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Room at the Top as well as at the Bottom: Structure of Functional Food Inclusion Compounds

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<http://dx.doi.org/10.5772/intechopen.74162>

Abstract

Cyclodextrins (CDs) have been hanging around research laboratories, since their discovery by Villiers. When Schardinger identified the three naturally occurring forms— α , β , γ , alpha; β , beta; and γ , gamma—they were called “Schardinger sugars.” Then it was found that CDs have the ability to bind with many different types of molecules in their cavities. Cyclodextrins are oligosaccharides obtained by enzymatic means from starch-containing raw materials such as corn. The characteristic feature of cyclodextrins is their ring-shaped, three-dimensional structure, with a hydrophobic cavity in the center, which is capable of receiving a lipophilic “guest” molecule. The hydrophilic outer surface ensures compatibility with aqueous systems. The specific properties of CDs opened up a wide range of application in food fields. Molecular encapsulation of food ingredients through cyclodextrins is intended to improve the stability of the ingredients, by extending the shelf life of the products. The results of accelerated and long-term stability tests have demonstrated that the stability of food ingredients encapsulated by cyclodextrins has outpaced those of traditionally formulated ones. The technological advantages of using cyclodextrins in food systems and food processing technologies are also manifested in the improvement of sensory and nutritional properties. Examples of food products are presented to demonstrate the importance of cyclodextrin-based molecular inclusion technology in the food industry.

Keywords: cyclodextrins, Global Paradox, functional foods, novel food ingredients, inclusion compounds, supramolecular chemistry

1. Introduction

The Neolithic Revolution marked the end of nomadic peoples and the beginning of sedentarization of *Homo sapiens*, having originated 10,000 years of food inventions. Nowadays, it produced sufficient food to feed each of the 7 billion human beings. However, malnutrition and food waste related to production and consumption are big issues that pose major challenges for the future. The big question then arises: why exists malnutrition, if there is enough food quantity and quality for all people around the world?

The Global Paradox of Malnutrition (**Figure 1**), i.e., the conditions of malnutrition and overweight/obesity, have causes and consequences strongly related with the existence of inadequate food systems. This Global Paradox of obesity *versus* undernutrition is portrayed through the numbers: around 33% of the world population suffers from malnutrition. While one part of the world population has no access to food in quantity and quality necessary for a healthy life, another large group of people chooses to excessively high-calorie foods low in nutrients and fiber. Metabolic disorders as obesity and related diseases can be prevented but recently became pandemic. Even more serious is the fact that recently the number of children suffering from these metabolic disorders (155 million) exceeded the number of children suffering from malnutrition (148 million). If this process is not stopped, through appropriate measures at the community level and at the individual level, it is expected that the economic and social impact will be catastrophic.

One approach to reduce malnutrition is the development of functional foods or novel food ingredients to reduce the risk of disease, providing longevity and a healthy lifestyle. In this context, glucose cyclic oligosaccharides, the cyclodextrins, play an important role.

Cyclodextrins (CDs) are compounds derived from starch, modified industrially produced enzymatically. These starch derivatives are nontoxic ingredients, are not absorbed at the level of the upper gastrointestinal tract, and are completely metabolized by colonic microflora.



Figure 1. The Global Paradox: Obesity and Malnutrition. Obesity has doubled since 1980; In 2014 there were more than 1.9 billion adults overweight, of which 600 million people are obese; most people live in countries where overweight causes more mortality than malnutrition (WHO Fact sheet n°311 2015).

CDs can be used in food as supports for molecular encapsulation of flavors and other ingredients, and there is a huge scope that goes beyond food applications.

2. Cyclodextrins discovery

Over 100 years have elapsed, since Villers first described the isolation of a crystalline substance from a medium of *Bacillus amylobacter* starch culture, corresponding to what is now recognized as cyclomalto-oligosaccharides or cyclodextrins. This crystalline substance was then called “cellusine” because of its similarity with the cellulose. Over the next 60 years, progress in purification products, elucidation of structures, and identification of unusual properties were remarkable and surprised the pioneering researchers in the field. Contributions from Schardinger, Pringshein, Freudenburg, and Cramer, in Germany, and from French in the United States of America are presented in a review article that has become a true classic, published in *Advances in Carbohydrate Chemistry* [1]. In this article, French anticipated that the cyclodextrins would serve, teach, delight, and intrigue the scientific community. It was from this time that the scientific community recognized one of the most characteristic properties of cyclodextrins: the ability to form inclusion compounds with a wide variety of substrates or guest molecules.

However, the path taken by the pioneers in the area was not easy. Cramer felt strong opposition when mentioned that cyclodextrins in solution could include other molecules. M.L. Bender recognized the synthesis of inclusion compounds based on cyclodextrins and the ability to discriminate enantiomers during the inclusion process and the catalytic capacity in reactions on bound substrates for the very first time. The result of these discoveries fascinated a large number of researchers: Bender and Breslow in the United States, Saenger in Germany, and Tabushi, Komiyama, and Hirai in Japan. They felt captivated by scientific research involving cyclodextrins [2].

