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A COMPREHENSIVE OVERVIEW OF CYCLODEXTRINS IN TERMS OF PRODUCTION, PROPERTIES, AND APPLICATIONS

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Cyclic oligosaccharides, production, structure, properties, applications

ABSTRACT

Cyclodextrins (CDs) are cyclic oligosaccharides formed through the enzymatic transformation of starch into glucose, catalyzed by cyclodextrin glucanotransferase (CGTase). They are composed of six (α-CD), seven (β-CD), or eight (γ-CD) glucose molecules, interconnected by α-1,4 glycosidic bonds. Cyclodextrin glucanotransferase has been declared safe for use in food applications by the European Food Safety Authority (EFSA). CGTase is an extracellular enzyme that is found in nature on a cellular level and is generated by a variety of microorganisms, such as fungi, bacteria, and archaea. Approximately 90% of bacteria that generate CGTase belong to the genus Bacillus. A number of glucose units joined covalently by oxygen atoms form cyclodextrins. CDs have a truncated cone shape with a hydrophilic outer wall and a less hydrophilic inner wall. Due to their numerous health benefits, CDs are regarded as advantageous nutrients and biologically active dietary supplements. CDs and their derivatives have diverse applications across the food, cosmetics, and pharmaceutical industries, with their use being most prominent in the food sector. Within the food industry, CDs serve primarily as auxiliary agents, acting as technological enhancers to improve the physicochemical properties of various food components. For example, they can be used to stabilize aroma and flavor compounds, polyunsaturated fatty acids (PUFAs), and poorly water-soluble vitamins and nutrients, as well as to improve medication solubility and bioavailability. Studies on their toxicity have also revealed that CDs are safe to use orally. Many studies have examined the insertion of conventional medications or naturally occurring bioactive substances into CDs cavities in an effort to better understand their effects on various cancer cell lines in vitro. CDs are used in cosmetics products to extend their shelf life, stabilize volatile chemical ingredients, lessen offensive tastes or smells, and prevent or lessen topical irritation. Cyclodextrins remain a focal point of research due to their ability to encapsulate molecules and function as catalysts and carriers for a wide range of chemical compounds.

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ПОДРОБНЫЙ ОБЗОР ПРОИЗВОДСТВА, СВОЙСТВ И ПРИМЕНЕНИЯ ЦИКЛОДЕКСТРИНОВ

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КЛЮЧЕВЫЕ СЛОВА:
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АННОТАЦИЯ

Циклодекстрины (ЦД) — это циклические олигосахариды, образующиеся в результате ферментативного преобразования крахмала в глюкозу, катализируемого циклодекстринглюканотрансферазой (ЦГТазой). Они состоят из шести (α-ЦД), семи (β-ЦД) или восьми (γ-ЦД) молекул глюкозы, соединенных между собой α-1,4-гликозидными связями. Европейское агентство по безопасности пищевых продуктов (EFSA) считает циклодекстринглюканотрансферазу безопасной для использования в пищевых продуктах. ЦГТаза — это внеклеточный фермент, который встречается в природе на клеточном уровне и вырабатывается различными микроорганизмами, такими как грибки, бактерии и археи. Примерно 90% бактерий, вырабатывающих ЦГТазу, принадлежат к роду Bacillus. Циклодекстрины образуются несколькими молекулами глюкозы, ковалентно соединенными атомами кислорода. Они имеют форму усеченного конуса с гидрофильной внешней частью и менее гидрофильной внутренней частью. Благодаря многочисленным преимуществам ЦД считаются полезными для здоровья питательными веществами и биологически активными пищевыми добавками. ЦД и их производные находят разнообразное применение в пищевой, косметической и фармацевтической промышленности, причем наиболее распространено их использование в пищевых продуктах. В пищевой промышленности ЦД в первую очередь служат в качестве вспомогательных ингредиентов, таких как добавки для улучшения физико-химических свойств различных пищевых компонентов. Например, их можно использовать для стабилизации ароматических и вкусовых соединений, полиненасыщенных жирных кислот (ПНЖК) и плохо растворимых в воде витаминов или питательных веществ, а также для улучшения растворимости и биодоступности лекарственных средств. Токсикологические исследования показали, что ЦД безопасны для перорального применения. Во многих исследованиях изучалось введение обычных лекарственных средств или природных биологически активных веществ в полости ЦД с целью лучшего понимания их воздействия на различные линии раковых клеток in vitro. ЦД используются в косметических продуктах для продления срока их годности, стабилизации летучих химических ингредиентов, уменьшения неприятного вкуса или запаха и предотвращения или уменьшения местного раздражения. Циклодекстрины остаются в центре внимания исследований благодаря своей способности инкапсулировать молекулы и выполнять функции катализаторов и носителей для широкого спектра химических соединений.

1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides synthesized through the enzymatic conversion of starch into glucose by cyclodextrin glucanotransferase (CGTase). They are composed of six (α-CD), seven (β-CD), or eight (γ-CD) glucose units linked by α-1,4 glycosidic bonds [1,2]. Cyclodextrin glucanotransferase (CGTase; EC2.4.1.19) is an endoenzyme that catalyzes the breakdown of starch derived from sources such as potatoes, corn, and rice, facilitating CD production. [3]. Cyclodextrin glucanotransferase has been declared safe for use in food applications by the European Food Safety Authority (EFSA) [4]. Regarding starch, the US Food and Drug

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Administration (FDA) also declared its products, which are represented by the cyclodextrins α, γ, and β, to be safe (GRAS) [2]. This enzyme is produced by bacteria, fungi and archaea. CDs may be kept for several years at room temperature without experiencing any discernible deterioration [5,6].

