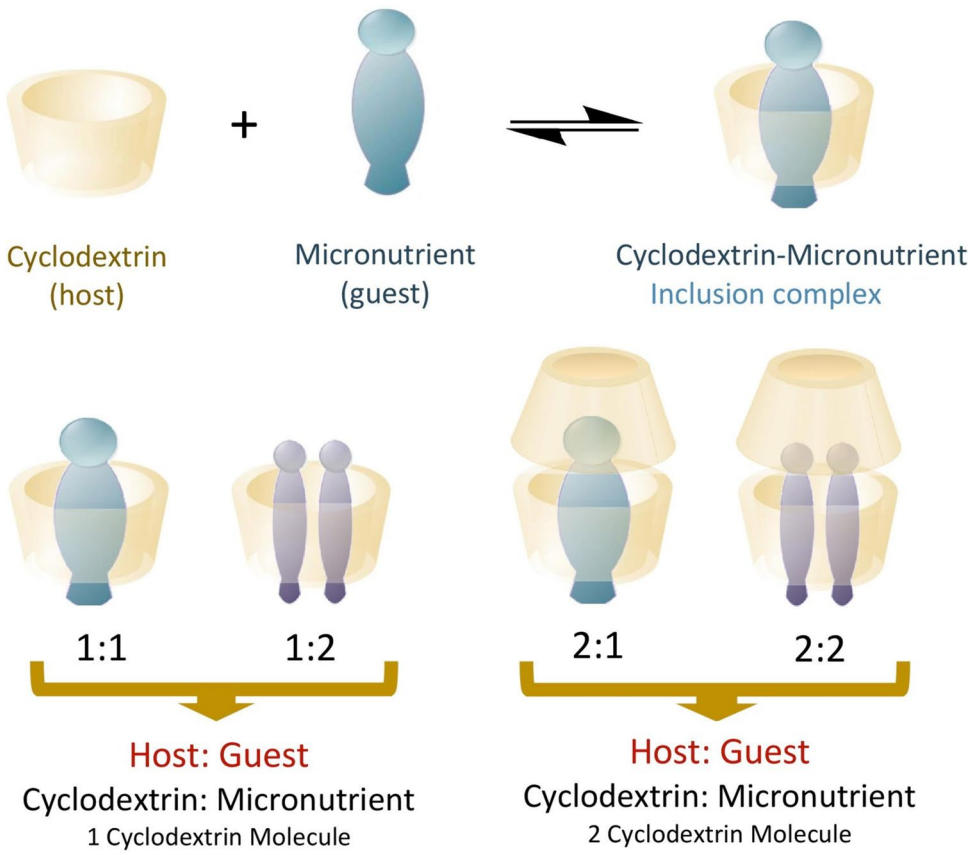


Fig. 2 Different stoichiometries for Cyclodextrin (CD) (host): Micronutrient (guest) inclusion complex formation [3]

Preparation techniques

CDs and their inclusion complexes with guest molecules can be prepared through several techniques such as *co-precipitation* [41, 42], *kneading* [40, 44, 45], *spray drying* [46, 53, 110], *freeze-drying* [34, 42], *grinding* [40], *co-evaporation* [40], *sealed heating* [40], *microwave irradiation*, or with the assistance of a *supercritical fluid* such as carbon dioxide (CO_2) [6, 111]. The most commonly applied techniques for the preparation of CDs and their inclusion complexes with micronutrients are discussed in the following.

The *Co-precipitation* method is the commonly applied technique for the preparation of CD inclusion complexes with micronutrients [41, 42, 46, 99, 105–109]. In this method, the guest molecule dissolved in a co-solvent e.g. ethanol or other alcohols is added to the cyclodextrin aqueous solution and the solution mixture is gently heated for the formation of the complex. It is followed by cooling the solution and precipitation of the complex. The resulting complex is vacuum filtered and washed for removal of the unbound surface guest molecules. The washed filtrate is then oven-dried. This technique is commonly employed at lab-scale due to its simplicity and efficiency [6, 41, 99, 111].

The *Kneading* method involves the preparation of a CD paste through dissolving it in water in a mortar, followed by addition of a micronutrient as the guest molecule and grinding the mixture with a pestle. The obtained solid is then washed with a small quantity of solvent to remove free unbound micronutrients [40, 44, 45]. Although this technique is easy and simple, it might lead to low yields. Therefore, it is less commonly applied than the co-precipitation technique [6, 111].

Spray drying can be also used for the preparation of CD inclusion complexes. First, a solution of a mixture of CD and the guest micronutrient in the presence or absence of other biopolymers is prepared and an inclusion complex is formed following three steps: (a) Atomization of the liquid feed at optimized spray drying conditions by adjusting several parameters such as feed flow rate, inlet, and outlet temperatures (b) Mixing and drying of the atomized feed with the hot air stream (c) Collection of the dried powder. This technique is suitable for water-dispersible carrier materials and is applicable for large-scale operations. However, it requires expensive equipment and has high energy consumption [6, 46, 53, 110, 111].

The *Grinding* method consists of the preparation of CD inclusion complexes through kneading followed by applying mechanical force to break further the formed crystals to reduce the particle size and increase the contact surface to facilitate the interaction of the guest micronutrient with the CD molecule. This technique is simple, fast and is solvent-free, suitable for poorly water-soluble micronutrients. However, similar to the kneading method, it might lead to low yields and impact the loading efficiency [6, 40, 111].

The *Co-evaporation* technique includes the preparation of a mixture of an aqueous solution of CD and a dissolved micronutrient in an alcoholic solution, e.g. ethanol, and evaporating the solvent to dryness under vacuum followed by collection of the sample powder and further air drying of the sample at room temperature [40].

The *Sealed heating* method involves the preparation of a physical mixture of CD and the guest micronutrient in a closed container and heating the mixture for some duration. It is then followed by cooling the container to room temperature and collection of the formed inclusion complex powder. The collected powders are then air-dried at room temperature. This technique is a solvent-free method and is easy to implement. It can result in micronutrient loading comparable to or higher than that obtained with grinding or co-evaporation techniques [40].

The latter two techniques are less suited for the preparation of inclusion complexes of CDs with heat-labile micronutrients and therefore the co-precipitation technique is the most preferred method for their preparation.

Delivery systems and their preparation methods

CDs form inclusion complexes with vitamins, iron, and iodine and these can be used as delivery systems in foods, pharmaceutics, and cosmeceutical products. The most common delivery systems for vitamins, iron, or iodine are illustrated in Fig. 3. CDs and their inclusion complexes can be used directly as a delivery system but these can be also electrospun into nanofibers, nanowebs, or mats in the presence or absence of biopolymers during an electrohydrodynamic process (electrospinning/electrospraying) [34, 52, 83, 112]. The electrospinning process includes the elongation and stretching of a polymeric/ polymer-free solution of a CD inclusion complex at the tip of a needle and under the applied voltage and electrostatic field, see Fig. 3a [83]. The produced nanofibers can be collected at a certain distance from a collector. The electrospinning process is easy to operate, adaptable to several polymeric systems, and capable of producing nanofibers in different diameters and structures [83, 113] without the requirement of utilizing high temperatures or pressures [114]. An adjustment of several parameters such as flowrate (0.1 to 1 mL h^{-1}), voltage (7–30 kV), needle tip to collector distance (8 to 15 cm), temperature (20 to 26 °C), and relative humidity% (RH%) (17 to 50%) [34, 39, 43, 52, 69, 102, 115], assures the formation of stable, small-sized nanofibers of micronutrients- CD inclusion complexes. The high surface area and large pore size of electrospun nanofibers or nanofibrous films make them adaptable delivery systems of micronutrients and other functional ingredients. Simultaneously, they can find their applications in active packaging for preserving foods and extending their shelf-life [34, 52, 114].

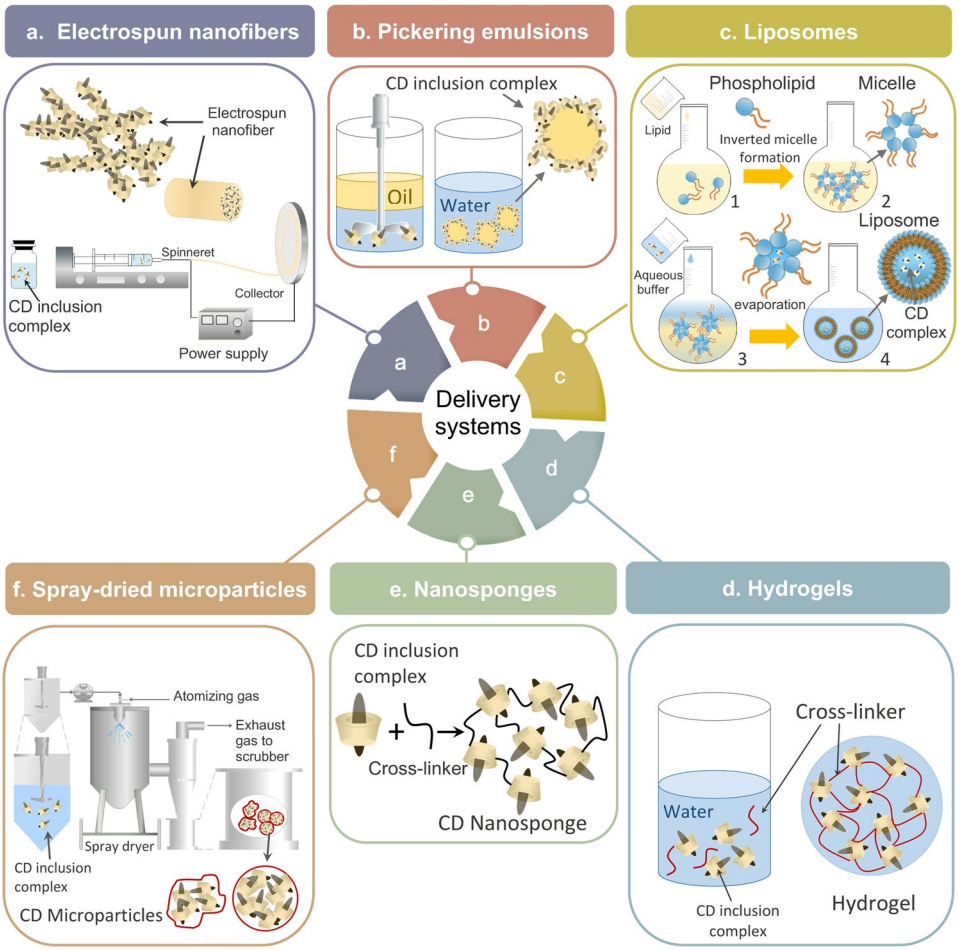


Fig. 3 Delivery systems of cyclodextrin (CD) inclusion complexes with micronutrients; **a** Electrospun nanofibers (CD inclusion complexes can be electrospun into nanofibers/mats through electrospinning technique) [83, 116]; **b** Pickering emulsions (CD inclusion complexes can be used as emulsion stabilizers) [117]; **c** Liposomes (CD inclusion complexes can be incorporated into liposomes) [118–120]; **d** Hydrogels (CD inclusion complexes can be used for formulating hydrogels using cross-linkers [68, 109]; **e** Nanosponges (CD inclusion complexes can be used for formulating nanosponges using cross-linkers [121]; **f** Spray-dried microparticles (CD inclusion complexes can be spray dried to form microparticles using spray drying) [122, 123]

This technology has the potential for scale-up using High-speed electrospinning [124]. Micronutrients encapsulated in CDs have been used in designing colloidal systems such as emulsions [41, 51, 107, 117, 125, 126], liposomes [71, 72], or colloidal gels [68, 109, 127]. They can be used to formulate particle-stabilized Pickering emulsions as they can assemble at the interface of the emulsions and enhance the accessibility of the encapsulated micronutrient (Fig. 3b). These emulsion systems are constructed from aqueous and organic phases and commonly prepared through homogenization using high-speed Ultraturrax mixers or under high pressures adopting a high-pressure homogenizer [107, 125, 126]. CDs can also be used to stabilize micronutrient-loaded emulsion systems enabling co-delivery of several nutraceutical compounds [41, 51, 117]. The amphiphilic nature of CDs makes them suitable candidates for formulating emulsions for the delivery of antioxidants in foods [107, 125]. Some studies also attempted incorporating micronutrients and their inclusion complexes with CDs into the aqueous phase of liposomes, colloidal delivery systems prepared from phospholipids, to protect the encapsulated micronutrient, while enhancing its stability and bioavailability (Fig. 3c) [71, 72]. Liposomes can be prepared through the *thin film hydration* method using organic solvents such as dichloromethane, chloroform, or ethanol to dissolve lipids. The solvent can then be evaporated under vacuum to form a thin lipid film, which will be further hydrated using an aqueous media while stirring at temperatures of 60 to 70 °C to swell and form rounded liposomes [118]. The formation of hydrogel nanocomposites of CD inclusion complexes with micronutrients is also reported using (ethylene glycol) diglycidyl ether (PEGDGE) polymer as a cross-linker [127]. The preparation of a supramolecular hydrogel of CD and tri-block copolymer of poly-ϵ-caprolactone (PCL)-polyethylene glycol (PEG)-PCL was also attempted for co-delivery of a drug compound or a micronutrient [68]. Lu et al. [109] attempted the preparation of hydrogels through the suspension of cross-linked cyclodextrin-metal organic frameworks (CD-MOFs) into hydroxyethyl cellulose gels for the delivery of a micronutrient. Figure 3d illustrates the formation mechanism of CD-based hydrogels. Additionally, CD nanosponges can be prepared using carbonyls, diisocyanates, dianhydrides, or carboxylic acids as cross-linkers, as shown in Fig. 3e [44, 121, 128]. The resulting porous nanosponges carrying the

amphiphilic nature of CDs can bind several lipophilic and hydrophilic micronutrients [44, 121]. CDs and their inclusion complexes formed with micronutrients can also be spray-dried alone or in the presence of other biopolymers used as an additional coating to produce microparticles, see Fig. 3f [46, 53]. Optimization of the spray drying conditions such as the feed flow rate (reported between 7 and 9 mL/min), inlet air temperature (T_{inlet}) (110 to 180 °C), and outlet air temperature (T_{outet}) (60 to 80 °C) can assure the formation of powders with a desired morphology (i.e. absence of cracks, wrinkles, collapsed, or crumbled particles) from micronutrients and their CD inclusion complexes [46, 53, 110]. These spray-dried powders can be easily handled during processing. Additionally, spray drying, a technique with short operation time compared with the other drying techniques has the potential for scale-up for the preparation of CD inclusion complexes [129].