During the decades of 60 and 70 of the last century, cyclodextrins have been widely studied as simulants enzyme systems (cyclophanes) or very similar to the behavior of the various enzymes. The advent of high-pressure liquid chromatography techniques (HPLC), fast atom bombardment mass spectrometry atoms (FAMS), and nuclear magnetic resonance spectroscopy (NMR) has made possible the characterization of chemically modified cyclodextrins (e.g., methylated cyclodextrins). A complete and unambiguous characterization of the structures was made by X-ray diffraction and neutron diffraction techniques.

On the other hand, the commercial interest in cyclodextrins has grown and is growing at a phenomenal rate, particularly in Japan and Hungary, where Professor Joseph Szejtli's contribution was enormous. The pharmaceuticals, agrochemicals, food, and cosmetics industries have been influenced by these outstanding molecules to a lesser or greater extent [2].

Scientific and technological impact of cyclodextrins are associated, on the one hand, the diversity of situations in which they operate and on the other hand, the enormous challenge that its use has caused in the design of new molecular systems reminiscent functions of biological, chemical, or physical nature.

3. Chemistry and structure and cyclodextrins

3.1. Biological synthesis of cyclodextrins

The CDs are produced by degradation of the prehydrolyzed starch and their subsequent cyclization-mediated cyclodextrin glucosyltransferase enzyme (CGTase, EC 2.4.1.19) produced by bacteria that belong to the genus *Bacillus*. Due to the helical structure of the starch molecules, the primary cleavage product undergoes an intermolecular reaction forming cyclic products joined by α -1,4 linkages, generally designated by cyclodextrins. To distinguish them, Greek letters are used to specify the number of D-glucose units (in brackets): α (6) β (7) γ (8) δ (9) ϵ (10) ξ (12) η (13).

The shapes α , β , and γ are the natural cyclodextrins and most commonly used (**Figure 2 (c)**). Higher numbers of counterparts of glucose units also exist but are difficult to purify, with weaker inclusion properties. Cyclodextrins with a number of glucose units less than 6 do not exist, probably due to steric hindrance.

The preparation of cyclodextrins can be subdivided into the following main stages:

- Culture of the producing microorganism CGTase enzyme
- Separation of the enzyme from the medium, their concentration, and purification
- Enzymatic conversion of prehydrolyzed starch a mixture of cyclic and noncyclic dextrans
- Separation of the CDs are from the conversion mixture, purification and crystallization

In industrial production of cyclodextrins, the most frequently used source of enzyme is *Bacillus macerans*, renamed as *Paenobacillus macerans*. Other enzymatic sources used are *Klebsiella pneumonia* and *Alkalophilic bacterium* 38–2. The forms α , β , and γ are dependent from the source of CTGase enzyme. The *Bacillus macerans* and *Klebsiella pneumonia* CTGase mainly produce the α form. *Alkalophilic bacterium* 38-2 mainly produces β -cyclodextrin. However, the relationship between the CD formed also depends on the incubation time of the enzyme in starch medium culture because most CTGases initially produce the α form, while the synthesis of other forms is slower [3].

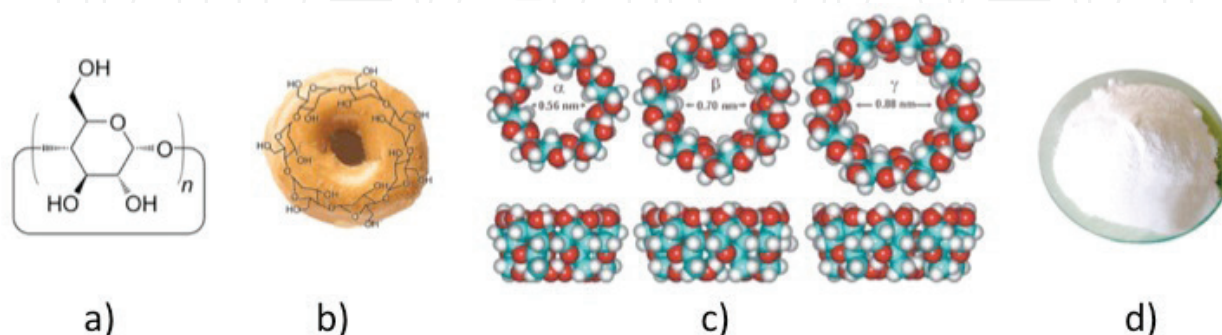


Figure 2. Structure of a cyclic oligosaccharide, cyclodextrin, CD (a); The “donut” Molecular (b); Paragraph equal to six, seven or eight rings of D-glucopyranose, joined by glycosidic linkages of the type α -1.4, representing α -CD, β -CD and γ -CD, respectively (c); white crystalline powder β -CD (d).

