The Applications of Cyclodextrins in Food

Subjects: Pharmacology & Pharmacy

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Cyclodextrins (CDs) are a group of cyclic oligosaccharides produced from starch, consisting of a hydrophobic interior cavity and hydrophilic exterior. Cyclodextrins have gained significant and established attention as versatile carriers for the delivery of bioactive compounds derived from natural sources in various applications, including medicine, food and cosmetics. Their toroidal structure and hydrophobic cavity render them ideal candidates for encapsulating and solubilizing hydrophobic and poorly soluble compounds. Most medicinal, food and cosmetic ingredients share the challenges of hydrophobicity and degradation that can be effectively addressed by various cyclodextrin types.

cyclodextrins bioactive compounds carriers hydrophobic hydrophilic food inclusion complex

1. Introduction

Natural compounds have been used since ancient times for their beneficial properties and have played a crucial role in drug discovery. Such natural, biologically active compounds are derived from plants, animals or mineral sources and include, among others, vitamins, phenolic compounds, alkaloids and terpenoids. These groups of bioactive compounds possess antitumor, neuroprotective, antioxidant, anti-inflammatory and antimicrobial properties, so they have numerous applications in the medical, pharmaceutical, food and cosmetic industries [1][2][3]. However, despite their biological activities, they are characterized by poor solubility, bioavailability and stability in their bulk form, so their incorporation in various commercial health-related products is challenging. These drawbacks can be resolved through their encapsulation in delivery systems, one of which are cyclodextrins (CDs) [4].

CDs are a group of cyclic oligosaccharides produced from starch, consisting of a hydrophobic interior cavity and hydrophilic exterior. They were first described by Antoine Villiers more than one hundred years ago. In his work, Villiers reported that potato starch fermentation, under certain incubation conditions with *Bacillus amylobacter*, could lead to the recovery of dextrins [5][6]. However, the current term ‘cyclodextrin’ was adopted many years later and is attributed to Friedrich Cramer at the end of the 1940s [7]. Since then, an increasing number of scientific publications has been focusing on studying their structure, physicochemical properties and applications, as well as the development of new CD-based systems (e.g., nanoparticles) [8][9][10].

The most common types of CDs used in the delivery of bioactive molecules are alpha-cyclodextrin (α-CD), beta-cyclodextrin (β-CD) and gamma-cyclodextrin (γ-CD). α-CD is the smallest CD with six glucose units in the ring. It has a relatively small hydrophobic cavity and is commonly used for complexing small lipophilic molecules. β-CD is one of the most widely used CDs in bioactive compound delivery. It consists of seven glucose units in the ring, providing a larger hydrophobic cavity than α-CD. It can form inclusion complexes with a wider range of molecules including both lipophilic and hydrophilic compounds. γ-CD has eight glucose units in the ring, offering an even larger hydrophobic cavity compared to β-CD that can encapsulate larger molecules. Apart from the above three commonly used CDs, their derivatives have been introduced and applied to enhance the drug-binding capabilities of native CDs. In the first case, CDs can be chemically modified by adding methyl groups to the hydroxyl groups on the glucose units through a process called O-methylation. Examples of such CDs include heptakis (2,6-di-O-methyl)-β-cyclodextrin (DIMEB) and heptakis (2,3,6-tri-O-methyl)-β-cyclodextrin (TRIMEB). It is interesting to note that methylation affects the hydrogen bond network of CDs, thus influencing the intermolecular interactions' strength and the host: guest flexibility. This could offer increased inclusion complex (IC) stability through stronger hydrogen bonds and/or Van der Waals interactions [11]. With another process, called acetylation, hydroxypropyl groups are added to the hydroxyl groups of CDs. So, for example, (2-hydroxy)propylated β-CD (HPβCD) can be produced from β-CD. Similarly to methylation, the degree of substitution (DS) in this case affects the CD's properties. For example, DS-differentiated HPβCDs present various molecular recognition abilities, while their catalytic abilities also differ regarding organic reactions in water [12]. The selection of a specific CD type for the delivery of bioactive molecules depends on the physicochemical properties of the latter, the desired release profile and the intended route of administration [10].

