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Fundamentals of Cyclodextrin Chemistry: Structural Features, Anchoring and Varied Applications

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ABSTRACT:

Cyclodextrins (CDs) stand as versatile molecules with a rich history and transformative impact across scientific and industrial domains. This review unfolds the captivating evolution of cyclodextrin chemistry, from its discovery in the late 19th century to its current status as indispensable molecular tools. CDs, cyclic oligosaccharides with a torus-like structure, play crucial roles in drug development, offering solutions to challenges related to solubility, permeability, stability, and controlled release. The anchoring of cyclodextrins onto surfaces represents a novel approach, enhancing stability, versatility, and practical applicability. Various anchoring methods, including chemical bonding and physical adsorption, contribute to improved stability and controlled release. Cyclodextrins excel in enhancing drug solubility, dissolution, and bioavailability, reducing toxic effects, and providing controlled drug release. They find applications in diverse industries, including pharmaceuticals, food, cosmetics, and environmental sciences. Characterization techniques, such as spectroscopy and chromatography, ensure precise analysis of cyclodextrins and their interactions. This comprehensive exploration underscores the pivotal role of cyclodextrins in advancing drug development and delivery, emphasizing their adaptability and multifaceted contributions.

1. Introduction:

1.1 History:

The captivating history of cyclodextrin chemistry unfolds through three distinct and transformative stages, each characterized by pivotal discoveries and remarkable progress. The initial Discovery Period, spanning from 1891 to the 1930s, marked the emergence of crystalline substances from starch digestion. Notably, Schardinger's foundational work during this period laid the groundwork for cyclodextrin chemistry, differentiating between α and β crystallized dextrins based on their iodine reaction. Moving into the Systematic Studies phase, spanning from the 1930s to the 1970s, researchers, including Freudenberg and co-workers, delved into the structural intricacies of crystalline dextrins. The discovery of γ-CD in 1948-50 expanded the cyclodextrin family, and intense research in the 1950s focused on enzymic production, fractionation, and the complex-forming properties of these intriguing molecules.

Despite these advancements, the scientific community faced a setback due to misinformation on cyclodextrin toxicity in the literature, particularly from French's early experiments with rats. This erroneous information, suggesting high toxicity, deterred many scientists from further developing CD-containing products for human use for nearly a quarter of a century.

The subsequent Industrial Production and Utilization era, emerging in the 1970s, proved transformative. Rigorous toxicological studies dispelled concerns about inherent CD toxicity, paving the way for their widespread utilization. The first International Symposium on Cyclodextrins in 1981 marked a turning point, bringing together experts and fostering increased interest. As industrial production scaled up, the price of

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cyclodextrins plummeted, making them not only economically viable but also safe for various applications.

In the current landscape, cyclodextrins have transcended their initial characterization as expensive and potentially toxic substances. Instead, they have become indispensable molecular tools with diverse applications across scientific, industrial, and commercial realms. Today, the story of cyclodextrin chemistry stands as a testament to perseverance, overcoming challenges, and the transformative power of scientific discovery. [1, 2]

1.2 Background and Significance of Cyclodextrins:

Cyclodextrins, a family of cyclic oligosaccharides, have emerged as versatile molecules with unique properties that make them pivotal in various scientific and industrial applications. Initially discovered in the late 19th century by Villiers and further studied by Schardinger, cyclodextrins are cyclic structures formed from glucopyranose units derived from starch through enzymatic conversion.

Cyclodextrins exhibit a torus-like structure, with a hydrophobic cavity and hydrophilic outer surface. This unique structure allows them to form inclusion complexes with a wide range of guest molecules, resulting in altered physicochemical properties of the encapsulated compounds. The three major types of cyclodextrins, namely α, β, γ-cyclodextrins, differ in the number of glucopyranose units (six, seven, and eight, respectively) forming their cyclic structure. [3]

The significance of cyclodextrins lies in their ability to solubilize poorly soluble compounds, enhance stability, and modify the release profile of encapsulated substances. This property has found applications in various industries, including textile, [4] pharmaceuticals, [5] biotechnologies, [6] food, [7]cosmetics, personal care, and toiletry [8] chemical industry [9] and environmental sciences. [10] Cyclodextrins have been employed in drug delivery systems to improve the bioavailability of drugs, mask undesirable tastes or odors, and protect sensitive compounds from degradation.[11]