3.2. The structure of cyclodextrins

The native cyclodextrin molecules (α -CD, β -CD, and γ -CD) have the shape of a short truncated cone with a cavity inside, i.e., a toroidal shape. The length is determined by the height of the glucose unit ($7.9 \text{ \AA} = 0.79 \text{ nm}$), and the diameter of the cavity is determined by the number of glucose units (**Figure 2 (a) and (c)**).

The glucose rings linked together by α -1,4 linkages as in amylose. They are oriented in the same direction, and thus, the narrow end of the torus is formed by the primary hydroxyl groups (O (6) H), while the wider edge of the truncated cone is occupied by the secondary hydroxyl (O (2) H, O (3) H) groups. These peripheral hydroxyl groups confer hydrophilic properties to the CD surface. Moreover, the internal cavity has mainly hydrophobic characteristics due to the methine group (CH) and the oxygen atoms of the ether type (O (4) and (5)).

The CDs may crystallize in the form of hydrate or inclusion compound, and the crystal structure was mainly determined by the following factors:

1. The nature and size of the cavity included in the molecule;
2. Hydrogen bonding between the included molecules and between CD and CD drives.

The interstices between the CD units are occupied by water molecules incorporated in the overall structure (see **Figure 3**) [3, 4].

The CDs cavity in the center, with predominantly hydrophobic character, is large enough to hold, accommodate, or include other molecules. When this occurs, there is the formation of an inclusion compound. These compounds, or complexes, may be described as a molecular-level nanoencapsulation. Food ingredients formulated with cyclodextrins become stable to heat and oxidation processes and are not affected by dispersion forces and are readily dispersed for use in liquid products [5].

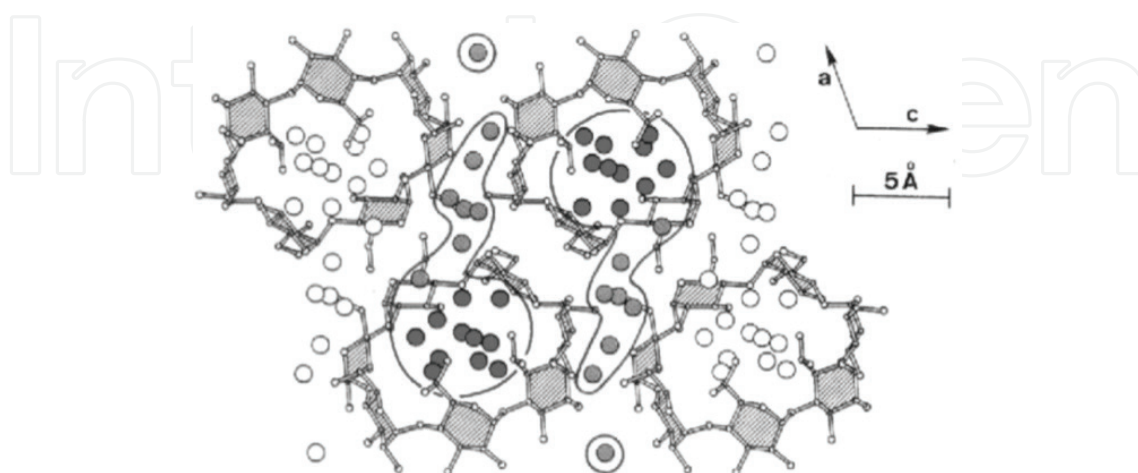


Figure 3. The crystalline hydrate of β -CD. The blue are represented statistical locations of the interstices water molecules; red are represented statistical locations of cavity water molecules [3, 4].

The food industry uses the native cyclodextrins in different ways owing to the above-described properties, being used in various applications due to their ability to form inclusion compounds. The α -cyclodextrin acts even as prebiotic. Thus, formulations with CDs are used in food and also in the designated functional food markets in order to circumvent the problems of stability, taste, and flavors of special ingredients. In this context, natural functional foods are food systems enriched, e.g., with bacterial cultures, omega 3 fatty acids, anthocyanins, dietary fibers, etc., which can contribute to the maintenance of health and reduction of disease risk. [6]

4. α -CD as a novel food ingredient

α -cyclodextrin was approved in Europe as a novel food ingredient for use as a prebiotic in 2008 [6, 7]. The term prebiotic is used to describe nondigestible carbohydrates necessary to maintain healthy intestinal flora [7, 8].