Administration routes

The encapsulated guest molecule inside the cavity of CDs can be delivered to body tissues orally [130], transdermally [131], topically [43], nasally [132], ocularly [133], or parenterally [22, 134]. The most frequently employed administration routes are schematically shown in Fig. 4.

CDs have been used as adjuvants in formulating vaccines for intradermal, intravenous, subcutaneous, or intramuscular delivery of drugs and antivirals to the human body [22, 139]. Simultaneously, they have found their applications for the ocular delivery of several therapeutics and drugs through eyedrops or contact lenses [140, 141]. HP-βCD and SBE-βCD are examples of modified CDs, which can be used for ocular delivery of drugs without showing toxicity towards the ocular tissue [142, 143]. CDs and their inclusion complexes with several drug compounds have been also tested for the development of nasal sprays to facilitate rapid drug delivery through nasal mucosa [132, 144].

Micronutrients incorporated into natural or modified CDs are mostly delivered orally through dietary supplements [145, 146] or fortified foods [41, 53] through designing appropriate delivery systems. They can be also delivered topically or transdermally through cosmeceuticals and skin care products, micro-needles, or patches [43, 131]. The skin permeability of micronutrients can be enhanced by delivery systems such as colloids, e.g. emulsions, liposomes, or colloidal gels.

Safety of cyclodextrins

Among the natural CD forms, βCD has been mostly applied for the delivery of bioactive ingredients due to its suitable cavity size and economy [41, 147]. α- and γCDs are approved as food-grade with the "not specified" ADI (allowed daily intake). Therefore they can be used in formulating foods at any concentration [41, 148, 149]. Comparatively, an acceptable daily intake of 5 mg per kg body weight per day was allocated to βCD by the Scientific Committee on Food (SCF) [150]. Natural CDs are Generally Recognized As Safe (GRAS) and can have applications in the food, pharmaceuticals, or cosmeceuticals industries. Their food applications include the production of low-cholesterol dairy products [26, 30, 151] and the delivery of antioxidants and antimicrobials in meat [152, 153]. They have also found their applications for fortification of foods with micronutrients to enhance their nutritional profile [50, 154]. Natural CDs can be also used in the development of orally bioavailable drugs and solubilized parenteral formulations [155, 156].

The US Food and Drug Administration (FDA) approves the modified type cyclodextrins, HP-βCD and 2-hydroxypropyl-γ-cyclodextrin (HP-γCD) as inert materials with the former suited for intravenous and oral administration [157, 158] while the latter can only be used in topical applications at a maximum concentration of 1.5% w/v [159, 160]. Among the methylated CDs, TRIME-βCD is reported as unsafe for human use due to its renal toxicity and hemolytic action. Although DIME-βCD also showed liver toxicity it can be used at low concentrations in injectable vaccines [160, 161]. SBE-βCD (Captisol®) has also been utilized in the formulation of several FDA-approved injectables and clinical candidates [162, 163].

Statistical analysis of recently published works

A statistical analysis of the published works on CDs and their inclusion complexes identified by searching the database of *Scopus* with the keywords "Cyclodextrin" AND "Complex" within articles, book chapters, reviews, and editorials hit 9685 publications. Limiting the search to the application of CDs for vitamin, iron, or iodine delivery by adding the keywords AND "Vitamin" OR "Iron" OR "Iodine" results in 413 publications among which 119 belong to vitamins (AND "Vitamin"), 239 belong to iron (AND "Iron"), and 58 belong to iodine delivery (AND "Iodine"), please see Table S1 in the Supplementary information section. The distribution of the number of publications between the years 2013 and 2023 is shown with the data points in Fig. 5a, also summarized in Table S1. In the presented raincloud plot, wider kernel density shows a higher probability of occurrence for a specific number of publications. In the boxplot underneath the raincloud plot, the median value of the number of publications is also presented. The number of publications on the application of CDs for vitamin delivery has increased during the years 2021 and 2022 (see Table S1). The results of the statistical analysis show a higher median value of the number of publications for the micronutrient iron, compared with vitamins, or iodine.

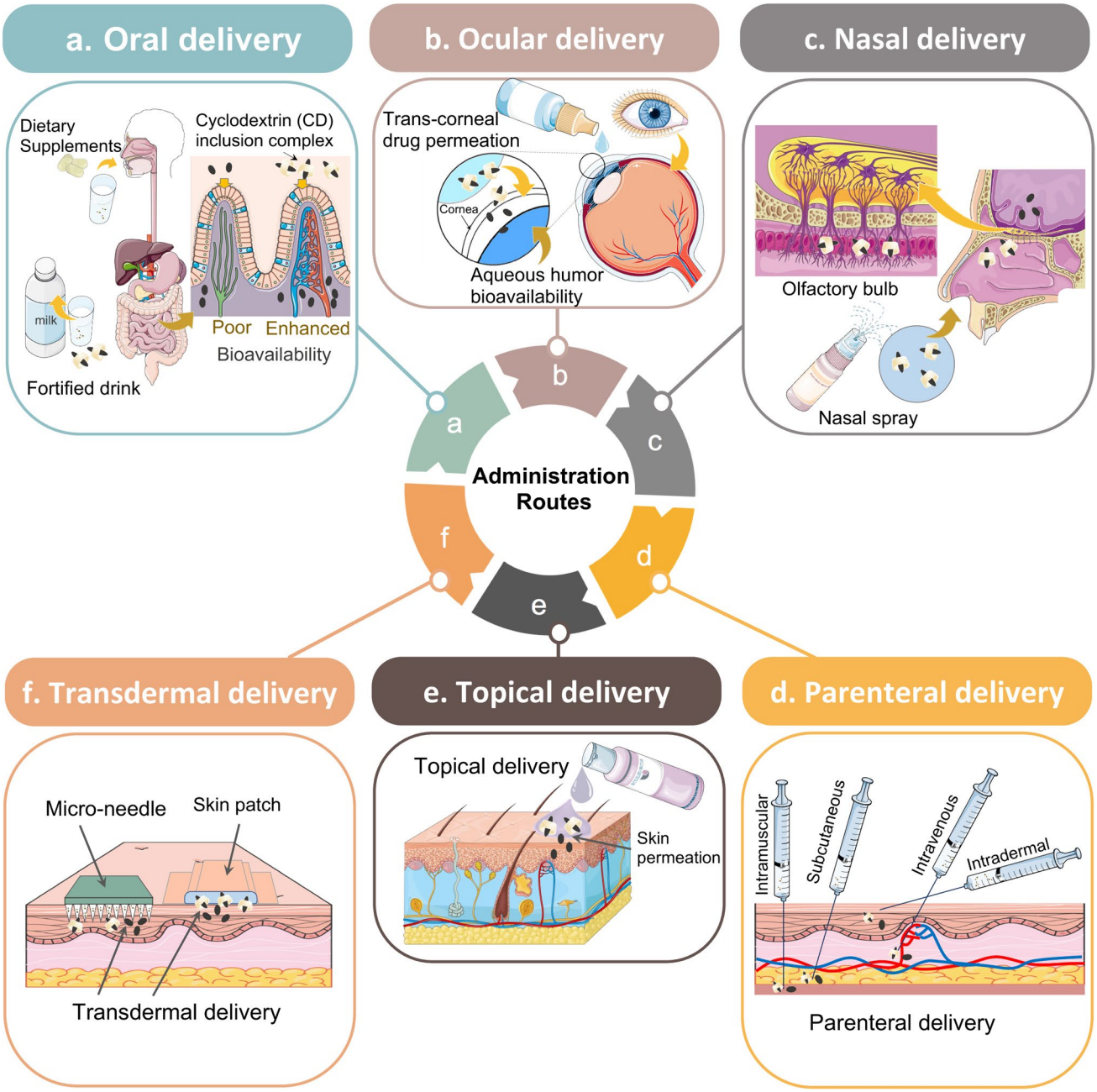


Fig. 4 Different administration routes of cyclodextrin (CD) inclusion complexes [135–138]; Graphical elements are partly adapted from Servier medical art repository (https://smart.servier.com)

The reported number of publications includes published works on the conjugation of CDs with minerals, which improves the solubility and targeted delivery of drugs. However, most reported works published on iron are relevant to iron oxide magnetic nanoparticles prepared with CD. Iron oxide magnetic nanoparticles enable controlled and targeted drug delivery while facilitating magnetic resonance imaging (MRI) to monitor the delivery of drug compound [164–167]. Additionally, several works explored folic acid-modified or conjugated cyclodextrins and reported the application of folic acid as a targeting ligand for cancer therapy as it binds to folate receptor overexpressed on cancer tissues and enables the targeted delivery of drugs [168–170]. In comparison, the number of works on the application of natural CDs and their modified forms for inclusion complex formation with vitamins, iron, or iodine and their delivery as micronutrients is limited. Specifically, only a few studies are reported on iron delivery in foods or pharmaceutical

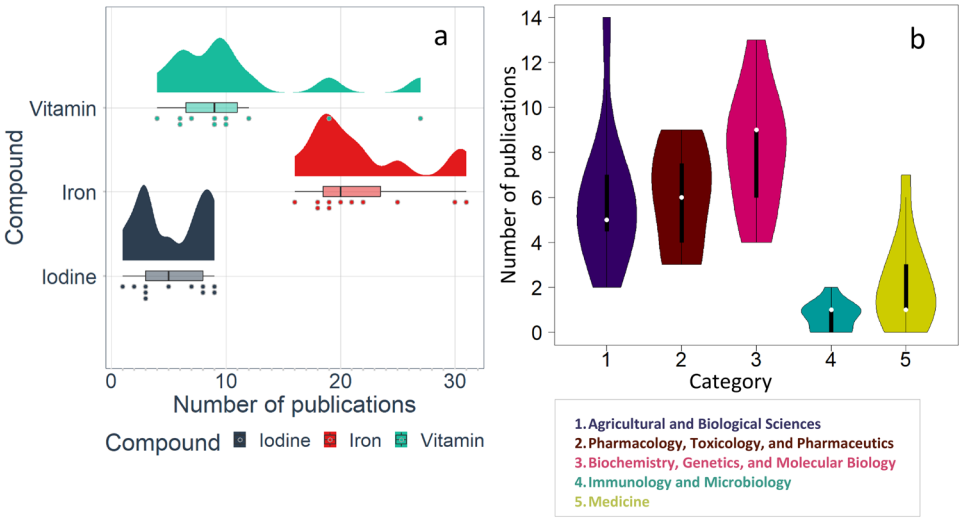


Fig. 5 Statistical analysis of number of publications **a** Raincloud plot showing the kernel density of the data of number of publications on CD inclusion complexes with three micronutrients, i.e. vitamin, iron, or iodine **b** Kernel density estimates of the number of publications in five categories of (1) Agricultural and Biological Sciences, (2) Pharmacology, Toxicology, and Pharmaceutics, (3) Biochemistry, Genetics, and Molecular Biology, (4) Immunology and Microbiology, and (5) Medicine; (data is acquired for the years 2013 to 2023)

products through inclusion complex formation with CDs. Figure 5b shows the distribution of the number of publications in five different categories. It can be observed that the number of publications in the category of *Agricultural and Biological Sciences* has increased during the year 2022 (see "Statistical data" in Table S1 in the supplementary information). Although the median value of the number of publications in this category is lower than that of categories 2 and 3, i.e. published works in the domain of *Pharmacology, Toxicology, and Pharmaceutics* and *Biochemistry, Genetics and Molecular Biology*. This category covers studies relevant to nutritional therapy, food fortification, or enhancement of shelf-life and photostability of micronutrients, specifically vitamins. An increased interest in the application of CDs in *Medicine* can also be observed as the number of publications has increased in this category during the last 2–3 years. It can be concluded from this statistical analysis that CDs have emerged in the Agricultural and Pharmaceutical industries finding increasing applications for the delivery of micronutrients.

Cyclodextrins (CDs) and their inclusion complexes for delivery of vitamins

An inclusion complex between a CD and vitamins can be formed to enhance the solubility and bioavailability of vitamins and increase their stability through protecting them from oxidation and light, or variations in environmental conditions such as pH or temperature. An extensive number of studies contribute to our enhanced understanding of the application of CDs for the encapsulation of fat-soluble vitamins including, *vitamin E* [52, 71, 125], *vitamin A* (retinol) [39, 42, 126], *vitamin D* [44, 72, 99], and *vitamin K* [171, 172]. CDs can simultaneously form inclusion complex with aqueous-soluble vitamins including *vitamin C* (ascorbic acid) [43, 51], and *vitamin B complex* [68, 69, 108]. Recently reported studies on the application of CDs and their inclusion complexes for the delivery of vitamins as vital micronutrients are discussed in the following and presented in Table 2.