Moreover, the environmentally friendly production of cyclodextrins from starch, their biodegradability, and the ability to include a wide range of compounds without forming covalent bonds contribute to their eco-friendly profile. As a result, cyclodextrins have become indispensable in modern research and industry, prompting continuous exploration of their applications and modification for specific uses. [12]

1.3 Rationale for tailored Cyclodextrins:

The rationale for employing anchored cyclodextrins extends beyond the intrinsic properties of free cyclodextrins, introducing a novel approach to enhance their stability, versatility, and practical applicability. Anchoring cyclodextrins to surfaces or matrices enhances their stability, facilitating sustained and controlled release of encapsulated guest molecules. This immobilization onto substrates prevents leaching, ensuring prolonged functionality in different environments. Moreover, the anchoring of cyclodextrins onto surfaces enables the modification of material properties, providing tailored functionalities to substrates, particularly relevant in materials science. This immobilization also plays a crucial role in the development of controlled release systems, offering finely tuned release kinetics for applications in drug delivery, agriculture, and beyond. Furthermore, cyclodextrins are strategically deployed for targeted applications, allowing for site-specific drug delivery in the pharmaceutical industry and minimizing systemic exposure. In essence, the rationale for anchored cyclodextrins revolves around harnessing the unique characteristics of cyclodextrins while introducing additional functionalities through immobilization, unlocking new possibilities for tailored applications across diverse scientific and industrial domains[13][14][15].

2. Fundamentals of Cyclodextrin Chemistry:

The fundamentals of cyclodextrin chemistry encompass the unique structural features that define these cyclic oligosaccharides. Cyclodextrins exhibit a torus-like structure formed by the arrangement of glucopyranose units, leading to a hydrophobic interior cavity and a hydrophilic exterior. The three major types are α, β, and γ-cyclodextrins differ in the number of glucopyranose units, influencing their size and interaction capabilities. Cyclodextrins' remarkable ability to form inclusion complexes through non-covalent forces, such as hydrophobic and hydrogen bonding interactions, is central to their diverse applications. This understanding of their structural intricacies forms the basis for harnessing cyclodextrins

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in drug delivery, materials science, and various scientific and industrial realms.[16]

2.1 Structural Features of Cyclodextrins:

Cyclodextrins, pivotal in host-guest interactions, exhibit unique structural features that underpin their versatile applications. This section delves into the fundamental aspects of cyclodextrin structures, shedding light on their torus-like shape, hydrophobic cavities, and the arrangement of glucopyranose units.[17]

2.1.1 Torus-like Structure:

Cyclodextrins possess a distinctive torus-like structure formed by the cyclic arrangement of glucopyranose units. The resulting toroidal shape contributes to their ability to encapsulate guest molecules within the central hydrophobic cavity. [18]

2.1.2 Hydrophobic Cavity:

A defining feature of cyclodextrins is their hydrophobic interior cavity, formed by the glycosidic oxygen bridges and hydrogen atoms. This cavity serves as a host for guest molecules, allowing for the formation of inclusion complexes through hydrophobic interactions. [19]

Types of cyclodextrin ((α, β, γ) and their properties, inclusion complex formation:

Cyclodextrins (CDs) represent a family of unique sugar molecules arranged in the form of rings. The specific sugar molecules constituting CDs are known as "Glucopyranosides," which are essentially glucose molecules arranged in a pyranose configuration. The discovery of cyclodextrin dates back to 1891 when Villiers isolated a crystalline substance during enzymatic digestion of starch. Subsequently, Schardinger delved into the details of cyclodextrin molecules, laying the foundation for our understanding [20].

Chemical Structure:

Chemically, cyclodextrin molecules are cyclic oligosaccharides composed of alpha-1→4 linked D-glucopyranose units. Depending on the number of glucopyranosides, CDs are categorized into alpha α , β, and γ-cyclodextrins. [21].