Currently, there is considerable interest in these food ingredients, since that the common diet only consumes half the indigestible portion of carbohydrate necessary to maintain the intestinal flora. The properties of the smaller native cyclodextrin make it particularly suitable for this function, since it is soluble in water, does not affect the solution viscosity or change its taste, and can be added to beverages. Thus, the daily intake of dietary fiber essential to the health can be increased. Soluble fibers also have a beneficial effect on the levels of fat and sugar in blood. Apart from adding the liquor, the α -cyclodextrin may also be added to pasta to baking or other finished products, since it is stable even at high temperatures. The Maillard reactions (a kind of browning reaction) are not supported, since the α -cyclodextrin is not a

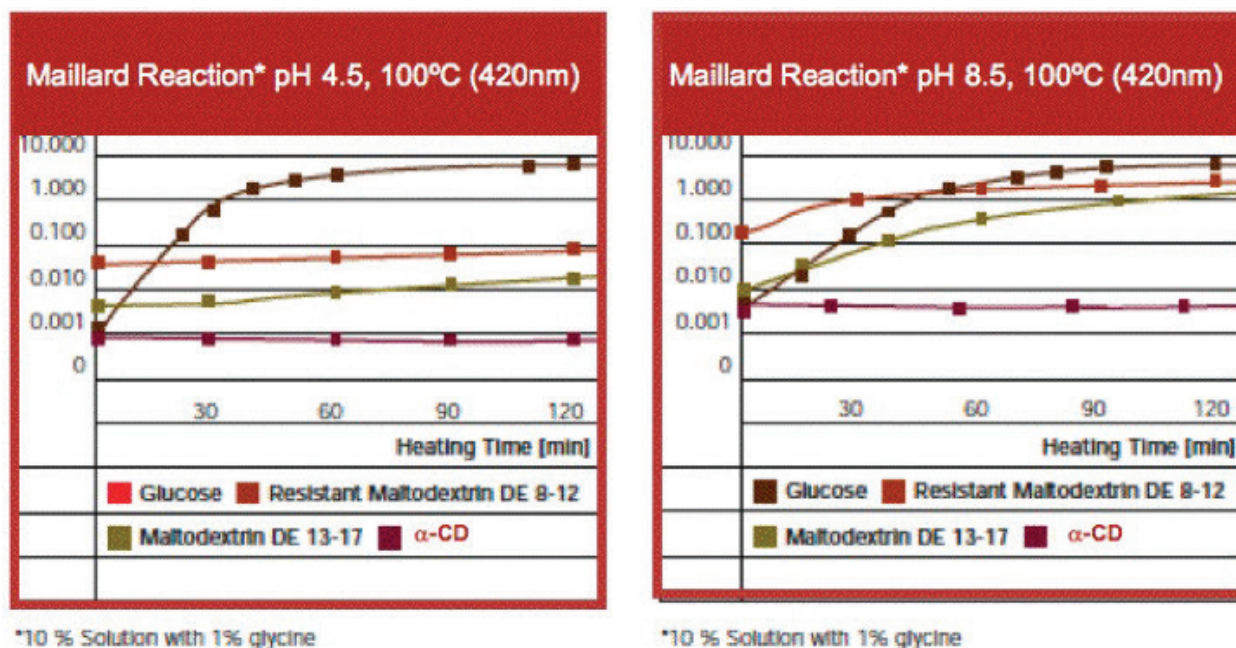


Figure 4. Speed of the Maillard reaction as measured by the formation of HMF ([HMF]/(mg/kg)); $\lambda_{\max} = 420$ nm, pH = 4.5 and 100°C. The α -cyclodextrin does not take part in Maillard reactions [10].

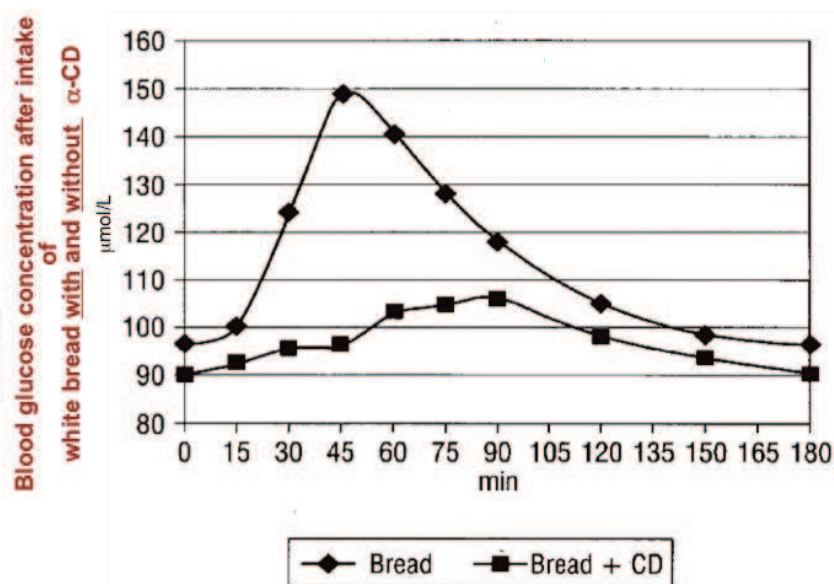


Figure 5. Effect of addition of α -cyclodextrin white bread glycemic index (GI ratio between the area calculated in bread curve (100 g) and the area calculated in bread curve (100 g) + α -CD (10% (m/m)) [10].

reducing oligosaccharide. The same is not true with glucose and maltodextrin that react with glycine in the formation of undesirable pigments, in addition to nutritional loss (**Figure 4**) [9].