Cyclodextrins, specifically α and β types, were first discovered in 1891 as byproducts of potato starch digestion by the bacterium *Bacillus amylobacter*, according to a report by a French chemist. Later, Franz Schardinger, an Austrian microbiologist considered the "founding father" of cyclodextrin chemistry, successfully isolated these compounds from various starch sources after digestion by *Bacillus macerans*. Due to their ability to encapsulate molecules and their qualities as catalysts and carriers of various chemicals, cyclodextrins remain a subject of interest for many researchers. These attributes make them excellent candidates for both basic and advanced applications in a variety of industries. This has led to significant theoretical and experimental research into their physicochemical behavior and applications [7]. Over 44,000 articles have been reported according to Scopus and Web of Science. Some great CD evaluations of food science have emerged in tandem with the rapid growth of CD research [2,8]. CDs have been employed for a range of purposes because of their biocompatibility, biodegradability, and very inexpensive manufacture [9]. Given their adaptability, they may be used as excipients in a variety of industries, including biotechnology, agriculture, chemicals, cosmetics, and the food sector. Additionally, CDs have been used as antigen vectors, vaccination adjuvants, antibody stabilizers, and antiviral activity enhancers, as well as to improve medication solubility and bioavailability [10]. Studies on their toxicity have also revealed that CDs are safe to use orally [11]. For β-CD, the acceptable daily consumption has been established to be between 0 and 0.5 mg per kg of body weight, however the acceptable daily intake for α- and γ-CD is not indicated [12,13]. Both α-CD and β-CD function as dietary fibers that contribute to regulating blood lipids and body weight. While γ-CD is easily broken down, α-CD and β-CD are largely resistant to digestion by human amylase enzymes in the digestive system [14]. Furthermore, more than 10,000 metric tons of cyclodextrins are annually produced, with β-cyclodextrin accounting for 70 %, α-cyclodextrin 15 %, γ-cyclodextrin 5 %, and various cyclodextrin derivatives 10 % [15]. The increasing applications of CDs across various industries are driving market demand, which is projected to reach approximately $390 million by 2027 [6].

2. Materials and methods

The search for literature in the Web of Science database was conducted using the keywords "β- cyclodextrin" or "cyclodextrin". In the Web of Science and Scopus, 51,085 research, review articles, book chapters, letters and conferences were identified for this review (Figure 1). The main goal of the present study is to have a detailed overview of the knowledge gained over the years regarding cyclodextrin. The structure, source, manufacture, and features of cyclodextrin were thoroughly covered. Additionally, possible applications of cyclodextrin in various food industries as well as its advantages for improving health were covered.

3. Production of cyclodextrins

When starch is broken down by the enzyme cyclodextrin glucanotransferase (CGTase), cyclodextrins (CDs) are produced as a result of the initiation of the intramolecular glucose conversion pathway [16]. Nevertheless, a mixture of cyclodextrins with bigger rings and higher proportions of β-, α-, and γ-CDs is produced by all known CGTase enzymes [17]. Various enzymes, such as CGTase, dextranase, pullulanase, β-galactosidase, and isomaltase, can catalyze transglycosylation reactions. However, CGTase is preferred due to its advantages over alternative enzymes, which often suffer from lower yields, partial hydrolysis of glycosidic compounds, poor regioselectivity, and the formation of undesirable byproducts. In contrast, CGTase provides higher conversion yields of glycosylated products, exhibits minimal hydrolytic activity, demonstrates enhanced transglycosylation efficiency with specific acceptors and maintains high regioselectivity, specifically catalyzing α-(1→4)-glycosyl transfer reactions [6,18]. Currently, only two commercially available cyclodextrin glycosyltransferases (CGTases) exist. The first, Toruzyme, originates from *Thermoanaerobacter* sp. ATCC53627 and produces a mixture of cyclodextrins (CDs); it is marketed by Novozyme in Denmark. The second, Amano, is derived from *Paenibacillus macerans*, also yielding a CD mixture, and is distributed by Amano Enzyme Europe Ltd. in Milton, UK. This highlights the need for developing large-scale production processes for CGTases to meet increasing demand [6].

Cyclodextrin glucanotransferase is an extracellular enzyme that occurs in nature at the cellular level and is produced by a variety of microorganisms, including fungi, bacteria, and archaea. CGTases are a unique member of the α-amylase family, which have been isolated from a majority of *Bacillus*, *Paenibacillus*, *Klebsiella*, *Thermoanaerobacterium*, *Geobacillus*, *Gracibacillus*, and *Actinomycetes* species [6,18]. Approximately 90 % of bacteria that produce CGTase belong to the genus *Bacillus*. Different fermentation techniques, including solid-state, submerged, and surface culture, as well as different modes of fermentor operations such as batch, fed-batch, and continuous fermentation, have been developed and utilized for the production and enhancement of various fermentation processes [19] as shown in Table 1.

The characteristics of the enzyme are mainly determined by the microorganism that produces it. Its mechanism is influenced by the production conditions. CGTases have been identified with a molecular mass ranging from 33 to 110 kDa. Additionally, based on their product specificity, CGTases are divided into three main classes: α-, β-, and γ-CGTases. The type and amount of cyclodextrin produced generally depends on several factors, including the source of cyclodextrin glucanotransferase, the substrate utilized, the incubation or reaction time, as well as temperature, pH, and the presence of complexing agents. As a result, researchers seek out or enhance CGTase enzymes to improve production yield and specificity [6,19] as shown in Table 2.