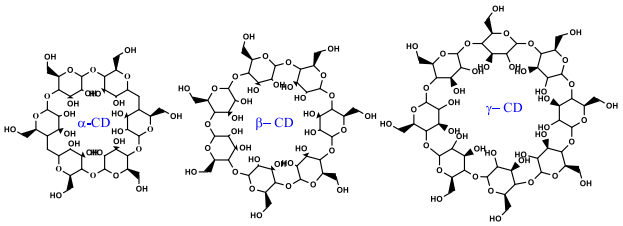

Figure 1: Chemical structure of the α-, β-, and γ-cyclodextrins [22]

Cyclodextrins, despite their complex-sounding nature, are relatively easy to obtain. They are typically derived from starch through enzymatic treatments, employing enzymes like amylase or glucosyl transferases. The source of starch can vary, leading to different ratios of α, β, and γ cyclodextrins. However, due to stoichiometric constraints, obtaining cyclodextrins with fewer than six glucopyranoside residues is not feasible. On the other hand, those with higher glucose residues, while reported, face challenges like poor yield and limited complexing ability, making them unsuitable for pharmaceutical use [23,24].

2.2.2 Structure and Properties:

In terms of structure, CDs have a basket or truncated cone-like structure, with the diameter of the inner cavity determined by the glucopyranose units (Figure 2) [25]. The spherical arrangement of glucose units imparts a basket-like shape, with primary OH groups on the narrower end and secondary OH groups on the wider end. The hydrophilic exterior surface is formed by H-atoms bonded to CH groups and OH groups, while the internal cavity presents a hydrophobic microenvironment surrounded by carbon and ether oxygen [26].

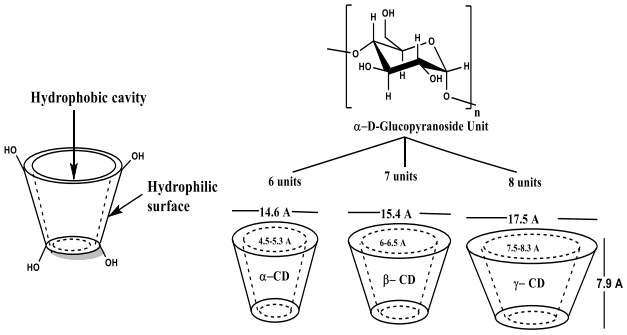

Figure 2: Schematic diagram of the shape and dimensions of parent cyclodextrin [27,28]

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There are three main types of cyclodextrins: Alpha α, Beta β, and Gamma γ, also known as the first or parent generation CDs. Physicochemically, all cyclodextrin molecules share characteristics such as being large, hydrophilic, stable in basic media, hydrolysable in acidic media, and capable of modifying the physical, chemical, and biological features of drugs through the formation of inclusion complexes (Table 1) [29].

Table 1: Important characteristics of parent cyclodextrin [28]

Property	α- CD	β- CD	γ - CD
Glucose subunits	Hexa	Hepta	Octa
Synonyms	Cyclo-hexaamylose	Cyclo-heptaamylose	Cyclo-octaamylose
Height (Å)	7.9	7.9	7.9
Cavity diameter (Å)	4.5-5.3	6-6.5	7.5-8.3
External diameter (Å)	14.6	15.4	17.5
Solubility in water (mg/ml)	145	18.5	232
Molecular weight (g/mol)	972	1135	1297

Despite their hydrophilic nature, the aqueous solubility of natural CDs and their complexes is restricted, particularly in the case of β-CD. This limitation arises from strong molecular bonding in CD crystals. However, modifying OH-groups, for instance, by substituting with methoxy groups, significantly enhances solubility. It is noteworthy that while derivatives may have increased solubility, they often have lower molecular weights compared to parent cyclodextrins.[30]

2.2.3 Derivatives of Cyclodextrins:

Due to the lower aqueous solubility of natural CDs, researchers have explored various derivatives with medicinal applications. These derivatives are produced by polymerizing or substituting with methyl, carboxymethyl, ethyl, hydroxyethyl, sulfabutyl, or saccharides. The goal of these derivatizations includes improving solubility, enhancing host-guest association, stabilizing the guest, and reducing reactivity and movement. While numerous CD derivatives have been successfully produced and analyzed, only a select few, such as methylated, hydroxyalkylated, and ether-substituted derivatives, have found applications in novel pharmaceutical studies [31].