2. Food Applications

The applications of CDs as carriers for bioactive compounds and their incorporation in various food products has been widely studied in the literature. Although CDs were initially tested and applied as drug delivery systems [8], their characteristics enabled food researchers to also widen their applications in various food matrices. Either as carriers for single bioactive compounds or as carriers for crude essential oils (EOs), CDs are effectively applied in many food products. Usually, such products are fresh, easily perishable ones (e.g., fruits, juice, fresh meat) since their composition (e.g., high moisture content) enables their microbiological and physicochemical degradation [13]. As delivery systems, CDs offer a variety of advantages in the final food product, mainly by preserving or enhancing the activities of the entrapped bioactive compounds. Firstly, the formation of inclusion complexes with CDs promotes the easier solubility of bioactive compounds in aqueous matrices [14]. This is of key importance since most of the food products that require preservation are water-based systems. In addition, encapsulation in CDs offers increased stability to the bioactive compounds as they are protected from adverse conditions (e.g., oxygen, heat) during food processing and storage. In this way, their biological activities are prolonged [15][16]. Especially for volatile compounds such as EOs and their constituents, which are most commonly applied as natural antimicrobial and antioxidant agents in foods, encapsulation in CDs decreases their evaporation rate and promotes their controlled and sustained release in the food matrix [17]. Moreover, one of the main advantages of bioactive compound encapsulation in CDs is the masking of their intense odor and taste, thus decreasing their negative effect on the organoleptic properties of foods [18].

The most widely studied and applied CD in food products is β-CD due to its affordability and compatibility with a variety of molecules [19]. β-CD is essentially odorless and white/whitish, while its aqueous solution is clear and colorless. Although β-CD is moderately soluble in water, it can easily be dissolved in warm water, whereas its solubility in ethanol is low (Regulation (EU) No 231/2012) [20]. As an approved food additive, β-CD is listed in Annexes II and III of Regulation (EC) No. 1333/2008, under the code E 459 [21]. Derivatives of β-CD, such as HPβCD, are also used. As reported by [22], CDs do not passively diffuse through biological membranes due to their hydrophilic nature, characterized by numerous hydrogen bond donors and acceptors and very low octanol–water partition coefficients. In addition, CDs present very low bioavailability when administered orally; β-CD, α-CD and their derivatives are mainly digested by bacteria in the colon, and γ-CD is completely digested in the gastrointestinal tract. In this way, they are practically nontoxic, and no CD accumulation is observed in healthy individuals with normal kidney function, even at high doses, whereas caution is recommended in the case of severely renally impaired patients [22].

Many studies in the literature have evaluated the effect of IC incorporation, between CDs and bioactive compounds, in the final food product in terms of microbiological, oxidative, color stability, and organoleptic characteristics. Guest moieties commonly studied are EOs (e.g., clove, rosemary, lemongrass) and their constituents (e.g., cuminaldehyde, thymol, citral) and phenolic compounds that are mainly hydrophobic (e.g., resveratrol, oxyresveratrol, ferulic acid, gingerols, curcumin). All the above are well-known natural compounds with important antioxidant and antimicrobial activities. Apart from direct incorporation of ICs in the food products, there are also indirect applications via active food packaging [23]. This method of preservation has been widely studied through the last years, where edible materials can be used to form a film/coating incorporating various bioactive compounds and applied externally in the food product of interest. In this way, the respective products are protected from external factors and can be preserved for a longer period of time (extension of shelf-life) [24]. Applications of active food packaging containing CD-based ICs or ICs directly incorporated in different food systems and their main effects are presented in **Table 1** and **Table 2**, respectively.

Table 1. Applications of active packaging containing CD-based ICs in different food systems and their main effects.

CD Type	Bioactive Compound/Guest Moiety	IC [1] Preparation Methods	Packaging Material	Food System/Model	Effects in the Final Product	Reference
β-CD	Cinnamaldehyde (CIN)	Mixing and freeze-drying	Non-woven polyethylene terephthalate (PET)	Cold fresh pork	Packaged pork samples with the highest tested CIN concentration were preserved for 11 days under	[25]