Delivery of vitamin E

Vitamin E is a group of lipophilic molecules consisting of a chromanol head and a hydrophobic phytyl tail and includes four tocopherols and four tocotrienols [173]. α-tocopherol is the most biologically active form of vitamin E with low aqueous solubility, shown by its high partition coefficient in octanol/water solution (*log P* of 10.51) [90]. It is sensitive to oxygen, light, and alkaline conditions, which might reduce its biological activity [34, 52, 106, 127]. The ester form of α-tocopherol, α-tocopherol acetate, (*log P* of 10.42) [90], is less active and more stable. It has a longer shelf-life, finding its application in dermatology and skin treatment [106, 174, 175]. Vitamin E plays a major role in treating free radical-induced diseases, such as cardiovascular, neurodegenerative, or inflammatory diseases, and can interfere with lipid oxidation, and reduce oxidative stress [105].

Some studies explored the application of CDs for delivering vitamin E as an antioxidant while studying its increased solubility and cytoprotective activity [105, 106]. The possibility of complex formation between vitamin E and α, β, or γCD was explored by Ogawa et al. [105]. They showed that βCD could encapsulate a higher amount of vitamin E, approximately 2.6 mM higher than that complexed with α- or γCD. The complexes formed with γCD were stable at concentrations above 20 mM while forming aggregates at low concentrations. In addition, αCD was not able to form a complex with vitamin E as the phytyl chain of the vitamin E molecule could not be positioned

Table 2 Summary of studies performed on the application of CDs for the delivery of vitamins, iron, or iodine

Micronutrient	Carrier Type	Encapsulation technique	Average diameter (nm)	Main findings	Ref.
Vitamins					
Vitamin E	α-cyclodextrin (αCD) β-cyclodextrin (βCD) γ-cyclodextrin (γCD)	CD inclusion-complexes were prepared with co-precipitation technique (mixing at room temperature and for 16 h)	---	• Formation of the most stable complex with γCD. • Concentration-dependent aggregation behaviour of γCD • A high and slow radical scavenging activity of Vitamin E-γCD inclusion complex • Potential application of the complex for clinical use and reducing oxidative stress	[105]
Vitamin E acetate	Large-ring CD (LR-CD), CD22-CD50 (CD with 20 to 50 glucose units)	CD inclusion complexes were prepared with co-precipitation technique (mixing at 50 °C and for 4 h)	---	• The highest encapsulation yield of 80.1% at vitamin E acetate: CD of 1:10 • Enhanced vitamin E acetate solubility (up to 814 fold) • A 30% reduction in antioxidant radical scavenging activity of vitamin E acetate-LR-CD compared with the free vitamin	[106]
α-tocopherol (α-TC)	βCD Zein	Spray dried α-tocopherol-zein complex with βCD Zein-α-TC complex formation (30 min stirring at 200 rpm at room temperature) Spray drying with βCD (Feed flow: 7–9 mL/min, T = 23 °C, T_{inlet}=110, 150, or 180 °C)	For α-TC-βCD-zein inclusion complex: 10000 For α-TC-zein inclusion complex: 1523.3 ± 377.2 (110 °C, 0.01 g mL^{-1} solid) 8534.0 ± 240.4 (150 °C, 0.04 g mL^{-1})	• Optimized temperature and zein concentration for the formation of α-TC-zein inclusion complex • A higher cell viability and less cytotoxicity with β CD addition and implementing spray drying • Phase separation of fortified strawberry juice due to the presence of free or released α-TC during a 10-day storage	[53]
Vitamin E	Hydroxypropyl-βCD (HP-βCD)	Electrospinning and nanofiber production Vitamin E: HP-βCD solution (ratio 1:1 and 1:2) were electrospun *Electrospinning condition*: Feed flow: 0.5 mL/h, needle diameter: 0.45 mm, voltage: 15 kV, needle tip to collector distance: 10 cm, humidity: 30%, T = 24 °C)	630 ± 285 (ratio 1:1) 735 ± 345 (ratio 1:2)	• Improved photostability of vitamin E • Enhanced water-solubility of vitamin E • Prolonged shelf-life of vitamin E • An ~11% loading of vitamin E into electrospun vitamin E-HP-βCD inclusion complex nanofibers	[52]

Table 2 (continued)

Micronutrient	Carrier Type	Encapsulation technique	Average diameter (nm)	Main findings	Ref.
α-tocopherol (α-TC)	Polycaprolactone (PCL)- βCD	Electrospinning and nanofiber production α-TC:βCD-PCL (α-TC:βCD ratio 2:1), α-TC: PCL and PCL solutions were electrospun *Electrospinning condition*: Feed flow: 0.5 mL/h, needle diameter: 0.8 mm, voltage: 15 kV, needle tip to collector distance: 8 cm, humidity: 17–20%, T = 22–26 °C)	255 ± 130 (PCL) 205 ± 115 (PCL-α-TC) 345 ± 140 (PCL-α-TC-βCD inclusion complex)	• A linear change in solubility of α-TC with an increase of βCD up to 0.012 M. • A higher antioxidant activity of the inclusion complexes in methanol, approximately 96%. • A decrease in the amount of total released α-TC and a higher photostability with the presence of βCD inclusion complex in the nanofiber • Potential application of the complex for topical delivery	[115]
α-tocopherol (α-TC)	Poly lactic acid (PLA)- γCD	Electrospinning and nanofiber production α-TC-γCD inclusion complex was prepared by freeze drying α-TC:γCD-PLA, α-TC: PLA and PLA solutions were electrospun *Electrospinning condition*: Feed flow: 1 mL/h, needle diameter: 0.8 mm, voltage: 15 kV, needle tip to collector distance: 10 cm, humidity: 18%, T = 25 °C)	395 ± 120 (PLA) 555 ± 205 (PLA-α-TC) 430 ± 170 (PLA-α-TC-γCD inclusion complex)	• A linear change in solubility of α-TC with an increase of γCD up to 30 mM • A high antioxidant activity of the inclusion complexes in methanol, approximately 97% • A reduction in lipid oxidation over 10 days of storage when used for meat packaging • A higher release of α-TC from PLA-γCD nanofibers compared with PLA-nanofibers	[34]
Vitamin E	βCD Sodium caseinate (NaCas)	Vitamin E-βCD inclusion complex incorporated into liposomes coated with NaCas Liposomes were prepared from lecithin and ethanol using thin film hydration Liposomes were coated by addition of NaCas (ratio 1:1), stirring at 300 rpm followed by sonication of the coated liposomes	173.9 ± 42.4 (Coated Vitamin E-βCD inclusion complex) 201.2 ± 9.7 (Complex loaded liposomes)	• A decreased particle size with incorporation of Vitamin E-βCD inclusion complex into liposomes and NaCas coating • A high encapsulation efficiency of 84% of vitamin E for coated liposomes • A lower gastric release and a sustained intestinal release for coated liposomes	[71]

Table 2 (continued)

Micronutrient	Carrier Type	Encapsulation technique	Average diameter (nm)	Main findings	Ref.
Vitamin E	βCD (Octenyl Succinic anhydride (OSA)-βCD	Complexes formed by solvent evaporation followed by freeze-drying Emulsions were stabilized by the complex prepared with high speed homogenization using Ultra-Turrax T18, 24,000 rpm, 3 min followed by ultrahigh pressure homogenization at 30 MPa	~170-300 (vitamin E-OSA-βCD stabilized emulsion) ~300-350 (Vitamin E-βCD stabilized emulsion) ~200-320 (OSA-βCD stabilized emulsion) 4500 βCD stabilized emulsion)	• Formation of a stable vitamin E-OSA-βCD shown by low binding energy Enhanced complex formation at 35–45 °C • An optimized complex formation at ratios of CD: vitamin E of 12:1 and mixing time of 5 h • A higher stability and smaller droplet size for emulsions stabilized with vitamin E-OSA-βCD • Improved oxidative stability of oil with vitamin E • Potential application for reducing lipid oxidation in foods	[125]
Vitamin E	Octadecenyl (ODS)-βCD	CD inclusion complexes were prepared with the co-precipitation technique (mixing at 50 °C for 2 h) Emulsions were prepared by high speed homogenization at 17,000 rpm for 4 min	Rod-like βCD-vitamin E particles: 80 (dimeter) 300 (length) ODS-βCD-Vitamin E: 200 (diameter) 80 (thickness)	• Increased loading of vitamin E (75 mg/g) for ODS-βCD compared with 11 mg/g for unmodified βCD • A higher decrease in lipid oxidation with positioning vitamin E complex at emulsion interface compared with positioning vitamin E in oil • A higher stability of emulsions during gastric digestion compared with the intestinal condition	[107]
Vitamin E	βCD Soy-soluble polysaccharide (SSPS) Poly (Ethylene glycol) diglycidyl ether (PEGDGE) crosslinker	Hydrogel nanocomposites (HGNCs) were prepared with vitamin E-βCD complex, SSPS, and PEGDGE as a cross-linker	114 ± 4 (βCD: SSPS of 10:20) 134.3 ± 2 (βCD: SSPS of 15:20) 174.3 ± 3 (βCD: SSPS of 20:20) 202.9 ± 12 (βCD: SSPS of 25:20)	• Preparation of HGNCs by incorporating vitamin E-βCD into SSPS • A larger pore size and higher swelling of the HGNC at lower βCD content of 10% • A slower release of vitamin E during in vitro digestion with increase of βCD content to 20–25% • A 7.5 and 6.2 fold increase in bioavailability of vitamin E at low βCD concentrations of 10 and 15%	[127]

Table 2 (continued)

Micronutrient	Carrier Type	Encapsulation technique	Average diameter (nm)	Main findings	Ref.
Vitamin A palmitate (VAP)	βCD	CD inclusion complexes were prepared by freeze-drying technique (mixing at room temperature for 4 days) followed by lyophilization Oil-in-water (O/W) emulsions were homogenized by an Ultra-Turrax IKA at 8500 rpm, 3 min, and stabilized by βCD or VAP-βCD inclusion complex	32.4 (βCD-stabilized emulsion) 15.2 (VAP-βCD inclusion complex stabilized emulsions)	• A linear increase in solubility of VAP at low concentrations of βCD (0.25-2 mM), and a decrease at concentrations > 12 mM • An increased degradation temperature to 230 °C upon complexation • UV protection of VAP for inclusion complex, with a reduction during first hour due to the presence of free VAP	[126]
Vitamin A Vitamin A acetate (VAA) Vitamin A palmitate (VAP)	βCD	CD inclusion complexes were formed using co-precipitation technique followed by freeze drying (mixing at 50 °C for 7 h)	---	• A linear increase in VAA and VAP concentration with βCD (ratio βCD: vitamin of 1:1) with a quadratic increase for vitamin A (ratio βCD: vitamin of 2:1) • A 23, 35.9 and 20.9% loss of VAA, VAP and vitamin A after complex formation and during storage • A 4470 times improvement in the aqueous solubility of complexed VAA compared with its free form • The weakest binding to βCD for VAP due to its longer isoprenoid chain	[42]
Vitamin A Palmitate (VAP)	γCD Polyethylene glycol (PEG) 2000	γCD-Metal organic framework (MOFs) were prepared by reacting γCD with potassium hydroxide in water solution followed by vapour diffusion of methanol with addition of PEG VAP and γCD-MOF were added to ethanol (mixing at 40 °C for 2 h)	2000–5000 (Micro-γCD-MOFs) 200–500 (Nano-γCD-MOFs)	• A higher loading of VAP for micro-sized washed carriers compared with the unwashed • Increased loading of VAP with its content up to 40 mg mL^{-1} and only at 40 °C • Up to 71.3% preservation of VAP in γCD-MOFs during a 10-day storage period • A 1.6 fold enhanced half-life of VAP	[54]

Table 2 (continued)

Micronutrient	Carrier Type	Encapsulation technique	Average diameter (nm)	Main findings	Ref.
Vitamin A acetate (VAA)	Hydroxypropyl-βCD (HP-βCD) Hydroxypropyl-γCD (HP-γCD)	Electrospinning and production of nanowebs VAA-CD solutions (ratio 1:1) were electrospun *Electrospinning condition*: Feed flow: 0.5 mL/h, 21 G metallic needle, voltage: 15 kV, needle tip to collector distance: 12 cm, humidity: 50%, T = 20 °C)	195 ± 85 (VAA-HP-βCD) 610 ± 275 (VAA-HP-γCD)	• A 16.1 folds enhanced solubility of VAA with HP-βCD compared with 2.3 for HP-γCD • A higher antioxidant activity of 99% for HP-βCD compared with 51.6% for HP-γCD • An improved thermal stability of VAA • A higher release of VAA (94%) from HP-βCD complex compared with 55% from HP-γCD complex during 30 s	[39]
Cholecalciferol Ascorbic acid α-tocopherol (α-T)	αCD βCD γCD Hydroxypropyl-βCD (HP-βCD)	CD inclusion complexes were prepared with co-precipitation technique CD-vitamin solutions were prepared in molar ratios of (2.5:1, 5:1, and 10:1) in ethanol (for cholecalciferol) and in acetone (for ascorbic acid and α-T) (mixing at room temperature for 16, 18, 20, and 40 h)	---	• The highest inclusion efficiency (IE%) (82%) for ascorbic acid-βCD (ratio of βCD: vitamin of 2.5:1) • The highest IE% (78% and 72%)) for cholecalciferol-βCD, and γCD (βCD: cholecalciferol of 2.5:1 and 5:1 respectively) • The least favourable complexation with αCD and low IE% for cholecalciferol and HP-βCD • A higher insertion depth of cholecalciferol in βCD, and γCD • Dependency of cholecalciferol and ascorbic acid solubility on βCD concentration • A low IE% of 8.9% for α-T-βCD inclusion complex	[99]
Vitamin D_3	βCD	CD inclusion complex incorporated into Nanoliposomes (NLP) coated with gelatin Vitamin D_3 and βCD solution was prepared in ethanol (mixing at 25 °C for 24 h) Liposomes were prepared from lecithin and ethanol using thin film hydration Liposomes were coated by addition of gelatin (ratio 1:1), followed by sonication of the coated liposomes	165.13 ± 6.16 Uncoated NLP) 104.33 ± 5.36 (1 mg/mL gelatin coating) 130.18 ± 7.92 (2 mg/mL gelatin coating) 151.1 ± 7.58 (4 mg/mL gelatin coating)	• A sustained and controlled release of vitamin D_3 in a simulated gastrointestinal digestion • An improved antioxidant activity of vitamin D_3 • A high encapsulation efficiency of vitamin D_3 approximately 89%	[72]

