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Physicochemical Features And Applications Of Cyclodextrin As A Prominent Host In Inclusion Complex Formation

Pankaj Meshram[1*], Rajendra Dongre[2]

[1*]Research scholar, PGTD of chemistry, RTM Nagpur University, Nagpur (M.S.) India. punkaj99@gmail.com
[2]Professor, PGTD of chemistry, RTM Nagpur University, Nagpur (M.S.) India

***Corresponding Author:** Pankaj Meshram
*Research scholar, PGTD of chemistry, RTM Nagpur University, Nagpur (M.S.) India. punkaj99@gmail.com

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Abstract

Cyclodextrins (CDs) are natural compounds with a cyclic structure composed of 6-to-8 glucopyranose units. They have a rich history dating back to their recognition for inclusion complex formation in 1938 and pharmaceutical patent filings in 1953. CDs have a well-established safety profile, allowing their use in drug products. Different CD types, including α-CD, β-CD, and γ-CD, have varying properties and applications. β-CD is widely used in pharmaceuticals for enhancing drug solubility and stability, while γ-CD is ideal for poorly water-soluble drugs. CDs play a crucial role in scaffold development, tissue regeneration, and additive manufacturing. They can reinforce hydrogels, self-assemble into supramolecular networks, and serve as depots for disease management and tissue repair. CD-modified scaffolds facilitate prolonged gene vector delivery and contribute to additive manufacturing by enhancing bioinks and enabling rapid photopolymerization. CDs have a cone shape with a hydrophilic outer surface and hydrophobic cavity, offering conformational flexibility. They find applications in drug delivery, cancer treatment, chromatography, food industry, cosmetics, textiles, and industrial processes. They are also valuable in environmental science for removing pollutants and enhancing wastewater treatment. Concerns about CD toxicity have been addressed, primarily focusing on medical applications. CDs are versatile molecules with multifaceted applications across different fields, driven by their unique structural and chemical properties.

Keywords: Cyclodextrins, Classification of CDs, Host-guest complexes, Self-Assembly and Aggregation of Cyclodextrins, Applications of CDs

1. Historical Events:

In 1952, during investigations into the properties and structure of cyclodextrins (CDs), Cramer foresaw the potential utility of these nanometer-sized, apolar, and chiral cavities in analytical chemistry, especially in separation science [1]. Approximately three decades later, Armstrong provided compelling evidence supporting Cramer's prediction and laid the foundational principles for utilizing cyclodextrins in separation science [2-4]. Between 1980 and 1988, Armstrong and his collaborators pioneered the development and optimization of analytical techniques suitable for isomer separation using CDs. They even introduced CD-bonded chromatographic columns for highly selective and efficient enantiomer separation [5]. Throughout the 1980s and 1990s, various

types of cyclodextrins became commonplace in separation science, serving as additives to enhance sensitivity and selectivity in different analytical methods [6].

Li and Purdy conducted a comprehensive review in the field, focusing on how cyclodextrin structures contributed to improving various chromatographic separations and enhancing the precision and sensitivity of analytical spectrometric methods, such as luminescence spectroscopy and electrochemical analyses [7]. In 1998, a similar survey explored the nonchromatographic applications of CDs [8]. The prospective applications of CDs as reagents in analytical chemistry and diagnostics were compiled by Hinze and coworkers [9]. The adaptable function of CDs as chiral selectors in various separation procedures has been highlighted in more recent reviews [10,11].

This paper's goal is to provide a comprehensive study of "Anchored Cyclodextrin: A Multifaceted Host for Enhancing Physicochemical Characteristics with Guest Moieties."

2. Introduction:

Cyclodextrins (CDs) are a series of extremely adaptable natural substances with a special cyclic structure made up of six to eight glucopyranose units and hydrophilic groups on the outside. These interesting compounds were first identified over a century ago, and it was revealed in 1938 that they could form inclusion complexes. Their first patent application for a pharmaceutical product was submitted in 1953 [12,13]. The exceptional capacity of CDs to host hydrophobic compounds, hence changing their physicochemical properties, makes them one of the first known drug nanocarriers [14]. Additionally, CDs are viewed as molecular devices capable of displaying movements similar to those of machinery [15]. When they are placed in watery conditions, their full potential is shown. CDs can spontaneously self-assemble into nanoparticles or form inclusion complexes with other substances, including polymers, when they are discharged from their solid crystalline form into aqueous solutions [16–18]. Furthermore, CDs can be chemically grafted onto both natural and synthetic polymers or inorganic particles to leverage multiple noncovalent interactions, closely resembling natural molecular recognition mechanisms and enhancing binding affinity with various molecules and substrates [19–23].

The diverse range of guest molecules and resulting supramolecular structures have led to growing interest in CDs across various sectors, including pharmaceuticals, cosmetics, and food, as well as emerging fields like regenerative medicine [24–26]. Importantly, CDs have well-established safety profiles and clearance mechanisms from a regulatory perspective and have been utilized as components of approved drug products for many years [27,28]. This established safety profile is advantageous when compared to novel materials for scaffold development. For example, while natural β-CD may cause renal toxicity after intravenous administration, the Permitted Daily Exposure (PDE) for α-CD is 0.2 mg/kg/day, equivalent to 10 mg for a human weighing 50 kg. In contrast, γ-CD is safe for continuous administration at up to 600 mg/kg/day for three months, and derivatives like hydroxypropyl-β-CD (HP-β-CD) and sulfobutylether-β-CD (SBE-β-CD) are components of parenteral formulations, administered daily in amounts of 16 g and 14 g, respectively, without causing adverse effects in humans older than 2 years. Even scaffolds based on α-CD are expected to erode slowly in vivo, potentially leading to non-adverse effect levels [29]. Hydrogels, consisting mainly of hydrophilic polymers forming a 3D network, closely mimic the water content and mechanical properties of human soft tissues, making them biocompatible platforms [30]. Combining the properties of hydrogels with those of CDs results in synergistic advantages. In physically cross-linked gels, CDs can act as structural agents, reinforcing viscoelasticity and extending residence time at the application site [31, 32]. Amphiphilic

copolymers can thread along CD units, creating various poly(pseudo)rotaxane structures that self-assemble into supramolecular networks based on interactions between neighboring CDs [33]. Furthermore, polymers with side chains containing suitable guest moieties can form zipper-like assemblies with polymers carrying pendant CDs [34-36]. Notably, both polypseudorotaxane- and zipper-based supramolecular assemblies can be easily disrupted under mild shear conditions and rapidly regain their structure at rest, making them ideal for the preparation of injectable depots. Additionally, host-guest interactions are sensitive to various internal and external stimuli, facilitating the development of responsive materials that can adapt their properties as needed and exhibit self-healing capabilities [37-39]. In chemically cross-linked gels, the covalent attachment of CDs to the 3D network promotes the cooperative binding of guest molecules and prevents dilution upon contact with physiological fluids. CD-rich domains within the network allow the hosting of hydrophobic active substances while maintaining compatibility with the aqueous environment of the hydrogel. Moreover, CD domains impart affinity-driven loading and release properties, demonstrated in various gel formats ranging from nano- to macro-scale [40, 41]. This hosting ability extends to CDs chemically grafted onto medical devices, offering new avenues for designing drug-eluting devices, particularly to prevent biofilm formation [42,43].

Extensive literature already exists on the excellent performance of both CD-based physically and chemically cross-linked gels as depots for managing a range of diseases [44,45]. Ongoing efforts are focused on optimizing designs and implementing novel strategies to create mechanically robust networks for advanced cell scaffolds in tissue regeneration [46]. Besides sustaining the release of growth factors, CD-based supramolecular gels can facilitate the delivery of gene vectors capable of modifying mesenchymal stem cells (MSCs) within the host [47] or act as carriers for genetically modified MSCs [48], thereby enhancing tissue repair and angiogenesis. In this context, modified CDs can serve as non-viral vectors themselves [49, 50], or the CD-structured scaffold can serve as a platform for the prolonged delivery of both non-viral and viral gene vectors [51].