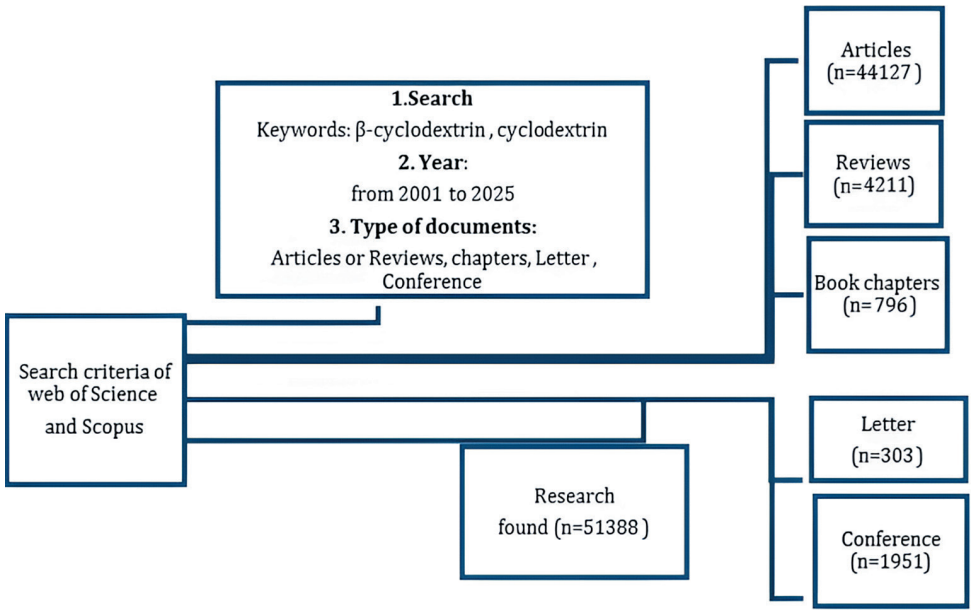

Figure 1. **Total of 51,388 research, review articles, book chapters, letters and conferences referred in paper by searching keywords "β-cyclodextrin" or "cyclodextrin" in the Web of Science and Scopus**

Рисунок 1. **В Web of Science и Scopus найдено 51388 исследований, обзорных статей, глав книг, писем и конференций с упоминанием ключевых слов «β-циклодекстрин» или «циклодекстрин»**

Table 1. **CGTase production by *Bacillus* spp. and other microorganism**

Таблица 1. **Продукция ЦГТазы бактериями рода *Bacillus* и другими микроорганизмами**

Microorganism	Optimal fermentation conditions				CD produced	References
	Substrate	pH	Temp. (°C)	Time (h)		
Bacillus circulans DF 9R	Cassava starch	8.3	37	48	β	[20]
Bacillus licheniformis	Soluble starch	8	37	24	B	[21]
B. pseudalcaliphilus 20RF[a]	Raw starch	9.8	40	24	β/Y	[22]
B. lehensis	Rice starch	10.5	37	24	β	[23]
Bacillus circulans	Cassava starch	7.6	37	48	β	[24]
Bacillus megaterium	Amaranth starch	8	50	36	β	[25]
Bacillus sp. NR5 UPM[e]	—	—	37	24	β/Y, α	[26]
B. circulans ATCC21783[a]	Soluble starch	9.8–10	40	24	β	[18]
B. macerans 15[a]	Potato starch	7	37	48	α	[18]
B. sphaericus 41[a]	Soluble starch	10.3	37	48	β	[18]
B. pseudalcaliphilus 8SB[a]	Soluble starch	9.8–10	40	24	β/Y	[18]
B. *halodurans*[a]	Soluble starch	10.5	37	72	β	[18]
B. agaradhaerens LS-3C[a]	Soluble starch	9	37	30	α/β	[18]
B. halophilus BIO-12H[a]	Potato starch	7–7.2	37	24–30	β/Y	[18]
Bacillus sp. T1[g]	Soluble starch	—	37	72	α/β	[27]
Evansella caseinilytica[c]	Soluble potato starch	9	37	48	Y	[6]

Table 2. **Optimal reaction parameters for maximizing CD production using cyclodextrin glucanotransferase**

Таблица 2. **Оптимальные параметры реакции для максимизации продукции ЦД посредством циклодекстринглюканотрансферазы**

Source of enzyme	Type of substrate	Temperature	pH	Time of reaction (h)	% of conversion or quantity	Ref.
Bacillus circulans DF 9R	Cassava starch	56	6.4	4	66%	[20]
Bacillus agaradhaerens KSU-A11	Potato starch	55	10	1	66.4%	[28]
Bacillus sp.	Starch of corn	50	7	3	4.1 g/L	[29]
Microbacterium terrae KNR9	Potato starch	60	6	1	13.46 gm/L	[30]
Bacillus licheniformis	Potato starch	40	6	4	12.41 mg/ml	[31]
Bacillus lincheniformis	Potato starch	45.2	5.6	24	5.65 mg/ml	[32]