2.2.4 Effect of CDs on Formulation Properties:

The most significant attribute of CDs is inclusion complexation, allowing them to host therapeutic agents or the hydrophobic portion of medicinal moieties in their internal cavities [32].

2.2.5 Mechanism of Inclusion Complexation:

Cyclodextrins exhibit a remarkable ability to form inclusion complexes with a diverse range of guest molecules. This interaction occurs through non-covalent forces such as van der Waals, hydrophobic, and hydrogen bonding interactions, resulting in the modification of the properties of the encapsulated substances [19,20] In the process of inclusion complexation, water molecules are removed from the lipophilic cavity of cyclodextrins, leading to increased hydrogen bonds, decreased repulsive interaction between the guest and aqueous environment, and enhanced hydrophobic interaction. This results in the formation of a stable complex in an aqueous solution (Figure 3) [33].

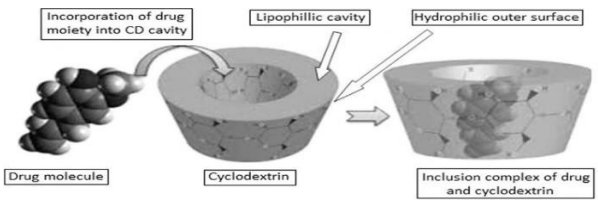

Figure 3: Schematic illustration of the drug-CD inclusion complexation [22]

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When a complex is formed, covalent bonds remain unchanged, and the drug molecules are in equilibrium between the complex and the solution. The stability and dissociation constant of complexes are crucial indicators of how a compound's physicochemical characteristics change after inclusion. Complexes can be categorized into A-type, B-type, and non-inclusion types like complex aggregation [34].

In general, there are four energetically favourable interactions that help inclusion complex formation.

The displacement of polar water molecules from the apolar cyclodextrin cavity.

The increased number of hydrogen bonds formed as the displaced water returns to the large pool.

A reduction of the repulsive interaction between the hydrophobic guest and theaqueous environment.

An increase in the hydrophobic interactions as the guest inserts itself into the apolar cyclodextrin cavity.

Anchored Cyclodextrins:

Anchored cyclodextrins represent a class of molecular structures where cyclodextrin molecules are covalently attached to another molecular entity. This unique configuration imparts distinctive characteristics and functionalities to cyclodextrins, extending their applications in various fields. The anchoring process involves the formation of stable bonds between cyclodextrins and a substrate, leading to novel structures with enhanced properties.[35]

3.1 Characteristics:

3.1.1 Enhanced Stability:

cyclodextrins exhibit improved stability, attributed to the covalent bonds formed during the anchoring process. This enhanced stability allows these structures to withstand environmental factors such as temperature variations and exposure to light.

3.1.2 Functionalization:

The anchoring of cyclodextrins facilitates functionalization, enabling the introduction of specific chemical groups during the attachment process. This functional versatility opens avenues for tailored applications, including drug delivery and materials science.

3.1.3. Improved Solubility:

Cyclodextrins often display enhanced solubility compared to their free counterparts. This property is particularly valuable in pharmaceutical applications, where increased solubility can positively impact drug delivery systems.

3.1.4. Targeted Delivery Systems:

The structure of cyclodextrins allows for the design of targeted delivery systems. By attaching cyclodextrins to specific carriers or substrates, it becomes possible to direct the release of encapsulated molecules to precise locations within biological systems.

3.1.5. Versatility in Applications:

Cyclodextrins find applications across diverse fields, including drug delivery, materials science, and nanotechnology. Their versatility makes them adaptable to various requirements in these domains.

3.1.6. Controlled Release Formulations:

The configuration enables the development of controlled release formulations. This controlled release is valuable in pharmaceuticals, ensuring a sustained and regulated delivery of active compounds. [36]

3.2 Methods of Anchoring Cyclodextrins:

Cyclodextrins are cyclic oligosaccharides composed of glucose units, and they are widely used in various applications, including drug delivery, chromatography, and sensor development. Anchoring cyclodextrins involves attaching them to a solid support or incorporating them into a matrix for enhanced stability and functionality.