Table 2 (continued)

Micronutrient	Carrier Type	Encapsulation technique	Average diameter (nm)	Main findings	Ref.
Vitamin D_3	βCD nano-sponges	Ball milling was used for nano-sponge preparation CD inclusion complexes were prepared with the kneading method Nanosponges were prepared using carbonyl diimidazole as a cross-linker with ratio of CD: carbonyl diimidazole of 1:4	---	• An enhanced thermal stability of vitamin D_3 with βCD nano-sponges • A higher bioavailability of Vitamin D_3 nano-sponge (up to 53%) compared with the physical mixture	[44]
Vitamin K_3 (menadione, or 2-methyl-1,4-naphtoquinone)	γCD	Inclusion complexes of vitamin K_3 and γCD were prepared Interaction of the complex with Herring sperm Deoxyribonucleic acid (DNA) was studied	---	• Formation of vitamin K_3-γCD complex with stoichiometric ratio of 1:1 • Existence of hydrophobic and intercalative interaction between DNA and vitamin K_3-γCD inclusion complex • DNA binding to vitamin K_3-γCD complex in the ratio of 1:2 • Positive entropy and negative Gibbs energy promoting the spontaneous interaction of DNA and the complex	[171]
Vitamin K_3 Vitamin K_3 bisulfate Vitamin K_3 sodium bisulfate Phthiocol (2-hydroxy-3-methy-1,4-naphtoquinone)	βCD	Computational study on the interaction of vitamin K_3 and its analogues with βCD	---	• Positive values of Gibbs energy for both *a* and *b* orientations of vitamin K_3 when forming complex with βCD • A favourable interaction for vitamin K_3 bisulfate or sodium bisulfate with βCD for *a* and *b* orientations and *S* and *R* enantiomers shown by negative value of Gibbs energy • A more stable complex at *a* orientation	[172]

Table 2 (continued)

Micronutrient	Carrier Type	Encapsulation technique	Average diameter (nm)	Main findings	Ref.
Vitamin K_3 Vitamin A Vitamin E Vitamin D (cholecalciferol)	Cycloamylose (CA) polymerization degree: 23–45 βCD Maltodextrin (MD)	Fat-soluble vitamins (5 mM) solutions prepared in ethanol were added to βCD (0–30 mM) or CA or MD (0–60 mM), reaction for 3 days at 30 °C and 180 rpm mixing speed, centrifugation and lyophilization of the powders	---	• A lower solubility for CA complexes compared with βCD at concentrations≤20 mM • An increased solubility of vitamin A, D, E, and K_3, up to 5.8, 29, 4.3, and 3.6 fold after complexation with CA • A continuous linear increase in the solubility of fat-soluble vitamins even at 60 mM CA • A decrease in solubility of vitamin K_3 in MD at high MD concentration > 20 mM • A decreased loss of all vitamins (85 to 45% after 4 h irradiation) after complexation with 40 mM CA • A longer half-life and prolonged shelf-life of vitamins encapsulated with CA	[183]
L-ascorbic acid	HP-βCD	Electrospinning and nanofiber production L-ascorbic acid: HP-βCD solution (ratio 2:1) was electrospun *Electrospinning conditions*: Feed flow: 0.5 mL/h, 21 G metal needle, voltage: 15 kV, needle tip to collector distance: 15 cm, humidity: 50%, T = 20–25 °C)	339.32 ± 41.93	• Formation of a complex with stoichiometry of L-ascorbic acid: HP-βCD of 2:1 • Encapsulation of ~97% L-ascorbic acid • An elevation of the degradation temperature of L-ascorbic acid from 190–240 to 220–310 °C • Approximately 96% radical scavenging activity of the complex at highest L-ascorbic acid content (30 μM) • Potential application in food packaging	[102]

Table 2 (continued)

Micronutrient	Carrier Type	Encapsulation technique	Average diameter (nm)	Main findings	Ref.
Vitamin C	βCD Polyvinyl alcohol (PVA) Cellulose acetate (CellA)	Electrospinning of vitamin C or vitamin C-βCD loaded PVA (Feed flow: 0.1 mL/h, 210 µm needle, voltage: 7.3–10.6 kV, needle tip to collector distance: 13 cm) Electrospraying of vitamin C-βCD inclusion complex on CellA and on PVA nanofibers (Feed flow: 0.7 mL/h, 210 µm needle, voltage: 10.5 kV, needle tip to collector distance: 15 cm)	209 ± 37 (PVA NFs loaded with vitamin C) 128 ± 30 (PVA NFs) 10,900 ± 1500 (CellA-βCD-vitamin C inclusion complex)	• An enhanced thermal stability up to 350 °C for Vitamin C-βCD complex • A sustained release of vitamin C up to 96% during 48 h • Moderation of hydration by immobilizing the complex on CellA • Burst release of vitamin C from swollen PVA NFs • Potential application in skin patches for topical delivery of vitamin C	[43]
Vitamin C	βCD Tween 80 Polyglycerol polyricinoleate (PGPR)	Water-in-oil-in-water ($W_1/O/W_2$) double emulsions were prepared using mechanical stirring (400 rpm, 15 min at 25 °C)	~35000 (4% w/w βCD) ~32000 (6% w/w βCD) ~28000 (8% w/w βCD)	• An Increased number of smaller emulsion droplets with increased βCD content • An improved retention rate of vitamin C • Release of vitamin C up to 85.38% during 2 h of in vitro digestion • An increase of in vitro skin permeation with increase in βCD content	[51]
Vitamin B_2	βCD-co-guanidine Epichlorohydrin (EP) as crosslinker	Complexes were prepared with co-precipitation technique Guanidine powder was added to βCD and EP was added as crosslinker (polymerization at 30 °C, 3 h, 50 min)	1281 (vitamin B_2) 255 (particles ratio CD: guanidine 1:5) 388 (particles ratio CD: guanidine 1:15)	• Synthesis of cationic βCD by guanidine as building blocks and EP as a crosslinker • A significant improvement in solubility of βCD after polymerization with EP • An enhanced complex solubility with increased guanidine • A lower sustained in vitro release at pH 7.4 followed by pHs 1.2 and 10, and for complexes with a higher guanidine content	[108]

Table 2 (continued)

Micronutrient	Carrier Type	Encapsulation technique	Average diameter (nm)	Main findings	Ref.
Vitamin B_2	PeracetylβCD polymer	Electrospinning and nanofiber production βCD was crosslinked with epichlorohydrin and acetylated with pyridine Electrospinning of the solution (Feed flow: 0.5 mL/h, 1.473 mm needle, voltage: 30 kV, needle tip to collector distance: 8 cm)	83–177	• Improved encapsulation of vitamin B_2 and its sustained release during 170 h at the neutral pH. • Increased release of vitamin B_2 compared with the case of using only βCD as carrier.	[69]
Vitamin B_9 (Folic acid)	βCD Indian horse chestnut starch	Preparation of 10% βCD or starch solution with 4% folic acid (pH 11.5), ratio folic acid: βCD of 1:5, mixing 10 min Spray drying of the solution, air flow 140 L/h, inlet and outlet temperature: 130 and 80 °C	Folic acid-βCD microcapsules: 30090–145930 (25–90% samples) Folic acid-starch microcapsules: 28260–227340 (25–90% samples)	• A higher encapsulation efficiency of 76.10% for βCD compared with 57.29% for starch • Smaller particle sizes of microcapsules for βCD • A lower water activity for βCD microcapsules providing microbiological and oxidative stability • A lower gastric and intestinal release for βCD microcapsules • A higher antioxidant and radical scavenging activity for βCD microcapsules	[110]
Vitamin B_{12} Naltrexone hydrochloride	αCD Polycaprolactone (PCL)-polyethylene glycol (PEG)-PCL copolymer	Supramolecular hydrogels prepared from PCL-PEG-PCL, and αCD aqueous mixture Tri-block copolymer was prepared with ring-opening polymerization Loading of vitamin B_{12} or Naltrexone hydrochloride	---	• Preparation of supramolecular hydrogels from PCL-PEG-PCL and αCD • Sustained release of vitamin B_{12}, 25–35%, during 600 h with burst release < 5%	[68]
Iron					
Iron(II) fumarate	βCD 2-hydroxypropyl-βCD (HP-βCD)	Iron(II) fumarate complexes were prepared by mixing with βCD or HP-βCD at room temperature for 72 h followed by evaporation of solvent at 50 °C and drying in a desiccator Physical mixtures prepared at ratio 1:1 (host: guest)	---	• Synthesis of Iron(II) fumarate through conversion of fumaric acid to disodium fumarate • A higher aqueous solubility of Iron(II) fumarate when complexed with HP-βCD (2.71 mg/cm^3) compared with 2.05 mg/cm^3 for βCD	[45]

Table 2 (continued)

Micronutrient	Carrier Type	Encapsulation technique	Average diameter (nm)	Main findings	Ref.
Ferric sodium EDTA Ferrous ammonium phosphate	βCD	CD inclusion complexes were prepared using co-precipitation technique Ferric sodium EDTA and CD solution was prepared in 10, 30, or 50 wt% alcohol (majorly ethanol), stirring for 24–72 h at room temperature, ratios of iron: βCD (1:4, 1:6, and 1:10) Ferrous ammonium phosphate ratio 1:4, stirring for 6 h	---	• A synergistic/antagonistic effect of concentration of βCD and alcohol and mixing duration on inclusion rate% (IR%) • A 77% IR of hydrophilic ferric sodium EDTA at low alcohol concentration (~25% v/v), longer mixing time (72 h), and iron: βCD of 1:6 • A 96% IR of ferrous ammonium phosphate at alcohol concentration (~25% v/v), 6 h mixing and iron: βCD of 1:4 • A significant increase in melting temperature of ferrous ammonium phosphate from 172 to 294 °C after complexation	[41]
Ferric sodium EDTA Curcumin	βCD Sodium caseinate (NaCas) Sodium alginate (NaAlg)	iron-loaded $W_1/O/W_2$ double emulsions were stabilized with NaCas-curcumin-βCD complex or NaCas-NaAlg-curcumin-βCD complex Iron and curcumin loaded emulsion was stabilized by NaCas-βCD, homogenization at 6700 rpm, 20 min	8700±7510 (NaCas-NaAlg-curcumin-βCD inclusion complex) 8030±11470 (NaCas-βCD)	• An increase in bioaccessibility of curcumin from ~33–69% when complexed with βCD positioned at emulsion interface and complexed with NaCas and NaAlg • An improvement in stability of NaCas-βCD stabilized emulsion with NaAlg addition • A low gastric (37%) and sustained intestinal (80%) iron release for emulsions stabilized with NaCas-NaAlg-curcumin-βCD inclusion complex	[117]
Iron bisglycinate	βCD Zein	Zein pseudolatex was prepared using antisolvent co-precipitation Spray drying of the pseudolatex including iron bisglycinate (T_{inlet}=115 °C, T_{outlet}=60 °C, pump 10%, aspirator level 90%)	~600–2200 (at βCD of 1% w/v, zein of 2–6% w/v) ~-850 (at zein 4% w/v, βCD of 0.5 to 1.5% w/v)	• Prevention of zein's aggregation and precipitation using βCD • An increase in the pseudolatex diameter from 500 to 800 nm with an increase of βCD upto 1.5% w/v • An increased yield upto 90% at inlet temperature of 115 °C during spray drying • Protection and 30% release during gastric digestion • A sustained release in the SIF upto maximum 7 h digestion time	[46]

Table 2 (continued)