The multifaceted capabilities of CDs have also found applications in the rapidly evolving field of additive manufacturing technologies. One significant challenge in 3D printing is the development of cytocompatible bioinks that can withstand processing conditions and result in 3D structures mimicking the shape of the target tissue [52]. Recent advancements suggest that CDs can enhance bioinks by providing the required flowability for extrusion through nozzles and maintaining the necessary consistency for shape fidelity. Furthermore, CDs can be surface-functionalized to induce rapid curing of 3D structures or act as solubilizers for hydrophobic photoinitiators, enabling rapid photopolymerization [53]. These properties can also be leveraged to produce electrospun fibers for tissue regeneration [54]. Finally, CDs are particularly suitable for creating composites with inorganic salts similar to bone constituents, opening the possibility of developing cements that induce calcification while delivering growth factors or other active substances [55]. Figure 1 summarizes the versatile roles of CDs in scaffold applications.

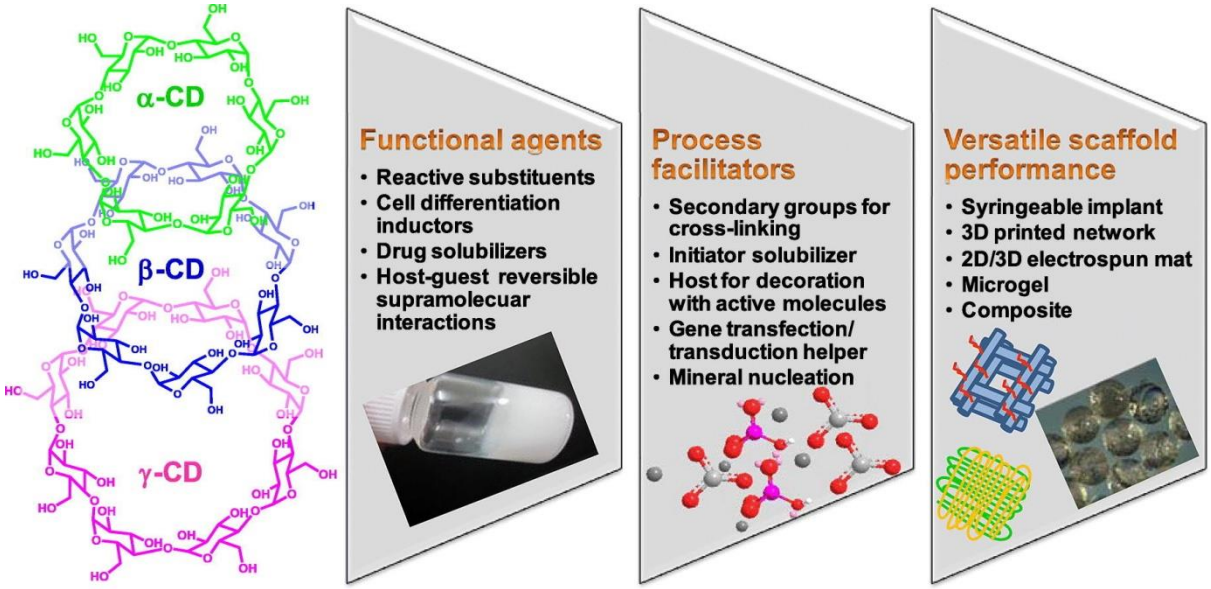


Figure 1: Some of the role played by cyclodextrins as functional agents, process facilitators and structural components of advanced 2D and 3D architectures for regenerative medicine. [56]

In this review, we will provide an in-depth analysis of physicochemical characteristics, self-assembly abilities, inclusion complexation, and potential applications of CDs.

3. Classification of CDs:

3.1 α-CD:

Cyclodextrins (CDs) are primarily categorized based on the number of glucose units within their structure. For instance, CD molecules composed of 6 glucose units are referred to as α-CD [57]. These CDs exhibit weak hydrogen bonding, particularly between the 2-OH and 3-OH groups located at the outer edge. This bonding interaction is relatively weak in α-CD but becomes stronger in γ-CD. In α-CD, the 3-OH group acts as a hydrogen bond donor, while the 2-OH group serves as the acceptor. In the case of β- and γ-CD, this bonding pattern switches, with the 3-OH group acting as the acceptor and the 2-OH group as the donor.

Cyclodextrins possess amphipathic structures, where the wider rim displays 3-OH and 2-OH groups, while the narrower rim exhibits 6-OH groups. The molecular cavity within cyclodextrins is surrounded by hydrophilic groups, while the inner part is hydrophobic, covered by ether-like anomeric oxygen atoms. It's worth noting that the cavity size of α-CD is often insufficient for accommodating drugs within its cavity [58-60]. Interestingly, α-CDs are highly effective in extracting phospholipids.

3.2 β-Cyclodextrin (β-CD):

β-CD has traditionally found extensive use in the early stages of pharmaceutical applications due to its readily accessible cavity size, making it suitable for a wide range of drugs. This particular cyclodextrin possesses a cavity size that is well-suited for encapsulating a diverse array of molecules. The utilization of β-CD has a well-established history in pharmacy, primarily driven by its ability to enhance drug solubility, bioavailability, safety, stability, and its role as a carrier in drug formulations through the formation of inclusion complexes with drug molecules [61].

Comprised of seven glucopyranose residues, β-CD exhibits only moderate solubility in water due to intermolecular hydrogen bonding. However, modified forms of β-CD, such as randomly methylated-β-cyclodextrin (M-β-CD), disrupt this hydrogen bonding network, rendering them

considerably more water-soluble. These alkylated CDs also demonstrate reduced toxicity compared to the parent β-CD. Notably, β-CD features a hydrophilic outer surface and a lipophilic central cavity, allowing it to accommodate a variety of lipophilic drugs. This accommodation results in increased solubility of the incorporated drug, improved permeation for macromolecular drugs, and the inhibition of certain protease activities [62].

3.3 γ-CD:

γ-CD possesses a notably spacious internal cavity, offering a distinct advantage in encapsulating larger molecules that may not fit within the confines of α- and β-CDs. One of its standout features is its superior aqueous solubility compared to other natural cyclodextrins, which arises from its noncoplanar and flexible molecular structure. This remarkable solubility property positions it as an excellent host for enhancing the solubility of poorly water-soluble drugs, further expanding its applications across various industries.

However, it's important to note that γ-CD exhibits low bioavailability because it struggles to permeate biological membranes easily. Additionally, it is rapidly digested in the gastrointestinal tract and is excreted unchanged through urine after parenteral administration. Despite these drawbacks, -CD is a promising candidate for enhancing therapeutic characteristics due to its high water solubility, bigger cavity size, and favourable toxicological profile. Saokham and Loftsson recently offered a thorough assessment of -CD that covered topics including formulation, physicochemical characteristics, toxicological profile, and its various uses in various domains [63].

4. Structural and Chemical Properties of Cyclodextrins :

The distinctive structural properties of cyclodextrins (CDs) can be primarily blamed for the wide range of novel uses for them. Therefore, it is essential to start with an explanation of their physicochemical features in order to understand their versatility and prospective uses.

4.1 The Shape of the Native Cyclodextrins:

Non-toxic sugar polymers called cyclodextrins (CDs) are renowned for their stability in organic solvents and water. With reported pKa values ranging from 12.1 to 13.5, they demonstrate great resistance in alkaline conditions. Low pH levels, however, make CDs susceptible to acid hydrolysis, which causes their rings to open and the production of different linear oligosaccharides and individual glucose units [64]. CDs are non-reducing cyclic oligosaccharides made up of -D-glucopyranose subunits joined together by -1,4-glycosidic linkages. They have a hydrophilic, round truncated cone shape with a hydrophobic, hollow conical cavity that extends to a depth of 7.9 as its distinctive geometric feature. This cavity is well-suited for accommodating appropriately sized hydrophobic guest molecules [65-68].

The three primary native cyclodextrins, namely alpha CD (α-CD), beta CD (β-CD), and gamma CD (γ-CD), consist of six, seven, and eight D-glucose subunits, respectively. Their structural representations are provided in Figure 2. The D-glucose subunit typically adopts a 4C1 chair conformation (as depicted in Figure 3), occasionally transitioning into the 1C4 chair conformation, although less frequently [69-73]. This chair conformation of the D-glucose subunit contributes to the overall angular stability of the CD molecule. Additionally, it positions the "bulky" oxygen groups, such as hydroxyls and glycosidic groups, within the equatorial plane, further enhancing the stability of the CD structure.