CD Type	Bioactive Compound/Guest Moiety	IC [1] Preparation Methods	Packaging Material	Food System/Model	Effects in the Final Product	Reference
					refrigerated storage compared to control samples (7 days).	
Methyl-β-CD	*Satureja montana* L. essential oil (SEO)	Mixing, ultrasonication and freeze-drying	Soy soluble polysaccharide (SSPS) hydrogel	Meat slices	Methyl-β-CD/SEO-SSPS hydrogel effectively reduced *S. aureus* counts by 3.5 log CFU/g after 7 days of storage at 4 °C.	[26]
β-CD	Octyl gallate (OG)	Co-precipitation and freeze-drying	Chitosan film	Fresh fruits vegetables (blueberries and asparagus)	Lower weight loss was reported in coated asparagus samples containing 0.5%, 1.0% and 2.0% β-CD/OG (3.87%, 3.12% and 2.85%, respectively), compared to control (7%) after 25 days storage at 4 °C. TVC [2] was maintained close to the initial 10^2–10^3 CFU/g in the coated asparagus samples compared to control (10^7 CFU/g) after 25 days of storage at 4 °C. Coated blueberries with	[27]

CD Type	Bioactive Compound/Guest Moiety	IC [1] Preparation Methods	Packaging Material	Food System/Model	Effects in the Final Product	Reference
					films containing 1.0% and 2.0% β-CD/OG presented lower weight loss (2%) compared to control (7%) after 25-day storage at 4 °C. Films containing 2.0% β-CD/OG effectively preserved freshness in blueberries with a 6% rotting rate compared to control (20%).	
β-CD	*Trans*-cinnamaldehyde (TC) and citral (CI)	Co-precipitation and vacuum-drying	Ethylene vinyl alcohol copolymer (EVOH) film	Beef	Shelf-life of EVOH-β-CD-CI and EVOH-β-CD-TC coated samples was extended about 4 days at 4 °C, compared to control and coated samples without ICs.	[28]
β-CD	Curcumin (Cur)	Mixing and freeze-drying	κ-Carrageenan (κ-Car) film	Chilled pork	Extension of chilled pork shelf life from 4–5 days to 10 days with application of κ-Car-β-CD-Cur film combined with light treatment, compared to pure κ-Car film and other treatments.	[29]

CD Type	Bioactive Compound/Guest Moiety	IC [1] Preparation Methods	Packaging Material	Food System/Model	Effects in the Final Product	Reference
β-CD	Lemongrass essential oil (LEO)	Co-precipitation and drying	Chitosan–gelatin (CS-Gel) coating	Fresh cherry tomatoes	CS/Gel coating with 7% β-CD/LEO presented high antibacterial activity against *P. aurantiogriseum* in cherry tomatoes artificially during 20 days of cold storage at 8 °C.	[30]
α-CD	Benzyl isothiocyanate (BITC)	Mixing, ultrasonication and vacuum freeze-drying	Chitosan (CS) film	Beef	CS-α-CD-BITC-coated beef samples presented lower TVC, TVB-N [3] and TBARS [4] values and higher overall acceptability score, compared to PET- [5] and CS-coated samples after 12 days of refrigerated storage.	[31]

[1] ICs: inclusion complexes; [2] TVC: total viable count; [3] TVB-N: total volatile base nitrogen; [4] TBARS: thiobarbituric acid reactive substances; [5] PET: polyethylene terephthalate.

Films/coatings incorporating ICs have been applied in meat products (beef, pork) for preservation (**Table 1**). Zhou et al. reported the extension of refrigerated storage of fresh pork packaged with non-woven PET containing CIN-β-CD ICs by 4 more days compared to the control (non-packaged samples) [26]. Similar results were reported by Wu et al., where κ-carrageenan films containing Cur-β-CD ICs, combined with light treatment, extended the shelf-life of chilled pork by 5 days, compared to pure κ-carrageenan films (no extension) [29]. Chitosan-based films with ICs of benzyl isothiocyanate–a compound found in the plants of the *Brassicaceae* family, and α-CD effectively preserved beef samples after 12 days of refrigerated storage. These coated samples were less oxidized after storage (lower TVB-N and TBARS values) and more microbiologically stable (lower TVC) compared to samples coated with pure chitosan films or PET [31]. Chen et al. used films from ethylene vinyl alcohol copolymer (EVOH) incorporating ICs of β-CD with two essential oil constituents, namely, *trans*-cinnamaldehyde and citral, for the preservation of beef [28].

