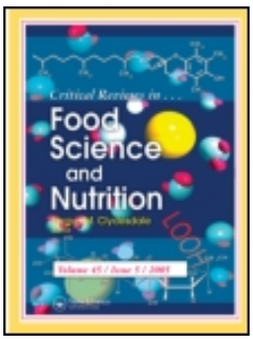

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Cyclodextrins in Food Technology and Human Nutrition: Benefits and Limitations

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Cyclodextrins are tasteless, odorless, nondigestible, noncaloric, noncariogenic saccharides, which reduce the digestion of carbohydrates and lipids. They have low glycemic index and decrease the glycemic index of the food. They are either non- or only partly digestible by the enzymes of the human gastrointestinal (GI) tract and fermented by the gut microflora. Based on these properties, cyclodextrins are dietary fibers useful for controlling the body weight and blood lipid profile. They are prebiotics, improve the intestinal microflora by selective proliferation of bifidobacteria. These antiobesity and anti-diabetic effects make them bioactive food supplements and nutraceuticals. In this review, these features are evaluated for α-, β- and γ-cyclodextrins, which are the cyclodextrin variants approved by authorities for food applications. The mechanisms behind these effects are reviewed together with the applications as solubilizers, stabilizers of dietary lipids, such as unsaturated fatty acids, phytosterols, vitamins, flavonoids, carotenoids and other nutraceuticals. The recent applications of cyclodextrins for reducing unwanted components, such as trans-fats, allergens, mycotoxins, acrylamides, bitter compounds, as well as in smart active packaging of foods are also overviewed.

Keywords Blood lipid profile, body weight control, digestion, glycemic index, nutraceuticals, packaging, prebiotic, soluble fiber

INTRODUCTION

Cyclodextrins (CDs) are enzyme-modified starch derivatives produced industrially. Due to the slightly hydrophobic inner surface of these ring-shaped molecules, they are able to form inclusion complexes with molecules of low hydrophilicity and proper geometrical size. The variants of these cyclic oligosaccharides consisting of 6, 7 or 8 glucopyranose units (α-, β- and γ-CDs, respectively) differ in their size (0.5–0.9 nm in diameter) that determines the geometrical fit of the guest molecules into the cavity. The versatile applications including pharmaceutical, food, cosmetic, environmental, agricultural, etc., fields are based on inclusion complex formation.

The structure of the βCD can be seen in Fig. 1.

The food application started as early as in 1970 by recognizing the retention of volatile food flavor ingredients by complexation (Gray and Roberts, 1970). CDs have been utilized in food technology mainly as *carriers of food related lipophiles* (such as flavors, aromas, colorants, fats, etc.) inhibiting the light- and heat-induced transformations of these sensitive food ingredients. The molecular encapsulation of flavors, vitamins, colorants, unsaturated fats, etc., with CDs improves the stability of these lipophilic food components both in physical and chemical sense leading to extended product shelf life. The active ingredients are protected against oxidation, light-induced reactions, heat-promoted decomposition, loss by volatility, and sublimation. The results of accelerated and long-term storage stability tests showed that the stability of CD-entrapped food ingredients surpassed that of the traditionally formulated ones. The moisture-triggered release of the included lipophiles makes these complexes useful in food application. *Technological advantages* of the use of CDs in foods and food processing technologies, such as reduction of foaming, stabilization of emulsions, decrease of enzymatic browning, are also manifested in improved sensory, nutritional and performance properties. Further technological advantages include stable, standardizable compositions, simple dosing and handling of dry powders, reduced packing and storage costs, more economical, technological processes, manpower saving. *Elimination of undesirable tastes* and odors by

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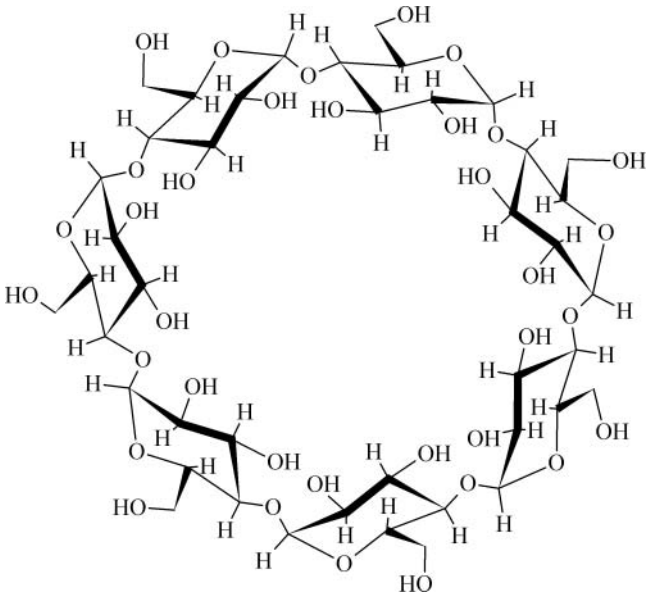

Figure 1 Chemical formula of β-cyclodextrin.

complexing the unwanted components further improves the quality of food contributing the market success.

All these, now considered "traditional" food applications are well documented in the literature: we can find about 1,400 entries on food applications including approximately 800 patents in the *Cyclodextrin News Literature Database* containing approximately 50,000 entries on CDs. The most published area is the stabilization of flavors and aromas (780). Also, fatty acids (650), carotenoids (130) and vitamins (620) are in the focus of the development in relation to CD application for stabilization, solubilization, decreasing the off-taste (600) and unpleasant odor (100). The everyday consumers are not aware how many marketed products contain CDs, such as chocolate bars, chewing gums aromatized with slow releasing aroma/CD complexes, vitamin-enriched dry beverages with CD-stabilized vitamins, debittered juices, sea-food and fermented soy products deodorized with CDs, etc.

Reviews on food applications published in the past 10 years summarize these features (Szente and Szejtli, 2004; Szejtli and Szente, 2005; Cravotto et al., 2006; Hashimoto, 2008; Klein and Zoeller, 2008; Astray et al., 2009; Cabral Marques, 2010; González-Barreiro et al., 2012; Martina et al., 2013).

The global market of CDs is continuously increasing. The production is estimated to reach 250,000 tons per year with Japan sharing the 40% of it (Zhiyuan Bio-tech, 2013). Even if this estimation is exaggerating, it should be around 10^5 tons. In Asia, also China, South Korea and India produce CDs. In China there are around 50 companies producing various CDs, 20 of them contribute with more than 1,000 tons per year. In Japan nearly 90% of CDs were used for foods in 1988 (Hashimoto, 1988), in the US 14% of CD production was utilized by the food industry in 2008 (Frost and Sullivan, 2008). The reasonable price (βCD: 4–5 Euro/kg) and well documented safety profile give way to the extending food applications.

The present review intends to overview how CDs influence the digestion and absorption of basic nutrients, such as fats, carbohydrates and proteins, and the bioavailability and stability of specific nutrients, such as vitamins, flavonoids, as nutraceuticals and functional food components. We tried to collect the literature data on the secondary effects based on the properties of CDs as soluble fibers and prebiotics. Products with enhanced/reduced lipid content (e.g. cholesterol free and phytosterol rich), based on the solubilizing/precipitating effect of complexation on various dietary lipids, are listed. Various CD-based technologies for the removal of harmful components, such as trans-fat, allergens and cancerogens are summarized. The recent developments on CD applications in active food packaging are also reviewed.

Authorization and Evaluation of CDs as Food Additives

It was only a recent finding that branched type (glucosylated and maltosylated) CDs can be detected in various food products containing enzyme- and heat-processed starch (Szente et al., 2006). Beer samples, corn syrups and bread can contain minute amounts of the enzyme-modified CDs. HPLC/MS analyses evidenced the presence of all the three, α- β- and γ-branched CDs. Based on these results the humankind has been presumably consuming CDs for thousands of years. Even so, the authorization process has only a 35-year history.

In Japan, the CDs were declared to be enzymatically modified starch and, therefore, their use in food products has been permitted since 1978. In Hungary, the Ministry of Health approved the use of βCD for stabilization of natural flavors (flavor/β-CD complexes) in 1983. In France, S.A.L. International in cooperation with Chinoin (Hungary), received a limited approval for the use of βCD as a flavor carrier in 1986.

In the Netherlands, the Ministry of Health officially declared βCD to be an enzymatically modified starch in 1986, and, as such, applicable in all those food products in which, according to the already existing regulations, (positive lists of ingredients) the use of enzymatically modified starch is permitted. The corresponding authorities of the Benelux (Belgium, Luxemburg, and the Netherlands) countries followed this act with identical decisions.

In 1987, the Spanish authorities also approved the utilization of βCD in foods.

Due to intensive toxicological and physiological studies, α- and γCDs have been approved for food worldwide. No toxicological findings were filed for any of these two CDs at FDA. Joint FAO/WHO Expert Committee on Food Additives (JECFA) checked the data and classified both CDs as "ADI not specified" (ADI = Allowed Daily Intakes) which means both CDs can be used in food at any concentration and quantity (JECFA, 1999, 2001). GRAS (generally recognized as safe in a wide range of intended use in food) approvals were obtained in the US and Novel food applications are filed in Europe (FDA, 2000, 2001,

Table 1 JECFA Evaluation of parent cyclodextrins (JECFA, 1995, 1999, 2001)

	Functional class	ADI	INS number	JECFA report	Latest studied
αCD	Carrier; encapsulating agent for food additives, flavorings and vitamins; stabilizer; absorbent	"Not specified"	457	TRS 928-JECFA 63/16	2001
βCD	encapsulating agent for food additives, flavorings and vitamins; thickening agent	0–5 mg/kg bw	459	TRS 859-JECFA 44/28	1995
γCD	Stabilizer and thickener	"Not specified"	458		1999

2004). For βCD ADI of 0–5 mg/kg body weight (bw) was allocated based on the NOEL (no effect level) of 1.25% in the diet (equal to 470 mg/kg bw/day) in a 1-year study in dogs and a safety factor of 100. It has been classified as GRAS for the use as a flavor protectant in human food (Wacker Chemie, 2013). In Australia and New Zealand α- and γCDs are regarded as Novel Food.

The three parent CDs, α-, β- and γCDs are registered in the Codex Alimentarius of Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2013) with International Numbering System (INS) No. 457, 459 and 458, respectively, among the General Food Standard Additives (GFSA) (Table 1). βCD is registered in EU as E-459 additive (Commission Directive 2003/95/E, 2003).

The food categories and use levels accepted as GRAS are listed in Table 2. The maximum use levels were determined according to the expected consumption of the food.