Micronutrient	Carrier Type	Encapsulation technique	Average diameter (nm)	Main findings	Ref.
Iodine					
Iodine	βCD βCD	Solution of KI_3 and CD was stirred for 5 h at 25 °C and retained at 4 °C for 10 h	---	• Formation of αCD and *β*CD complexes with I_2 in a 1:1 molar ratio • A 16.7–16.9% and 18-19.9% I_2 loading into *β*CD and *α*CD respectively • A 9% I_2 loss during 1-year storage at 4 °C from *β*CD	[247]
Iodine	2-Hydroxypropyl-*β*-CD (HP-*β*CD) 2-Hydroxypropyl-*α*-CD (HP-*α*CD) 2-Hydroxypropyl-*γ*-CD (HP-*γ*CD)	Iodine CD inclusion complexes were prepared with three techniques: *Liquid-assisted grinding (LAG)*: Mixing of iodine and CD with ethanol, kneading followed by pulverization of the dry powders *Co-evaporation (COE)*: Mixing of iodine and CD with ethanol, drying at 30 °C under vacuum, further drying at 25 °C in ventilated hood *Sealed heating (SH)*: Physically mixing iodine and CD in a closed vial at 60 °C for 6 h, cooling to room temperature and drying at 25 °C in ventilated hood	---	• Dependence of iodine in HP-βCD and HP-*γ*CD on the preparation method changing in the order: SH > COE > LAG • Less variation for HP-*α*CD with preparation method • A 8.3–10.8% iodine complexation with CDs in the order HP-αCD > HP-βCD > HP-*γ*CD (SH method and 60 °C) • An increased degradation temperature with increased host: guest ratio in SH method • A 61% of iodine loss from HP-*γ*CD compared with 18–33% for the other CD types during a 28-day storage with a faster decrease in the first week • A lower variability in iodine content for samples prepared with LAG and COE • An effective reduction in bacterial cell vitality for all inclusion complexes	[40]
Iodine Potassium iodide (KI)	*β*CD	KI was mixed with I_2 and CD solution was stirred for 5 h at 25 °C and retained at 4 °C for 10 h.	---	• Formation of iodine and KI complexes with *β*CD in stoichiometric ratio of 1:1 • A 19.91% iodine content in iodine/*β*CD complex • An elevated content of hormones T3 and T4 and Thyroid-stimulating hormone (TSH) (in vivo tests on rats)	[79]

Table 2 (continued)

Micronutrient	Carrier Type	Encapsulation technique	Average diameter (nm)	Main findings	Ref.
Iodine Potassium iodide (KI)	βCD	KI and I_2 were dissolved in water to form KI_3, then were added to CD solution and mixed for 5 h at 25 °C then retained for 10 h at 4 °C.	---	• A 16.9% iodine incorporation in βCD • An increased iodine status in human subjects during a 10-day trial with consumption of the boiled fortified sausages • An elevation of 3,5-diiodotyrosine (DIT) level with antioxidant and anticancer properties through fortified sausages	[47]
Iodine	βCD	Iodine was mixed with CD, stirred for 3 h, stored then for 12 h in ice bath, Brown precipitate was collected, washed, and oven-dried	---	• A decrease in iodine content in the complex with elevation of pH to alkaline • A binding constant of 1286 M^{-1} and stoichiometry of 1:1 for I_2:βCD • A 17.3% iodine complexation with βCD • Protection of iodine from early sublimation after complexation • A strong inhibitory effect of 1.5 wt% iodine on Aspergillus niger	[248]
Iodine Potassium iodide (KI)	γCD Polyethylene glycol (PEG 20,000) Hydroxyethyl cellulose (HEC)	CD metal organic framework (CD-MOF) was prepared using PEG 20,000 Cross-linking CD-MOF with diphenyl carbonate to produce cross-linked CD-MOF (COF) then loading with iodine followed by precipitation to obtain I_2@COF I_2@COF was suspended in hydroxyethyl cellulose gels (I_2@COF-HEC hydrogel)	11800 ± _29.2 (I_2@COF)	• Sustained slower iodine release from I_2@COF-HEC hydrogels compared with COF in a 5-day in vitro study • Effectiveness of I_2@COF-HEC in decreasing periodontal pocket depth	[109]
Radioactive iodine I^{123} and I^{131}	αCD	Iodine was mixed with saline and αCD solution	---	• A sustained release of iodine and prevention of volatilization after complexation • A 40% reduction in iodine uptake after complexation (in vivo tests on mice)	[48]

Table 2 (continued)

Micronutrient	Carrier Type	Encapsulation technique	Average diameter (nm)	Main findings	Ref.
Radioactive iodine I^{131}	Hydroxypropyl-βCD (HP-βCD) Hydroxypropyl-αCD (HP-αCD)	Iodine was dissolved in CD solution or glucose solution	---	• A 1/3 – 1/4 reduction in volatilization of iodine when complexed with CD • An increased retention rate of iodine with elevated CD content • A consistent retention rate after exposure to high radiation doses of 30,000 Gy.	[249]

inside the cavity of αCD. The complexes formed with 10 mM βCD and 30 mM γCD showed radical scavenging activity and the latter also showed cytoprotective activity demonstrated by improved cell viability due to its high and gradually increasing radical scavenging activity compared with βCD. This makes γCD a potential candidate to be used as an antioxidant delivery system for clinical applications and for reducing oxidative stress. The synthesis of large-ring CDs (C22-C54) from tapioca starch and its application for vitamin E acetate encapsulation was studied by Kuttiyawong et al. [106]. The authors showed that vitamin E acetate to CD ratio of 1:10 resulted in the highest yield of vitamin E acetate encapsulation equal to 80.1%. The complex significantly increased the solubility of vitamin E acetate (by up to 814 fold).

Saldanha Do Carmo et al. [53] studied spray drying for the preparation of microparticles from α-tocopherol and a zein complex, utilizing βCD as a protecting agent. The authors additionally explored the possibility of adopting the resulting microparticles for formulating strawberry juices. The addition of βCD to a zein-α-tocopherol complex could enhance cell viability during 48 h and decrease cytotoxicity. However, this fortified beverage had a tendency to phase separate after 10 days of storage.

A number of research studies highlight the application of the electrospinning technique for the encapsulation and delivery of vitamin E incorporated into CDs [34, 52, 115]. To enhance the photostability of vitamin E, Celebioglu and Uyar [52] studied the formation of inclusion complex between vitamin E and HP-βCD. Incorporation of vitamin E into HP-βCD and electrospinning of the solution into nanofibers resulted in approximately 11% loading of vitamin E and an increase in the stoichiometric molar ratio of vitamin E: HP-βCD from 1:1 to 1:2 increased the size of the produced nanofibers (see Table 2). The electrospun nanofibers enhanced the solubility of vitamin E, and preserved its antioxidant properties while prolonging its shelf-life. Aytac and Uyar [115] showed that the electrospun nanofibers prepared with polycaprolactone (PCL)-βCD and their inclusion complex with α-tocopherol can improve the antioxidant activity by up to 96% in methanol. The solubility of α-tocopherol changed linearly with an increase in βCD content from 0 to 0.012 mM. The lower sustained release achieved with the incorporation of PCL makes the nanofibers suitable carriers for topical delivery of lipophilic drugs. The authors also explored [34] the possibility of complex formation between polylactic acid (PLA), α-tocopherol, and γCD. The solubility of α-tocopherol increased linearly with an increase in γCD concentration from 0 to 30 mM. The difference in the size of the produced nanofibers in the absence or presence of γCD (see Table 2) impacted the release of α-tocopherol and a higher release was observed in the presence of γCD, which additionally improved the solubility of the vitamin.

The antioxidant activity of the complex was approximately 97%. The nanofibers were used for meat packaging and could reduce lipid oxidation for 10 days of storage at 4 °C.

Some studies enhance our knowledge of the application of vitamin E-CD inclusion complexes for designing colloidal systems including liposomes, emulsions, or hydrogels [71, 107, 125, 127]. Souri et al. [71] demonstrated the possibility of enhancing the thermal stability of vitamin E through the incorporation of vitamin E-βCD inclusion complex into liposomes coated with sodium caseinate. Approximately 84% encapsulation efficiency was achieved for vitamin E in liposomes and CD. Coating of the liposomes with sodium caseinate reduced the size of the liposomes (presented in Table 2) and lowered vitamin E release during gastric digestion from 52% for the complex to 15 and 5% for the uncoated and coated liposomes respectively. Similarly, sustained release was obtained during intestinal digestion and the coated liposome released only 36% compared with 87% release by the complex.

Ke et al. [125] shed light on the application of vitamin E-CD inclusion complex for the stabilization of emulsions and enhancing the oxidative stability of the oils. They showed that vitamin E complexes can be formed with βCD or octenyl succinic anhydride (OSA)-βCD when the temperature was elevated from 35 to 45 °C and the ratio of vitamin E: OSA-βCD was increased from 1:30 to 1:12. Vitamin E-βCD complex was formed with the hydrophobic tail of vitamin E positioning inside the CD cavity and the benzene ring positioning outside. The addition of OSA to βCD decreased the emulsion droplet size (see Table 2) and could impart a higher degree of oxidative stability to the emulsions stabilized with the complex. Xi et al. [107] explored the modification of βCD with octadecenyl succinic anhydride (ODSA) for the stabilization of emulsions and delivery of vitamin E. They studied two different positions of vitamin E: (a) vitamin E was complexed with modified octadecenyl (ODS)-βCD and positioned at the emulsion interface and (b) vitamin E was positioned inside the oil phase. The modification of βCD could improve the loading of vitamin E into (ODS)-βCD increasing it from 11 to 75 mg/g and vitamin E was successfully included inside the cavity of modified βCD with its hydrophobic tail inside the cavity. The incorporation of vitamin E in the complex and positioning it at the emulsion interface could inhibit lipid oxidation at 45 °C for 7 days. Similar observations on the ability of OSA-βCD to enhance the oxidative stability of the oil at elevated temperatures were reported by Ke et al. [125]. The modification of cyclodextrin with OSA through esterification and substitution of hydrophobic octenyl and hydrophilic carboxyl groups imparts an amphiphilic nature to the CD molecule and improves its emulsifying behaviour [176]. The reported studies demonstrated the potential application of OSA-modified CDs for the delivery of antioxidants and reducing lipid oxidation in foods when employed as emulsion stabilizers. Eid et al. [127] discussed the application of hydrogel nanocomposites prepared with vitamin E-βCD complex and a soy-soluble polysaccharide using polyethylene glycol (PEG) diglycidyl ether (PEGDGE) as a cross-linker for improving the solubility of vitamin E. An increase in the βCD content from 10 to 15% elevated the viscoelasticity of hydrogels and an elevation of the CD content to 20 and 25% lowered the in vitro vitamin release to 48 and 44% after 230 h. The results of in vivo studies on rats showed that low βCD concentration (i.e. 10 and 15%) and high soy-soluble polysaccharide content (i.e. 20%) could increase the bioavailability of vitamin E up to 7.5 and 6.2 fold.

The reported studies highlight the efficacy of CDs in improving the solubility, stability, and bioavailability of vitamin E. Delivery systems designed with vitamin E-CD inclusion complexes enable the delivery of the vitamin as an antioxidant while enabling its sustained release. Therefore, they can find their applications in preventing lipid oxidation in foods and extending the shelf-life of food products or in the development of dietary supplements or cosmeceutical products for sustained oral or topical delivery of this macronutrient.

Delivery of vitamin A

Vitamin A (retinol) is another vital lipophilic vitamin that can be ingested from animal or plant sources. Inadequate intake of this vitamin can result in impaired immunity and cause ocular disorders such as xeropthalmia [177, 178]. Vitamin A molecule is a C20 diterpenoid including four isoprene units [179]. It is comprised of a cyclohexenyl/beta-ionone ring and a tetraene side chain with different groups positioned at Carbon 15, either a hydroxyl group (retinol), aldehyde group (retinal), carboxylic acid (retinoic acid), or an ester group (retinyl ester) [180]. The hydrophobicity of vitamin A molecule shown by the value of its partition coefficient in octanol/water solution (*log P* of 4.69) [90] limits its absorption and bioavailability. It is prone to oxidation and should be protected from air [181]. Vitamin A exists in two synthetic forms, retinyl acetate or retinyl palmitate, that are commonly used for the fortification of foods [182].

A number of research studies shed light on the application of CDs and their inclusion complexes for enhancing the solubility and stability of vitamin A [39, 42, 54, 126]. Rho and Kim [183] discussed and compared the solubility of vitamin A in βCD and cycloamylose synthesized from amylose with a polymerization degree of 23–45. They showed that at lower βCD concentrations (< 20 mM) stronger complexes could be formed with βCD and as the concentration increased further reaching the maximum solubility of βCD, a plateau was observed for the solubility of the vitamin. In contrast, the solubility of vitamin A continuously increased up to 5.8 fold when complexed with cycloamylose even at

high concentrations of the biopolymer (60 mM). The flexible structure of the cycloamylose molecule and its higher solubility compared with βCD facilitated the formation of inclusion complex. The application of βCD for inclusion complexation with vitamin A palmitate was explored by Vilanova and Solans [126]. At low βCD concentrations (0.25-2 mM) the solubility of vitamin A palmitate increased linearly with the stoichiometric ratio of vitamin A palmitate: βCD of 1:1. While at intermediate βCD concentrations (5–12 mM), closer to the maximum solubility of βCD and similar to previous observations for vitamin A [183], the content of vitamin A palmitate remained constant; at higher concentrations of vitamin A palmitate above 12 mM, the solubility of vitamin A palmitate decreased and with the elevation of the content more βCD and the stoichiometric ratio of 1:2 was required for inclusion complexation. The formation of inclusion complex elevated the thermal stability of vitamin A palmitate up to 230 °C. The formed complex could also protect vitamin A palmitate from UV light, although a 20% reduction in vitamin A palmitate during the 1st hour of exposure was observed due to the decomposition of the vitamin A palmitate. Comparatively, Xu et al. [42] compared the application of βCD for inclusion complexation with vitamin A, vitamin A acetate, or vitamin A palmitate. The concentration of vitamin A acetate and vitamin A palmitate increased linearly with βCD with a stoichiometric ratio of 1:1. In contrast, the concentration of vitamin A increased quadratically and two molecules of βCD were required for the formation of inclusion complex for 1–4 mM CD content. The weakest binding was observed for vitamin A palmitate with the highest Gibbs energy due to the presence of long isoprenoid chains, which prevented the positioning of the ring inside the cavity of βCD. In comparison, the solubility of vitamin A acetate increased up to 4470 times compared with the free vitamin. In another study, Zhang et al. [54] studied the application of γCD-metal organic frameworks (MOFs) for the delivery of vitamin A palmitate. A higher loading of vitamin A palmitate could be obtained for the nano-sized γCD-MOFs and they could load more vitamin A palmitate due to the larger surface area. The polarity of the solvent also impacted the loading of vitamin A palmitate and too low or too high viscous solvents did not facilitate the formation of an inclusion complex. Additionally, lower temperatures facilitated the loading of vitamin A palmitate. The incorporation of vitamin A palmitate in γCD-MOFs could prolong the shelf-life of the vitamin: after 10 days of storage 71.3% of vitamin A palmitate was preserved. The half-life of vitamin A palmitate also increased up to 1.6-fold.