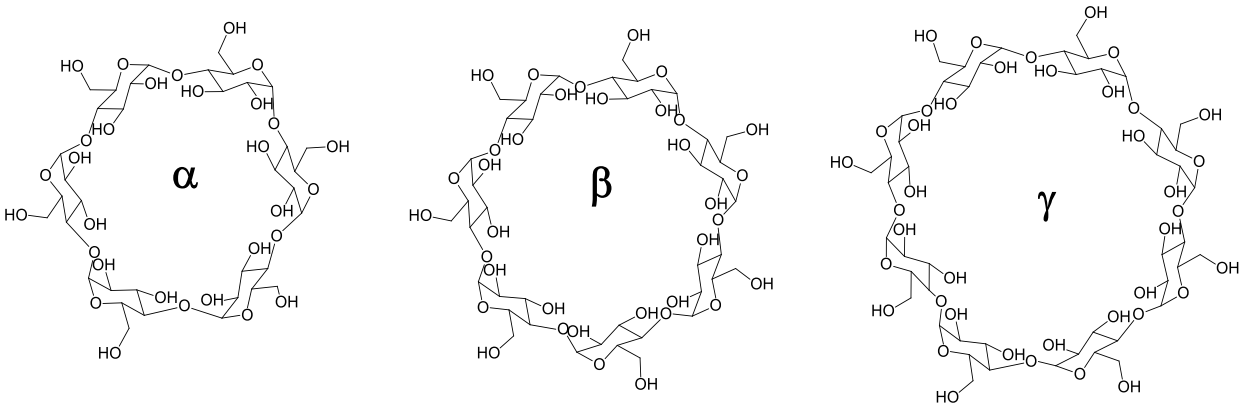


Figure 2: Structure of the native cyclodextrins [74]

The chair conformation of the D-glucose subunit introduces another structural feature that leads to the formation of a "truncated" cone shape in the three native cyclodextrins [75,76], as opposed to a straight, symmetrical cylinder. This truncated cone structure brings about a change in the orientation of the free hydroxyl groups. Specifically, the hydroxyl groups extend outward from the cyclodextrin molecule, with the C2 and C3-OH groups projecting toward the wider rim and the C6-OH groups directed toward the narrower rim. This external arrangement of hydroxyl groups enables cyclodextrins to engage in hydrogen bonding with water molecules, contributing to their limited aqueous solubility. In contrast to the polar exterior of cyclodextrins, the interior cavity is hydrophobic in nature. This hydrophobicity arises from the lining of the cavity with non-polar groups, including the C3, O4 glycosidic bond (resembling ether), and C5-CH (similar to aliphatic) groups.

The hydrophobic cavity possesses the unique ability to partially or completely encapsulate small organic molecules [77]. This encapsulation capability has proven highly valuable across various applications, spanning medicine, industry, food, textiles, cosmetics, and more.

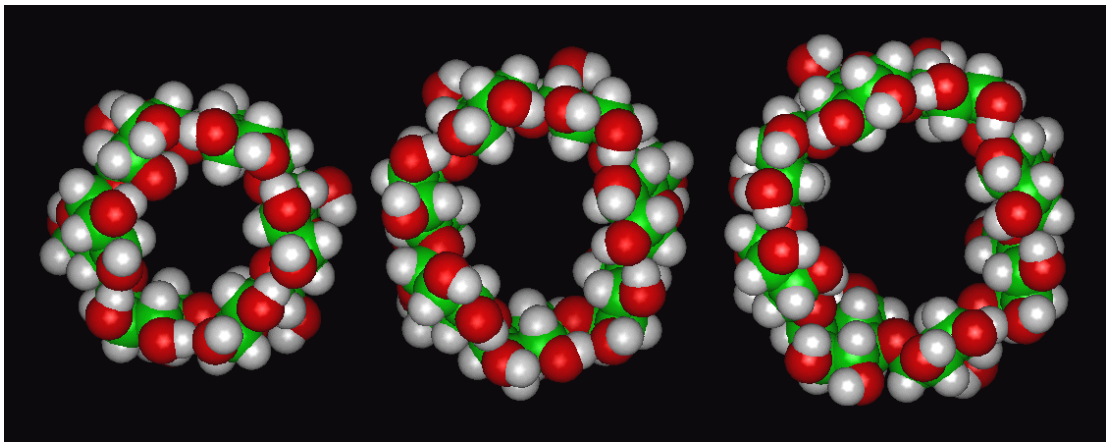


Figure 3: CPK model of α-, β- and γ- cyclodextrins [78]

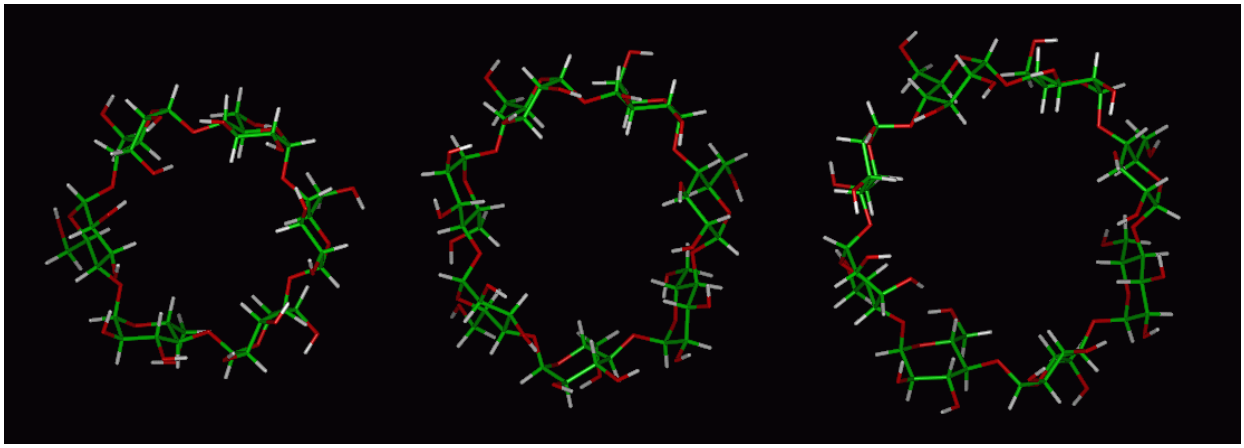


Figure 4: Upper view of α–, β– and γ– cyclodextrins [78]

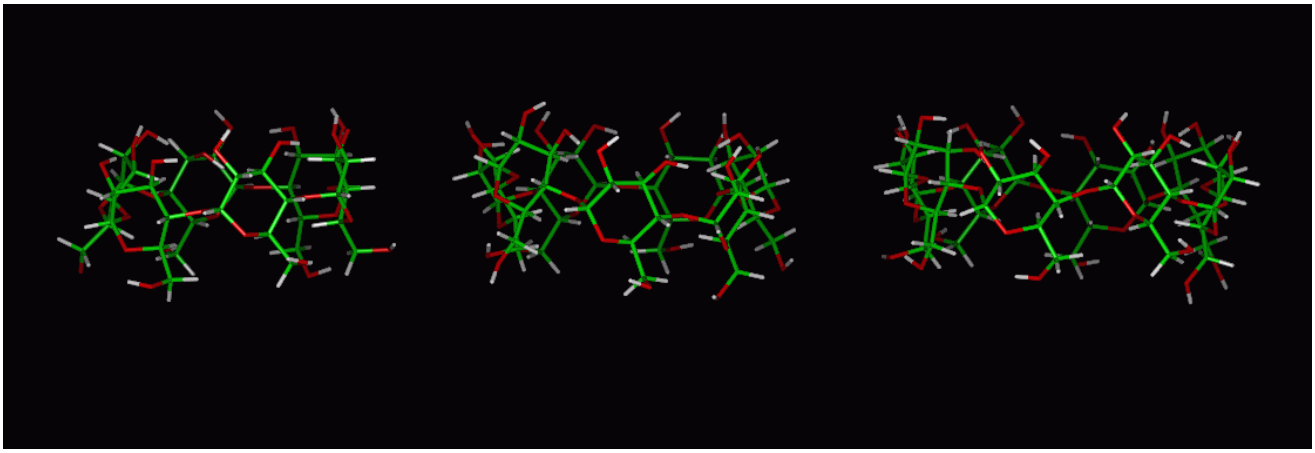


Figure 5: Side view of α–, β– and γ– cyclodextrins [78]