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7. Cramer, F. EINSCHLUSSVERBINDUNGEN VON CYCLODEXTRINEN UND DIE JOD-REAKTION DER STARKE. Angew. Chem. 1951, 63, 487.

8. Jansook, P.; Ogawa, N.; Loftsson, T. Cyclodextrins: Structure, physicochemical properties and pharmaceutical applications. Int. J. Pharm. 2018, 535, 272–284.

9. Pandey, A. Cyclodextrin-based nanoparticles for pharmaceutical applications: A review. Environ. Chem. Lett. 2021, 19, 4297–4310.

10. Morin-Crini, N.; Fourmentin, S.; Fenyvesi, É.; Lichtfouse, E.; Torri, G.; Fourmentin, M.; Crini, G. 130 years of cyclodextrin discovery for health, food, agriculture, and the industry: A review. Environ. Chem. Lett. 2021, 19, 2581–2617.

11. Chen, H.; Ji, H. Effect of Substitution Degree of 2-Hydroxypropyl-β-Cyclodextrin on the Alkaline Hydrolysis of Cinnamaldehyde to Benzaldehyde. Supramol. Chem. 2014, 26, 796–803.

12. Geue, N.; Alcázar, J.J.; Campodónico, P.R. Influence of β-Cyclodextrin Methylation on Host-Guest Complex Stability: A Theoretical Study of Intra- and Intermolecular Interactions as Well as Host Dimer Formation. Molecules 2023, 28, 2625.

The results showed that EVOH-coated samples containing ICs were preserved for 4 more days in refrigerated storage compared to both control, samples and EVOH-coated samples, without ICs. It can be concluded that encapsulation of bioactive compounds in the cavity of CDs prior to their incorporation in the film/coating-forming solution enhances their solubility and preserves their biological activities. However, for comparison reasons, it would be also useful to prepare films/coatings containing the pure compounds (without CDs). In this way, an overall conclusion can be drawn regarding not only the extension of biological activities of bioactive compounds, but also the other advantages that CDs offer (sustained release, odor masking, etc.).

Table 2. Applications of CD-based ICs in different food systems and their main effects.

CD Type	Bioactive Compound/Guest Moiety	IC [1] Preparation Methods	Food System/Model	Effects in the Final Product	Reference
β-CD	Cuminaldehyde (CUM)	Ultrasonication, cold nitrogen plasma (CNP) treatment and freeze-drying	Vegetable juices (tomato and cucumber)	CNP-treated ICs decreased the *E. coli* O157:H7 population from 3.5 log CFU/mL to 2.51 (12 °C) and 1.29 log CFU/mL (4 °C) on cucumber juice, and to 2.58 (12 °C) and 1.33 log CFU/mL (4 °C) on tomato juice after 3 days of storage, compared to control (no added ICs).	[32]
β-CD	Ferulic acid (FA)	Crosslinking of β-CD with diphenyl carbonate (nanosponges preparation), agitation and freeze-drying	Pomegranate juice	Highest TPC [2] and antioxidant activity of pomegranate juice treated with FA-CD-NSs [3] containing 500 mg/L FA was reported after 30 days of storage at 4 °C compared to control and samples containing free FA. Total anthocyanins were better stabilized in pomegranate juice treated with FA-CD-NSs containing 250 mg/L FA after 30 days of storage at 4 °C, compared to control and samples containing free FA, through co-pigmentation effect.	[33]

13. Mozuraityte, R.; Kristinova, V.; Rustad, T. Oxidation of Food Components. In Encyclopedia of Food and Health; Caballero, B., Finglas, P.M., Toldrá, F., Eds.; Academic Press: Oxford, UK, 2016; pp. 186–190. ISBN 978-0-12-384953-3.

14. Ho, S.; Thoo, Y.Y.; Young, D.J.; Siow, L.F. Cyclodextrin encapsulated catechin: Effect of pH, relative humidity and various food models on antioxidant stability. LWT Food Sci. Technol. 2017, 85, 232–239.

15. Nguyen, T.A.; Liu, B.; Zhao, J.; Thomas, D.S.; Hook, J.M. An investigation into the supramolecular structure, solubility, stability and antioxidant activity of rutin/cyclodextrin inclusion complex. Food Chem. 2013, 136, 186–192.

food packaging. Trends Food Sci. Technol. 2016, 48, 51–62.