Celebioglu and Uyar [39] studied the application of modified type HP-βCD and HP-γCD for the delivery of vitamin A acetate with polymer-free electrospun nanofibers. This encapsulation system could enhance the solubility of vitamin A acetate and improve the thermal stability of the complex. The solubility was increased 16.1 fold with HP-βCD compared with 2.3 with HP-γCD as the formation of a complex with the former was more favourable determined by the higher value of binding constant for vitamin A acetate-HP-βCD of 387.8 M^{-1} compared with 41.4 M^{-1} for vitamin A acetate- HP-γCD. Release studies also showed a higher release of vitamin A acetate, approximately 94%, from nanowebs prepared with HP-βCD compared with approximately 55% from HP-γCD during the first 30 s followed by a steady release for 10 min. The authors explained the observed behaviour by the lower absorption intensity of vitamin A acetate when complexed with HP-γCD due to the presence of undissolved or uncomplexed vitamin A acetate. Simultaneously, 99% antioxidant activity was observed for HP-βCD compared with 51.6% for HP-γCD.

The reported studies show the potential application of CD based delivery systems for enhancing the solubility of vitamin A while increasing its thermal or oxidative stability.

Delivery of vitamin D

Vitamin D is an essential micronutrient with several functions in the human body. It contributes to bone health, and regulates serum calcium and phosphate while affecting cell proliferation through modulating cell differentiation and apoptosis [184, 185]. Deficiency of this vitamin results in osteoporosis in adults and rickets in children, and can cause common cancers and autoimmune diseases [186]. This vitamin can be synthesized in skin with the exposure to sunlight or obtained from the diet [187]. Vitamin D is a fat-soluble vitamin consisting of vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). While vitamin D_2 can be commonly acquired from plant sources, vitamin D_3 is abundantly found in animal foods or synthesized in the skin through the photochemical conversion of provitamin D_3 [188]. Vitamin D is a hydrophobic molecule with low aqueous solubility (*log P* of 7.13) [90] and susceptibility to oxidation or heat degradation [189]. Therefore, the development of delivery systems is required to protect this compound. Vitamin D_3 has been preferred as a food fortificant or dietary supplement [190].

A number of research studies highlight the application of CDs as carriers of vitamin D_3 to enhance its solubility, heat, or oxidative stability [44, 72, 99]. Braithwaite et al. [99] shed light on the influence of CD type and concentration in addition to the duration of mixing on the inclusion complex formation with cholecalciferol. Up to 78% inclusion efficiency of vitamin D_3 with βCD was obtained for the ratio of βCD: vitamin D_3 of 2.5: 1 while a slightly lower inclusion efficiency of 72% was derived with γCD for the ratio of 5:1. Complexes with αCD and HP-βCD were the least favourable. The solubility of vitamin D_3 in βCD increased when the concentration of βCD was increased up to 3 mM and with the further increase of the concentration from 4 to 11 mM

a decrease in the solubility of cholecalciferol was observed. Similar observations on the limited solubility of vitamin A [183] or vitamin A palmitate [126] were also reported earlier with the elevation of the βCD concentration to a similar range closer to its maximum solubility. At low βCD concentrations of 0.25–1.75 mM, prolonging the mixing duration from 24 to 72 h facilitated the inclusion of vitamin D_3 into the βCD cavity and increased the inclusion efficiency by 5 to 8 times [99]. Positioning of vitamin D_3 showed a different behaviour in the tested CDs as was revealed by molecular simulations. The aliphatic end of vitamin D_3 was positioned close to the primary face of αCD and its aromatic ring stayed outside closer to the secondary face. Conversely in βCD, γCD, and HP-βCD, the aliphatic end was closer to the secondary face and the aromatic ring was positioned inside the cavity closer to the primary face. Higher insertion depths of vitamin D_3 molecule were observed inside β and γCD, which explains the observed higher inclusion efficiencies for these CD types. Some research studies explored the application of vitamin D_3-CD inclusion complexes for designing different delivery systems such as liposomes or nanosponges. Ebrahimi et al. [72] discussed the application of βCD for inclusion complex formation with vitamin D_3 and the incorporation of the formed complex into liposomes coated with gelatin. Maximum, encapsulation efficiency of 81.09% could be achieved with this system and at the concentration of 1 mg/mL of gelatin, the smallest particle size of approximately 104 nm could be obtained. The coated liposomes showed higher antioxidant activity and a slow controlled in vitro release of vitamin D_3, 14.65% release after 2 h in the gastric phase. In contrast, a higher release rate of 43.55% was observed in the intestinal phase due to the lipolysis of phospholipids for the coated liposomes compared with 57.15% for the uncoated ones. Similar observations were also reported on the application of CD inclusion complexes incorporated into liposomes for achieving controlled and sustained release of vitamin E [71]. In another study, Uberti et al. [44] explored the application of nanosponges for the delivery of vitamin D_3. Nanosponges were prepared using the ball-milling technique and carbonyl diimidazole as a cross-linker. A higher thermal stability of vitamin D_3 could be achieved with the developed nanosponges. Simultaneously, a higher bioavailability of cholecalciferol could be obtained without toxicity to epithelial cells. Vitamin D_3 nanosponges could be absorbed into the blood plasma more than twice than that for physical mixtures (53% compared with 22%).

The reviewed studies demonstrated the efficiency of CDs, specifically βCD for enhancing the solubility and stability of vitamin D_3. Nanosponges and colloidal liposomes can facilitate the permeation of vitamin D_3 through epithelial cells and its uptake by the bloodstream. Therefore, they might find their applications in fortified foods, dietary supplements and cosmeceutical products.

Delivery of vitamin K

Vitamin K consists of a group of fat-soluble molecules characterized by the 2-methyl-1,4-naphthoquionone ring. There exist two natural forms of vitamin K, i.e. K_1 (phylloquinone or phytonadione) and K_2 (menaquinone) [191]. While the former consists of a phytyl side chain, the latter possesses a polyprenyl side chain at the C3 position [191, 192]. Vitamin K_1 is commonly isolated from plants whereas vitamin K_2 is synthesized by bacteria and gut flora [193]. Synthetic and water-soluble form of vitamin K includes vitamin K_3 known also as menadione. Vitamin K_3 does not contain an isoprenoid chain and is not recommended for clinical use as it can cause hemolytic anaemia or allergic reactions [194, 195]. Due to the absence of side chains at the C3 position, vitamin K_3 is highly reactive and can bind to thiol groups to form toxic thioethers [196, 197]. Other forms of aqueous-soluble menadione are synthesized such as menadione bisulfate, menadione sodium bisulfate, or menadione nicotinamide bisulfate. They are commonly used in animal feed in the recommended doses by the US Food and Drug Administration (FDA), i.e. maximum of 2 g per ton of complete feed in chicken and turkey feed and 10 g per ton of complete feed in swine feed [198–200]. Deficiency of vitamin K can cause significant bleeding or haemorrhage [201], low bone mass, or osteoporosis [202], or elevate the risk of cardiovascular diseases [203]. Therefore, natural forms of vitamin K are commonly utilized for formulating oral drugs and supplements to address vitamin K deficiency [191]. Although the synthetic Vitamin K_3 is not recommended for clinical use in humans, studies exist in the literature, which explore its potential anticancer effects. The inhibitory effect of vitamin K_3 is related to its interaction with deoxyribonucleic acid (DNA), and inhibition of enzyme activity [204]. Another form of vitamin K, phthiocol (2-hydroxy-3-methyl-1,4-naphthoquinone), is synthesized from menadione and possesses antifungal, anticancer, and antihaemorrhagic properties [205].

A number of research studies explored the application of cyclodextrins for inclusion complex formation with vitamin K_3. These studies investigated the inclusion complexation of vitamin K_3 and its analogues with cyclodextrins and examined the mechanism of the interaction of menadione and its complexes with the DNA molecule. Petkova et al. [172] studied the interaction of vitamin K_3 and its analogues, menadione bisulfate, menadione sodium bisulfate, and hydroxylated menadione (i.e. phthiocol) with βCD. They examined the impact of different orientations of menadione, i.e. *a* and *b*, and its different enantiomers on the inclusion complex formation. In position *a*, the C=O group of the vitamin K_3 molecule could form an H-bond with the OH group from the βCD rim whereas in the *b* orientation, the C=O groups were located far from the βCD rim. Therefore, orientation *a* showed a more stable complex as the K_3 molecule

was able to form hydrogen bonds with the βCD wider rim. For both *a* and *b* orientations, positive values of Gibbs energy were obtained for the vitamin K_3-βCD complex. In comparison, for the aqueous-soluble menadione bisulfate and menadione sodium bisulfate, the values of Gibbs energy were negative for both *a* and *b* orientations and different enantiomers showing the favourable interactions in the water environment. For phthiocol, the presence of hydroxy groups facilitated the complex formation and orientation *a* showed a higher preference for complex formation.

Tang et al. [171] explored the interaction of vitamin K_3 with γCD and Herring sperm DNA. Vitamin K_3 could form a complex with γCD in the stoichiometric ratio of 1:1. With the addition of DNA to the resulting complex, some degree of intercalation was observed between the complex and the DNA that could limit the quenching from water molecules. The complex could bind to DNA in the stoichiometric ratio of DNA: vitamin K_3-γCD of 1:2. The negative value of the Gibbs energy showed a spontaneous interaction between the vitamin K_3-γCD complex and DNA. In addition, the positive value of the entropy was a driver for the interaction of the complex with the DNA molecule. The interaction of vitamin K_3 with DNA molecules and its anticancer properties makes it a potential candidate to be used together with anthracyclines or anthraquinones for cancer therapy [205, 206].

There is a limited number of published studies on the application of CDs for the delivery of vitamin K. Considering the important role of vitamin K in blood coagulation and its potential use in cancer therapy, further studies on the application of CDs and their inclusion complexes for the delivery of this vitamin seem worthwhile.

Delivery of vitamin C

CDs are also explored for the delivery of water-soluble vitamins to enhance their shelf life, or improve their thermal stability. However, the number of publications on CD inclusion complexes with hydrophilic vitamins is limited as CDs have a higher tendency to form inclusion complexes with hydrophobic guest molecules. Vitamin C is a six-carbon molecule similar to glucose and is a water-soluble vitamin (*log P* of -1.9) [90], which is not synthesized in the human body due to the lack of gulonolactone oxidase enzyme [207, 208]. Therefore, it should be obtained from fruits, vegetables or supplements. Deficiency of vitamin C can cause scurvy characterized by perifollicular haemorrhages, or swollen bleeding gums [209]. It can also aggravate skin diseases such as atopic dermatitis often referred to as eczema [210, 211]. Different isomers of vitamin C exist including L-ascorbic acid, erythorbic acid, or D-ascorbic acid, among which the L isomer is the most active form [196, 212]. L-ascorbic acid is commonly added to foods to enhance their nutritional value, while simultaneously adding citrus flavor to some products and preserving them from spoilage by enhancing their oxidative stability [213]. Due to its antioxidative properties, it is also commonly added to skin-care products and have numerous applications in cosmeceuticals [214].