4. Structure and properties of cyclodextrins

Cyclodextrins are formed by several glucose units joined together by oxygen atoms. These molecules have a hollow, truncated cone shape, with hydrogen bonds forming between secondary hydroxyl groups on adjacent units at the broad edge of the cavity [33]. The primary hydroxyl groups, composed of six glucose units, are located at the narrow end, while the secondary hydroxyl groups, made up of two and three glucose units, are positioned at the wide end. Due to their unique structure, cyclodextrins are highly soluble in water and contain hydrophobic cavities. This allows them to encapsulate hydrophobic compounds and form inclusion complexes without changing their structure or chemical makeup [2]. Cyclodextrins have a truncated cone shape with a hydrophilic outer wall and a less hydrophilic inner wall. The inner wall forms a more apolar internal cavity, which enables cyclodextrins to simultaneously host lipophilic guest molecules and make them soluble in water. This unique design allows for increased water solubility of lipophilic compounds when incorporated into cyclodextrins (Figures 2 and 3). Cyclodextrins have several benefits, including greater resistance to hydrolysis and enzymatic destruction, better complexing capabilities, and larger solubilizing potential compared to linear dextrins [34,38]. According to [35], a study was conducted on the structure of original CDs, and they found that although the outer part of CDs takes the shape of a truncated cone, the inner cavity takes the shape of a conical hourglass. The shape of cyclodextrins results from the inward emission of glycosidic oxygen. The hydrophobic inner cavity facilitates the formation of inclusion complexes with host molecules, primarily through van der Waals forces, hydrogen bonds, and hydrophobic interactions. These host-guest complexes are highly dynamic, with their stability depending on the size, polarity, and structure of the guest molecule in relation to the cavity. Cyclodextrins can accommodate hydrophobic molecules or portions of larger molecules, stabilizing them by isolating the encapsulated guest from the aqueous environment, which improves solubility, bioavailability, and resistance to degradation [36]. The flexibility and encapsulation ability of cyclodextrins enable for host-guest interactions, which alter the chemical, biological, and physical characteristics of the guest molecules [37]. According to [38], the three most common CDs are α, β, and γ, which are composed of six, seven, and eight glucose subunits with widths of 0.5, 0.6, and 0.8 nm, respectively. As seen in Table 3, the differences in their structures account for their disparate physical and chemical characteristics. Additionally, the chemical properties of cyclodextrins can be modified through functionalization of the hydroxyl groups to form derivatives (e. g., hydroxypropyl-β-cyclodextrin, methylated cyclodextrins), allowing for tailored properties such as enhanced solubility, complexation efficiency, and targeted applications. Cyclodextrins are relatively thermally stable, with decomposition occurring at temperatures above 250 °C. This stability is linked to the glycosidic bonds in their glucose units. Due to their low toxicity, biocompatibility, and capacity to form stable complexes with a variety of organic, inorganic, and biological molecules, cyclodextrins have been studied extensively for their use as solubilizing agents, molecular encapsulants, and drug delivery systems [27].

Table 3. **The three natural CDs' physical and chemical characteristics**

Таблица 3. **Физические и химические свойства трех природных ЦД**

Physical and chemical properties	α-CD	β-CD	Y-CD	References
Glucose units	6	7	8	[33]
Molecular weight (kDa)	972.84	1134.98	1297.12	[19]
Chemical formula	$C_{36}H_{60}O_{30}$	$C_{42}H_{70}O_{35}$	$C_{48}H_{80}O_{40}$	[8]
Diameter of central cavity (nm)	0.57	0.78	0.95	[2]
Outer diameter (nm)	1.4–1.5	1.5–1.6	1.7–1.8	[8]
Melting point (°C)	275	280	275	[8]
pKa at 25 °C	12.3	12.2	12.1	[8]
Internal water molecules	6–8	11–12	13–17	[8]

α-CDs have smaller cavities, restricting their capacity to host a large number of molecules. They primarily accommodate smaller molecules compared to γ-CDs. Additionally, the payloads within hydrophobic CDs struggle to interact effectively, which complicates complex formation. The cavity of β-CDs, however, is more suitable for molecules like vitamins, hormones, and other substances typically used in tissue and cell culture applications. Because of these characteristics, β-CDs are often the preferred choice for complexing agents [39]. The structure of cyclodextrins has key features:

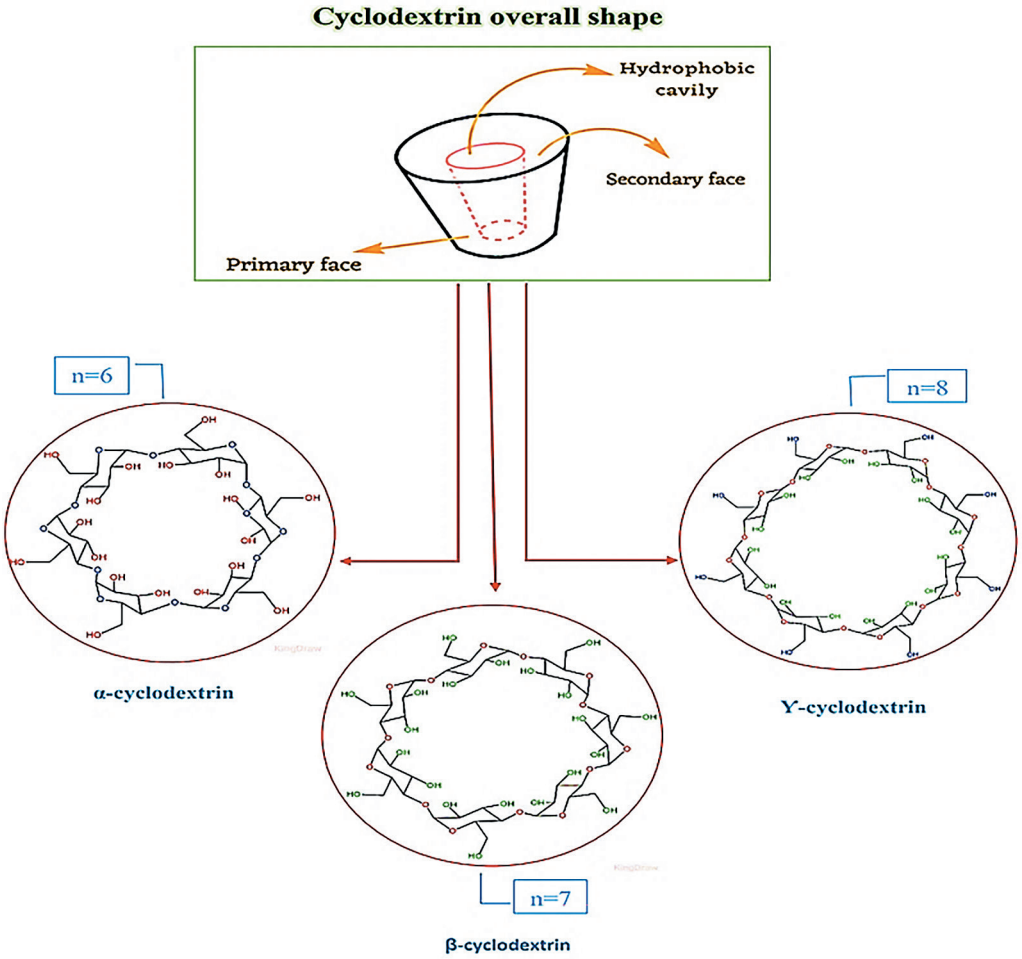

Figure 2. **Structure of cyclodextrins. Monomeric units of sugar molecules organized in rings are called cyclodextrins. The amount of sugar molecules (6, 7, or 8) determines the classification of the cyclodextrins as α, β, or Y, respectively**