Ezaki Gliko Ltd. (Osaka, Japan) asked for the approval of branched cyclic dextrin. This product is a mixture of branched oligosaccharides composed of α-D-glucose monomers with at least 80% of cyclic dextrin molecules with molecular weights ranging from 30,000 to 1,000,000. Cyclic dextrin is a partially degraded maize starch that is a white, odorless powder. Cyclic dextrin contains short linear chains that are composed of α-(1,4)-linked glucose units with branching through α-(1,6) glucosidic bonds. The cyclic α-glucan moieties of cyclic dextrin are linked to adjacent branched clusters through an α-(1,6) glucosidic bond. Ezaki notes that cyclic dextrin also contains smaller amounts of single glucose molecules and other saccharides with molecular weights outside the range of the cyclic dextrin. Ezaki states that the metabolic fate of cyclic dextrin is similar to that of γCD. In 2012, this product received also the GRAS status (FDA, 2012).

Some chemically modified CDs, such as the hydroxypropyl α-, β- and γCD (HPαCD, HPβCD, HPγCD), random methylated α-, β- and γCD (RAMEα, RAMEβ, RAMEγ) and sulfobutyl βCD (SBEβCD), are approved as drug excipients, but they have not been recognized as food ingredients yet.

Dietary Lipids

The dietary lipids include triacylglycerols (triglycerides) containing saturated and unsaturated fatty acids, and sterols such as cholesterol and phytosterols (Fig. 2) (Michalski et al., 2013). Triglycerides are the main constituents of vegetable oils and animal fat; cholesterol can be found in dairy products, meat, animal fat, shrimps, etc. Some vegetable oils and nuts contain cholesterol-like compounds called phytosterols (β-sitosterol, stigmasterol, ergosterol, etc.).

In humans, triglycerides are responsible for storing unused calories, and their high concentration in blood correlates with the consumption of high carbohydrate foods (Welsh et al., 2010). High levels of triglycerides in the bloodstream have been linked to atherosclerosis as well as the risk of heart disease and stroke.

The polyunsaturated fatty acids (PUFAs) called omega-6 and omega-3 fatty acids are important for hormone synthesis, cell membrane structure and healthy brain and vision, and they may help lowering the blood cholesterol levels. Some of them (α-linolenic acid C18:3 ω3 and linoleic acid C18:2 ω3, having a carbon chain length of 18 carbon atoms with 3 and 2 double bonds, respectively, starting at the 3rd carbon atom from the ω end) are essential lipids, the mammalians cannot synthesize them but have to consume by food. The omega-6 fatty acids are found in vegetable oils and nuts, while omega-3

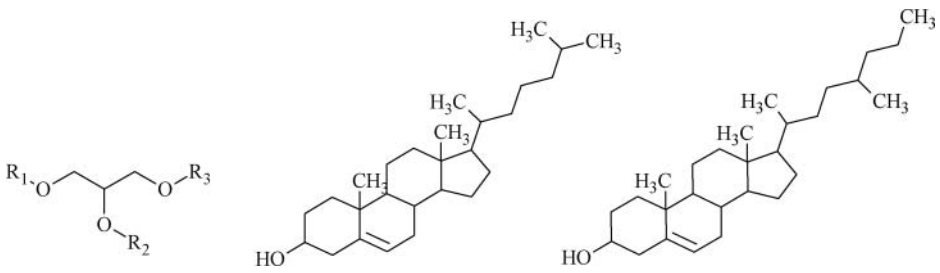

Figure 2 Structure of triglycerides (R_1, R_2 and R_3 are fatty acids), cholesterol and β-sitosterol.

Table 2 Food categories and use levels approved for the CDs

Food category	Maximum use level, percent (w/w)		
	αCD (FDA, 2004)	βCD (FDA, 2001)	γCD (FDA, 2000)
Breads, rolls, cakes, baking mixes, refrigerated dough	5	2	1
Brownies and bars	7		
Crackers (sweet and nonsweet)	10	0.5	1
Diet soft drinks, beverage mixes, fruit juices, instant coffees and teas, coffee whiteners (dry), formula diets, meal replacements, and nutritional supplements	1	1	1
Vegetable juices, soy milk and non-soy (imitation) milk	2		2
Ready-to-eat breakfast cereals	2 to 9	2	1
Instant rice, pasta, and noodles (prepared)	2		
Condiments	3		
Reduced fat spreads	20		20
Dressings and mayonnaise	5		
Yogurt, milk beverage mixes, and frozen dairy desserts	2.5		
Pudding mixes (dry)	1	1	
Snack foods	1		1
Canned and dry soups (prepared)	2	0.2	
Hard candy	15	2	1
Chewing gum	10	2	1
Cheese		1	3
Spices and seasonings			1
Carrier for vitamins as dietary supplement			90
Carrier for polyunsaturated fatty acids (PUFA) as dietary supplement			80
Fat-based fillings, Fruit-based fillings			5/3
Dairy desserts			3
Baked goods			2

fatty acids are also in fatty fish. The main constituents of the fish oil are the eicosapentaenoic acid (EPA, C20:5 ω3) and docosahexaenoic acid (DHA, C22:6 ω3), both especially important for human health due to their benign effects. They reduce the risk of heart disease by decreasing the level of blood triglycerides, improve mental conditions, are beneficial for macular degeneration, cystic fibrosis, diabetes, enhance the response to chemotherapy, etc. (Chen et al., 2014). Both are usually administered together in the form of acylglycerols in fish oil.

Trans fats are triacylglycerols containing the trans-isomers (or E-isomers) of unsaturated fatty acids (Fig. 3).

Trans fats are formed also naturally (in ruminants and in some vegetables and fruits, such as pomegranate) or during the processing of polyunsaturated fatty acids (PUFAs) in food production, for example, hydrogenation of vegetable oils. The latter trans-fats are blamed to increase the incidence of coronary heart disease due to changing unfavorably the balance between HDL and LDL (high density and low density lipoprotein) cholesterol in blood (Willett et al., 1993).

Cholesterol is an important constituent of the mammalian cell membranes and a starting material for hormone and vitamin D synthesis, but high cholesterol level in the blood can cause atherosclerosis and cardiovascular disease. Cholesterol consumed by food is esterified in our body and is poorly absorbed. The body also compensates for any absorption of additional cholesterol by reducing cholesterol synthesis. For these reasons, cholesterol intake in food has little, if any, effect on total body cholesterol content or concentrations of cholesterol in the blood (Kratz, 2005). Anyhow, there is a big market of the cholesterol-free or reduced cholesterol products.

In a wider context some further organic compounds having long alkyl chains similarly to fatty acids are also classified as lipids: natural fat-soluble colorants such as carotenoids (hydrocarbon carotenoids, hydroxyl carotenoids and carotenoid carboxylic acids) (Fig. 4), curcuminoids and capsaicin (Fig. 5) as well as fat-soluble vitamins (Fig. 6) belong to this group of compounds.

It is a general feature of the lipids that they do not dissolve in water, and the compounds with double bonds in their structure, such as PUFAs, carotenoids and vitamins are highly

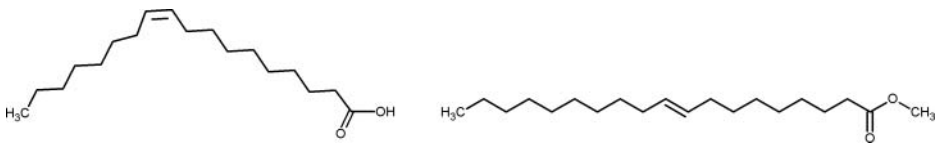

Figure 3 Structure of two monounsaturated fatty acid isomers: oleic acid (*cis* C18:1) and elaidic acid (*trans* C18:1).

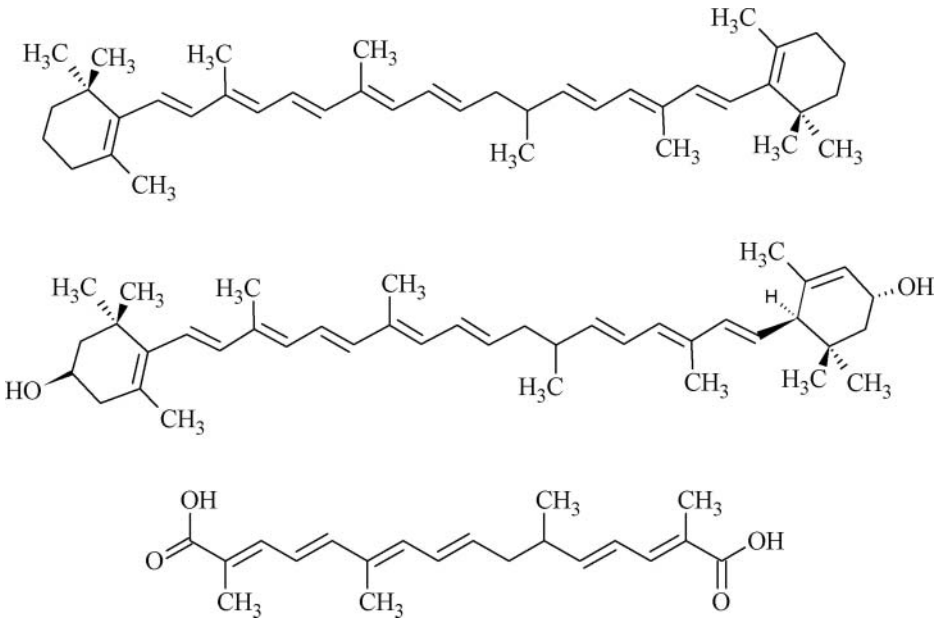

Figure 4 Structure of β-carotene (β, β-carotene), lutein ((3*R*,3′*R*,6′*R*)-β,ε-carotine-3,3′-diol) and crocetine (8,8′-diapocarotine-8,8′-dicarboxylic acid).

sensitive to oxidation. Their solubilization and protection against oxidation can be achieved by molecular encapsulation with CDs (Szejtli, 1982).

CDS TO MOBILIZE AND IMMOBILIZE CHOLESTEROL

Cholesterol forms complexes only with βCD and its derivatives, but there is practically no interaction with α- and γCD because of adequate steric fit into the cavity. The structure of the cholesterol/βCD complex obtained by molecular dynamics optimization can be seen in Fig. 7.

While cholesterol is precipitated with βCD, the complexes with the βCD derivatives are well soluble in water therefore these derivatives can be used for removal and delivery of cholesterol from and into cell cultures. Especially the methylated derivatives have high cholesterol-solubilizing effect (Table 3) (Kiss et al., 2010). The α- and γCD derivatives do not enhance the solubility of cholesterol.

The cholesterol precipitating effect of the parent βCD is utilized in the production of various food products with reduced cholesterol content, the cholesterol-solubilizing effect of the βCD derivatives has not been used in food so far.