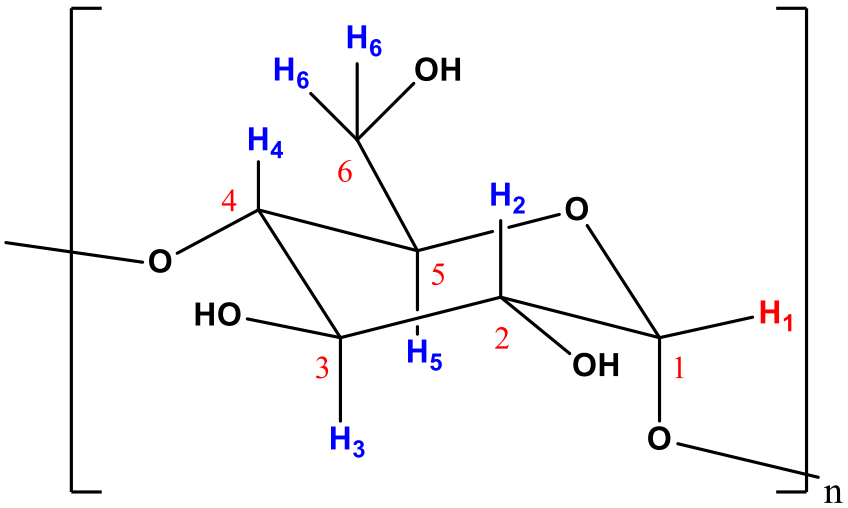


Figure 6(a): Structure of the glucose unit in cyclodextrin; [79]

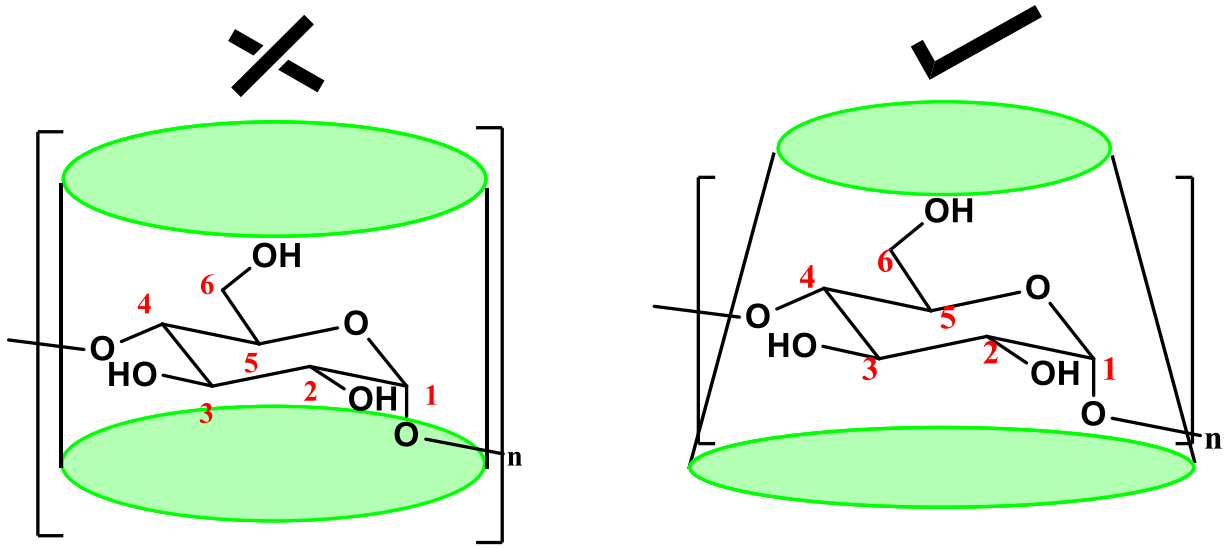


Figure: 6(b) Native CDs form a truncated cone (right) instead of the symmetrical cone (left). Reproduce from ref.[80]

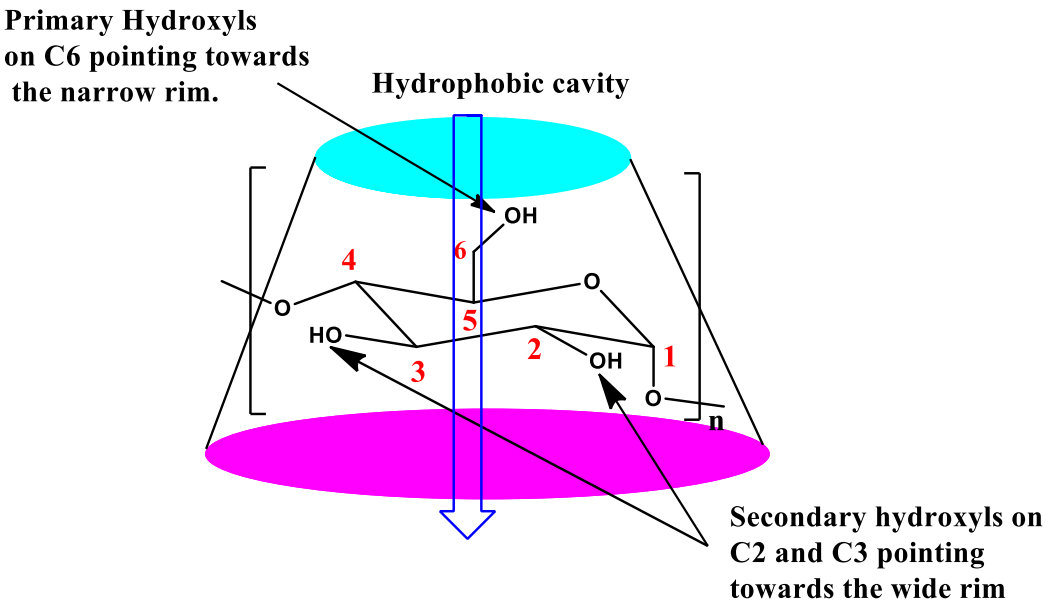
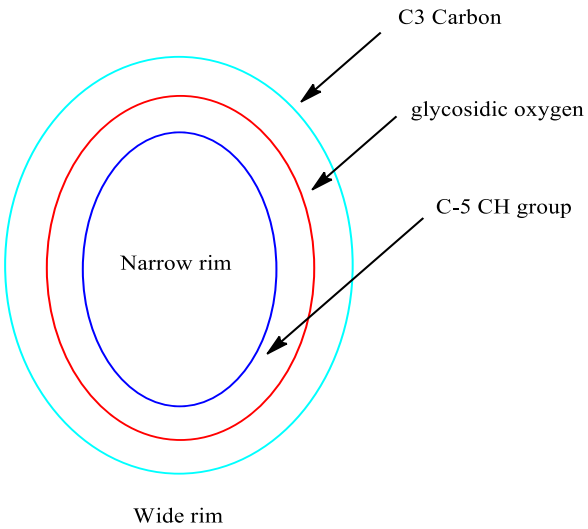


Figure 7 (a): primary and secondary hydroxyl point towards the outside of the CDs molecule. Reproduce from ref. [80]



7(b) Interior lining of α-CD, β-CD, γ-CD. Reproduce from ref. no. [80]

5. Cyclodextrin Size Properties and Overall Flexibility:

The hydrophobic cavities found in α-CD, β-CD, and γ-CD exhibit variations in size, with the smallest CD being α-CD and the largest being γ-CD. These size differences are a direct consequence of the varying numbers of glucose units present in the three native CDs. The size characteristics of α-CD, β-CD, and γ-CD are detailed in Table 1 and visually depicted in Figure 8. It's worth noting that in both Table 1 and Figure 8, the inner diameter lengths are presented as a range rather than a single value. This range representation aligns more accurately with the inherent flexibility observed in CDs. While scientific literature often reports inner cavity diameters as single values, using a range is more appropriate as it acknowledges the inherent structural variability of CDs [80,81].