Рисунок 2. **Структура циклодекстринов. Мономерные единицы молекул сахара, организованные в кольца, называются циклодекстринами. Количество молекул сахара (6, 7 или 8) определяет классификацию циклодекстринов как α, β или Y соответственно**

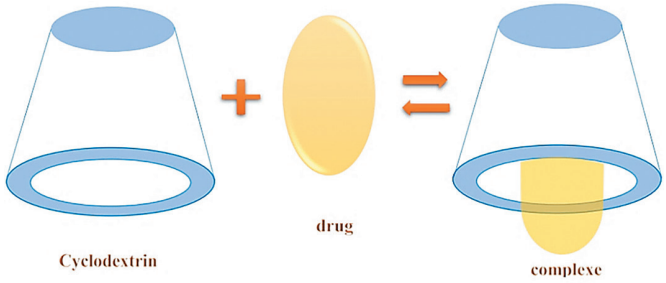

Figure 3. **Formation of cyclodextrin inclusion complexes**

Рисунок 3. **Образование комплекса с включением в полость циклодекстрина**

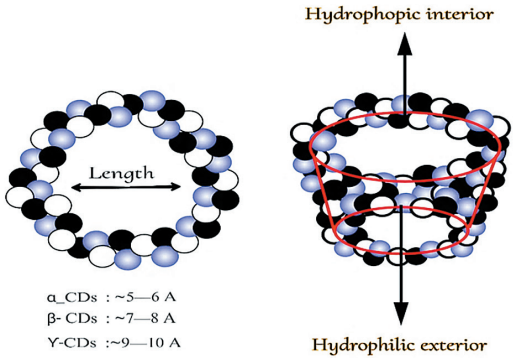

Figure 4. **Cyclodextrin schematic representations**

Рисунок 4. **Схематические изображения циклодекстринов**

1. Hydrophilic surface: The outer surface of cyclodextrin is composed of hydroxyl groups (–OH) attached to glucose units. The primary hydroxyl groups are positioned at the narrow end of the cone, particularly on carbon 6 of the glucose molecules, while the secondary hydroxyl groups are located on carbons 2 and 3 at the broad edge. This hydrophilic surface enables cyclodextrins to interact effectively with water, making them soluble in aqueous solutions [40].

2. Creation of a hydrophobic cavity: Within the ring structure, the hydrogen atoms and ether-like oxygen atoms in the glucose units contribute to forming a relatively nonpolar, hydrophobic cavity. This inner space can accommodate various hydrophobic guest molecules, making cyclodextrins excellent for encapsulation. The cavity's hydrophobic nature allows the inclusion of nonpolar substances while keeping the polar exterior exposed to the surrounding water [41,42] (Figure 4).

5. Characterization of CD inclusion complex

Encapsulation induces several notable changes in both host and guest molecules. The solubility of the guest molecules significantly increases, whereas the concentration of dissolved cyclodextrins (CDs) may remain unchanged or decrease depending on the solvent used. Additionally, the spectral properties of the encapsulated molecule, including UV absorption bands, fluorescence, and NMR spectra, undergo modifications. Encapsulation also reduces the reactivity and volatility of the guest molecule. Furthermore, hydrophobic guest molecules acquire hydrophilic characteristics, altering their mobility in chromatographic analyses [2,36].

Due to the importance of cyclodextrins complexes, different methods have been used to diagnose and study the properties of these complexes, such as spectroscopic (ultraviolet/visible, fluorescence, nuclear magnetic resonance, electrons spin resonance, Fourier-transform infrared), electroanalytical (polarography, voltammetry, conductimetry, potentiometry), separative (high-performance liquid chromatography, gas chromatography, thermal, differential scanning calorimetry (DSC), thermal gravimetric analysis, X-ray, single crystal X-ray diffraction, powder

X-ray diffraction, polarimetry [8,40]. These methods rely on variations in physical or chemical properties of the guest molecule useful for tracking complex formation [40]. A comprehensive set of advanced analytical techniques is employed to study and characterize inclusion complexes, providing a precise understanding of their structural and physicochemical properties. Fourier-transform infrared spectroscopy (FTIR) is a fundamental tool for analyzing these complexes by examining molecular vibrational energy level transitions, which reveal structural modifications and molecular interactions occurring during complex formation. In addition, nuclear magnetic resonance (NMR) spectroscopy serves as an effective method for determining the molecular structure of inclusion complexes. This technique is based on the absorption of radiofrequency radiation by atomic nuclei in the presence of a strong magnetic field. The formation of an inclusion complex is confirmed by shifts in the chemical environment of nuclei, reflected in the NMR spectrum as changes in chemical shift values, which indicate interactions between the host and guest molecules. Furthermore, X-ray diffraction (XRD) is a crucial technique for detecting structural modifications associated with the formation of inclusion complexes. This method relies on analyzing diffraction patterns generated by the crystalline lattice of materials when exposed to X-rays. The presence of distinct diffraction peaks, which differ significantly from those of the original functional ingredient, serves as strong evidence of complex formation, confirming changes in the crystalline structure resulting from molecular encapsulation. Beyond spectroscopic and structural analyses, thermal analysis techniques provide critical insights into the thermodynamic properties of inclusion complexes. Thermal analysis is used to investigate the relationship between a substance's physicochemical properties and its thermal-induced transformations, such as phase transitions, melting, decomposition, and oxidation. These changes are monitored by measuring variations in mass or energy under controlled temperature conditions. The most commonly employed thermal analysis techniques include differential thermal analysis (DTA), thermogravimetric analysis (TGA), and differential scanning calorimetry (DSC). These methods allow for qualitative and quantitative assessments of the crystallinity of substances during the melting process, offering valuable information about the thermal stability and phase behavior of inclusion complexes with high precision [8].