3.2.1 Chemical Bonding:

Cyclodextrins can be covalently attached to a substrate through chemical reactions. This involves modifying the hydroxyl groups of cyclodextrins and linking them to functional groups on a surface.

3.2.2. Physical Adsorption:

Cyclodextrins can be physically adsorbed onto surfaces through non-covalent interactions, such as van der Waals forces or hydrogen bonding. This method is relatively simple and can be reversible. [37]

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3.2.3. Crosslinking:

Crosslinking involves forming stable networks within a matrix by connecting cyclodextrin molecules. This method enhances the stability and mechanical strength of the cyclodextrins.

3.2.4. Polymer Matrix Incorporation:

Cyclodextrins can be incorporated into polymeric matrices, where the polymer serves as a support. This method is advantageous for applications in controlled drug release and separation processes. [38]

3.2.5. Inclusion Complex Formation:

Cyclodextrins can form inclusion complexes with guest molecules, and these complexes can be anchored onto surfaces. This method is employed in various fields, including drug delivery and environmental remediation.

3.3 Factors Influencing the Anchoring Process:

3.3.1. Substrate Surface Properties:

The nature and properties of the substrate surface play a significant role in the anchoring process. Factors such as surface chemistry, roughness, and charge can impact the attachment of cyclodextrins. [39]

3.3.2. Cyclodextrin Modification:

The modification of cyclodextrins, such as derivatization or functionalization, can influence their reactivity and ability to form stable bonds with the substrate. [40]

3.3.3 Solvent and Reaction Conditions:

The choice of solvent and reaction conditions, including temperature and pressure, can affect the efficiency and specificity of the anchoring reaction.

3.3.4. Crosslinking Agents:

When employing crosslinking methods, the choice of crosslinking agents and their concentrations can influence the structure and stability of the cyclodextrin network.

3.3.5. pH and Ionic Strength:

The pH and ionic strength of the reaction medium can impact the electrostatic interactions and hydrogen bonding between cyclodextrins and the substrate.[41]

3.3.6. Influence of Guest Molecules:

In cases where cyclodextrins form inclusion complexes with guest molecules, the nature and properties of these guest molecules can affect the anchoring process.

3.3.7. Temperature and Time of Reaction:

Reaction temperature and the duration of the reaction can impact the kinetics and thermodynamics of the anchoring process. [42]

4. Physicochemical Characteristics Enhancement:

4.1 Solubility Enhancement through Cyclodextrin Complexation:

Cyclodextrins, a family of cyclic oligosaccharides with a hydrophobic core and hydrophilic exterior, have emerged as pivotal agents in the field of pharmaceuticals for enhancing the solubility of poorly water-soluble drugs. This complexation strategy holds immense promise in improving drug bioavailability and therapeutic efficacy.

4.1.1. Mechanism of Solubility Enhancement:

The fundamental mechanism underlying solubility enhancement through cyclodextrin complexation lies in the formation of inclusion complexes. Cyclodextrins encapsulate the hydrophobic portions of drug molecules, thereby reducing the free energy of the drug in the aqueous medium and subsequently enhancing its solubility.

4.1.2. Types of Cyclodextrins Used:

Various types of cyclodextrins, including α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin, are strategically employed based on the specific physicochemical properties of the drug under consideration. [43]

4.1.3. Factors Influencing Complexation Efficiency:

Several factors influence the efficiency of complexation, including the size and shape of the drug molecule, the type of cyclodextrin selected, and the intricacies of the preparation method. [44]

4.1.4. Methods of Complexation:

The methods employed for complexation encompass physical mixing, kneading, co-evaporation, and freeze-drying. The choice of method is contingent upon the

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unique characteristics of both the drug and the selected cyclodextrin. [45]

4.2 Stability Improvement with Cyclodextrins:

Cyclodextrins, owing to their unique molecular structure, have proven instrumental in stabilizing various compounds. Anchoring cyclodextrins to surfaces or matrices enhances their stability, presenting a versatile strategy for improving the shelf-life and performance of sensitive substances. [46]

4.2.1. Mechanisms of Stability Improvement:

cyclodextrins impart stability through encapsulation, shielding the encapsulated compound from environmental factors such as light, oxygen, and moisture. The protective environment created by the cyclodextrin enhances the stability of the guest molecules.