Table 1: Dimensions of α-CD, β-CD, γ-CD [82]

Cyclodextrin	No. of Glucose Units	Molecular Weight	Cavity Diameter (Å)	Outer Diameter (Å)	Height (Å)	Cavity Volume (Å^3)
A	6	972	4.7-5.2	14.6	7.8	174
B	7	1135	6.0-6.4	15.4	7.8	262
Γ	8	1297	7.5-8.3	17.5	7.8	427

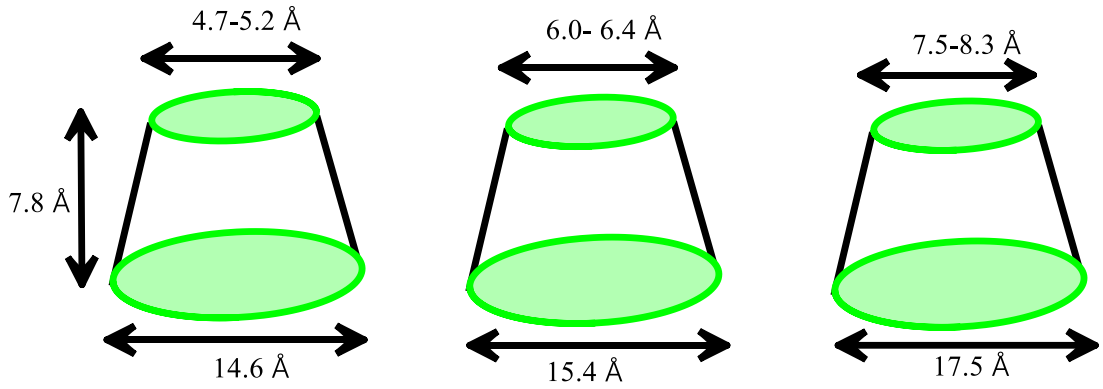


Figure 8: Dimensions of α-CD, β-CD, γ-CD [82]

The glucose subunit has been described as "rigid," which imparts a similar attribute to the entire subunit. This assertion finds support in X-ray crystallography studies, which originally unveiled the structure of cyclodextrin (CD) molecules, ultimately revealing their truncated cone shape. However, it's important to note that X-ray crystallography is limited to solid-state samples. Consequently, relying solely on this technique falls short of substantiating the claim that CDs are inherently rigid molecules. Furthermore, it doesn't fully explain why CDs are capable of forming stable complexes with a wide range of molecules [83]. Therefore, additional analytical methods are necessary to establish the conclusion regarding the rigidity of CDs.

For instance, Vibrational Raman Optical Activity and Nuclear Magnetic Resonance (NMR) Spectroscopy have provided evidence of considerable conformational flexibility within CDs. Recent studies, excluding X-ray crystallography, also align with this notion. Various molecular dynamics studies have explored the conformational flexibility of CDs, offering valuable structural insights into these molecules. Consequently, it is more accurate to refrain from characterizing CDs as

entirely "rigid," hence the rationale for representing the inner cavity diameter as a range, rather than a single value.

Larger cyclodextrins, containing as many as 31 glucose units, have undergone extensive study and characterization. These larger CDs exhibit considerably greater conformational flexibility compared to their smaller counterparts, such as α-CD, β-CD, and γ-CD. However, this increased flexibility comes at the cost of reduced overall stability, which significantly limits their ability to form complexes, unlike α-CD, β-CD, and γ-CD [84].

6. Self-Assembly and Aggregation of Cyclodextrins and Their Complexes:

The native cyclodextrins (CDs) and their complexes adopt structures that resemble cages or channels. Within the category of cage-like structures, further distinctions can be made, including "herringbone" and "brick wall" arrangements. Likewise, channel-like structures can be categorized based on different orientations, such as head-to-head or head-to-tail configurations. For the reader's convenience, these structures and their respective categories are visually presented in Figure 9.

In solution, the self-assembly and aggregation of cyclodextrins and their complexes can either promote or hinder the formation of these complexes. The outcome depends on the specific experimental conditions. It's worth noting that CD aggregation has the potential to distort the accurate determination of the binding constant of the guest molecule [85].

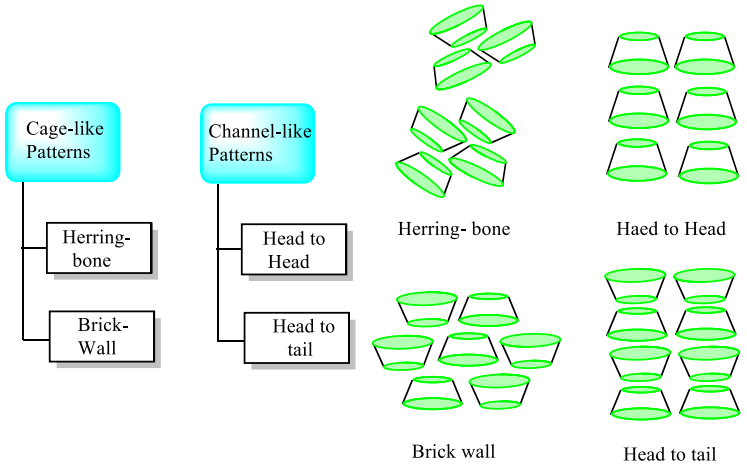


Figure 9: Standard aggregation categories and structures of CD and CD complexes. [86, 87]

Circular dichroism, Differential Light Scattering (DLS), Nuclear Magnetic Resonance (NMR), Different Microscopy Methods, and other techniques have all been used to look into the aggregation of cyclodextrins (CDs) and how it affects complex formation. Despite the availability of these techniques, it is still unclear how CDs aggregate, and experimental results occasionally seem to contradict one another. Some of these inconsistencies can be due to the approaches' built-in limitations.

Circular dichroism, for instance, can be significantly impacted by CD aggregation, which can increase turbidity, and is particularly sensitive to the turbidity of a solution. However, more trustworthy findings involving CD aggregation have been obtained using methods like DLS (Differential Light Scattering) and electron transmission microscopy [86].

Despite our lack of comprehension of the subject, several widely acknowledged facts have emerged. These facts include the findings that native CD aggregates can form at concentrations ranging from 3 to 12 mM, much below their aqueous solubility thresholds, and that aggregate size rises with increasing CD concentrations. Additionally, for -CD, -CD, and -CD, respectively, the

critical aggregation concentrations, or the lowest concentrations below which aggregation cannot occur, have been reported to be 25 mg/mL (26 mM), 8 mg/mL (7 mM), and 9 mg/mL (7 mM) [88].

7. Aggregation of CDs with Small Molecules:

It's crucial to consider the impact of cyclodextrin (CD) aggregation on molecular binding, as it can, in some cases, influence binding strength. A study by Bikádi et al. (2006) [89] explored this influence in the context of CD binding to carotenoids. They found that the aggregation tendencies of CD derivatives significantly affected their complexation with carotenoids, which are pigments present in various natural sources. Among the CD derivatives studied, randomly methylated β-CD exhibited the lowest aggregation tendency and the highest affinity for carotenoids. Molecular modeling experiments conducted by Bikádi et al. suggested that lower CD self-aggregation correlated with stronger binding affinities with carotenoids.

Similarly, Huang et al. (2019) [90] investigated the effects of CD aggregation on the binding of glipizide to various CDs (β-CD, γ-CD, HP-β-CD, Me-β-CD). They observed glipizide/CD aggregation in all cases, especially at higher concentrations. However, altering the CD structure (e.g., from β-CD to Me-β-CD or HP-β-CD) had a significant impact on the tendency of the glipizide/CD complex to aggregate. The glipizide/Me-β-CD complex exhibited the strongest binding affinity among the complexes, presumably due to its lower aggregation tendency. This study partially supports the hypothesis that increased CD aggregation can lead to decreased molecular binding.

While it might seem reasonable to extend this hypothesis to other types of CD/small molecule complexes, each host-guest system must be considered individually, as exceptions may arise. Two such cases are explored below:

For instance, Chun et al. (2012) [91] examined the diffusion rate of eugenol through β-CD to assess the extent of CD complex aggregation. They induced eugenol/β-CD complexation through agitation for various durations and observed larger aggregate particles formed during longer shaking times (24 hours) compared to shorter shaking times (8 hours). Interestingly, the diffusion rate of the larger aggregated particles (eugenol/β-CD complex) was lower than that of the smaller aggregated particles, indicating that aggregation hindered the release of eugenol from the β-CD cavity. While this study doesn't directly support the hypothesis of a correlation between diffusion rate and binding affinity, it underscores the importance of considering and analyzing the effect of CD aggregation on CD complexation.

Similarly, Jo et al. (2015) [92] explored the relationship between the concentrations of trans-cinnamaldehyde and β-CD and trans-cinnamaldehyde/β-CD aggregation. Increasing concentrations of both components led to more aggregation and the formation of larger particles. However, β-CD encapsulation exceeded 90%, and β-CD retained more than 80% of trans-cinnamaldehyde at higher β-CD concentrations due to increased aggregation of the trans-cinnamaldehyde/β-CD complex. This study presents seemingly contradictory results, indicating that the relationship between CD aggregation and binding strength is not straightforward.