6. Types of cyclodextrins

Cyclodextrin glucanotransferase catalyzes four reactions: hydrolysis, cyclization, coupling, and disproportionation. This is achieved by breaking α-1,4-glycosidic bonds found within the inner part of a polysaccharide chain. Among these reactions, cyclization is the specific enzymatic process that produces three types of cyclodextrins (CDs) from starch and its derivatives [18,19], including:

6.1. Alpha-cyclodextrin (α-CD)

α-Cyclodextrin is composed of six glucose units, with a molecular weight of 972.84 Da and a chemical formula $C_{36}H_{60}O_{30}$. Due to its narrow cavity and strong resistance to enzymatic hydrolysis, α-cyclodextrin is utilized in various industries, especially in the food sector. At 25 °C, α-cyclodextrin exhibits moderate water solubility, approximately 1.6 times lower than γ-CD but several times higher than β-CD. Its limited digestibility and lower risk of causing indigestion make it suitable for use in large quantities. Several chemical derivatives of α-CD have been developed through modifications of its hydroxyl groups. For example, cyclodextrin glycosyltransferase catalyzes the enzymatic conversion of starch or its derivatives into α-CD. However, α-CD holds a smaller market share compared to β-CD, largely due to its higher cost and lower yield [43,44].

6.2. Beta-cyclodextrin (β-CD)

β-Cyclodextrin is a chemical compound with the formula $C_{42}H_{70}O_{35}$ and a molecular weight of 1135 Da. Its cavity size is ideal for accommodating many drugs with molecular weights ranging from 200 to 800 Da, and its melting point can exceed 280 °C [45]. Composed of seven glucose units, β-CD has a stable average cavity size, enabling it to form complexes with a variety of guest molecules efficiently and at a reasonable cost. Among the three types of cyclodextrins, β-CD has the lowest solubility and the strongest hydrogen bond strength, owing to the flexible hydroxyl groups located on its narrow edges, which facilitate hydrogen bond formation [36,44].

6.3. Gamma-cyclodextrin (γ-CD)

γ-CD has a molecular weight of 1297 Da and the chemical formula $C_{48}H_{80}O_{40}$. It consists of eight glucose subunits connected end-to-end by α-1,4 bonds, forming a tapered cylinder with 8 primary alcohol groups on one side and 16 secondary alcohol groups on the other side [36,46]. Cyclodextrin's inner core is hydrophobic, while its outside surface is moderately hydrophilic. γ-CD has the largest cavity, making it well-suited to accommodate larger biomolecules and other guests, with maximum solubility and the best level of safety among the three CDs. However, the high expense associated with the manufacture and purification of enzymes restricts the large-scale production of γ-CD [44].

7. Application of CDs

There are a variety of applications for CDs and their derivatives in the food, cosmetics, and pharmaceutical industries (Figures 5 and 6), though they are more prevalent in the food industries [11].

In the food industry, CDs are usually used as an adjuvant, a technological tool that improves the physical and chemical characteristics of food components. For instance, they can be used to stabilize aroma and flavor compounds, polyunsaturated fatty acids (PUFAs), and poorly water-soluble vitamins and nutrients. This allows the complex food components made of cyclodextrin to be incorporated into automated food processing systems on an industrial scale. Additional examples include taste masking and the elimination of undesirable ingredients like cholesterol from dairy products and eggs [9,40,46]. Cholesterol and CDs can combine to create inclusion complexes, which trap the cholesterol molecule inside the CD cavity. This complexation makes cholesterol more soluble, which

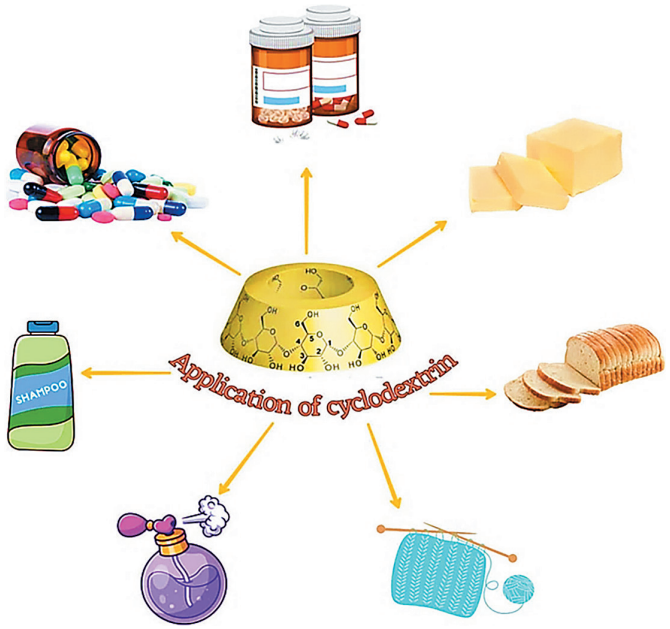

Figure 5. **CDs and their derivatives' applications**
Рисунок 5. **Применение ЦД и их производных**