CD Type	Bioactive Compound/Guest Moiety	IC [1] Preparation Methods	Food System/Model	Effects in the Final Product	Reference
β-CD	Clove essential oil (CEO)	β-CD-metal organic frameworks (β-CD-MOFs) preparation through methanol vapor diffusion, mixing and freeze-drying	Chinese bacon (preserved meat product)	The lowest MDA [4] and POV [5] values were reported in Chinese bacon preserved with CEO-β-CD-MOFs in all tested concentrations, after 3 days of preservation and 15 days of fermentation compared to control, samples containing free CEO or BHT [6].	[34]
β-CD	Fish oil (FO)	Homogenization for emulsion formation and ultrasonication	Yogurt	FO-IC-treated yogurt presented greater syneresis reduction and lower POV values, but higher DHA [7] and EPA [8] content, after 21 days of storage at 4 °C compared to control and samples containing free FO. FO-IC-treated yogurt was significantly better accepted regarding sensory characteristics compared to the free-FO-treated one.	[35]
γ-CD	Resveratrol (RSV)	Mixing, snap-freezing and freeze-drying	Lemon juice	RSV encapsulation in γ-CD improved its solubility in lemon juice by nine times compared to free RSV (43.1% and 4.8% dissolution, respectively) at day 0. Higher RSV content was reported in γ-CD-RSV-treated lemon juice after 28 days of storage under dark conditions (room temperature or 4 °C).	[36]
HPβCD	Apple polyphenols (AP)	Mixing and freeze-drying	Lamb	Frozen-stored lamb treated with 1.6 mg/mL AP/HPβCD-ICs	[37]

35. Ghorbanzade, T.; Akhavan-Mahdavi, S.; Kharazmi, M.S.; Ibrahim, S.A.; Jafari, S.M. Loading of fish oil into β-cyclodextrin nanocomplexes for the production of a functional yogurt. Food Chem. X

CD Type	Bioactive Compound/Guest Moiety	IC [1] Preparation Methods	Food System/Model	Effects in the Final Product	Reference
				presented the lowest carbonyl content (protein oxidation parameter) and improved muscle tissue structure after 40 days of storage compared to control and other tested IC concentrations.	
γ-CD	Epigallocatechin-3-gallate (EGCG)	Co-precipitation and freeze-drying	Shrimp surimi products	γ-CD-EGC-treated shrimp surimi products were better preserved regarding lipid oxidation phenomena and browning effects from EGCG oxidation after 5 weeks under refrigerated storage compared to control and free-EGCG-treated samples.	[38]
γ-CD	Gingerols (GINs)	Co-precipitation and drying	Yogurt	Lower ΔE in γ-CD-GIN-treated yogurt compared to the free-GIN-treated one regarding L*, a* and b* color parameters (control used as reference).	[39]
				γ-CD-GIN-treated yogurt presented higher ABTS radical scavenging activity compared to control and the free-GIN-treated one.	
HPβCD	Thymol (Th)	Ultrasonication and freeze-drying	Tomatoes	A 66.55% lower disease incidence from *B. cinerea* in tomato samples treated with 30 mg/mL HPβCD-Th-ICs compared to control after storage for 3 days at 25 °C.	[40]

No. RU2366292C2, 30 September 2005.

47. Gebreselassi, P.; Luo Shiukh, D.; Bogkhani, N. Stain Removing Chewing Gum Composition. Patent No. US20050008732, 11 July 2003.

CD Type	Bioactive Compound/Guest Moiety	IC [1] Preparation Methods	Food System/Model	Effects in the Final Product	Reference
β-CD and HPβCD	Oxyresveratrol (Ox)	Agitation and spray-drying	Grape juice	Ox-β-CD- and Ox-HPβCD-treated samples, combined with ascorbic acid, presented the lowest L* and ΔE value differences (compared to 0 h) after 24 h of storage at room temperature, indicating an anti-browning effect.	[41]
β-CD	Rosemary essential oil (REO)	Co-precipitation and drying	Tomato juice	In REO-β-CD-treated tomato juice, the population of *S. pastorianus* decreased from 5.5 log CFU/100 mL (day 0) to 2 log CFU/100 mL after 15-day storage at 5 °C, and this difference was significantly higher compared to control and free-REO-treated samples.	[42]

[1] ICs: inclusion complexes, [2] TPC: total phenolic content, [3] NSs: nanosponges, [4] MDA: malondialdehyde, [5] POV: peroxide value, [6] BHT: butylated hydroxytoluene, [7] DHA: docosahexaenoic acid, [8] EPA: eicosapentaenoic acid.