Moreover, it's important to note that guest molecules can also influence CD aggregation. For instance, in pure aqueous solution, γ-CD exhibits a critical aggregation concentration of 4.2% (w/v). However, when carbamazepine, an epilepsy drug, is present in the solution, the critical aggregation concentration of γ-CD decreases to 2.5% (w/v) [93].

While various studies have explored the influence of CD aggregation or CD/small molecule aggregation on CD complexation, a clear trend linking CD aggregation to CD complexation has not emerged. These observations highlight the need for further investigations in this area.

Additional studies could provide valuable insights into the CD complexation process, especially in the context of drug delivery, where many of the small molecules involved are drugs, and aggregation may affect the ability of CDs to effectively bind to and release these drugs.[94]

8. Chemical Properties of the Guest Molecule:

The binding strength of the CD/molecule complex is significantly influenced by the chemical properties of the guest molecule. Several of these properties come into play, including the charge of the guest molecule (whether it's neutral, cationic, or anionic), the types of intermolecular interactions involved (such as hydrogen bonding, van der Waals forces, and dipole-dipole interactions), and the size and shape of the guest molecule. It's important to note that depending on the class or type of guest molecules under consideration, the effect of each of these parameters on CD complexation can change. It would therefore be premature to claim that one component has an absolute impact on CD-molecule binding, even though this factor may frequently have a dominant influence. Ionic charge, intermolecular interactions, and the size and structure of the guest molecules all have important and necessary roles to perform. We will examine each of these elements in more detail in the sections that follow.

9. Ionic Charge of the Guest Molecule:

The chemical characteristics of the guest molecule have a substantial impact on the CD/molecule complex's ability to bind. The charge of the guest molecule—neutral, cationic, or anionic—the kinds of intermolecular interactions involved (such as hydrogen bonds, van der Waals forces, and dipole-dipole interactions), as well as the size and shape of the guest molecule—all of these factors are relevant. It's important to note that depending on the class or type of guest molecules being studied, the effects of each of these parameters on CD complexation can change. Therefore, while one factor may often be a dominant influence on CD-molecule binding, it would be premature to assert that this factor's contribution is absolute. Nevertheless, each of these factors, namely ionic charge, intermolecular interactions, and guest molecule size and shape, plays a significant and indispensable role. In the subsequent sections, we will delve into each of these factors.

Table 2: Ionic charge and its effect on CD complexation

Guest	Host (s)	Type of Charge (i.e., Positive and/or Negative)	Effect on CD Binding	Reference
Adamantane derivatives	β-CD, DM-β -CD, TM-β -CD	Positive, Negative	Positively charged end of guests pointed out the wide rim, negative charge had no effect	[95]
Trifluoperazine	β -CD, DM-β -CD, HP-β -CD	Less positive (i.e., more negative)	Stronger binding	[96]
Imatinib	β -CD	0, +1, +2, and +3	Weakest binding at +1, strongest binding at +3	[97]
p-nitrophenol, p-nitrophenolate	α-CD, β -CD	0 (p-nitrophenol) -1 (p-nitrophenolate)	Anionic guest bound more strongly	
Some carboxylic acids and their conjugate bases	α -CD	0 (carboxylic acids) -1 (conjugate bases)	Negligible effect	[98] [99]
nitrobenzene, carboxybenzene,	α -CD	0 (nitrobenzene) 0 (carboxybenzene)		[100] [101]

benzoate,	−1 (benzoate)	Negligible effect
4-nitrophenol,	0 (4-nitrophenol)	
4-nitrophenolate	−1 (4-nitrophenolate)	

The presence of an ionic charge can indeed influence the orientation of a guest molecule within the CD cavity. For instance, in the case of adamantane derivatives featuring positively charged groups, these charged groups tend to extend outward from the broader end of β-CD and its derivatives, such as DM-β-CD and TM-β-CD. Conversely, adamantane derivatives with negative charges do not exhibit a distinct preference for orientation within the CD cavity. In these instances, the negatively charged groups can simultaneously protrude from either the narrow end or the wider end of the cavity within the same sample, although it's important to note that this occurs at the level of the CD/adamantane derivative complex molecules and not within individual complexes [102].

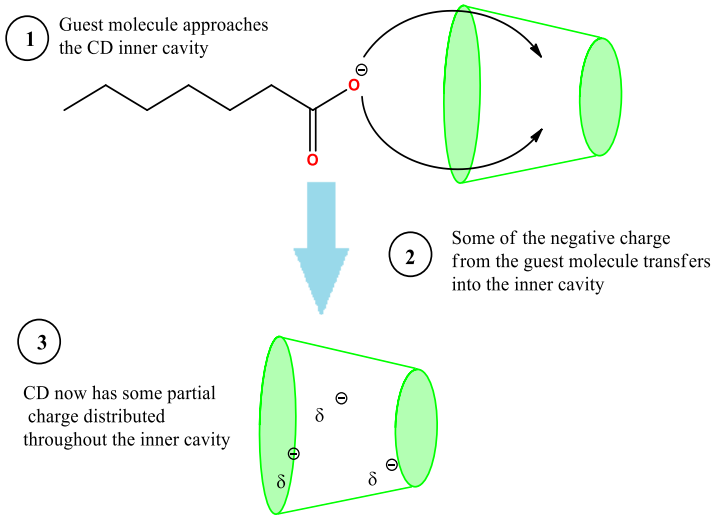


Figure 10: Illustration of charge transfer between a hypothetical guest molecule and a CD. Reproduce from ref. [80]

10. Intermolecular Forces between Guest and Host:

Effective binding between the guest molecule and the cyclodextrin cavity relies on the presence of suitable organic functional groups within the guest. Given the hydrophobic nature of the CD cavity, it predominantly forms strong interactions with organic molecules that exhibit hydrophobic characteristics, mainly through van der Waals forces. Conversely, molecules featuring hydrophilic or polar organic functional groups are less likely to establish robust binding with the CD cavity.

10.1 The Dominating Van Der Waals Forces in CD Complexation:

In many instances, the primary forces that stabilize CD-guest complexes are van der Waals forces . For instance, in the study by Cai et al. (2006), they observed that the binding energies between α-CD and the acyl groups of phospholipids were notably lower than the binding energies with the phospholipid head groups. Since the acyl groups predominantly rely on van der Waals forces, it suggests that these forces are the primary driving factor behind the complexation of phospholipids with α-CD [103]. Similarly, research by Du et al. (2020) revealed that the primary binding force between β-CD and geranyl acetone, a commonly used flavoring compound, is primarily van der Waals forces [104]. Furthermore, Wang et al. (2009) found that van der Waals forces played a significant role in the complexation of Litsea cubeba essential oil with β-CD and some of its derivatives (DM-β-CD, HE-β-CD, and HP-β-CD) [105].

While other intermolecular forces also contribute to CD complexation, van der Waals forces consistently emerge as the dominant force influencing the stability of inclusion complexes. For instance, in the case of β-CD complexation with certain sunscreen agents (oxybenzone, octocrylene, and ethylhexyl-methoxycinnamate), a combination of various forces, including electrostatic, van der Waals, bond angle bending, and dihedral angle bending forces, were at play [103]. However, van der Waals forces accounted for 90% or more of the total binding energy between the sunscreen agents and β-CD. These findings underscore the prominent role of van der Waals forces in binding guest molecules to CDs.

10.2 Hydrogen Bonding between Guest and Host:

In solution, hydrogen bonding represents the primary polar intermolecular force that comes into play for cyclodextrins, as the native cyclodextrins typically lack ionizable groups under most conditions, except in extremely acidic or basic environments. Nevertheless, the hydrogen bonding capacity of the external hydroxyl groups found on native CDs is somewhat limited, particularly in the case of β-CD, due to the presence of a robust network of intramolecular hydrogen bonds. Additionally, the inner cavity of CDs lacks the ability to engage in hydrogen bonding interactions with guest molecules, as it lacks hydrogen donors or acceptors, such as hydroxyl groups. In essence, hydrogen bonding plays a relatively minor role in stabilizing CD complexes, and its influence tends to diminish at higher temperatures, while van der Waals forces remain relatively consistent.