Products with Reduced Cholesterol

The cholesterol complex of the underivatized βCD is water-insoluble. This phenomenon has been utilized for the removal of cholesterol from dairy products and eggs, etc., for 20 years (Roderbourg et al., 1990; Smith et al., 1995; Awad et al., 1997). The research is, however, continued especially in the Far East. For instance, treating milk with 0.6% βCD, butter with reduced cholesterol content (by 95%) and no significant change in the fatty acid composition is obtained (Alonso et al., 2010). Treating butter with βCD is another option using the coprecipitation technique, which is more efficient than kneading (Dias et al., 2010). The quality of whipping cream (Shim et al., 2003), Mozzarella cheese (Kwak et al., 2001), Cheddar cheese (Kwak et al., 2002), cream cheese (Kim et al., 2005; Jeon et al., 2011; Jeon et al., 2012), Blue cheese (Kim et al., 2008), Camembert cheese (Bae et al., 2008; Kim et al., 2008a), Feta cheese (Bae et al., 2009), lard (Kim et al., 2007), processed cheese spread (Kim et al., 2009), ghee (Soni, 2010), etc., was not changed significantly when milk with reduced cholesterol (treated with crosslinked βCD) was used for their production, but accelerated ripening was observed (Seon et al., 2009).

The low cholesterol egg yolk obtained by treatment with βCD contained less lipid and protein and more carbohydrate

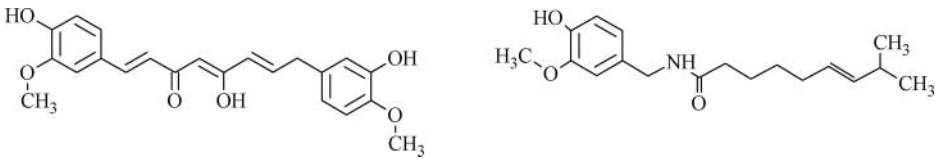

Figure 5 Structure of curcumin (left) and capsaicin (right).

Table 3 Solubility of cholesterol (mg/ml) in 5% aqueous solutions of CD derivatives

	αCD	βCD	γCD
Hydroxypropyl (HP)*	<0.01	0.3	<0.01
Random methyl (RAME)**	<0.01	3.6	<0.01
Dimethyl (DIME)	<0.01	4.2	<0.01
Trimethyl (TRIME)	<0.01	3.8	<0.01

*Number of substituents/CD is in the range of 3–6.
**Number of substituents/CD is in the range of 10–15.

and ash than the original egg yolk. Both free and esterified cholesterol in cholesterol-reduced egg yolk were reduced by about 90%. Triglycerides became the major lipid class in the product, which contained more oleic acid and less linoleic acid than the control. The low cholesterol egg yolk was less yellow than the original egg, because βCD also removed a considerable fraction of β-carotene (Awad et al., 1997). More economic technologies were worked out by using βCD immobilized in chitosan beads or crosslinked βCD (Chiu et al., 2004; Jung et al., 2005). The cholesterol reduced egg yolk can be used for foods such as mayonnaise (Isono et al., 1993) without causing any toxicity (Rao et al., 2000).

The regeneration of CD from its cholesterol complex is easier when water-insoluble cross-linked βCD (Kim et al., 2004; Jung et al., 2005; Kwak et al., 2007) or immobilized βCD (Kang et al., 2003; Chiu et al., 2004; Kwak et al., 2004) is used as specific sorbent for cholesterol. A recent development is a CD-containing film in the food packaging, which can scavenge the undesirable components such as cholesterol from milk (Lopez-de-Dicastillo, 2011, 2011a).

A Korean Patent claims that hens fed with βCD laid eggs with reduced cholesterol (Kang et al., 2004). Although the feed intake and egg production decreased with a diet of enhanced βCD content, the cholesterol content of egg yolks was significantly decreased by 0.7–4.2 mg in eggs from hens maintained on 2–8% βCD supplemented feed (Park et al., 2005).

Similarly to cholesterol removal, the residual phospholipids causing off-flavour can be removed from soy protein isolate with βCD (Akshay and Srinivasan, 2011).

Products with Enhanced Phytosterols

Phytosterols and their derivatives have been known for many years for their cholesterol-lowering properties and thus

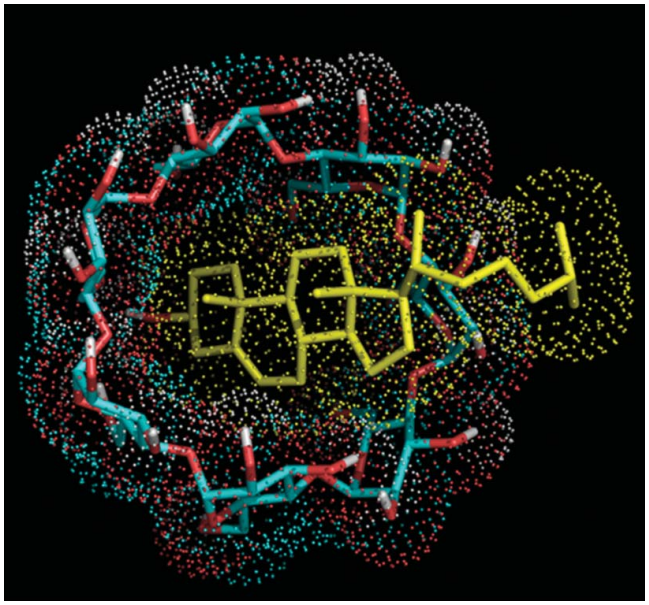

Figure 7 Molecular model of cholesterol/βCD complex.

preventing cardiovascular diseases. Phytosterols reduce cholesterol levels by competing with cholesterol absorption in the gut. The mechanism is based on the inhibition of 27-hydroxycholesterol generation, the self-priming component of cholesterol absorption (sitosterol solubilized by CD complexation was used for this study) (Brauner et al., 2012). Phytosterols (β-sitosterol and campesterol) protect from atherosclerosis by reducing the prostaglandin release from macrophages (Awad et al., 2004). Phytosterols have anticancer effect, too, as it was shown in experiments using sitosterol solubilized by HPβCD (Awad et al., 1996).

These compounds are insoluble in water and poorly soluble in fats and oils, therefore CD complexation is one of the most feasible ways to include them into foods. The most commonly occurring phytosterols in the human diet, β-sitosterol, campesterol and stigmasterol form complexes with β- and γCDs. In model experiments, βCDs were proved to improve the absorption of plant sterols through biological membranes (Castelli et al., 2006).

Various phytosterol complexes to enhance the nutraceutical value of food were patented (Stewart et al., 1999) and stable solid dispersions containing phytosterols and CDs easy to disperse in beverages, such as milk and orange juice have been disclosed (Schwarzer et al., 2011). Phytosterols of corn germ oil were stabilized by complexation (Wang et al., 2012). In

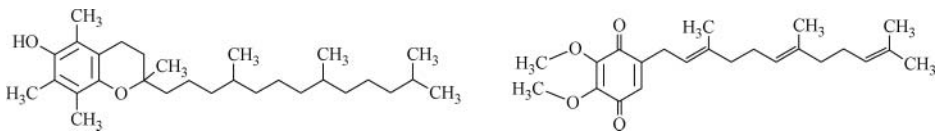

Figure 6 Structure of Vitamin E (α-tocopherol) and Q10 (ubiquinone).

addition to phytosterol and saponine complexes, L-arabinose is also a constituent of the food supplement for reducing cholesterol, treatment of obesity and prevention of diabetes (Ono and Yamamoto, 2006). Other patents describe products with phytosterols, phytosterol esters, γ-oryzanol, isoflavones, vitamin D, vitamin E, and vitamin K stabilized by γCD (Hashimoto and Han, 2010), plant sterols, PUFAs, carotenoids and other antioxidants encapsulated by CDs (Mazed and Mazed, 2011). The complexation decreases the bitter taste, as well. βCD is used to improve the taste in chocolates containing nutraceuticals, such as phytosterols, vitamins, flavonoids, PUFAs, etc. (McKee and Karwic, 2009). Various plant extracts containing also phytosterols in addition to other components are formulated by using phytosterol esters and CDs (Hashimoto et al., 2010). The health promoting effect of activated *Lactobacillus plantarum* is enhanced by phytosterols and CDs (Yu et al., 2011).

SOLUBILIZATION AND STABILIZATION OF FATTY ACIDS AND ACYLGLYCEROLS

Solubilization of Saturated and Unsaturated Fatty Acids

The complexation of fatty acids and their esters has been reviewed up to 1996 (Fenyvesi et al., 1996).

The underivatized (parent) CDs form water-insoluble complexes with the fatty acids as βCD with cholesterol, while the derivatives form soluble complexes. About 6 CH_2 units of the alkyl chain of fatty acids are covered by one CD molecule resulting, for instance, in 1:3 fatty acid/CD stoichiometry for the stearic acid (7–9% fatty acid content in the complex) (Schlenk and Sand, 1961). Others say that the C18:2 and C20:5 form complexes with 1–2 and 3–4 CDs, respectively, independently of the cavity size (Ishiguro et al., 1995).

To solubilize the fatty acids the well soluble CD derivatives, such as hydroxypropyl α-, β- and γCD (HPαCD, HPβCD, HPγCD) and random methylated α-, β- and γCD (RAMEα, RAMEβ, RAMEγ) can be used. The methylated derivatives (both RAMEβ and DIMEβ) are better solubilizers than HPβCD for fatty acids independently of the degree of unsaturation (Szente et al., 1993).

Figure 8 shows how the cavity size (α-, β- or γCD) affect the solubilizing capacity of the hydroxypropyl derivatives (Bálint et al., 2012). In addition to the dimensions of the CD ring the solubilizing effect depends also on the chain length and the degree of unsaturation of the fatty acid. By increasing chain length of the saturated fatty acids the solubilizing effect is decreased. In the case of HPαCD the solubilizing effect is decreased with increasing number of double bonds, while for HPβCD the highest solubility was obtained for α-linoleic acid (C18:3) and eicosapentaenoic acid (C20:5). HPαCD is better solubilizer than HPβCD for the saturated fatty acids, while HPβCD performs better for the polyunsaturated fatty acids (PUFAs) (Bálint et al., 2012). HPγCD hardly has any solubilizing effect. These results are in agreement with those of Meier et al. (2001), who found that βCD forms more stable complexes with fatty acids compared to γCD, but the anionic form of capric acid (C10:0) was preferred to that of caprylic acid (C8:0).

The solubility of ω3 PUFAs most abundant in fish oil: eicosapentaenoic acid (EPA, C20:5 ω3) and docosahexaenoic acid (DHA, C22:6 ω3) is also highly enhanced with HPβCD. In the control (without CD) experiment dissolved lipids could not be detected not only because of the insolubility of these fatty acids in water but also because they are decomposed during the solubilization experiment (1 day equilibration) without the protection of the CDs (Bálint et al., 2012).