In contrast to the active food packaging containing ICs, which has been mainly applied to meat products, pure ICs containing bioactive compounds have been commonly used for juice preservation (**Table 2**). This is expected, since ICs are in solid, water-soluble form (powder), thus enabling their solubilization in aqueous matrices. In addition, due to the high amount of sugars and water present in juices, the incorporation of antioxidant and antimicrobial agents is crucial for their preservation during storage. CUM-β-CD ICs that were treated with cold nitrogen plasma were added in vegetable juices for evaluation of their antibacterial activity against *E. coli* O157: H7. The results showed that ICs were effective against *E. coli*, since its population decreased both in 4 °C and 12 °C compared to control samples (no added ICs). The decrease was bigger in the case of 4 °C, implying a synergy between cold storage and the antibacterial agent, cuminaldehyde [32]. Garcia-Sotelo et al. evaluated the application of REO-β-CD ICs in tomato juice regarding the antimicrobial activity against the yeast *S. pastorianus* [42]. The population of *S. pastorianus* decreased by 3.5 log CFU/100 mL in the IC-treated samples after 15 days of storage at 5 °C, whereas control and samples treated with free (non-encapsulated) REO did not present the same population decrease. In a study by Amani et al. [33], the incorporation of FA-β-CD ICs in pomegranate juice was studied in terms of anthocyanin content, among other factors. The results showed that, in the presence of ICs containing 250 mg/L FA, total anthocyanins were better stabilized in the juice after 30 days of storage at 4 °C compared to control and samples containing free FA due to a co-pigmentation effect. Oxyresveratrol, a natural stilbenoid with high antioxidant activity, was complexed with β- and HPβCD and added in grape juice for elimination of browning phenomena responsible for the product's degradation [41]. The application of both ICs and ascorbic acid in grape juice effectively preserved the color (in terms of lightness L* and ΔE) after 24 h of storage at room temperature.

The importance of CDs as carriers for bioactive compounds is also highlighted by the number of patented works regarding applications of such complexes in various food systems. Indicatively, the preparation of ICs of at least one CD, or derivatives, complexed with terpene glycosides (e.g., steviol glycosides) for the production of beverages in the food industry has been patented [43]. The complexation of such glycosides with CDs is expected to increase their solubility in the beverage matrix. Another patented invention regarding non-alcoholic beverages focuses on the reduction and future replacement of conventional preserving agents in such products by suggesting an antimicrobial system based on CD complexes with natural compounds (e.g., limonene, cinnamaldehyde) that will not increase the beverage pH higher than 7.5 [44]. In another patent, the development of ICs of sucralose (sweetener) with CD is described [45]. Later on, another patented invention focused on the development of gum containing the above ICs, aiming to preserve the activity of sucralose, i.e., the sweet taste of gum, throughout chewing [46]. One more very interesting, patented invention describes the production of CD complexes with colorant-eliminating agents and their incorporation in confections (e.g., gum) in order to remove colorants from teeth surfaces [47]. The researchers suggest the incorporation of such ICs in the final stages of gum production. The preparation and preservation of a bakery product containing ICs of natamycin with CD is presented in another patented invention. For antimicrobial effectiveness, the ICs should be applied on the surface of the bakery product and the amount of natamycin should range from 0.1 pg/cm^2 to 7.0 pg/cm^2 [48]. Last but not least, the development of ICs between carotenoids, such as astaxanthin or lycopene, with CDs for the improvement of their storage stability compared to carotenoids in their free form is described in another patent [49]. The researchers highlight the ability of the ICs containing carotenoids to also improve pigmentation in animal tissues (e.g., salmon), and be used as feed or food supplement. It can be observed that the CD-based complexes can be used in various food products. The interest of researchers is basically focused on the delivery of bioactive compounds that can act as preservatives, while in most cases the ability of CDs to eliminate the taste, aroma or color of bioactive compounds is taken into consideration for the development of novel formulations.