For bakery products remain fresh and crispy during the storage period, the ingredients should not have hygroscopic characteristics. In this respect, and contrary to inulin, the α -cyclodextrin has a low hygroscopicity.

Beyond the benefits of not participating in browning reactions and low hygroscopicity, this soluble fiber also has beneficial effects on the levels of fat and sugar in the blood. Two months clinic studies performed by researchers of the University of California, Davis, CA (UC Davis), was used controlled placebo in 28 volunteers who were overweight (25 > Body Mass Index >30) but not obese, there was the following: after ingesting 6-cyclodextrin daily for a period of 2 months, these people lost weight without changing diet or lifestyle. During the study, blood parameters as total cholesterol and low density lipoprotein (LDL) decreased along with insulin level. The positive effect of α -cyclodextrin on the glycemic index (GI) was also confirmed by other studies [9].

Figure 5 shows the effect on glycemic index after adding α -cyclodextrin to the white bread.

5. Inclusion compounds based on cyclodextrins: applications in food and food processing

The three-dimensional nature of native CDs makes these molecules very important, since these starch derivatives are ingredients that do not have toxic characteristics; they are not absorbed in the digestive tract and are completely metabolized by the intestinal microflora. These CDs have the necessary requirements to be neutral in terms of aroma and flavor,

although they are made from glucose units; the α -CD and β -CD have no sweet taste, while the γ form only has a slight sweet taste. Since the CDs are occurring in the form of a colorless powder, it makes them easier to process [4, 11].

The molecular inclusion phenomenon is one chemistry field also called supramolecular chemistry. Jean-Marie Lehn, Nobel Prize in 1997, is one of the creators of this area of chemistry that deals with complex entities resulting from the association of two or more chemical species held together by non-covalent intramolecular bonds. Lehn, paraphrasing Richard Feynman (and his well-known speech on nanotechnology “There is plenty of room on the bottom”) with the expression “There's even more room at the top”, has indicated that chemistry not only has to look toward the extremely small but can also go beyond the molecular size, studying the supramolecular complexity.

The main advantage of using CDs in food systems lies summarized in **Table 1**. The prolongation of the shelf-life of the compositions and standardization and ease in dosing and transport of inclusion compounds are very important features of this inclusion nanotechnology.

Cyclodextrins can encapsulate biocides that can be applied to food packaging materials. By changing humidity conditions, there is controlled release of the biocide thus preventing, for example, the proliferation of microorganisms (bacteria, fungi, and yeasts). The CDs are good carriers for flavors and fragrances. In bakery products, it can be reduced to one-third the amount of aroma needed, if they are CD encapsulated. The CDs can also improve the bread dough and the crispy effect of rice crackers. The aroma of fresh vegetables can also be preserved by reduction of the degradation rate and preventing discoloration. Mixed

Benefit	Food system
Stabilization effect	
Protection against deterioration of sensitive substances	<ul style="list-style-type: none">• Fats,• Terpenos• Flavors
Elimination or reduction	
Unpleasant flavors/aromas	<ul style="list-style-type: none">• Removal of bitter taste in grapefruit juices
Microbial contamination; Hygroscopicity	<ul style="list-style-type: none">• Smell of Vitamin B1
Selective cholesterol removal	<ul style="list-style-type: none">• Cheese• Butter
Improvement of the solubility of lipophilic ingredients	<ul style="list-style-type: none">• Carotenes• Curcumin
Improvement of emulsion stability	<ul style="list-style-type: none">• Mayonnaise• Dairy products
Improvement in the uniformity of content	<ul style="list-style-type: none">• Standard flavors

Table 1. Summary of some beneficial effects of the use of cyclodextrins in food systems.

with spices, the CDs can help stabilize emulsions (mayonnaises and salad dressings). Cyclodextrins may act as sweetener by aspartame encapsulation to make it more water soluble (**Table 2**).

In beverages, the CDs allow the use of aromas, control the dissolution of aspartame preventing its breakage, maintain the color of fruit juices, and also allow the encapsulating of carbon dioxide.

In Japan, CDs are considered a natural product, used to deodorize meats and fish, improving the defrosting properties through water and red pigments retention and reduction of undesirable aromas.

Some of the foods that contain plant extracts have undesirable bitter flavors. The CD molecules are suitable to encapsulate these components. For example, grapefruit juice can be treated during preparation CD are to remove the bitter taste caused by naringin and the limonene (**Figure 6**). The other grapefruit aromas are encapsulated in a small extent, and the treatment does not alter the contents acid or vitamin C [11].

The polymers of cyclodextrins are used to prevent the juice to precipitate. The polymer molecules are synthesized using a bifunctional crosslinking agent (*e.g.* glutaraldehyde). The CD loaded polymer naringin, adding sodium hydroxide and subsequent washing regenerate limonene.