Complexation of branched chain fatty acids, such as 4-methyloctanoic acid explains the reduced off-flavor and odor of goat milk after treatment by βCD (Luiz and Fett, 2000; Young et al., 2012). The sensory value of goat milk and yoghurt was remarkably improved by adding βCD. Displacement experiments with phenolphthalein showed that there is

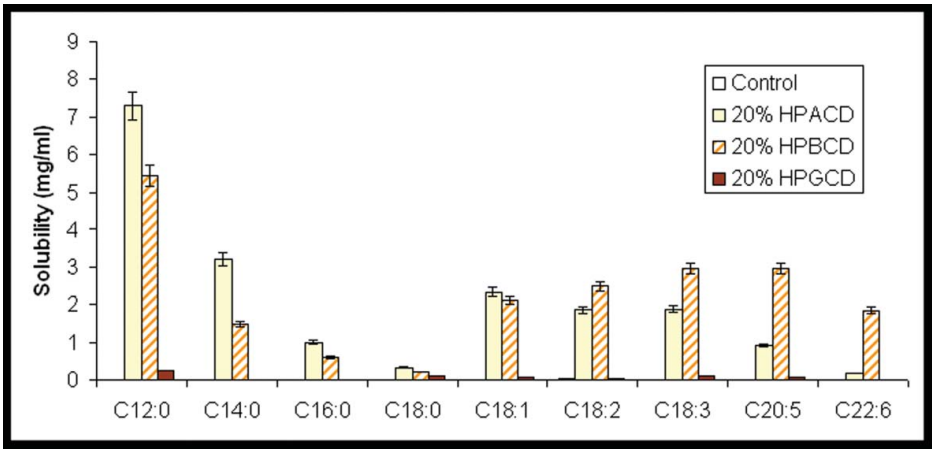

Figure 8 Solubility of water-insoluble fatty acids in 20% aqueous solutions of hydroxypropyl α-, β- and γCD measured by HPLC (Bálint et al., 2012).

no preferential binding of straight-chain fatty acids as it was supposed earlier.

The pasting properties of rice starch were improved by adding fatty acids and βCD (Liang et al., 2002).

α- and βCD-solubilized medium-chain fatty acids used as feed additives for ruminants changed significantly the food metabolism, reduced the hydrogen and methane production (Ajisaka et al., 2002).

Stabilization of PUFAs as Nutritional Supplements

The conjugated double bonds in PUFAs are sensitive to autooxidation. As a result of oxidative processes, many detrimental substances are produced that might be harmful on health. Some of them are responsible for the rancid, undesirable smell and taste of food products. A significant improvement of the stability of linoleic acid (C18:2) and linolenic acid (C18:3) was achieved in the form of a water-insoluble complex with βCD compared to that of the nonencapsulated acids (Cao et al., 2011; Gorska et al., 2011). Enhanced thermal and acid stability of linoleic acid complexed by amylose/βCD mixture has been recently published (Yang et al., 2010).

The rapid oxidation of eicosapentaenoic acid ethyl ester was reduced by complexation with γCD, while no sign of decomposition was observed within 30 days when complexed with α- or βCD (Yoshii et al., 1997). The degree of autooxidation depends on the molar ratio of the CD to the fatty acid resulting in practically complete protection at 3:1 CD: fatty acid ratio (Ishiguro et al., 1995).

Linoleic acid (C18:2, ω6) and arachidonic acid (C20:4, ω6) complexed with βCD were protected against enzymatic oxidation by lipoxygenase (Lopez-Nicolas et al., 1997).

βCD was used as sorbent and stabilizer of linolenic acid extracted from flaxseed oil (Lin et al., 2012) or other seeds (Zheng et al., 2012; Wang et al., 2012a). Imprinted polymers prepared by crosslinking linolenic acid/βCD complex and subsequent removal of linolenic acid showed enhanced binding of this specific fatty acid (Wang et al., 2012b).

The soluble fatty acid complexes prepared with RAMEβ are well protected as it was proved in a 6-month stability study showing that even the α-linolenic and eicosapentaenoic acids (C18:3 and C20:5) with 3 and 5 conjugated double bonds preserved >80% and >70% of their original content for 6 months, respectively (Fig. 9) (Szente et al., 1993). These unsaturated fatty acids decompose in a few hours if uncomplexed.

Advantages of CD-stabilized/solubilized PUFAs as nutraceuticals:

- Exact dosing can be realized.
- No need of further antioxidants, because of the stabilizing effect.
- Reduced rancid/fishy smell.

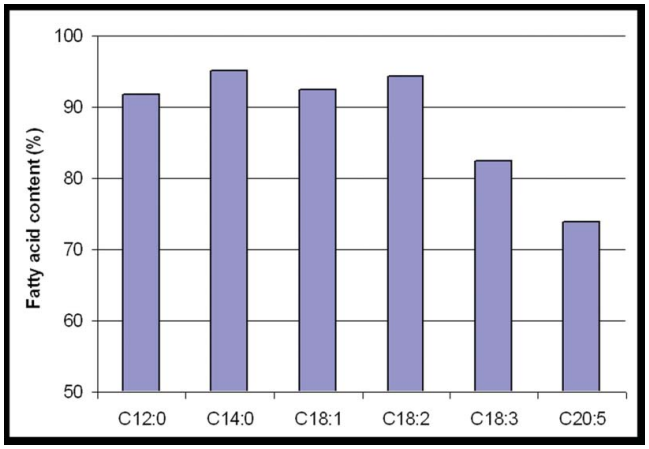

Figure 9 Residual fatty acid content in RAMEβ complexes stored for 6 months at 60°C in open glass vials under normal humidity (Szente et al., 1993).

- As nutraceuticals, the use of the proper highly soluble CD derivatives would result in improved absorption of fatty acids (as it is usual in the case of poorly soluble drugs complexed with highly soluble CD derivatives).

COMPLEXATION OF TRIACYLGLYCEROLS

CDs form complexes with the triglycerides at the oil/water interface with a molar ratio depending on the chain length of the fatty acids (Shimada et al., 1992). The association constants (the affinity to form complexes) decrease in the order of:

Fatty acid > monoglyceride > diglyceride > triglyceride.

When mixing CDs with vegetable oils in a proper ratio a multiple emulsion is formed (Hamoudi et al., 2009): oily microdomains dispersed in a crystalline matrix of αCD can result in beads (Fig. 10). The triglyceride/CD complexes stabilize the oil/water interfaces both at the surface of the beads and in the inner surface of the tiny aqueous droplets within the beads (Trichard et al., 2008).

According to Canadian patents, αCD is used as an oil thickening ingredient (Plank and Staeger, 2006). By avoiding hydrogenation to solidify the oil into a solid fat at room temperature, finished popcorn products desirably low in trans-fatty acid content were provided (Plank et al., 2006; Teoh et al., 2006).

The rapid autocatalytic oxidation of oils can be prevented by complexation. Some examples for seed oils rich in PUFAs and stabilized by CD complexation are listed in Table 4. These stabilized plant oils are used as nutraceuticals or feed additives.

Fish oil, such as seal blubber oil is protected from oxidation by encapsulation with βCD (Wanasundara and Shahidi, 1995). At a mixing ratio of 1:2 (βCD: fish oil, w:w) a product with

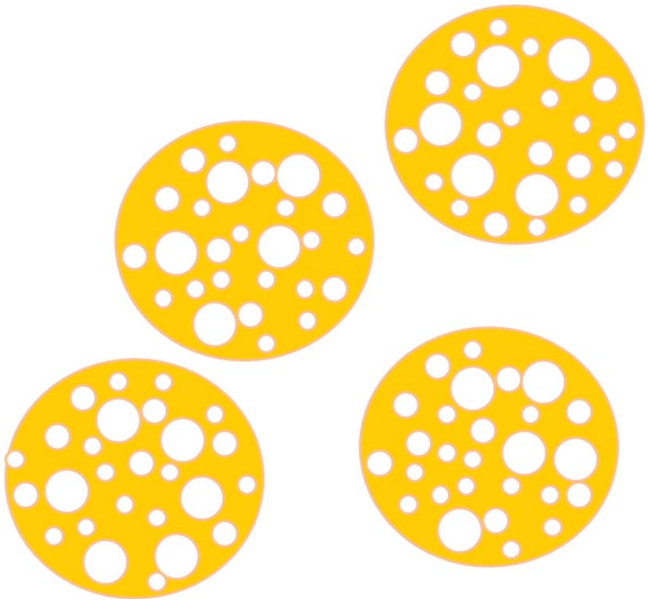

Figure 10 Scheme on the multiple emulsions formed between vegetable oil (yellow) and CD solution (white) (Trichard et al., 2008).

optimal encapsulation efficiency, loading, and release was obtained (Choi et al., 2010). The freeze-dried complexes retained 97% of fish oil within the particles during 3 days at various relative humidity conditions.

The fish oil is protected from oxidation both by α- and βCD (Yoshii et al., 1996). The peroxide value of the non-complexed oil reached 160 meq/g after 2-week storage at 50°C, RH 75%, while remained around 20 and 70 meq/g when complexed with α- and βCD, respectively.

The oxidative stability of docosahexaenoic acid oil (containing 27% DHA in mixed triglyceride form) was enhanced by α- and γCD while βCD had no effect (Mikuni et al., 1999). In this experiment, however, the CDs were used at different ratios what can explain the unexpected results: the inefficiency of βCD can be due to the low (0.5) molar ratio to DHA. The αCD was more effective than γCD although it was used at lower molar ratio compared to γCD (1.2 vs. 2.5).

The αCD inclusion complex of DHA oil containing tridocosahexaenoin (tridocosahexaenoic acid glycerol ether, 45%) exhibited marked resistance against autooxidation for a long period, during storage at 4°C, and seemed to be effective for fortifying fish meal products (Yoshii et al., 1997).

Wacker Chemie has marketed a triglyceride/γCD formulation rich in PUFAs under OmegaDry® brand name (Wacker Chemie, 2013a). In a placebo-controlled double-blind study in 2007, ω3 PUFA/γCD complex (OmegaDry®, 660 mg EPA + 280 mg DHA/day) lowered the blood triglyceride levels in normal (35) and slightly hypertriglyceridemic (7) subjects while the cholesterol level remained unchanged. The smell and aftertaste of fish oil was slightly reduced by complexation with γCD (Kobayashi et al., 2007). Reduced odor intensity was observed also when the fish oil/γCD complex was encapsulated in whey protein (Na et al., 2011).

Powdered milk with CD-stabilized fat for long term storage is prepared according to the method of Terao et al. (2006a).