A few studies explored the application of CDs as carriers of vitamin C [43, 99] or as stabilizers of vitamin C-loaded delivery systems [51] to enhance the thermal stability, solubility, and permeation rate of the vitamin in skin-care products as an antioxidant. Braithwaite et al. [99] studied the application of βCD for inclusion complex formation with vitamin C. A high inclusion efficiency of 82% was obtained for the ratio of βCD: vitamin C of 2.5:1. The solubility of vitamin C was increased up to 3mM βCD concentration, which increased again for the 5–10 mM concentration range. The formed complexes were stable, as demonstrated by their lower total potential energy. Other studies explored the application of electrohydrodynamic technique, and electrospinning alone or combined with electrospraying, for the production of nanofibers from vitamin C-CD inclusion complexes [43, 102]. Khan et al. [102] studied the possibility of inclusion complex formation between L-ascorbic acid and HP-βCD to enhance the thermal and oxidative stability of the vitamin. They showed that L-ascorbic acid can form an inclusion complex with HP-βCD in a stoichiometric ratio of 2:1 with approximately 97% encapsulation efficiency in electrospun nanofibers with diameters of ~ 340 nm. Incorporation of L-ascorbic acid into the CD cavity could elevate its thermal degradation temperature from 190 to 240 to 220–310 °C. The formed complex also showed radical scavenging activity of ~96% compared with ~53% for its free form at 30 μM ascorbic acid concentration. Encapsulation of vitamin C and the formation of inclusion complex could protect the vitamin from oxidation and degradation at elevated temperatures. With preservation of the vitamin, its subsequent antioxidant and radical scavenging properties were elevated. Therefore, the prepared electrospun nanofibers can find their applications in formulating food packaging to prevent lipid oxidation. Calzado-Delgado et al. [43] investigated the application of βCD for inclusion complexation with vitamin C and subsequent immobilization of the formed complex on cellulose acetate followed by electrospraying of the stabilized complex on electrospun polyvinyl alcohol (PVA) nanofibers. While loading of vitamin C into electrospun PVA nanofibers could protect it during heating up to 180 °C, its inclusion into βCD could elevate its thermal resistance even more, up to 350 °C. A burst release of vitamin C (66 mg/g/h) was observed during the first 1 h. Conversely, the release rate was slower (6.3 mg/g/h) until the 48th hour when 96% of vitamin C was released. While the burst release of vitamin C could aid its skin permeation and diffusion, the vitamin C immobilization on cellulose acetate moderated skin hydration and enabled the controlled delivery of the vitamin. This system can be used in formulating

skin patches for controlled transdermal delivery of vitamin C through controlling moisture. Wang et al. [51] explored the application of βCD as the stabilizer of water-in-oil-in-water ($W_1/O/W_2$) double emulsions loaded with vitamin C. An increase in the concentration of βCD could elevate the number of emulsion droplets with smaller sizes. An increase in the content of βCD from 4 to 8% increased the retention rate of vitamin C from 58.3 to 83.3%. During an in vitro release study, 85.38% of vitamin C was released during 2 hours. Similarly, the permeation of vitamin C was increased in rat skin from approximately 6.6 to 10.4 $\mu g/cm^2$ during 12 h. The increase was observed with an elevation of the βCD concentration from 4 to 8%.

The reported studies highlight the application of designed electrospun nanofibers and emulsions as delivery systems for elevating the oxidative stability of vitamin C, moderating skin hydration, improving skin permeation and enabling sustained delivery of vitamin C. They can additionally be applied for formulating skin care products including creams or lotions for topical delivery, or utilized in skin patches and micro-needles for transdermal delivery of vitamin C. They can also be useful in food packaging to prevent lipid oxidation.

Delivery of vitamin B

CDs can have applications for the delivery of the vitamin B complex, which plays a key role in energy metabolism and proper function of the nervous system in the human body [215]. Vitamins belonging to B complex (B_1 (thiamine), B_2 (riboflavin), B_3 (niacin), B_5 (pantothenic acid), B_6 (pyridoxine), B_7 (biotin), B_9 (folic acid), and B_{12} (cobalamin), are essential water-soluble vitamins (*log P* value ranging from −3.2 to 0.32) [90] lack of which can cause fatal heart failure, impaired cognitive function, neurological disorders, skin rashes, or megaloblastic anaemia [216]. B vitamins are sensitive to heat, light, and acidic/alkaline environments [217]. Therefore, their inclusion complexation with CDs can protect them from changes in environmental conditions during processing. Food products can be fortified with different B vitamins to produce functional foods with added nutritional value [218–221]. Alternately, the status of B vitamins can be elevated through daily intake of supplements [222].

A number of research studies contribute to our enhanced understanding of the application of CDs for protecting vitamin B and enabling its controlled delivery and sustained release. Heydari et al. [108] studied the possibility of cationic βCD synthesis through the addition of guanidine as a building block and epichlorohydrin as a crosslinker during one-step polymerization. The resulting complex was utilized for encapsulation and delivery of vitamin B_2. The polymerization of βCD in the presence of epichlorohydrin significantly improved the solubility from 17.7 mg/mL to 875 mg/mL. The solubility was further increased with the insertion of guanidine in the structure and varied from 925 to 1285 mg/mL for ratios of guanidine: βCD of 5 and 15. Similarly, the solubility of the inclusion complexes prepared with the incorporation of vitamin B_2 was increased as the content of guanidine was increased. During the simulated in vitro digestion, a burst release was observed due to the release of free vitamin B_2. The released vitamin B_2 content was lower at neutral pH than at acidic and alkaline conditions, possibly due to the higher degree of electrostatic interactions between CD and the vitamin molecule. An increase in the guanidine content slowed down the release of vitamin B_2 and 71.5% of the vitamin was released from the complex prepared with the ratio of guanidine: βCD of 15:1. In another study [69], the authors explored the preparation of polymeric nanofibers from peracetyl-βCD and its complex with vitamin B_2 using the electrospinning technique. For the preparation of the polymer, βCD was crosslinked with the epichlorohydrin and acetic anhydride in the presence of pyridine. The produced nanofibers of peracetyl-βCD-vitamin B_2 had an average diameter of 122 nm and during 170 h at pH 7.4 showed a slower sustained release of 40% of vitamin B_2 compared with 97% from peracetyl-βCD polymer. The achieved sustained release makes the produced nanofibers potential carriers for the delivery of vitamin B_2 in drug formulations. The possibility of vitamin B_9 (folic acid) delivery through spray-dried microcapsules prepared with horse chestnut starch or βCD as wall materials was explored by Ahmad and co-workers [110]. They observed a higher encapsulation efficiency of folic acid in βCD compared with starch, 76.10% versus 57.29% respectively due to the large cavity size of βCD. Simultaneously, smaller particle sizes of microcapsules were obtained for βCD (see Table 2), due to the smaller molecular weight of βCD and the higher interaction of folic acid with this biopolymer. Folic acid in βCD had a lower water activity compared with starch, which provides the opportunity to formulate delivery systems with a higher oxidative and microbial stability. The βCD microcapsules also showed a higher antioxidant activity due to the presence of hydroxyl groups in the βCD molecule together with the radical scavenging activity of folic acid. The results of the in vitro simulated digestion showed a lower release of folic acid in the gastric phase compared with the intestinal for both microcapsules with a lower release for folic acid-βCD complexes (53.6 and 57.6% gastric release at 30 and 60 min, 71 and 84% intestinal release at 2 and 4 h) compared with folic acid-starch complexes (56.2 ad 60.5% gastric release at 30 and 60 min, 85.3 and 92.1% intestinal release at 2 and 4 h). Both formulations could provide the opportunity for sustained folic acid release. Therefore they can find their applications in fortifying foods with this micronutrient.

Tabassi et al. [68] studied the preparation of supramolecular hydrogels (SMGels) from tri-block copolymers of poly-ϵ-caprolactone (PCL)-polyethylene glycol (PEG)-PCL

and αCD and this formulation was used for the delivery of the drug naltrexone or vitamin B_{12}. Two different ratios of PCL: PEG of 2:1 and 1:4 were considered for the synthesis. For the ratio of 2:1 the hydrogels could not be formed due to the hydrophobicity of PCL, which prevented the threading of αCD onto the PEG polymer. Therefore, a ratio of 1:4 was selected for the preparation of hydrogels while changing the concentration of PCL-PEG-PCL (2, 4, 6, 8, 10, and 20%) and αCD (8, 12, 16, 20, and 24%). During an in vitro simulation study, sustained release of vitamin B_{12} (25–35%) was achieved during 600 h, with a burst release < 5%. In comparison, naltrexone released completely from the matrix during 350 h with a burst release of 10%. This system proved to be efficient for the delivery of the drug with sustained delivery of vitamin B_{12} during a longer period.

The discussed studies show the efficiency of CDs and their designed delivery systems for controlled and sustained delivery of vitamin B and highlight their potential applications in foods or dietary supplements.

Cyclodextrins (CDs) and their inclusion complexes for delivery of iron

Iron is a key micronutrient having the role of oxygen transport in the human body [223, 224]. It is not synthesized in the human body and must be obtained from dietary sources. The bioavailable dietary iron in the intestinal mucosa exists in two forms, haem or non-haem iron [224, 225]. Haem iron contained within haemoglobin or myoglobin of the animal tissue, can be absorbed easier than the non-haem iron. Non-haem iron exists in the ferrous (Fe^{2+}) or ferric state (Fe^{3+}) and for the absorption by the duodenal enterocytes, the ferric iron should be reduced to ferrous iron in the presence of the enzyme, cytochrome b reductase [224, 226]. Deficiency of iron as a result of its low intake or bioavailability to the human body causes iron-deficiency anaemia, which is more prevalent in children and lactating women of the developing world [227–229]. To elevate the intake and bioavailability of iron in the human body, strategies were developed for the fortification of foods and dietary supplements by micro/nanoencapsulation [230, 231]. Several iron sources have been utilized for formulating functional foods and supplements including mainly ferrous sulphate [232], ferrous fumarate [59, 232, 233], ferrous bisglycinate [234], ferrous gluconate [235], and sodium iron ethylenediaminetetraacetic acid (NaFeEDTA) [236–238]. The most widely utilized water-soluble iron source with high bioavailability is ferrous sulphate. Although it is highly bioavailable, it results in undesired changes in the colour or taste of food products [239, 240]. Iron bisglycinate is another much more expensive iron source with high bioavailability with applications in food fortification [241, 242].

Poorly water-soluble iron sources such as ferrous fumarate, or ferrous succinate are also employed in the fortification of foods [59, 233, 243]. Their low aqueous solubility can limit their bioavailability compared with other iron sources such as ferrous sulphate or ferrous bisglycinate [244]. The water-insoluble iron form ferric pyrophosphate is less bioavailable in comparison to soluble forms of iron but causes no organoleptic changes to the fortified food product [245]. Its solubility can be increased through co-delivery with other solubilizers such as the iron chelator, ethylenediaminetetraacetic acid (EDTA), or citric acid [246].

NaFeEDTA is a water-soluble form of iron with a high bioavailability more than that of ferrous sulphate or ferrous fumarate in a high-phytate diet due to the presence of EDTA in its molecular structure, which inhibits the binding of iron to polyphenols and phytates [117, 238, 240, 250]. This bioavailable iron source has received specific attention recently in food fortification [232, 238]. The other iron source with potential application in food fortification is ferrous ammonium phosphate prepared from iron(II), ammonium hydroxide, and phosphoric acid in a stoichiometric ratio of 1:1:1 [41]. This compound is generally recognized as safe (GRAS) [251] and shows a higher degree of bioavailability compared with ferric pyrophosphate, but lower than that of ferrous sulphate [41, 252]. To enhance the bioavailability of iron or mask its undesired taste and colour, encapsulation of iron is a strategy that is commonly applied in the food or pharmaceutical industry [230, 231, 253].

Although several research studies report the conjugation of CDs with iron for improving the targeted delivery of drugs and enabling the formation of magnetic nanoparticles for MRI applications [164, 254], the number of studies on the application of CDs for iron delivery in foods or dietary supplements is limited. Only a few studies report the application of CDs for the delivery of iron compounds such as iron bisglycinate, ferrous fumarate, ferric sodium EDTA, and ferrous ammonium phosphate. Kapor et al. [45] studied the application of βCD and HP-βCD for the delivery of ferrous fumarate. Ferrous fumarate has low water solubility but it is soluble in dilute acids or gastric fluid. The authors explored the synthesis of iron(II) fumarate based on the conversion of fumaric acid to disodium fumarate and attempted to enhance its solubility through inclusion complexation with βCD or HP-βCD. The highest solubility of ferrous fumarate up to 2.71 mg/cm^3 was achieved when it was complexed with HP-βCD compared with 1.4 mg/cm^3 in water. A lower solubility of iron(II) fumarate up to 2.05 mg/cm^3 was obtained when complexed with βCD after 72 h of mixing at room temperature. In a study on the application of βCD for iron delivery, Saffarionpour and Diosady [41] investigated the possibility of inclusion complexation between ferric sodium EDTA, or ferrous ammonium phosphate with βCD and studied the impact of iron to βCD ratio, duration of mixing, and the concentration of the co-solvent on the degree of complexation. The results

of the study showed that complexation of hydrophilic iron, ferric sodium EDTA, with βCD could only result in high inclusion rate of approximately 77% at lower alcohol concentrations (i.e. ~25% v/v) as a co-solvent, longer mixing duration of 72 h, and iron: βCD ratio of 1:6. At low βCD concentrations, an increase in the alcohol concentration facilitated the solubilization of CD and formation of inclusion complex and extension of the mixing duration slightly reduced the inclusion rate. In contrast, at CD concentrations close to its maximum solubility, an increase in the alcohol concentration reduced the inclusion rate as alcohol competed with iron to enter the CD cavity. Conversely, ferrous ammonium phosphate with lower aqueous solubility showed a higher degree of inclusion rate of approximately 96% at a shorter mixing duration of 6 h and a low alcohol concentration of ~25% v/v. The inclusion complex with ferrous ammonium phosphate could significantly enhance the melting temperature of iron (from 172 to 294 °C) which makes it an appropriate candidate for the fortification of foods processed at elevated temperatures [41]. In another study, Saffarionpour and Diosady [117] explored the application of βCD for the stabilization of water-in-oil-in-water ($W_1/O/W_2$) double emulsions for co-delivery of ferric sodium EDTA and curcumin as a nutraceutical compound. Higher stability of the emulsion could be achieved when curcumin-βCD inclusion complex was used as the emulsifier together with sodium alginate and sodium caseinate. The delivery system protected iron from the harsh acidic condition of the gastric phase while achieving sustained release of iron in the intestine with approximately 80% bioaccessibility. Esposito et al. [46] discussed the application of zein pseudolatex and the zein-βCD micropowders formed through spray drying for the delivery of iron bisglycinate. Spray drying of micropowders could result in encapsulation yields above 70%, which increased to 90% when zein 2% w/v and βCD of 0.5% w/v were used for formulating the micropowders. The formed inclusion complex limited the iron release in the gastric phase to 30%, which increased to 80% in the intestinal phase reaching its maximum at 7 h digestion.