However, it's worth noting that hydrogen bonding does contribute to the overall formation and stability of CD complexes, sometimes working in conjunction with van der Waals forces. For instance, Li et al. (2005) [106] proposed that both van der Waals forces and hydrogen bonding are responsible for the encapsulation of chloramphenicol, an antibiotic that targets ribosomes, by β-CD. They arrived at this conclusion based on calculated thermodynamic parameters related to the binding of chloramphenicol to β-CD. Likewise, Audino et al. (2005) [107] attributed the stability of the 1:1 Methoprene/β-CD complex to a combination of van der Waals forces and hydrogen bonding.

While hydrogen bonding does contribute to CD complexation and stability, its precise role remains somewhat elusive and can vary depending on the specific guest molecule and CD involved.

11. Characterization of Cyclodextrin complexes:

Several techniques are employed to assess the characteristics of cyclodextrin complexes, shedding light on the interactions between host and guest molecules, their structural attributes, the host's capacity to encapsulate the guest within its cavity, dissolution behavior, thermal properties, and various other properties.

11.1 Entrapment efficiency:

Entrapment efficiency is a measure of the quantity of drug encapsulated within host molecules. Greater entrapment efficiency indicates a larger quantity of drug successfully encapsulated within the host molecule. In cyclodextrin complexes, entrapment efficiency is primarily influenced by the dimensions of the guest molecules and the cavity size of the host molecules[108].

11.2 FTIR analysis:

FTIR spectra are valuable for discerning the nature of interactions, whether intramolecular or intermolecular, occurring between a drug and a polymer. When examining drug, polymer, physical

mixture, and formulation samples within the spectral range of 4000–400 cm−1, shifts in peak positions towards higher or lower wavenumbers can provide insights into the formation of hydrogen bonds between the drug and cyclodextrin. Such shifts also suggest that the drug becomes encapsulated within the polymer's cavity during inclusion complex formation [109].

11.3 Differential scanning calorimetry analysis:

Differential scanning calorimetry (DSC) is a valuable tool for investigating the thermal characteristics of drugs, including parameters like melting points and heat changes in formulations. When studying the melting point changes in the context of inclusion complex formation, it becomes evident whether guest molecules are entrapped within host molecules. The DSC thermogram obtained during thermal analysis offers insights into the crystal behavior and whether the reactions are endothermic or exothermic, shedding light on the formation of new compounds[110].

11.4 XRD analysis:

The X-ray diffraction (XRD) technique is employed for structural analysis by examining how X-rays scatter when interacting with materials. In the context of studying inclusion complexes, XRD offers insights into the solid-state structure of the substances. Advanced techniques within XRD provide confirmation of the formation of these inclusion complexes. Alterations in peak intensity and shifts in peak positions serve as indicators of the formation of a novel solid structure [111].

11.5 Dissolution studies:

Dissolution studies serve as a means to assess changes in the drug's solubility in an aqueous medium over time. The results obtained from these solubility investigations provide insights into the effectiveness of the inclusion complex in comparison to the pure drug. They reveal that the complexes formed between the drug and polymer significantly enhance the concentration of the drug dissolved during the dissolution process, ultimately leading to maximum dissolution [112].

11.6 Scanning electron microscopy (SEM):

Scanning electron microscopy (SEM) was employed to investigate the surface morphology of various formations. These SEM analyses were conducted to visualize alterations in the surface characteristics of the drug/polymer combination. They provided insights into the size and shape of the inclusion complexes and also validated the surface morphology of these complexes [113].

12. Application of Cyclodextrin

12.1 Drug delivery:

Over 30 licensed medications incorporate cyclodextrins as a constituent component. Cyclodextrins form complexes with hydrophobic substances due to their hydrophobic interior and hydrophilic exterior. The U.S. FDA has granted generally safe status to alpha, beta, and gamma-cyclodextrin. Medications like hydrocortisone, prostaglandin, nitro-glycerine, itraconazole, and chloramphenicol have been delivered effectively using these cyclodextrins. These drugs benefit from enhanced solubility and stability through their association with cyclodextrins. Cyclodextrin compounds, when combined with hydrophobic molecules, can infiltrate bodily tissues and, in specific situations, release biologically active compounds. Alterations in the pH of aqueous solutions often result in the disruption of hydrogen or ionic bonds between host and guest molecules, providing the basis for controlled release from such complexes. Additionally, heat or the action of enzymes

capable of cleaving the 1,4 links between glucose monomers can be employed to disassemble these complexes. Cyclodextrins have also been shown to enhance drug mucosal penetration [113].

12.2 Based on cancer treatment:

Due to their unique structural properties, cyclodextrins, recognized as safe excipients, find extensive application in pharmaceuticals through the formation of host-guest complexes with suitable molecules. Additionally, targeted or responsive materials are gaining attention as promising platforms for the development of advanced precision medicines. Furthermore, cyclodextrin-based polymers or assemblies have the capacity to condense DNA and RNA, making them valuable in genetic therapeutic applications. With an improved comprehension of diverse pharmaceutical mechanisms, particularly in the context of cancer treatment, researchers have made significant advancements in cyclodextrin-based drug delivery systems within the realms of materials chemistry and pharmaceutical science.

12.3 Chromatography:

Cyclodextrins are employed in the development of stationary phase media for high-performance liquid chromatography (HPLC) separations [114].

12.4 Application in food industry:

Due to their hygroscopic properties, cyclodextrins find extensive applications in the food industry for encapsulating desirable compounds and enhancing water retention [115]. Their utilization can offer several advantages in food processing, including improved standardization of formulations and uniformity. Cyclodextrins have a wide range of applications in food products, including improving sensory attributes by reducing or eliminating undesirable odors or flavors, prolonging the shelf life of food items, sequestering specific food components, and facilitating the formation of Pickering emulsions, among other functions.

12.5 Improving Sensorial Qualities :

a. Colour: Food color is a crucial quality factor that significantly influences consumers' perception of food products. Cyclodextrins (CDs) offer a versatile approach to modifying food color by enhancing the solubility and chemical stability of coloring compounds, whether natural or generated during food processing [116]. CDs can inhibit enzymatic browning reactions catalyzed by pro-browning polyphenol-oxidase enzymes by forming complexes with various substrates or cofactors, such as chlorogenic acid, polyphenols, cinnamic acid, and Cu^{2+}.

Several studies have highlighted the effectiveness of CDs in food science. For example, research has demonstrated that CDs can improve the solubility of natural colorants like curcumin and lycopene, reducing their susceptibility to oxidation compared to when used alone. In another study involving chopped ginger root, it was found that the addition of 1-4% of CDs could stabilize the sample against enzymatic browning for up to four weeks when vacuum-packed and stored at 5°C. Similarly, the use of maltosyl-β-CDs in apple and pear juices exhibited an inhibitory effect on ascorbic acid oxidation, preserving the color and nutritional quality of the juices. To enhance the color of finished food products, α-, β-, and γ-CDs, which are approved for use in the food industry by the EU and the US Food and Drug Administration, are frequently employed in the production of various juices.

b. Flavor: Flavoring chemicals utilized in food products have encountered several challenges, notably their high volatility and susceptibility to environmental factors like light and heat. Cyclodextrin (CDs)-based encapsulation of food odors has emerged as a common and effective approach to address these issues and preserve the stability of flavor compounds. This encapsulation method is particularly significant because flavor constituents typically consist of a diverse array of compounds, and it is essential that all these molecules can be incorporated into the complex without altering their sensory properties.
This encapsulation technique can also be extended to oils, allowing for the creation of a manageable powder form that can be easily incorporated into various food products.[117]

c. Taste: Bitterness can be a significant factor leading to the rejection of food products. However, there are exceptions to this rule, as certain items like coffee, beer, or wine are expected to possess a certain level of bitterness as part of their characteristic taste profiles. To mitigate or completely eliminate the bitter taste associated with some drugs, cyclodextrins (CDs) can be employed effectively. This is because complexed compounds do not interact with taste receptors in the oral cavity, rendering the bitter taste of certain substances imperceptible. This approach has been employed to address bitterness and astringency issues in various food and beverage components, including nicotine in cigarette smoke, naringin in citrus juice, and chlorogenic acid and polyphenols in coffee. [118]

d. Improving shelf life: Cyclodextrins (CDs) play a vital role in safeguarding food products against various deteriorative processes, including oxidation, light-induced reactions, heat-induced decomposition, self-decomposition, and losses due to volatility or sublimation. By encapsulating lipophilic food components with CDs, the stability of flavors, vitamins, colors, and unsaturated fats is significantly enhanced both physically and chemically. This protective action of CDs contributes to extending the shelf life of food products.