NUTRACEUTICAL UTILITY OF ALPHA- AND GAMMA-CDS

Fate of CDs in the GI Tract

αCD, similarly to βCD, is not digested in the gastrointestinal (GI) tract but is fermented by the intestinal microflora. In germ-free rats, αCD is almost completely excreted in the feces (Van Ommen et al., 2004). Orally administered αCD is absorbed intact at very low levels (approximately 1%) from the small intestine and then excreted rapidly in the urine. The majority of the absorption takes place after metabolism by the microflora in the cecum and colon (Van Ommen et al., 2004). The microbial degradation results in linear malto-oligosaccharides, which are then further hydrolyzed and fermented to absorbable and metabolisable short-chain fatty acids. Overall the metabolic fate of ingested αCD is similar to that of other nondigestible but fermentable carbohydrates such as resistant starch or inulin.

Table 4 Plant oils stabilized by CDs

Plant oil	Components stabilized	CD	References
Canola oil	Oleic, linoleic, linolenic acids, carotenoids, tocopherols	αCD	Basu and Del Vecchio (2001)
Cranberry seed oil	Oleic, linoleic and linolenic acid, tocopherols, tocotrienols, phytosterols and lecithin	γCD	Wacker Fine Chemicals (2005)
Evening primerose oil	PUFA	α-, β-and γCD	Regiert et al. (1996) and Park et al. (2007)
Nutmeg oil	PUFA	βCD	Liu et al. (2012a)
Perilla oil	α-linolenic acid	βCD	Wang and Wang (2010) and Yoo et al. (2010)
Prickly ash seed oil	PUFA (βCD: PUFA 6:1)	βCD	Tang and Xu (2009)
Olive oil	PUFA	βCD	Wang et al. (2007)
Sesame oil	Linoleic acid, oleic acid, sesamol, vitamin E	βCD	Sawano et al. (2010)
Tartary buckwheat bran oil	Oleic, linoleic and linolenic acid and eicosenoic acid (C20:1)	βCD	Ma (2010)
Walnut and flaxseed oil	PUFA, tocopherol	HPβCD	Wang and Wang (2010a)

Since αCD is essentially not digested in the small intestine, it is by definition a soluble, fermentable dietary fiber. Dietary fiber means carbohydrate polymers, which are not hydrolyzed by the endogenous enzymes in the small intestine of humans (Codex Alimentarius Commission, 2009).

αCD is a prebiotic. This term is used to describe nondigestible (non-completely digestible) carbohydrates, which are fermented by the gut flora and support the growth and activity of bacteria in the large intestine. *Lactobacillus casei* can multiply with αCD as carbon source without glucose. Taking 3 g αCD/day the concentration of bifidobacteria in the feces is enhanced from 10 to 35% (CycloChem, 2013).

The absorption of intact γCD is even lower than that of αCD: only 0.02% can be detected in the urine after oral administration (De Bie et al., 1998). On the contrary to α- and βCD it is readily digested to glucose by the luminal and/or epithelial enzymes of the GI tract. The hydrolysis by α-amylases is decreased, however, when the γCD cavity is not empty (when γCD is used as a carrier for drugs or other guests) (Lumholdt et al., 2012). The enzymatic digestibility by human saliva α-amylase was proved showing that the degradation starts already in the mouth (Harangi et al., 2012). γCD is metabolized and absorbed in the small intestine of dogs (Spears et al., 2005) and of humans (Koutsou et al., 1999), but subsequently results in a reduced postprandial glycemic response (reduced serum glucose level after meal) and insulin secretion compared to maltodextrin (Asp et al., 2005, 2006). A human study with 35 subjects consuming 50 g γCD or maltodextrin showed that consumption of γCD could lower postprandial glycemia and insulinemia compared to maltodextrin, without resulting in significant carbohydrate malabsorption. The plasma glucose AUC from baseline to 120 minutes was 55% of that after maltodextrin. The relative insulinemic response of γCD compared to maltodextrin from baseline to 120 minutes was 51% (Lai et al., 2005).

Although γCD is more readily digested by salivary and pancreatic amylases than α- and βCD, the metabolism is not complete in the upper region of the GI tract. The indigested portions are available for fermentation in the bowel altering the bacterial population: enhancing the number of bifidobacteria and lactobacilli resulting in concomitant decrease of pathogens such as *Clostridium perfringens* (Spears et al., 2005a). Based on these favorable changes in the gut microflora γCD is also considered as prebiotic.

Effect on Starch Digestion

It has been known for long that α- and βCDs are not only resistant to usual starch degrading enzymes but inhibit the hydrolysis of amylose by binding to the active sites of enzymes (Szejtli, 1982). Some recent studies showed that degradation of starch by barley α-amylase, bacterial amylases, porcine pancreatic amylases and intestinal amylases from fishes is inhibited by CDs (Fukuda et al., 1992; Koukiekolo et al., 2001; Moreau et al., 2001; Mitsuiki et al., 2005; Nielsen et al., 2012).

CDs interact not only with the enzymes but also with starch as evidenced by a reduced thermal stability of amylose in the amylose-βCD complex and a decrease of extractable βCD from 60 to 51% after their complexation suggesting that βCD is likely sandwiched between the helical amylose chains (Yang et al., 2010). In cereal starches, the amylose–lipid complex within the starch granules is disrupted by adding βCD, which forms complex with starch lipids, affecting a range of functional properties of starch (early swelling and decreased pasting temperature) (Gunaratne and Corke, 2007).

Several studies showed that CDs reduce the digestion of starch in the mammalian organism. They reduce the glycemic index of food.

Since the chronic and excessive consumption of high glycemic food is associated with an increased risk of diabetes, hyperlipemia, hypertension and atherosclerosis, food with a low glycemic index is to be favored over food with a high glycemic index. People with a pre-diabetic condition or patients with clinically manifest diabetes are advised particularly to consume low glycemic food.

The mechanism by which a high glycemic index diet increases the risk to develop diseases likely begins with increased postprandial glycemia, eventually leading to hyperinsulinemia and insulin resistance. Incorporation of low glycemic index foods into the diet may decrease the peak postprandial glucose concentration as well as insulin secretion (Venn and Green, 2007).

The low glycemic response to many carbohydrates is due to the presence of high amounts of dietary fiber or resistance to digestion in the small intestine. The carbohydrate which is slowly, but still fully digested in the small intestine could have important applications in the dietary management of diabetes (avoidance of night-time hypoglycemia), sports nutrition (sustained release of glucose for endurance events), and the management of glycogen storage disorders (reduction in fasting hypoglycemia).

Suzuki (1983) reported a study with a mixture of CDs containing 30, 15 and 5% of α-, β- and γCD in addition to 50% linear dextrins applied in 10–40% in the meal of rats fed for 1 month. While the body weight for the 10% group did not differ from that of the control, the 20, 30 and 40% groups showed reduced weight gain in a dose dependent manner. It proved that CDs hinder the digestion of carbohydrates and can be applied for body weight control. Reduced body fat deposition, plasma glucose, serum and liver triglyceride levels were noted after 110 days feeding compared to control, especially at diet containing higher CD content (Suzuki and Sato, 1985).

Adding as low amount as 2% βCD to potato starch, significant decrease in the plasma glucose and insulin levels in humans (65% and 25%, respectively) was measured compared to the control group getting starch only (Raben et al., 1997) showing that the starch digestion was slowed down. Significantly enhanced satiety feeling was also observed.

Slowly digestible starch was prepared by adding 3% βCD, maltosyl βCD or hydroxypropyl βCD to rice starch (Zan et al., 2013). In enzymatic digestion experiments βCD-modified starch was degraded the slowest and gave the lowest glycemic index.

In a human study 10 healthy subjects consumed boiled white rice containing 50 g of digestible carbohydrate to which 0 (control), 2, 5 or 10 g of αCD was added (Buckley et al., 2006). αCD was found to reduce the glycemic response in a dose-dependent manner (50% lower serum glucose levels were measured after consuming 10 g αCD). Higher doses of αCD resulted in greater satiety, but an increased incidence of minor GI complaints (stomach ache, nausea, bloating). In another study, a sucrose diet supplemented by αCD was given for healthy young humans to explore the role of inhibition of amylases by αCD. Sucrose is hydrolyzed by the enzymes in the intestine and not by pancreatic amylases (Gentilcore et al., 2011). The decreased glucose and insulin levels compared to control proved the hypothesis that αCD decreases the digestion of carbohydrates not only via inhibition of pancreatic amylases but also by slowing down the gastric emptying.

Hansen et al., reported that αCD reduced slightly the amylolytic hydrolysis of γCD and linear dextrins (2012).

The glycemia-lowering effect of αCD was patented by Wacker Chemie (Schmid et al., 2004). A double blind, randomized, crossover study with 10 healthy subjects consuming white bread containing 50 g of digestible carbohydrate (in the form of fresh white bread) and plain water with or without 10 g of αCD is described in the patent. The meal consumed together with αCD showed a reduced postprandial response regarding both glucose and insulin levels compared to the control. Calculations of the glycemic and insulinemic index showed a reduction of 57 and 55%, respectively (JECFA, 2006).

In a recently published scientific opinion of European Food Safety Administration (EFSA) a cause and effect relationship had been established between the consumption of αCD with starch-containing meals and reduction of postprandial glycemic responses that is the elevation of blood glucose concentrations after consumption of a food and/or meal. The health claim: "Consumption of α-cyclodextrin contributes to the reduction of the blood glucose rise after starch-containing meals" was accepted. The EFSA Panel on Dietetic Products, Nutrition and Allergies considered that in order to obtain the claimed effect, at least 5 g of αCD per 50 g of starch should be consumed (EFSA, 2012).

Similar effect of γCD was also patented by Abott Laboratories (Lai et al., 2005). γCD is rapidly metabolized and absorbed in the small intestine, but subsequently results in a surprisingly blunted postprandial glycemic response and reduced insulin secretion. γCD can be included in various foods and beverages used for reducing the appetite and control the body weight. However, we have not found data on how γCD, this slowly but completely digested carbohydrate changes the glycemic index of food.

Effect on Fat Digestion: Fat Binding, Cholesterol Lowering Mechanisms

Lipid bioavailability can be changed via complexation. In some cases, for example, in lipid absorption disorders (cystic fibrosis or pancreatitis) the enhancement of lipid bioavailability is an advantage (Fave et al., 2004). It is also important to increase the bioavailability of nutraceutical lipids, such as vitamins A, D, E, and K, ω-3 fatty acids, phytosterols, carotenoids. The lipid-droplet size exhibits a major effect on lipase activity during lipid digestion (Fave et al., 2004).

In other cases such as in obese people and those with the risk of cardiovascular diseases, the decrease of lipid bioavailability is desirable. The high-fat-diet-induced obesity triggers the metabolic syndrome, enhanced weight of liver and pancreas, malfunction of α- and β-cells, insulin resistance. Exposure to a chronic lipid challenge, such as a high fat diet results in changed composition and rigidity of cell membranes, and decrease in autophagic activity affecting not only the intracellular lipid metabolism but also the proteolytic pathway (Koga et al., 2010).