Brand	Type of food	CD'S function
Natural ^a	Cheese	Cholesterol removal
Cyroma-line ^b	Flavored sugar for baking	Preserve the flavor after heating
Balade ^c	Butter	Cholesterol removal
Simply eggs ^d	Eggs	Cholesterol removal
FlavorAktiv Standard Kit ^e	Patterns of beer aromas	Preserve the flavor
Flavono ^f	Chewing gum	Estabilize the flavor
Choco bar ^f	Chocolate	Emulsifier
Poder tea ^f	Instant tea	Preserve color
Gymet ^f	Dietary fiber drink	Mask flavor
Stick lemon ^f	Instant tea	Preserve the flavor

^aFrance.

^bHungary.

^cBélgium.

^dUSA.

^eGreat Britain.

^fJapan.

Table 2. Foods that include cyclodextrins in their formulation.

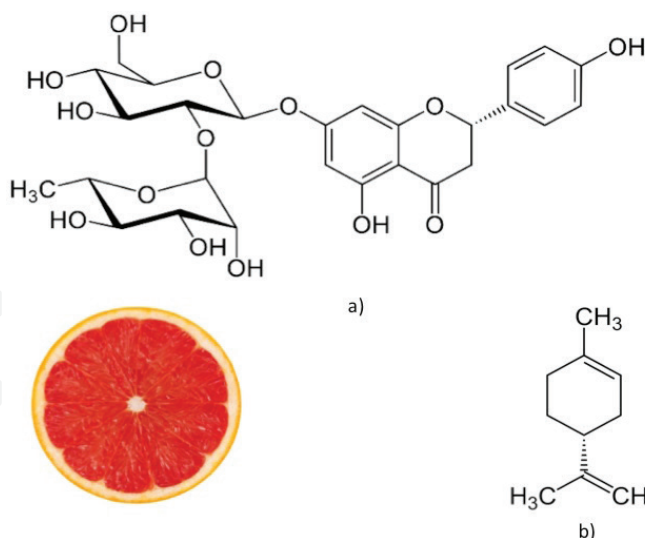


Figure 6. Naringin (a) and Limonene (b) give a bitter taste to grapefruit juice.

The ability to form inclusion complexes is also used for the production of cholesterol-free food due to the cholesterol molecule is retained in the cavity of seven glucose units from β -cyclodextrin (**Figure 7**).

The results of the preliminary study on the effect of β -cyclodextrin in removing red wine unpleasant smells have also been promising. This study was conducted triangle sensory analysis by 14 untrained panelists using a red wine enriched with 4-ethylphenol (5000 g/L) or a mixture of 4-ethylphenol (750 g/L) + 4-ethylguaiaicol (75 g/L) and different levels of β -CD concentration. According to the sensory panel, the concentration of 11.52 g/l CD- β (ratio 2:1) was sufficient to reduce the perception of red wine unpleasant odors. Additionally, an increase of colour intensity and the total polyphenol content of red wine treated with β -CD was measure and statistically significant [12].

β -cyclodextrin and γ -cyclodextrin are the most commonly used forms, because its size is usually more favorable. The complex formation facilitates controlled release of the encapsulated molecules, since the dissociation of the complex requires low humidity. For example, the flavors may be stored and released in a chewing gum, when it is chewed. An additional advantage of

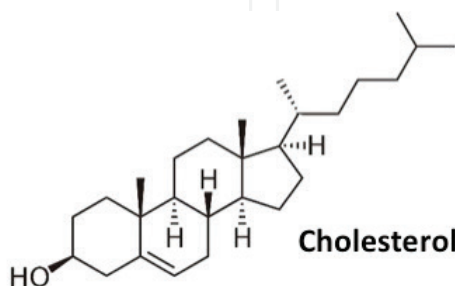


Figure 7. Cholesterol free butter is obtained by treatment with cyclodextrin to sequester (encapsulate) the cholesterol molecule.