e. Pharmaceutical Application: Cyclodextrins (CDs) find widespread applications in the field of medicine. They are utilized in pharmaceutical formulations to enhance bioavailability, solubility, stability, reduce hemolysis, prevent compatibility issues in mixtures, and serve as excipients. Enhancing solubility is particularly significant as it can lead to improved therapeutic effectiveness and reduced dosing requirements for drugs. Scientific research is actively exploring numerous anticancer medications based on CDs. CDs also play a crucial role in facilitating the transfer of proteins, oligonucleotides, oligosaccharides, and gene therapeutic drugs by interacting with cellular membranes, thereby enhancing cellular uptake. Additionally, CDs have demonstrated the ability to prolong the half-life of carbamates by protecting them in vitro. They can also sequester specific molecules, such as neuroactive steroids that modulate GABAA receptors. Furthermore, CDs are employed in constructing pickering emulsions for topical application in the preparation of antifungal econazole derivatives. These versatile applications make CDs valuable tools in the pharmaceutical industry [119].

f. Cosmetics and Personal Care: Cyclodextrins (CDs) have found applications in the cosmetics industry, offering various advantages such as stabilizing compounds, improving fragrances, enhancing the action of ingredients by converting liquid constituents into solid forms, reducing vapor pressure, altering solubility in water, and improving the thermal stability of oils. They are particularly valuable for controlling the release of scents in products like perfumes, air fresheners,

and detergents, thus reducing volatility. CDs are utilized in a range of cosmetic products, including paper towels, tissues, underarm shields, fabric softeners (both liquid and solid), toothpaste, and skin creams. Their inclusion in formulations enhances the overall performance of cosmetic products and addresses potential issues that may arise during production. Numerous studies have explored various cosmetic applications of CDs. For instance, in vitro research has demonstrated the effectiveness of CDs in delivering ferulic acid, a well-known antioxidant with photoprotective properties, while also improving its photostability, making it a valuable addition to cosmetic formulations [120].

g. Packing and textile Industry: The textile industry is actively pursuing sustainable and functional textile solutions. Cyclodextrins (-CDs) have emerged as valuable components in this pursuit, offering opportunities to create innovative textile products with enhanced properties. CDs can form complexes with various chemicals, leading to a diverse range of textile applications with advanced features such as antibacterial and photoprotective properties. Their incorporation into textiles can facilitate scent release, absorb unpleasant odors like sweat and smoke, improve color retention, thereby reducing color loss in wastewater, and even provide flame retardancy. Moreover, medical textiles incorporating CDs can release beneficial compounds with properties such as antibacterial, anti-allergic, antifungal, anti-inflammatory, and insect protection, either through topical or internal use.

h. Bioconversion and Fermentation: Because of the possible toxicity or inflammatory nature of the substrate or product, bioconversion and fermentation processes frequently encounter restrictions. Additionally, many organic substrates are lipophilic, which results in limited water solubility, which might compromise the efficiency of these processes. In addition, the catalyst utilised in these procedures is frequently very active. The biocatalyst can only interact with a small percentage of the substrate as a result of this combination. Cyclodextrins (CDs) have been used to improve the effectiveness of several chemical synthesis methods in order to overcome these difficulties.
For instance, CDs have contributed to better spiramycin manufacture. Additionally, customised CDs have been used to speed up the deacetylation of spironolactone [121].

12.6 Environmental Application of CDs:

By assisting in the augmentation and removal of organic contaminants and heavy metals from soil, water, and the atmosphere, cyclodextrins (CDs) play a key role in the field of environmental science. They have attracted attention from all over the world as cutting-edge adsorbents for wastewater treatment because they are very good at making organic pollutants more soluble. The preparation procedure has an impact on how CD-based adsorbents remove pollutants.
For instance, Singh et al. (2002) reported substantial reductions in the levels of aromatic toxic hydrocarbons, such as phenol, p-chlorophenol, and benzene, in wastewater after treatment with β-CD [122]. In addition to their role as adsorbents, CDs are utilized as non-toxic cyclic oligosaccharides in various environmental applications. They are integrated into the formulation of insecticides to enhance environmental safety. In one example, CDs are used in the preparation of a water-soluble neem seed kernel extract inclusion complex, encapsulating azadirachtin-A within a CD carrier molecule for the creation of a neem seed extract insecticide.
Furthermore, CDs contribute to the photodegradation process of organophosphorus pesticides in humid water by catalyzing the reaction of reactive radical pesticides formed by the humid photosensitizer and forming inclusion complexes with CDs. Silica beads containing CD molecules

have gained attention for their high mechanical properties and physical strength, serving as adsorbents for environmental purposes. These silica beads combined with CDs exhibit strong binding affinities for target pollutants and high pollutant adsorption capacities, offering a promising tool for environmental protection [123].

The versatile ability of CDs to form complexes with a wide range of chemicals makes them invaluable in various industries, and their potential applications in additional areas warrant further exploration and consideration.

13. Side Effect:

When cyclodextrins (CDs) were initially discovered, there were concerns about their potential toxicity, leading to cautious use in complex formation. Research on the toxicity of CDs has primarily focused on their applications in the field of medicine. Although the safety of each medication should ideally be thoroughly assessed during development and documented in the product information, this isn't always the case in practice. It's worth noting that excessive consumption of CDs can have adverse effects.

Despite having relatively low oral bioavailability, excessive CD doses can lead to reversible side effects such as diarrhea and hypertrophy of the cecum. The permeability of tissues, and consequently the bioavailability of the administered active compounds, may also be affected by the CD dosage. In animal studies with high systemic exposures, nephrotoxic effects have been observed, but there is currently no evidence to suggest that these effects are relevant to humans [124].

14. Conclusion:

Cyclodextrins (CDs) stand as remarkable molecules with a rich history and diverse applications across numerous industries. Initially recognized for their potential in analytical chemistry and separation science, CDs have evolved to become indispensable in drug delivery systems, enhancing the solubility and stability of pharmaceuticals. They play a significant role in chromatography, contributing to advancements in analytical chemistry. In the food industry, CDs find extensive use for encapsulating compounds, improving color, flavor, and taste, and extending the shelf life of products. They have also created a name for themselves in the cosmetics industry by boosting perfumes and stabilizing components. CDs help remove pollutants from many environmental matrices in the field of environmental protection. They are useful tools for a variety of applications because of their distinctive structural and chemical characteristics, as well as their capacity to build complexes through intermolecular interactions. Cyclodextrins continue to be adaptable and diverse molecules at the cutting edge of science and industry thanks to their well-established safety profile and continuous research that is broadening their possibilities.

15. Future Prospects:

In a variety of sectors, cyclodextrins (CDs) have a bright future. With a rising focus on personalized treatment, CDs are positioned to maintain their crucial position in the pharmaceutical industry's medication delivery. Assuring the best possible drug solubility, stability, and effectiveness while minimizing side effects may revolutionize the sector if CD-based formulations were tailored to specific patient needs and genetic profiles.

Another application for CDs is in the therapy of cancer. The capacity of CDs to form host-guest complexes with appropriate molecules opens up possibilities for more potent and less harmful treatments with continuing research in targeted therapies and precision medicine. The

development of CD-based drug carriers that can deliver treatments to cancer cells only while sparing healthy tissue gives patients new hope.

CDs will be used more frequently in the food business to enhance sensory attributes, shelf life, and food safety. In order to maintain flavour, colour, and nutritional value while lowering the need for artificial additives, CDs will become increasingly important as customer demand for healthier and more natural goods increases.

CDs will keep improving the sensory qualities and product stability in the cosmetics and personal care industry. The creation of new fragrances, lotions, and other goods will be driven by their capacity to regulate aroma release, stabilize components, and enhance photostability.

CDs will aid in the creation of more functional and sustainable textiles, improved bioconversion procedures, and effective pollution removal from soil, water, and the atmosphere in the fields of materials science and environmental applications. Their contribution to developing eco-friendly solutions is consistent with the increased focus on sustainability.

We can anticipate innovations in a variety of domains as study enhances our understanding of CDs' possibilities. Cyclodextrins are prepared to continue their diverse journey, providing creative answers to some of the most pressing issues in science and technology, from cutting-edge genetic treatments to environmentally friendly technologies. With their demonstrated safety, structural adaptability, and distinct host-guest chemistry, CDs are destined to remain essential tools in the search for better consumer goods, healthcare, and sustainable practices.

16. Conflicts of interests

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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