Knowing the high affinity of α- and βCDs to fatty acids and βCD to cholesterol, the decreased absorption of these lipids via consumption of α- and βCD together with high-fat or high-cholesterol diet was expected.

Férézou et al. (1997) feeding growing pigs with cholesterol-enriched diet containing 0%, 5% or 10% βCD for 4 weeks came to the conclusion that addition of βCD prevented the elevation of plasma cholesterol due to dietary cholesterol excess. Moreover, βCD produced a dose-dependent effect in reducing liver cholesterol storage, stimulating hepatic cholesterogenesis, increasing the proportion of primary bile acids in bile and in feces, and the fecal loss of neutral sterols and bile acids. Pigs receiving 10% βCD showed elevated hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase and cholesterol 7α-hydroxylase hepatic activities (5 times). Owing to the property of βCD to bind cholesterol and bile acids in vitro, these results suggest that it accelerates body cholesterol turnover by reducing cholesterol absorption, increasing cholesterol and bile acid synthesis, and altering the action of the intestinal microflora.

Pigs growing on βCD-containing diet produce meat of reduced cholesterol content (26.0%, 27.5%, 17.9% and 18.3%, respectively, decrease compared to control) in back fat, loin, belly and ham portions of swine especially in the 5% βCD-fed group (Park and Jang, 2007).

Addition of βCD to a cholesterol-rich diet of rats resulted in reduced plasma triglyceride level, enhanced bile acid synthesis and excretion, and normalized biliary lipid secretion, but produced a marked hepatotoxic effect (Garcia-Mediavilla et al., 2003). The hypocholesterolemic and hypotriglyceridemic effects of βCD in rats with low-fat diet were also proved (Levrat et al., 1993). The effect was more pronounced on triglyceride than on cholesterol levels (Favier et al., 1995). Similar results were obtained when rats on normal, high-fat and high-

cholesterol diet were fed with βCD (Park, 2003), so the impact on the plasma lipids seems to be independent of the diet. On the other hand, a very important side effect was also observed, which questioned the use of βCD as nutraceutical: βCD can induce cholesterol precipitation in gall causing gallstone (Juste et al., 1997).

The effect of αCD is similar to that of the βCD (significantly reduced weight gain, plasma triglyceride levels (−30%) and total cholesterol (−9%) in rats fed with a high-fat diet relative to rats fed with the high-fat control) (Artiss et al., 2005) except the hepatotoxicity. The bioavailability of fats in fat-containing food is reduced by αCD according to the patent of Artiss and Jen (2005).

The digestion of food lipid was simulated by adding water and αCD to French fries (Hansen et al., 2012). After centrifugation, a white emulsion was seen on the top containing the lipids. In preliminary digestion experiments with porcine pancreatic lipase, the free fatty acids were reduced by 95% compared to the control indicating that αCD was able to prevent the degradation of most of the lipids. The authors hypothesize that the lipid droplets are covered by αCD and the lipolysis of these stabilized droplets is hindered.

αCD, when given orally to rats being on normal-fat, low-fat, or high-fat diet, increased the fecal saturated fat excretion proving that fat passed through the gut without being metabolized (Artiss et al., 2005). Reduced blood total cholesterol and triglyceride levels as well as leptine levels (showing enhanced sensitivity to insulin) were observed in obese hypertriglyceridemic rats with type 2 diabetes mellitus. When given orally to low-density lipoprotein receptor knockout mice for 14 weeks there was no difference in body weight, but significant decreases were observed in plasma cholesterol (15.3%), free cholesterol (20%), cholesterol esters (14%), and phospholipids (17.5%) levels compared to control mice (Wagner et al., 2008). Furthermore, αCD improved the blood fatty acid profile, reducing the saturated fatty acids (4.5%) and trans-isomers (11%) while increasing (2.5%) unsaturated fatty acids. It has also been reported that αCD preferentially binds and reduces the absorption of saturated fatty acids and trans-fats from the diet (Gallaher et al., 2007). Because saturated fatty acids promote the hepatic synthesis of cholesterol and reduce its clearance, and reduction of saturated fat intake lowers blood cholesterol levels, the ability of αCD to lower plasma cholesterol may be related to its effect on saturated fatty acid absorption (Wagner et al., 2008). Other authors explain the suppression of serum cholesterol levels by α- and βCDs by the increasing acetate and propionate productions in the cecum (Kaewprasert et al., 2001).

There are hardly any data on the effect of γCD on lipid digestion. Adding 30% γCD to the diet of dogs, the digestibility of nutrients including proteins and fats was not influenced (Spears et al., 2005).

Based on these results, αCD was selected as dietary fiber for marketing in the US and Canada under the trade name of FBCx (Jen and Artiss, 2004) and in Australia under the trade name Calorees (SFI, 2013). According to the manufacturers by ingesting αCD in an appropriate amount with a fat-containing meal, or shortly before or after ingesting a fat-containing meal, CD may complex the ingested fat and inhibit its absorption by the body. In another patent addition of αCD to the food has beneficial hypocholesterolemic activity through increased bile acid and lipid binding activity (Plank and Lewandowski, 2004).

Body Weight Control

According to early Japanese studies rats fed diets supplemented with a mixture of α-, β- and γCD showed smaller weight gain and body fat deposition (Suzuki and Sato, 1985). The body weight of Japanese quail decreased, too with increasing dietary βCD levels, and feed intake was reduced (Murai et al., 1994). The use of βCD in pet foods at a level of 1–15% has been disclosed for the purpose of reducing the body weight of pets (Furuse and Sako, 2000).

A Korean scientist reported similar effects of oral administration of βCD to obese Korean women. After maintaining an antifat diet for 45 days there were significant reductions in body weight by 4 kg, obesity index by 5%, body mass index by 1 kg/m^2 and body fat mass by 7%. There were also significant reductions in arm, waist, hip and thigh circumferences. Furthermore, this antifat diet significantly reduced blood triglyceride, total cholesterol and LDL-cholesterol levels (Park, 2004). In spite of these promising results βCD is not recommended because of the possible gallstone formation. It accelerates body cholesterol turnover by reducing cholesterol absorption, and increasing cholesterol and bile acid synthesis (Férézou et al., 1997; Juste et al., 1997).

Body weight can be controlled by using empty αCD as dietary fiber without the risk of any damage in the liver.

According to the producers of FBCx tablets the recommended dose, six grams of αCD per day would bind and eliminate 54 g of dietary fat, which would be sufficient to decrease daily energy absorption by about 500 kilocalories a day corresponding to 4–6 pounds per month without the embarrassing side effects of lipase inhibitors (FBCx, 2013). The mechanism how αCD acts is, however, more complex: it not only can complex triglycerides, and inhibit lipases but can also inhibit the starch-degrading α-amylases, as well. The absorption of both the lipids and carbohydrates is hindered. The human experiments proved the blood lipid controlling effect, but the loss in body weight was not outstanding.

Overweight but not obese no diabetic healthy adults (41) participated in the 2-month, double-blinded, crossover human study to confirm the effects of αCD on both weight management and blood lipid levels (Comerford et al., 2011). In 28 compliant participants (8 males and 20 females), when the active phase was compared to the control phase, it was observed significant decreases in various parameters (Table 5).

In another study 66 obese people (body mass index, BMI > 30 kg/m^2) with type 2 diabetes taking 1 g αCD/meal without

Table 5 Changes in parameters of participants taking 2 g αCD/meal for 2 months (Comerford et al., 2011)

Parameter	Change
Body weight	−0.4 ± 0.2 kg, ($P < 0.05$)
Serum total cholesterol	−5.3% ($P < 0.02$)
Low-density lipoprotein (LDL) cholesterol	−6.7% ($P < 0.05$)
Apolipoprotein B	−5.6% ($P = 0.06$)
Insulin levels	−9.5% ($P = 0.06$)
Blood glucose	No change
Leptin	No change

any dietary restrictions maintained their body weight, while people in the placebo group continued to gain weight (about 2 kg in average) throughout the study (Grunberger et al., 2007). The decrease in the total cholesterol was the most significant in the hypertrigliceridemic group (−8.0 ± 5.4%), while it enhanced in those getting placebo (+6.7 ± 4.7%). The triglyceride level decreased significantly (−6%) compared to the control (+12.3%). Significantly increased blood levels of adiponectin indicated an increase in insulin sensitivity. αCD appeared to preferentially bind saturated over unsaturated dietary fats. In this study, the vitamin D level was also monitored to see if the fat soluble vitamins are also removed. There was no difference in the vitamin D level between the active and control group.

These human studies although very successful in beneficial changes of blood lipid profile gave disappointing results concerning body weight related to the expectations based on animal experiments. The reason is probably that the diet of animals was strictly controlled while the humans continued their dietary habits just supplementing their usual meals with αCD.

There are some antiobesity formulations in which CD is used in combination with some other components:

- A tablet formulation comprising cactus fiber and CD is claimed to prevent and treat obesity or hyperlipidemia (Chong et al., 2011).
- According to a Chinese patent antiobesity compositions containing HPβCD inhibit appetite through the decrease of food intake, reduction of body fat, the weight of liver, and inhibition of the rapid increase of blood glucose induced by the intake of glucose and maltose on an empty stomach (Han et al., 2011).
- Food supplement contains L-arabinose, phytosterols and CD as fat accumulation inhibitor (Ono and Yamamoto, 2006).
- Oleic acid and DHA solubilized with HPβCD when injected to rats resulted in reduced food intake and body weight for 48 h following injections, while no significant changes were observed in the palmitic acid group (Schwinkendorf et al., 2011).
- Starchy foods, such as noodles, bread, containing αCD are recommended for controlling postprandial blood sugar (Terao and Nakata, 2004; Wang et al., 2009).

A further effect of βCD in rats is the antithrombotic activity (2–3 times enhanced bleeding time, 1.5–2 times enhanced whole blood clotting time) is also worth for consideration (Park, 2003).

REDUCING UNWANTED COMPONENTS IN FOOD

Free Fatty Acids and Trans-fat

CD polymer is recommended for the removal of the free fatty acids from frying fat (Conte and Stauffer, 1996) and of animal fat (composed of unsaturated fatty acids and triglicerides) or of animal fat together with cholesterol from frying oil (Seo et al., 2011; Lee, 2012).

The addition of CD to products made from goat's milk could help mask "goaty" flavor caused by fatty acids, making more enjoyable such products without compromising the nutritional advantages (Luiz and Fett, 2000; Young et al., 2012).

CDs, especially αCD can reduce the beany flavor of soy milk (Suratman et al., 2004).

The residual phospholipids and free fatty acids can be removed from soy protein products thus avoiding the off-flavor (Akshay and Srinivasan, 2011).