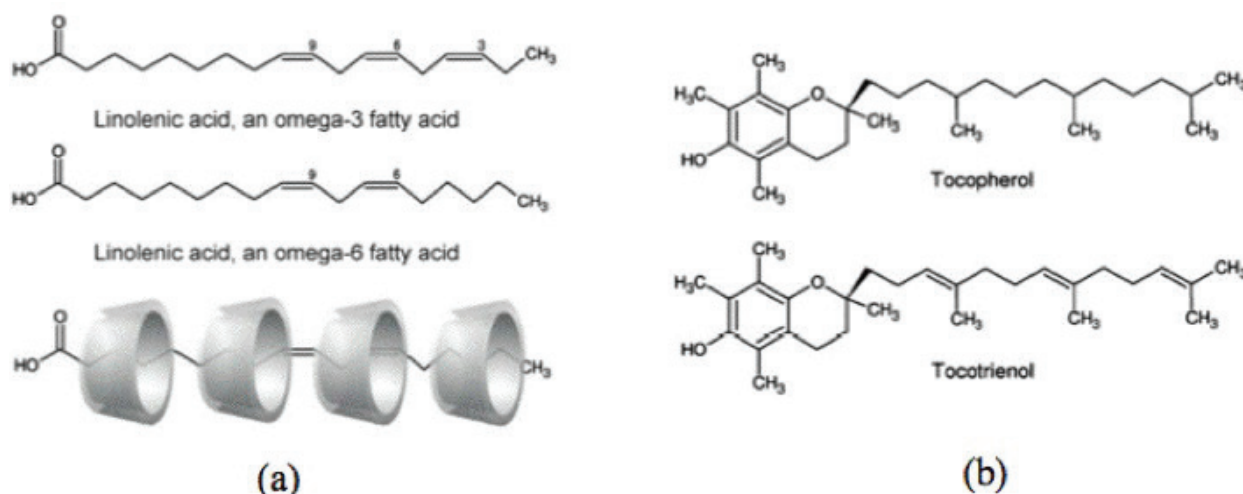


Figure 8. (a) Fatty acids ω^3 and ω^6 complexed with several cyclodextrin molecules; (b) The product contains OmegaDry® Cranberry inclusion compounds with components obtained from cranberry essential oil [13].

the inclusion of these molecules is the protection against oxidation, sublimation, and evaporation. The complexation may also be used to mask unpleasant flavors and odors. One of the advantages of cyclodextrins nanoencapsulation is exploited in the case of omega 3 (ω^3) and omega 6 (ω^6) fatty acids because they have proven positive effects in reducing fat levels in the blood plasma, with a consequent reduction in the risk of cardiovascular diseases. Although the ω^3 and ω^6 fatty acids are mostly derived from fish oils and algae extracts that in the native state have an unpleasant taste and aroma. Therefore, the encapsulation via CD is necessary to obtain a white odorless powder, which is easily processable, preventing also the oxidation reactions.

Currently, there is a product on the market, registered under the name OmegaDry® Cranberry, which contains several cranberry oil components encapsulated in γ -CD (**Figure 8 (a)**) [13]. There are also formulations with isomeric vitamin E with functional tocotrienols (**Figure 8 (b)**) and myricetin (3,5,7-trihydroxy-2- (3,4,5-trihydroxyphenyl) - 4-chromenone) and quercetin [14, 15]. Considerable interest in these formulations results of whether they are lipophilic substances with antioxidant properties, enabling the cell protection from oxidative degradation of lipid membrane structures of the molecules, preventing premature aging of the skin, caused by damage from ultraviolet radiation. Thus, the complexes with tocopherol and tocotrienol can be used in food systems and also in cosmetics.

6. Legal status and patents

From very early stages, cyclodextrins were used by the food industry. In Japan, cyclodextrins were considered natural products, and its use occurred in the late 70s of last century after the development of industrial manufacturing processes. In 1987, there were already 88 Japanese patents, making Japan the first country to functionalize food with CDs. Since 2000, the three native cyclodextrins can be used as food additives in the United States of America (USA). In

Australia and New Zealand, the α and γ forms were classified as new ingredient since 2003 and 2004, respectively.

However, there was no information on the legal situation of β -cyclodextrin in this region of the globe. In Europe, since 1998, β -cyclodextrin was approved under the designation E-459 in the list of food additives. More recently, α -cyclodextrin and γ -cyclodextrin were approved as new ingredient in 2008 and 2012, respectively. In **Table 3**, the information is gathered about the legal status of native cyclodextrins worldwide [16–21].

In 2014, Deorsola et al. presented a research paper on patents involving cyclodextrins. These authors used free databases: Espacenet, USPTO, PATENT SCOPE, INPI, and DERWENT. The

Cyclodextrin	α -CD	β -CD	γ -CD
WHO/FAO ¹	ADI = Not specified June 2001 to June 2004	ADI = 5 mg kg/day 4/1/1995	ADI = Not specified 1999 e 2000
USA	GRAS ² 2004	GRAS ³ 2001	GRAS ² 2000
CANADA	Filed for Novel food July 2006		
UE	Novel food Approved 2008	Carrier for food additives (< 1 g/kg) E-459	Novel food Approved 2012
JAPAN	Natural product	Natural product	Natural product
MEXICO	Approval of FDA Import licence	Follow FDA approvals with an import license	Approval of FDA Import licence
MERCOSUR ⁴	Approved		
FSANZ ⁵	Novel food 12/1/2004		Novel food 2003
COREIA	Approved for dietary supplement	Approved for dietary supplement	Approved for dietary supplement
PHILLIPINES	Approved		Approved
THAILAND			Approved for dietary supplement
TAIWAN	Approved for dietary supplement		

¹WHO/FAO – World Health Organization /Food & Agriculture Organization of the United Nations.

²GRAS in a wide range of intended use in food.

³GRAS as flavor protectant.

⁴State Mercosur – Argentina, Brazil, Paraguai, Uruguai & Venezuela.

⁵FSANZ – Food Standards Australia and New Zealand.

Table 3. Cyclodextrins approval status as food ingredients/additives [15–20].