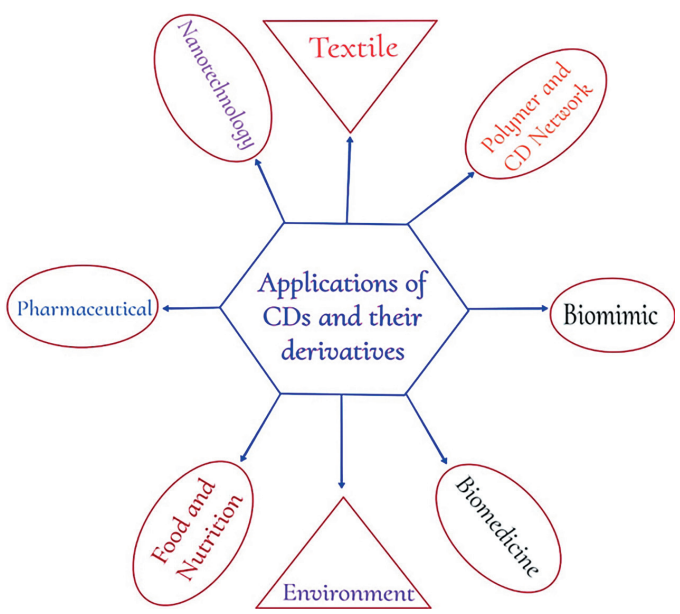

Figure 6. **Applications of cyclodextrins**
Рисунок 6. **Применение циклодекстринов**

may make it easier for the body to eliminate it. A cross-linked cyclodextrin made with adipic acid was employed to reduce the cholesterol content in butter. The treatment, which involved 10% cross-linked cyclodextrin, achieved a 90% reduction in cholesterol levels. Additionally, no significant adverse effects on the chemical, rheological, or sensory properties of the butter or cheese were observed [47]. Cyclodextrin has also been used in various hydrocolloids such as carrageen or starch, which has shown significant improvement in the properties and characteristics of the hydrocolloids. When combined with xanthan or guar gum, CDs can improve the viscosity of both hydrocolloids [40]. Additionally, microbial contamination can be removed using cyclodextrins [27]. Cyclodextrins are used in active packaging to improve food preservation by controlling the release of active substances like antioxidants, antimicrobials, and flavor compounds. They can encapsulate antioxidants such as ascorbic acid or tocopherols to prevent oxidation and spoilage of packaged food products. This type of packaging allows for a controlled release of compounds, allowing them to be released slowly over time, thus prolonging the shelf life of foods such as meat, oils and dairy products. Additionally, cyclodextrins can trap natural antimicrobial agents like essential oils (e. g., thyme, oregano) or bioactive compounds (e. g., nisin, lysozyme) in their hydrophobic cavity, helping to gradually release them. This gradual release inhibits microbial growth, thereby preventing foodborne illness and spoilage [48].

According to reports, bitter gourd (*Momordica charantia* L.) is useful for diabetes. The addition of β-CD to bitter gourd juice enhances its palatability, which suggests that it might be used as an additional treatment for diabetes. Momordicoside K and momordicoside L, two triterpene glycosides, are the active components of bitter gourd that give it its bitter flavor. It has been demonstrated that β-CD improves antioxidant activity and lessens bitterness, which increases consumer acceptability [9].

Through binding certain pigment compounds, such as anthocyanin, or the substrate of an enzymatic reaction, like phenolic compounds in the case of enzymatic browning, CDs have been used to either improve the stability of natural colorants in food during food processing and storage, or to prevent the formation of browning reactions [49]. Food-related activities that can be stopped using CDs include oxidation, light-induced reactions, heat-promoted breakdown, self-decomposition, and loss caused by volatility or sublimation [11].

CDs can be used to lower off-flavors. According to [50], authors investigated the impact of β-CD at concentrations of 0.05% — 0.25% on watermelon juice heat treatment in combination with other polymers. Of all the polymers analyzed, β-CD was found to be the most effective in reducing off-flavors after heat treatment. They also noted that the timing of β-CD addition had a significant effect, with addition after heat treatment being more effective in reducing off-flavors than addition before treatment [49].

Cyclodextrins improve the water absorption capacity of flour due to their numerous hydroxyl groups, which can form hydrogen bonds with water molecules. This reduces the availability of water, which in turn affects the formation of the gluten network. Consequently, changes in the dough's mixing and extensibility properties may occur. Additionally, CD can increase the proportion of α-helix in gluten protein and reduce the proportion of β-sheet, indicating that the secondary structure of gluten protein was affected by CD [51].

In the cosmetics industry, CDs are used in cosmetics products to extend their shelf life, stabilize volatile chemical ingredients, lessen offensive tastes or smells, and prevent or lessen topical irritation. CDs are widely used in treatments for dermatitis, psoriasis, acne, sun protection, and wound healing, as well as in deodorants and shampoos [49]. The cosmetics industry uses bioactive chemicals derived from natural sources because they often have a higher safety profile than synthetic ones. Even though their biological actions have been scientifically shown, they are difficult to handle, which limits their usage and activity. The bioavailability, solubility, and stability are among the problems that are resolved by using the CDs [39].

CDs are used in medicine as either therapeutic substances or excipients that improve the solubility and stability of drugs [5,52]. CDs and their derivatives provide advantages including enhancing the bioavailability and efficacy of current medications, which leads to a variety of applications in the pharmaceutical industry. Beta-cyclodextrin is a fundamental component in many pharmaceutical formulations, primarily used to enhance the solubility and bioavailability of drugs with poor water solubility. This compound forms inclusion complexes with pharmaceutical molecules, thereby facilitating increased drug absorption in the body. Additionally, it is employed to reduce irritation caused by certain drugs when applied topically or administered orally. Furthermore, beta-cyclodextrin plays a role in stabilizing drugs sensitive to environmental factors such as light and heat, prolonging their shelf life and maintaining their efficacy [41,53,54]. There are already more than 50 medicinal items on the market that include CDs [55].