The elongation of the αCD ring (substitution at both rims) makes it capable for selective complexation of the linear trans-fatty acid esters on the expense of the bending cis-fatty acid esters (Figs. 2 and 11) (Akashi et al., 2011). Having substituents only at one side was not efficient.

Acrylamide

In processed food, the reducing sugars react with asparagine at high temperature via Maillard reaction and form acrylamide, which is a possible carcinogen and has adverse effect on nervous system and fertility. As the CDs are not reducing sugars they do not result in acrylamide formation (Tsutsumiuchi et al., 2005).

Another mechanism is claimed by Plank and Novak (2007) and Plank et al. (2008): CDs bind asparagine moieties of proteins and in this way protect them from the reaction. The use of a combination of αCD and lysine in an extruded oat cereal reduced the acrylamide levels to 333 ppm vs. 1104 ppm in the control.

Allergens

βCD forms complexes with allergenic aroma compounds such as eugenol, isoeugenol, benzyl alcohol and anisyl alcohol (Decock et al., 2006).

Food allergens are naturally occurring proteins in food that cause abnormal immune responses. The key food allergens are peanuts, tree nuts, soy, milk, egg, cereals, seafood. Treating

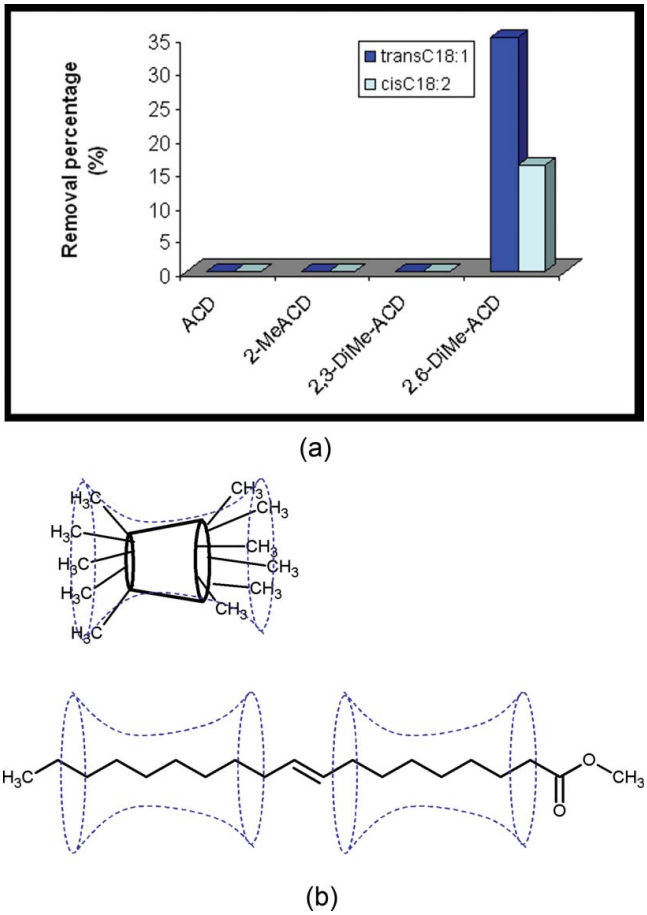

Figure 11 (a) Extraction of methyl elaidate (trans) from methyl oleate (cis) in N-hexane (Akashi et al., 2011). (b) Scheme of complexation of trans C18:1 by the elongated αCD.

soy milk with αCD results in lower content of the allergenic Gm30K protein content (Origasa and Ogawa, 2008).

Mycotoxins

Mycotoxins are the toxic chemical products produced by fungi that readily colonize crops. One mold species may produce many different mycotoxins, and the same mycotoxin may be produced by several species. Aflatoxins are naturally occurring mycotoxins that are produced by many species of Aspergillus. CD complexation enhances the sensitivity of detection of various mycotoxins, such as aflatoxin, ochratoxin, patulin, zearalenone, zearalenol, citrinin. For example, chemosensor based on the enhanced fluorescence upon the effect of CD complexation was developed for detecting mycotoxins such as aflatoxin B1 and ochratoxin A in food (Amadasi et al., 2007). Only a few technological applications of CDs for the removal of mycotoxins can be found in the literature. The treatment of apple juice with 1% βCD led not only to reduced enzymatic browning but also to reduction of aflatoxins and patulin by 70% and 75%, respectively (Essa and Ayesh, 2002). Polyurethane-βCD polymers were synthesized to remove patulin from apple juice (Appell and Jackson, 2010). CD complexation was found suitable to remove ochratoxin from cereals, coffee, beer, wine and cocoa (Verrone et al., 2007).

Bitter Components

Debittering of food and pharmaceutical formulations using CDs has been reviewed by Szejtli and Szente (2005). Debittering of various plant extracts, such as ginkyo (Yi, 2004), bergamot (Lu and Li, 2005), curcuma (Kishi et al., 2012), hop extract (Taniguchi et al., 2012; Wada and Yamamoto, 2012), lotus root extract (Wang et al., 2011), and whey protein hydrolysate (Yang et al., 2012) has been patented by researchers of the Far East.

βCD as bitter blocker may be of value in optimizing the flavor and acceptance of functional food and beverages fortified with phenolic compounds, such as catechin (Gaudette and Pickering, 2012).

NUTRACEUTICALS FORMULATED WITH CDs

Both malnutrition and over-nutrition have the deficient intake and uptake of important nutrients (trace elements, minerals, vitamins, omega-3 fatty acids, antioxidants, etc.). Dietary supplements provide nutrients, such as vitamins, minerals, fibers, fatty acids, amino acids, flavonoides, which are not consumed in sufficient quantities. The antioxidants (flavonoides, carotenoids, vitamins, polyphenols, etc.) scavenging the radicals have anti-inflammatory, anti-cancer, antiviral and anti-aging effects. The food supplements with proved beneficial impact on health are nutraceuticals.

CDs interact with the nutraceuticals enhancing the stability, solubility, reducing bitter taste, etc. (Mazzobre et al., 2010). It is clearly seen from the literature that the easily digestible γCD is an appropriate complex forming candidate for a lot of bio-active compounds, such as antioxidants, vitamins (Terao et al., 2006), carotenoids (Mele et al., 1999; Reuscher et al., 2004), and flavonoids (Koontz et al., 2009). Application of γCD in functional foods can hinder aggregation and improve the uptake of these important compounds therefore the nutrition-originated deficiency diseases can be successfully decreased (Uekaji et al., 2013). Bioavailability of α-lipoic acid stabilized by γCD was enhanced when added to rats orally (CycloChem, 2013a). Even a mineral, iron(II), can be stabilized and its bioavailability improved by γCD (Leite et al., 2003). Debittering of ginseng in energy drinks by γCD improves the sensory properties (Tamamoto et al., 2010). Vitamins Q10 and E as well as fish oil rich in omega-3 fatty acids stabilized by γCD are marketed by Wacker Chemie (2013, 2013a).

And α- and βCD are used for complexation of various vitamins in the B group (Zielenkiewicz et al., 2008), and fatty alcohols (policonasol) (Madhavi and Kagan, 2008). βCD is the most suitable for β-carotene (Polyakov and Kispert, 2009), antioxidants, such as chlorogenic, gallic and caffeic acids (Moreira da Silva, 2010), tea catechins (Folch-Cano et al., 2010), chrysin, apigenin and luteolin (Kim et al., 2008b).

The solubility and stability of some carotenoids, such as astaxanthin was enhanced by βCD (Chen et al., 2007), sulfobutyl ether βCD (Lockwood et al., 2003), HPβCD (Yuan et al., 2008; 2013), methylated βCD (Sueishi et al., 2012), β-carotene by methylated βCD (Szente et al., 1998), and crocetine by α- and βCDs and their derivatives (Zhao et al., 2009). Administering astaxanthin and other bioactive antioxidants such as tocotrienol complexed by γCD to *Caenorhabditis elegans* prolonged the nematode lifespan (Kashima et al., 2012). Bixin is protected from radicals by complexation with αCD (Ortega Lyng et al., 2005) and βCD (Marcolino et al., 2011). The solubility enhancement of some carotenoids with near zero intrinsic aqueous solubility via complexation with RAMEβ was encountered with increased stability of the solid complexes as well as of the solutions (Table 6) (Iványi et al., 2008). For instance, the RAMEβ-encapsulated lutein with 10.1% lutein content measured just after the preparation contained still 5.6% lutein after 1 month at 40°C/75% RH, which is a huge improvement compared to a formulation prepared with lactose of 8.4% starting lutein content reduced to 0.2% after 1 month.

The radical scavenging ability of quercetin solubilized by βCD or its derivatives was enhanced (Jullian et al., 2007). Encapsulation by βCD improved the stability of resveratrol and other polyphenols obtained by ultrasonic extraction of plants, but failed to improve the stability of matricine, the component of chamomile oil extracted by supercritical extraction (Kaiser et al., 2004; Mantegna et al., 2012). Saponins extracted from garlic and stabilized by CD are useful for tumor prevention (Liu et al., 2012b). Anthocyanins from chokeberry (Howard et al., 2013), natural antioxidants from papaya (Mi et al., 2009) are also prepared by CD to be used in health food. Mainly quercetin glucosides, catechin and quercetin and among anthocyanins, malvidin were extracted from *Hypericum perforatum* (St John's wort) and complexed by βCD to obtain flavonoids-rich food supplement (Kalogeropoulos et al., 2010). Capsanthin and capsaicin were extracted from capsicum in high yield by using βCD (Gao et al., 2011). Hesperidin-enriched juices were prepared by solubilizing hesperidin with βCD (Iwamoto and Iida, 2008). Blended carrot–orange juice with enhanced carotenoid content was obtained by addition of γCD during production prior to enzymatic clarification (Karangwa et al., 2012).

Herbal medicines are traditional in China. A huge number of nutraceuticals, health care beverages, pastes, pills containing various herb extracts and CDs, which are useful for improving the health conditions, have been patented.

Propolis extract rich in flavonoids, such as rutin, quercetin, apigenin, kaempferol, acacetin, chrysin, pinocembrine and cinnamic acid derivatives, such as caffeic acid was encapsulated by βCD (Coneac et al., 2008). Manuka honey (the honey from manuka bushes growing in New Zeeland) rich in methylglyoxal, a natural antibiotic, is marketed in CD-stabilized form (Manuka Health, 2013).

Application of curcumin/βCD in cheese and yogurt and bixin/βCD in curd did not alter the initial characteristics of the products, and both products were well accepted based on sensory evaluation (Marcolino et al., 2011). Complexation of these colorants with βCD promoted an intensification of color and increased water solubility; however, stabilization against the degradative effect of light occurred only for bixin.

Addition of βCD to orange juices did not change the vitamin C and carotenoids (lutein and β-cryptoxanthin) content, the color and antioxidant capacity (Navarro et al., 2011).