Cyclodextrin (CD)-based delivery systems, not only facilitated the controlled release and sustained delivery of iron but also enhanced its thermal resistance during processing. Therefore, they have potential applications in functional foods, food products processed at elevated temperatures, and in dietary supplements. However, the number of studies on the application of CDs for iron delivery is small and further exploration is warranted.

Cyclodextrins (CDs) and their inclusion complexes for delivery of iodine

Iodine is a vital micronutrient and an integral component of thyroid hormones required for cellular metabolism. It is essential for the synthesis of the thyroid hormones thyroxine (T4) and triiodothyronine (T3) [255]. Thyroid stimulating hormone (TSH) stimulates the release of T3 and T4 hormones which stimulate the thyroid gland to absorb more iodine from the blood and produce thyroid hormone. Low levels of TSH and subsequently T3, and T4 hormones can result in hypothyroidism [79]. The deficiency of iodine can also result in continuous stimulation of the thyroid gland for releasing TSH and its growth causing endemic goiter [78]. Abnormal concentrations of thyroid hormone can also induce periodontitis, marked by inflamed periodontal tissues, and destructed periodontal ligament [256, 257]. Strategies for fortification of foods with iodine were developed for addressing iodine deficiency [237, 238, 240]. Iodine is slightly water-soluble (*log P* of 1.36) [90] and is commonly dissolved in non-polar solvents. The formation of inclusion complex between iodine and CD molecule can enhance its water solubility [248] while preserving it from degradation or sublimation at elevated temperatures [40].

A number of studies report the application of CDs for iodine delivery. Polumbryk et al. [247] compared the application of α- and βCD for inclusion complexation with iodine. A higher degree of complexation with 18-19.9% iodine content was achieved using αCD. Comparatively, βCD resulted in the inclusion of less iodine (i.e. 16.7–16.9%) due to the adsorption of water which limited the inclusion of iodine. Needle-like iodine-CD inclusion complexes were formed in a stoichiometric ratio of 1:1 and the one prepared with βCD lost 9% of its iodine content during a 1-year storage period at 4 °C. In another study, Dattilo et al. [40] investigated the application of HP-αCD, HP-βCD, and HP-γCD for encapsulation and delivery of iodine. They compared the application of three different techniques of liquid-assisted grinding, co-evaporation, and sealed heating for the preparation of the complex. Similar to the observations of Polumbryk et al. [247] a higher degree of inclusion complexation was observed for the α-type CD, i.e. HP-αCD compared with HP-βCD or HP-γCD and the formation of an inclusion complex for the latter two depended on the preparation technique as the highest degree of complexation was observed for sealed heating (see Table 2). The inclusion complex formed between HP-βCD and iodine could improve the thermal stability of iodine and increase in the host: guest ratio increased the degradation temperature. During a 28-day storage period, all prepared samples showed an 18–33% decrease in iodine content except the one prepared with HP-γCD which retained only 39% of iodine. The iodine content decreased mostly during the first week after preparation. After 3 months storage, the iodine content remained almost unchanged for the complexes prepared with HP-α CD. All the formed complexes resulted in a high degree of reduction in bacterial cell vitality. Sharipov et al. [79] studied the application of βCD for inclusion complexation

with iodine and the role of the delivered iodine in regulating T3 and T4 hormones in Wistar rats. Iodine-βCD inclusion complex was formed with a stoichiometric ratio of 1:1 with 19.91% iodine content, similar to the results reported in the study of Polumbryk et al. [247]. Iodine complex could increase the level of T3, T4, and TSH hormones in rats. In another study, Polumbryk et al. [47] investigated the application of the iodine-βCD complex for the fortification of sausages and studied its impact on increasing the iodine status of 31 volunteers during a 10-day clinical trial. Similar to their previous study [247], 16.9% of iodine was complexed with βCD and the consumption of the fortified sausage could enhance the iodine status of the individuals from 60 to 110 μg/L while simultaneously increasing the T4 hormone level. Iodine reacts with tyrosine and forms 3,5-diiodotyrosine with anticancer and antioxidant effects. Results of the in vitro digestion studies showed that consumption of fortified sausages could increase the level of 3,5-diiodotyrosine with the potential of reducing the risk of cancer.

CDs can protect iodine from sublimation and the formed complex possessing antibacterial properties can find its medical applications. Wang et al. [248] studied the bacteriostatic effect of iodine-βCD inclusion complex and the impact of pH on the binding constant of iodine. They showed that alkaline condition was not favourable for the formation of inclusion complex as I_2 content decreased with an increase in alkalinity and iodine was mostly present in ionic forms of I^- and IO_3^- without ultraviolet (UV) absorption. Additionally, with an increase in βCD content a higher degree of iodine was encapsulated inside the CD molecule. Iodine-βCD complex with a stoichiometric ratio of 1:1 and 17.3% iodine content was prepared with a binding constant of 1286 M^{-1} for iodine. The percentage of complexed iodine in their study was slightly higher than that reported in the works of Polumbryk et al. [47, 247]. The formed iodine complex with 1.5% iodine content protected iodine from early sublimation and showed an inhibitory effect on Aspergillus niger. Relevant to medical applications of iodine-CD inclusion complexes, Lu et al. [109] investigated the application of γCD-metal organic frameworks (MOFs) for encapsulating iodine and the subsequent formation of iodine-γCD-MOF hydrogels prepared with hydroxyethyl cellulose for treating periodontitis, and inflammation of the gum tissue around the teeth. A more sustained release of iodine could be achieved during a 5-day in vitro study and hydrogels showed a more sustained release compared with iodine-γCD-MOF complexes. In vivo studies on rats showed the effective role of the prepared hydrogels in decreasing periodontal pocket depth.

A few studies discuss the application of radioactive iodine and its inclusion complex with CD in nuclear medicine [48, 249]. Radioactive isotopes of iodine I^{131} and I^{123} emit beta and gamma rays respectively. These can penetrate tumor cells and destroy them with localized radiation [258]. They are commonly applied for studying thyroid physiology and treating thyroid cancer. Nishi et al. [48] showed in their study that iodine-αCD can prolong the residence time of iodine while protecting it from volatilization and enabling its sustained release. The results of in vivo studies showed that the absorbed iodine bound to tyrosine and synthesized T3 and T4 hormones. Hirota et al. [249] showed similarly that volatilization of iodine can be reduced to 1/3 – 1/4 through inclusion complex formation between radioactive iodine isotopes I^{131} and I^{123} and HP-αCD or HP-βCD. The formed complexes could retain a higher amount of iodine when the CD content was elevated from 0.1 to 10 wt%.

The reported studies show the potential of CDs in medicine and in improving the thermal stability of iodine when used in fortified foods to address iodine deficiency. Concomitantly, iodine-CD inclusion complexes can have an efficient role in regulating thyroid hormones through controlled and sustained delivery of iodine while simultaneously protecting it from loss and sublimation.

Potential health applications of CDs for micronutrient delivery

CD inclusion complexes with vitamins have found their applications in the development of cosmeceutical and pharmaceutical products. To mention some examples, HP-βCD has been used for formulating L'Oreal's anti-ageing serum (ArtNaturals®) with vitamin C-retinol and hyaluronic acid [24]. The formulation of dermal filler hydrogels prepared with vitamin A, hyaluronic acid, and natural CDs and their inclusion complexes is also patented by Allergan Inc. [259]. CAVAMAX W8/Retinol inclusion complex produced by Wacker Chemie AG, is a complex of pharmaceutical-grade γCD and retinol and is applicable for formulating emulsions and skin care products [260]. CD inclusion complexes with micronutrients have also found their application in formulating dietary supplements. Liposomal vitamin C supplement, Cyclo-C, formulated with citrus bioflavonoids and CD with improved bioavailability was developed by Nature's Essentials™ [261].

Similarly, CDs and their inclusion complexes with micronutrients can find their applications in the food industry for the development of functional foods with enhanced nutritional properties. Inclusion complexes formed with vitamin D and FDA-approved CDs for food applications can be used for formulating fortified dairy products such as milk, butter, cheese, creams, or ice cream [262]. Moreover, functional beverages such as vitamin-fortified drinks, juices, vitamin or mineral-fortified water, energy drinks, or herbal drinks can be formulated through the delivery of micronutrients with CDs for boosting the immune system [263]. Vitamins with antioxidant properties such as α-tocopherol and their inclusion complexes with CDs can be used

for the fortification of meat or utilized in the formulation of food packages to prevent lipid oxidation and extend the shelf-life of products [115, 264]. Compared with vitamins, the applications of CDs are less explored for inclusion complexation with iron and iodine in the development of fortified foods with the prepared complexes. The increased thermal stability provided by the inclusion of iron in CDs makes CDs potential carriers for the delivery of iron in foods processed at elevated temperatures such as hot soups, or drinks (e.g. tea, coffee, or milk) [41]. Similarly, iodine and its complexes with CD can be used to formulate fortified foods to increase the iodine status and thyroid function in humans [47]. These delivery systems can enable the sustained and controlled release of iron or iodine and allow development of dietary supplements containing these micronutrients.

Conclusions

CDs are natural biopolymers that can form inclusion complexes with micronutrients, enhance their solubility, stability and shelf-life, mask their undesired taste or colour, and improve their bioavailability when delivered orally in foods and dietary supplements or topically and transdermally in pharmaceutical and cosmeceutical products. CDs and their inclusion complexes with vitamins as antioxidants enable the designing of delivery systems with radical scavenging and cytoprotective activity for reducing oxidative stress and treating several inflammatory, neuroprotective, and cardiovascular diseases. The reported studies show that modification of CDs with OSA can not only impart an amphiphilic nature to the CD molecule but also enhance the loading of vitamin E and emulsifying properties of βCD while enabling the design of emulsion systems with enhanced oxidative stability. Electrospun polymer-free nanofibers prepared with modified type cyclodextrins, i.e. HP-βCD or HP-γCD, or polymeric nanofibers prepared with PCL, PVA, or PLA, and CD inclusion complexes with vitamins show potential for enhancing the solubility and stability of vitamins and increasing their shelf-life while enabling their sustained and controlled release with simultaneous moderation of hydration. Therefore, they can find their applications for topical or transdermal delivery and formulating skin care products or for oral delivery and formulating fortified foods or dietary supplements. They can also be utilized in food packaging to prevent lipid oxidation. Incorporation of complexes formed between CDs and vitamins into liposomes provides the possibility of their controlled and sustained intestinal release while increasing their antioxidant activity. Coating of the liposomes loaded with vitamin-CD inclusion complexes with gelatin or caseinate can impart higher stability to the colloidal delivery system while protecting the active vitamin molecule from changes in environmental conditions such as pH or temperature. The design of βCD nanosponges using cross-linkers can enhance the thermal stability of vitamin D_3 while facilitating its permeation through epithelial cells and improving its bioavailability. The limited number of reported studies on the application of CDs for iron delivery shows the potential of CDs for the delivery of both hydrophilic and hydrophobic iron. While the latter shows a higher tendency to form complexes with CDs, the former can form complexes with CDs with elevated inclusion rates through optimization of several factors such as the concentration of CD and the utilized co-solvent, mixing duration and temperature. Spray-dried microcapsules prepared with βCD and zein can provide the possibility of controlled and sustained release of iron in the gastric and intestinal phases with potential applications for food fortification. Iodine-βCD inclusion complexes can regulate thyroid hormones while protecting iodine from sublimation. Hydrogels with γCDs-MOFs and hydroxyethyl cellulose have the potential to improve the sustained delivery of iodine and ameliorate periodontal pocket depth. Radioactive iodine and its inclusion complexes with αCD, HP-αCD or HP-βCD can synthesize thyroid hormones and find their applications in nuclear medicine. It can be inferred from the discussed studies that the formation of the inclusion complex between the micronutrient and the CD molecule is also dependent on the size of the molecule, its positioning, and its orientation inside the cyclodextrin cavity. For example, vitamin E and its phytyl chain could not be positioned inside the αCD cavity while it could be included into β- or γCD. A weak binding of vitamin A palmitate was also observed to βCD due to the presence of isoprenoid chains. A higher insertion depth of vitamin D_3 into β- or γCD is also reported with lower binding to αCD and HP-βCD in comparison with different orientations of the vitamin D_3 molecule. Different orientations and enantiomers of vitamin K_3 and its analogues also impacted the formation of an inclusion complex. Iodine had a higher tendency to form inclusion complexes with α-type CDs, i.e. αCD and HP-αCD. Therefore, to enhance the inclusion rate of micronutrients inside CDs, a suitable CD type should be selected considering the molecular size and structure of the guest molecule. CDs and their inclusion complexes with micronutrients, specifically vitamins have found their applications for the development of several cosmeceutical and pharmaceutical products already available in the market such as personal care products or drug supplements. Considering the increased interest in the use of CDs in the food and agricultural industry, further research is warranted on their applications for the delivery of micronutrients in fortified functional foods. Specifically, further exploration of their applications for iron delivery seems crucial due to the widespread deficiency of iron and the need for stable, organoleptically acceptable iron delivery systems. There is a need for the scale-up of different techniques for the preparation of CD inclusion complexes such as electrospinning or spray drying to an industrial scale.

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Declarations

Ethics approval and consent to participate Not applicable to this manuscript.

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Conflict of interest Shima Saffarionpour and Levente L. Diosady declare that they have no conflict of interest.

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