4.2.2. Types of Anchoring Strategies:

Various methods, including chemical bonding, physical adsorption, crosslinking, and incorporation into polymer matrices, are employed to anchor cyclodextrins. The choice of strategy depends on the nature of the guest molecules and the intended application. [43]

4.2.3. Impact of Substrate Properties:

The properties of the substrate surface, including surface chemistry, roughness, and charge, play a crucial role in the stability improvement process. The interaction between cyclodextrins and the substrate surface influences the overall stability of the system.

4.2.4. Guest Molecule Considerations:

The nature and properties of the guest molecules encapsulated by cyclodextrins influence the stability improvement. Understanding the specific interactions between cyclodextrins and guest molecules is paramount for optimizing stability.

4.2.5. Temperature and Time Effects:

Reaction temperature and the duration of the anchoring process can affect the stability of the cyclodextrins. Optimizing these parameters is essential for achieving the desired level of stability. [47]

Applications of Cyclodextrins:

The remarkable potential of Cyclodextrins (CDs) in the realm of pharmaceutical applications stems from their ability to exert a multifaceted influence on various properties that significantly impact the behavior and therapeutic outcomes of drugs. CDs are commonly utilized to enhance several key aspects, including solubility, permeability, stability, and mitigation of adverse effects such as irritation. These applications predominantly revolve around the unique capability of CDs to form inclusion complexes.

In practical terms, when CDs form inclusion complexes, they essentially encapsulate certain portions of drug molecules, leading to a variety of advantageous effects. For instance, by improving solubility, CDs address the challenge of poorly water-soluble drugs, thereby enhancing their bioavailability. The encapsulation process can also contribute to heightened drug stability, protecting against factors like light, oxygen, and moisture.

Moreover, CDs play a pivotal role in enhancing drug permeability, facilitating better absorption and distribution within the body. This aspect is crucial for optimizing the therapeutic impact of pharmaceuticals. Additionally, CDs can help mitigate adverse effects associated with drug administration, such as irritation, by providing a protective environment for the encapsulated drugs.

In essence, the versatility of CDs in forming inclusion complexes offers a comprehensive approach to addressing various challenges associated with drug development and delivery in the pharmaceutical industry. This capability underscores the significance of CDs as valuable tools in improving the overall performance and effectiveness of diverse pharmaceutical formulations.

5.1 Solubility and dissolution enhancement:

Cyclodextrins (CDs) find their most widespread application in enhancing the solubility of drugs in aqueous solutions. This increase in solubility is pivotal for improving bioavailability and, consequently, enhancing therapeutic efficiency. The unique capability of CDs to form inclusion complexes plays a crucial role in augmenting the solubility and dissolution of drug molecules in the solid state [48].

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Among various types of CDs, methylated CDs exhibit the highest potential for increasing solubility. This is attributed to their ability to reduce the crystallinity of drugs, thereby promoting enhanced dissolution. While literature extensively discusses the solubilization effects of all CD molecules, methylated CDs stand out for their exceptional efficacy in this regard.

Empirical observations in the field provide valuable insights into the factors influencing CD complexation and solubilization:

The water solubility of the drug inversely correlates with the effectiveness of CD complexation. Essentially, the poorer the water solubility of the drug, the more superior the solubility enhancement through CD complexation.

CDs with reduced molar substitution in derivatization offer superior solubilization compared to derivatives with higher molar substitutions. This suggests that optimizing the degree of derivatization is critical for achieving optimal solubilization effects.

The solubilizing ability of CDs is intricately linked to the proximity of charges to the cavity. The closer the charges are to the cavity, the better the solubilization ability exhibited by the CDs.

Incorporating various polymers within the group has been found to enhance complexation and, consequently, solubilization. This indicates the feasibility of leveraging polymer inclusion to augment the solubilization effects of CDs.

While the influences of CD complexation are often empirical, historical findings and systematic studies enable the inference of these crucial factors. These insights contribute to a deeper understanding of how CDs can be effectively employed to improve drug solubility, and hence, therapeutic outcomes.

5.2 Permeability across biological membranes:

The permeability across biological membranes is a complex process influenced by various factors, including molecular weight, molecular structure, and the partition coefficient. Notably, Cyclodextrins (CDs) play a unique role in this context. While CDs themselves don't contribute significantly to enhancing the permeation of hydrophilic drugs, their involvement in CD complexation alters this dynamic.