Table 6 Solubility of carotenoids complexed with RAMEβ and stability of RAMEβ solutions (Iványi et al., 2008)

	Solubility of the RAMEβ complex (mg/ml)	Half life time of the RAMEβ complex* (days)
Capsanthin	7.0	7
Capsorubin	8.0	7
Lutein	1.4	8

*Solutions of 20% RAMEβ complexes were stored in open container at room temperature under daylight.

CDS IN FOOD PACKAGING

An interesting and challenging food-related application of CDs in foods is the CD-containing food packaging materials. Traditional food packages are passive barriers designed to delay the adverse effects of the environment on the food product. Active packaging, however, allows packages to interact with food and the environment and play a dynamic role in food preservation.

Active packaging is primarily designed to extend shelf life, improve safety and/or enhance sensory properties in foods and beverages (Kerry and Butler, 2008; Brody et al., 2010). Recently, there has been an increasing interest in the use of CDs as a tool for inclusion and controlled release of compounds with aiming at

i) having the lowest concentration of preservatives, antimicrobial agents, etc. in the food, but high enough at the surface where the microbial attack is expected,
ii) moisture activated release of these compounds,
iii) capturing the unwanted components such as residual organic volatile contaminants in packaging materials,
iv) improving barrier properties (diffusion rate and transmission rate) of the package materials, thus improving

sensory properties while maintaining food quality and safety (Szejtli and Fenyvesi, 2005).

CD complexes of antibacterial hinokitiol, isothiocyanates, and carvacrol (Hirose and Yamamoto, 2001; Nakagawa and Sakai, 2006; Plackett et al., 2006, 2007; Raouche et al., 2011), antioxidant α-tocopherol, quercetin (Siro et al., 2006; Koontz et al., 2010), ripening agent 1-methylcyclopropene (Hotchkiss et al., 2007), ripening inhibitors, such as olefinic ethylene inhibitors (Wood et al., 2010), dyes (Kuwabara, 2006) or flavors (Koontz and Marcy, 2007) are used. The other main trend is incorporation of "empty CD" into the packaging films for improving the barrier function of the packaging material: entrapping both the penetrating volatiles, atmospheric pollutants migrating inward as well as the aroma substances escaping outward and odor adsorption (Wood, 2001; Wood and Beaverson, 2005). Ethylene-vinyl alcohol copolymer films with 10%, 20% and 30% of βCD content reduced the cholesterol content of packaged milk and aldehyde, such as hexanal content of packaged fried peanuts (Lopez-de-Dicastillo et al., 2010, 2011, 2011a).

Essential oils as natural preservatives and antimicrobial agents, such as garlic, cinnamon and thyme oils stabilized by CD complexation still show antimicrobial effect (Ayala-Zavala et al., 2008; Ayala-Zavala and Gonzalez-Aguilar, 2010; Del Toro-Sanchez et al., 2010). The active ingredients (allyl disulfide from garlic, eugenol from cinnamon and thymol from thyme) are released when the humidity is increased from the fresh cut vegetables and fruits.

CD is applied either by mixing it into the polymer blend before film casting/blowing or by grafting it onto the thermoplastic polymer. Films of polyethylene (PE) (Fenyvesi et al., 2007; Koontz and Marcy, 2007), polyvinyl alcohol (PVA) (Kostansek, 2002), polyvinyl chloride (PVC) (Fenyvesi et al., 2007; Kwak et al., 2007a), polyterephtalate (Ando et al., 2012), biodegradable polylactate (Plackett et al., 2006, 2007), and their composites (Deng et al., 2012; Jin et al., 2012) were modified by CDs or CD complexes. Incorporating CD complexes into the packaging material L-polylactide and L-polylactide–polycaprolactone co-polymer films compounded with nanoclays as a possible route to enhance barrier properties and/or with CD complexes were designed to provide slow release of encapsulated antimicrobials for control of mould growth on packaged cheeses (Plackett et al., 2006). The materials demonstrated complete biodegradation under controlled composting conditions and the extruded films had acceptable transparency. Tests indicated that a CD-encapsulated allyl isothiocyanate (AITC) incorporated in L-polylactide-polycaprolactone co-polymer films was effective in controlling fungi on packaged cheeses (Plackett et al., 2006). Imazalil/βCD complex incorporated in PVC films helped to extend the shelf life of fruits (Fig. 12) (Balogh et al., 2008).

Controlled release of α-tocopherol from low-density polyethylene (LDPE) film containing the active ingredient complexed by βCD was observed providing a long-lasting antioxidative effect of such kind of active packaging for food (Siro et al., 2006).

Gaseous 1-methylcyclopropene (1-MCP) an inhibitor of ethylene perception used extensively for apples and ornamental products was complexed by αCD to ensure controlled release (Neoh et al., 2008). 1-MCP/αCD complex was incorporated into several common packaging films by heat-pressing (dry-blend, lamination) and solution-casting methods. The rate of release depends on the humidity, temperature, 1-MCP load and the quality of the film.

The use of CDs to encapsulate volatile compounds facilitates the manufacturing of aroma emitters, because otherwise most of the added aroma would be released during the high temperatures experienced in polymer processing. βCD inclusion complexes with flavor volatiles such as, D-limonene, α-pinene, and 2-methoxy-3-methylpyrazine, have been incorporated into PE powder by dry mixing and then thermally pressed into films. The rate of flavor release from the polymer films was suitable for extended shelf-life food packaging (Koontz and Marcy, 2007). Grafting of CDs derivatives to cellulose surface, as in coffee filter paper, flavor components are stabilized and released in a controlled way (de Bergamasco et al., 2006). Tissue paper modified with CDs (by using monochlorotriazinyl βCD) is useful for tea bags and coffee bags to preserve the aroma and improve freshness (Wintersgill, 2004). Cellulosic web coated with a layer containing CD can be also used for this purpose (Wood and Beaverson, 1999).

Not only the volatile components can be captured by the CD-containing packaging, but also mycotoxin contamination of coffee beans occurring especially in green coffee beans and decaffeinated coffee can probably be reduced because of high affinity of CDs to interact with mycotoxins such as ochratoxin (Verrone et al., 2007).

A dye-modified CD film, such as a medicinal wafer or other packaging film containing p-methyl red-αCD conjugate exhibits a color change upon leakage of food (Kuwabara, 2006). This is an example of intelligent packaging responding on the changes in product or package environment: a color change from yellow to red can be observed

Figure 12 Bananas stored unpacked (1), in control PVC film (2) and in film contained 2.9% imazalil/βCD complex (3) for 12 days at 13°C (Balogh et al., 2008).

when the methyl red moiety is expelled from the αCD cavity by a competitive guest.

Incorporating "empty CD" into the films, PVC films with 0–2% βCD-content were prepared and their permeation properties were characterized using model flavors, such as carvone and vanillin. Much faster permeation of the selected flavors from the donor phase to the acceptor phase was measured through the films containing βCD than through those manufactured without it (Fig. 13). The difference was especially outstanding for vanillin, which practically cannot pass through the film without CD (Fenyvesi et al., 2007).

It is very important for the food safety that the presence of CD in the films results in reduced release of plasticizers (Fenyvesi et al., 2007; Yu et al., 2008). By applying a CD derivative (benzoyl βCD) in PVC film results in reduced endocrine-disrupting phthalate plasticizer contamination in the food (Kwak et al., 2007a; Chung et al., 2009).

Thermoplastic polymer compounds with grafted CD can scavenge impurities, permeants, or other undesirable volatile contaminants. A permeant or a contaminant can be complexed or trapped within the polymer and held within the film preventing the permeant from passing into the interior of the packaging material, or the contaminant can be scavenged from the enclosed headspace or surrounding environment (Wood and Baeverson, 2005; Wood et al., 2008). Bottle stoppers with reduced release of trichloroanisol are impregnated by silicone rubber-forming compounds containing CD (Angermaier, 2006). The offensive odor of trichloroanisol deteriorating the quality of the contents of the bottle is bound by CDs fixed into the cork with the silicone coating.

Polysaccharide-based multilayered antimicrobial edible coating enhances the quality of fresh-cut fruits (papaya, pineapple and watermelon). A trans-cinnamaldehyde/βCD complex was incorporated into a multilayered edible coating made of chitosan and pectin or sodium alginate. Coated fruits were firmer, maintained color, β-carotene content, and showed lower juice leakage. The coating inhibited the microbial growth (Brasil et al., 2012; Mantilla et al., 2013; Sipahi et al., 2013). A similar alginate film useful for preserving strawberries contains also *Cryptococcus laurentii* in addition to βCD (Fan et al., 2009). These microbes are antagonists of molds and significantly reduced the microbial decay, decreased the weight loss, maintained the firmness of the strawberries, and improved the quality and storage properties of the fruit without significant effects on external color parameters and anthocyanins of strawberries during storage.

Edible chopsticks made of konjac glucomannan and containing also βCD were invented by Chinese researchers (Pang et al., 2012).

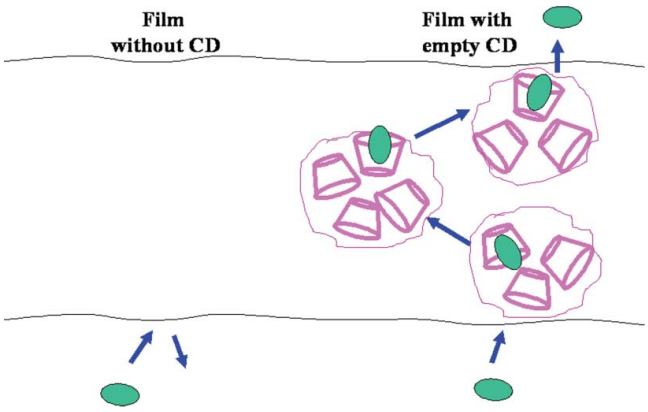

Figure 13 Permeation of flavors through films with and without empty CDs: the film without CDs is impermeable, but the film with CD can capture the volatile aroma components and will release them in a moisture-triggered, controlled way.

CONCLUSIONS

Although CDs have been used for foods for long, the focus of interest has changed in the past decade. The CD-stabilized flavors and aromas are already on the market and the research and development has found new targets:

- Empty CDs as nutritional supplements, their effect on the digestion of the macronutrients, such as carbohydrates and lipids, prebiotic effect, body weight and serum lipid control;
- CD-solubilized and stabilized nutraceuticals, mostly of plant origin, useful as antioxidants, antiproliferative agents, immune system strengthening materials, etc. applied as nutrition supplements or healthy food and beverages;
- Smart food packaging with controlled release of food preservatives, antimicrobial agents, etc., incorporated into the packaging material in the form of CD complexes.

This overview shows clearly that the development was significantly speeded up after the official approval of CDs by the competent authorities.

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