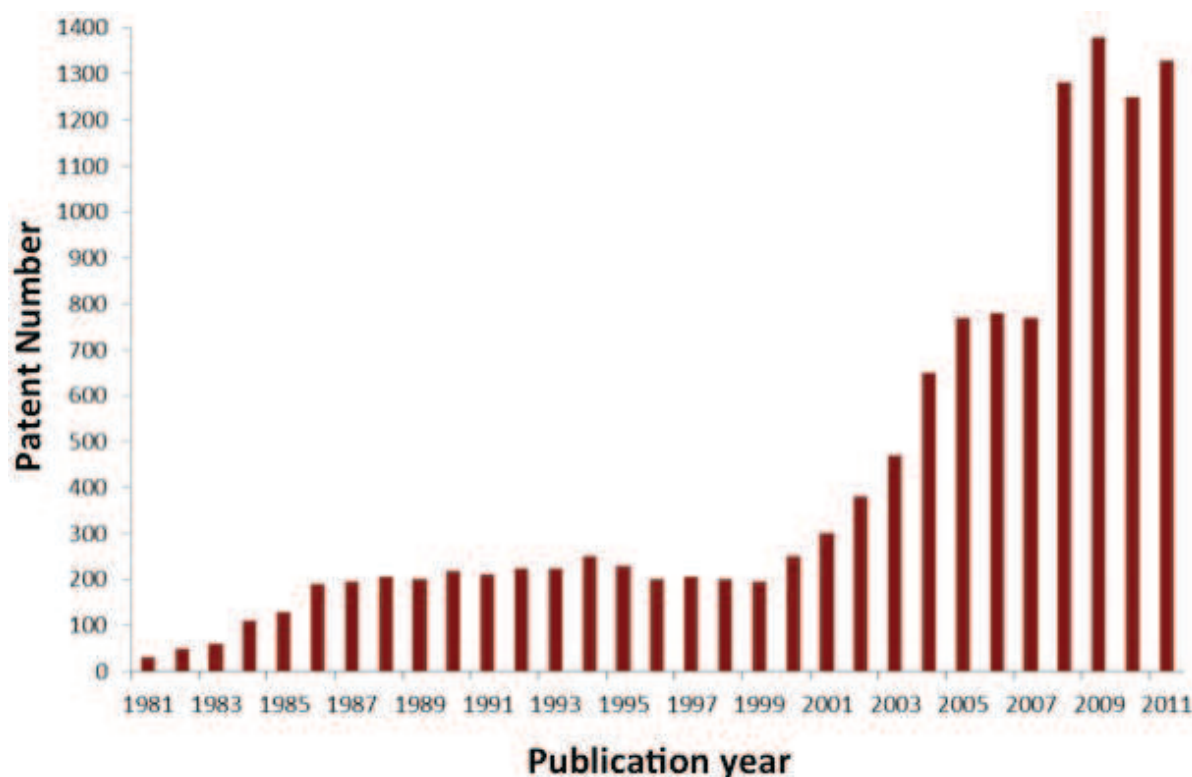


Figure 9. Number of cyclodextrin patents [22].

30-year evaluation period was from 1981 to 2011, having found 14,572 records. The increased number of patents in three stages: (I) to 1990 followed by a slight decline; (II) a faster growth 2000–2005 and remained for 2 years; and (III) from 2008 to 2011 the number nearly doubled patent (**Figure 9**).

Companies that recorded the highest number of cyclodextrin patents are Procter & Gamble Co. (>300), Kao Corp. (99), Schering AG (92), the Ensuiako Sugar Refining Co. (83), and Ono Pharm. Co. (79). The classification of patents allows an assessment of the topic of invention, and this analysis shows that the most selected classification relates to medicinal and/or food preparations [23].

7. Final notes

Cyclodextrins passed the benches of research and development laboratories (R&D) for industrial-scale production, since they were discovered by Villers in 1891. This is due to the fact that CDs had a very special feature: the ability to include different types of molecules in the cavity of the molecular “donut.”

Currently, the global market for cyclodextrins is estimated above 10 tons per year, mainly applied to food systems, or related to them (*e.g.*, retardant product of fruit maturation, SmartFresh® product from Agrofresh company).

Therefore, it is expected a huge increase in applications of CDs in this next century of research dedicated to cyclodextrins in food systems. This observation is supported on the exponential patent records, scientific publications, inclusion of the topic in school programs, and pedagogical manuals [21, 24], and also the growing organization of conferences devoted to the subject is globally widespread.

In conclusion, there is “*Room at the Top*” as well as “*Room at the Bottom*” for the use of cyclodextrins in food systems.

Acknowledgements

The author acknowledges financial support from the Portuguese Foundation for Science and Technology: PTDC/QEQ-MED/1890/2014, within Project 3599 – to Promote Scientific Production and Technological Development as well as the formation of thematic networks (3599-PPCDT) – jointly co-financed by the European Regional Development Fund (FEDER), through the partnership agreement Portugal2020—Regional Operation Program CENTRO2020, under the project CENTRO- 01-0145-FEDER-023631 SoSValor: Sustainable Solutions for the Valorization of Plant Natural Products and Industrial Waste.

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