The most important cyclodextrin in the pharmaceutical and medical industries is the β-CD, which is also the most often utilized. The popularity of cavity can be attributed to its ideal size for many common pharmaceutical drugs with molecular weights ranging from 200 to 800 g/mol, its straightforward production process, availability in pure form, efficient drug complexation capabilities, relatively low cost, and its ability to both enhance drug efficacy and reduce toxicity. Though it has some drawbacks over α-CD and γ-CD, such as reduced solubility in water, the β-CD makes up over 90% of all cyclodextrins that are made and ingested [40]. According to biosafety studies, CDs are useful for delivering lipophilic pharmaceuticals since they have helped to lessen the harmful side effects of numerous medications that arise from their poor solubility. CDs assist in controlled drug release, which can be regulated by solubility, osmotic pressure, or pH control [41,56]. CDs may help reduce the side effects of drugs that cause irritation or have a bitter taste or unpleasant smell [57].

The compressed tablets provide effective protection that enhances the stability of antioxidants and UV filters when exposed to sunlight and oxygen. In addition, studies have shown that these tablets can significantly increase the water solubility of poorly soluble antioxidants, enhancing their biological efficacy, particularly in the field of anti-cancer [53].

Since cyclodextrin may combine with drugs to create inclusion complexes, it is a useful tool in the development of more potent anti-cancer chemotherapy regimens. Many studies have examined the insertion of conventional medications or naturally occurring bioactive substances into CDs' cavities in an effort to better understand their effects on various cancer cell lines in vitro or as in vivo therapeutic possibilities in animal models [53,58].

Cyclodextrins (CDs) and their derivatives are widely used in various applications in analytical chemistry, particularly in analytical separations, due to their ability to distinguish between positional isomers, functional groups, homologues, and enantiomers. They are utilized in a range of applications, including chromatography, wastewater treatment, and other separation techniques [11]. A recent study has highlighted the potential of CD derivatives as vehicles for siRNA delivery. While a few of these derivatives have been approved for human use, others, such as TRIMEB (heptakis-2,3,6-tris-O-methyl β-CD) and SBE-β-CD (sulfobutylether β-CD), remain in the experimental phase [59].

Cyclodextrins have received wide attention due to their environmental applications, as they have the ability to form entrapment complexes with a variety of hydrophobic organic pollutants. These compounds have a unique structure, including a hydrophilic outer surface and a hydrophobic interior, which enables cyclodextrins to trap and remove pollutants from water, soil, and air. This makes them of great interest in the fields of environmental remediation and green chemistry [60]. Environmental scientists use CDs in several areas, such as enhancing the solubilization of organic pollutants and removing contaminants from wastewater, soil, and air. Since CDs are inexpensive and biodegradable, their usage in this industry is favored [6]. Through the use of chemistry with stimulating chemicals, such as functional golden nanotechnologies coupled with β-cyclodextrin, β-CD has been effectively used to eliminate organic contaminants, such as aromatic nitrogen. These nanoparticles produced with β-cyclodextrin may pave the way for the removal of pollutants from aquatic settings [61]. CDs are also useful for delaying seed germination. Grain treated with β-CD has a 20% to 45% higher harvest percentage because a part of the amylases that break down the starch storage in the seeds is inhibited [57].

In recent years, there have been a lot of research on the use of β-CD to encapsulate volatile materials with unstable chemical and physical characteristics, like essential oils [62]. Moreover, β-CD has been shown to be highly effective in improving the delivery characteristics of processed composite components in food systems, as well as in altering the density and texture of food products to enhance their mouthfeel.

The unique structural properties of cyclodextrins enable them to form inclusion complexes with a variety of guest molecules, including organic pollutants, pesticides, dyes, pharmaceuticals, and hydrocarbons. Cyclodextrins act as molecular sponges in water treatment, effectively trapping pollutants within their cavities. This process occurs through non-covalent interactions, such as hydrogen bonding, van der Waals forces, and hydrophobic interactions. When cyclodextrins are introduced to polluted water, they encapsulate contaminants within their cavities, forming stable inclusion complexes. This mechanism reduces the concentration of pollutants in the surrounding water, making cyclodextrins a powerful tool for decontamination. One notable advantage of using cyclodextrins in these applications is their reusability. These molecules can often be

regenerated and used multiple times, enhancing their cost-effectiveness in water treatment processes. Recent advancements have highlighted their potential across various scenarios of contaminant adsorption, showcasing their versatility and practicality [63].

8. Conclusion, prospective future, and suggestions for more research

The use of cyclodextrins (CDs) and their derivatives has expanded significantly in recent years, due to their diverse applications in food, cosmetics, and pharmaceuticals. The main reason behind their widespread use is their ability to form host-guest complexes with various chemicals. These complexes are formed as a result of the unique structural properties of cyclodextrins, such as their hydrophobic cavities. Moreover, the CDs can contribute to improved water solubility, as well as enhanced physical and chemical properties and the capacity to introduce various compounds. Molecular encapsulation with cyclodextrins can extend the shelf life of products by improving the physical and chemical stability of flavors, vitamins, pigments, unsaturated fats, and other lipophilic compounds. Additionally, this technique improves sensory qualities and aids in avoiding microbial contamination. Furthermore, CDs are regarded as advantageous nutrients and biologically active dietary supplements. Due to their low toxicity, these tablets may be utilized without endangering human health, leading to healthier products that are less likely to deteriorate.

The current uses of CDs emphasize the increasing demand for CD-based products in the future. The global CD market is expected to expand due to the substantial number of patents related to CD techniques and applications. Projections indicate that the market will grow from $180 million in 2019 to $210 million by 2024, eventually reaching approximately $390 million by 2027. The continued dominance of CDs in the market relies on the availability of robust CGTase enzymes with high product specificity.

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