In CD complexation, the free drug exhibits an increased affinity to penetrate biological membranes [49]. However, it's crucial to highlight that the success of delivery across biological membranes is contingent upon both the formulation of the drug and the specific barrier being encountered. In cases where the barrier is controlled by water diffusion layers, the presence of cyclodextrins can indeed influence the delivery process. However, this influence is limited when dealing with membranes that are predominantly lipophilic.

It's worth noting that there's an exception to this limitation, and it lies in the inclusion of hydrophobic cyclodextrins. These hydrophobic variants can effortlessly cross mucosal barriers, providing a unique capability that distinguishes them from their counterparts [50].

While CDs may not directly enhance the permeation of hydrophilic drugs, their involvement in CD complexation can significantly impact the penetration of free drugs across biological membranes. The success of this delivery method depends on the interplay between the drug formulation, the nature of the barrier, and the specific characteristics of the cyclodextrin utilized.

5.3 Photo- and thermal stability:

A significant attribute of cyclodextrins (CDs) lies in their capacity to enhance the photo- and thermal stability of pharmaceuticals, marking them as crucial excipients in drug formulations. The chemical stability of pharmaceuticals is paramount in the development of any drug formulation. Stability parameters and factors influencing them must be carefully considered, and suitable stability enhancers, such as CDs, should be incorporated based on specific requirements [51,52].

CDs are renowned for their ability to mitigate the impact of temperature, light, and oxygen, thereby elevating overall stability. The degradation of pharmaceutical products in the presence of light can lead to various adverse effects. Notably, the formation of a complex between CD and vitamin E demonstrated higher photo stability, showcasing the protective effect of CD in preventing light-induced degradation [53].

In addition to the protective influence of CDs on stability, it is crucial to conduct studies that delve into the extent to which an excipient, such as CDs, can

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prevent degradation of a given formulation. These investigations contribute valuable insights into the efficacy of CDs in safeguarding pharmaceutical products against deterioration caused by various environmental factors.

CDs serve as indispensable contributors to the chemical stability of pharmaceuticals, offering enhanced resistance to temperature, light, and oxygen-induced degradation. Their protective effects, especially in complex formations, highlight their pivotal role in ensuring the integrity and stability of drug formulations.

5.4 Improved drug safety:

The utilization of Cyclodextrins (CDs) in drug formulations not only enhances the solubility, dissolution, and bioavailability of drugs but also contributes to improved drug safety. When these parameters are positively influenced by CDs, it signifies that the drug can achieve the necessary residence time in the body without lingering excessively, thereby reducing the potential risks of toxic effects [54].

An illustrative example is a research study conducted on the antiviral drug ganciclovir when combined with CDs. The findings revealed a reduction in the toxic effects of the drug, accompanied by a significant improvement in efficacy. This emphasizes how the incorporation of CDs in drug formulations can contribute to enhancing therapeutic outcomes while minimizing potential harmful effects [55].

Furthermore, CDs have demonstrated their effectiveness in reducing irritation caused by both intravenous and ophthalmic products. This reduction in irritation adds an extra layer of safety and comfort for patients undergoing drug administration through these routes.

In essence, the incorporation of CDs in drug formulations not only optimizes drug performance but also plays a pivotal role in improving drug safety. By mitigating toxic effects, enhancing efficacy, and reducing irritation, CDs contribute significantly to the overall safety profile of pharmaceutical products.

5.5 Control of drug release:

Cyclodextrins (CDs) bearing ethyl and acyl groups exhibit a noteworthy capability to regulate drug release, presenting a valuable avenue in controlled drug delivery systems [56]. Among these, per-O-butanoyl β-CD is recognized for its mucoadhesive property, offering a potential alternative for controlling drug release through the epithelial surface of the gastrointestinal tract (GIT). Additionally, HP-β-CDs, known for their gel-forming property, prove instrumental in extending the release of drugs, contributing to controlled drug delivery systems.

In the realm of controlled drug release, osmotic pumps stand out as widely utilized devices due to their unique ability to provide a uniform concentration of the drug in the systemic circulation [57]. This ensures a controlled and sustained release over time.

Advanced forms of extended delivery systems can be achieved by incorporating CD conjugates with specific release formulations. An illustrative example is the combination of ketoprofen with β-CD, and the subsequent addition of this formulation to CD conjugates, resulting in a repeated release profile [58,53]. This strategy showcases the potential for tailored and controlled drug release achieved through the strategic integration of CDs into drug delivery systems.

CDs, particularly those with ethyl and acyl groups, play a pivotal role in the control of drug release. From mucoadhesive properties to gel-forming capabilities and integration with osmotic pumps, CDs offer diverse avenues for achieving controlled and sustained drug release in various pharmaceutical formulations.

5.6 Drug Delivery Systems:

5.6.1 Drug delivery by oral route:

The oral route has long been the primary and conventional means for drug delivery systems. Various mechanisms govern drug release in oral delivery, including dissolution, diffusion, pH, and osmosis [59]. Cyclodextrins (CDs) play a crucial role in enhancing oral drug delivery systems, primarily by accelerating the dissolution rate. The formation of inclusion complexes with CDs is instrumental in increasing the solubility of drugs, facilitating their transport across the aqueous phase to the lipid membrane in the gastrointestinal tract (GIT) [60]. Hydrophobic derivatives of CDs, such as ethylated CDs, are particularly employed to achieve this enhancement.

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For buccal and sublingual routes, rapid increases in drug concentration can also be attained through complexation. However, to exert the therapeutic effect, it is imperative that the drug is released from the complex. This poses a challenge in the sublingual route due to limited saliva volume and contact time [61].

Cyclodextrins, especially hydrophobic variants like ethylated CDs, play a crucial role in achieving site-specific or sustained drug release. Furthermore, CDs have been successfully employed in matrix tablets and osmotic pumps, providing effective control over drug release in various formulations [62].

CDs significantly contribute to the success of oral drug delivery systems by enhancing dissolution rates and facilitating the transport of drugs across biological barriers. The versatility of CDs in various drug delivery approaches underscores their importance in optimizing therapeutic outcomes for oral medications.

5.6.2 Ocular drug delivery:

The primary approach for treating ocular conditions typically involves the topical application of drugs in the form of aqueous solutions. Recent research confirms the valuable role of cyclodextrin molecules in ocular preparations, offering enhancements in solubility, stability, and consequently, the bioavailability of ophthalmic formulations [63]. Among the various cyclodextrins, hydrophilic variants, particularly SB β-CD and HP β-CD, stand out as the most compatible and non-toxic choices for ocular applications.

It is a well-established fact that only a limited amount of an ophthalmic drug reaches the systemic circulation. However, by employing cyclodextrin complexation, especially with hydrophobic drugs, it becomes feasible to increase the availability of a drug at the corneal surface. This enhancement in drug availability at the corneal level contributes to a substantial improvement in the ocular bioavailability of hydrophobic drugs [64].

The incorporation of cyclodextrin molecules in ocular formulations, particularly hydrophilic cyclodextrins like SB β-CD and HP β-CD, proves to be a valuable strategy. By addressing solubility and stability challenges, cyclodextrins enhance the overall efficacy and bioavailability of ophthalmic drugs, offering promising advancements in ocular drug delivery.

5.6.3 Nasal Drug Delivery:

To achieve effective systemic absorption through nasal administration, it's imperative that drugs exhibit optimal solubility in nasal fluids without compromising the defensive functions of respiratory cilia. Both hydrophilic and hydrophobic cyclodextrins play pivotal roles in nasal drug delivery. Their unique properties allow them to enhance solubilization and permeation, respectively, at low concentrations, all while maintaining a generally inert profile from a toxicological standpoint [65].

5.6.4 Transdermal Drug Delivery:

Overcoming the skin's primary barrier, the stratum corneum, is a key challenge in transdermal drug delivery. Cyclodextrins, owing to their hydrophobic nature, facilitate drug delivery across the water diffusion layer. However, their effectiveness in dermal drug delivery is contingent on the specific characteristics of the lipophilic barrier. Careful selection of an aqueous vehicle becomes paramount for success in transdermal drug delivery [66].

5.6.5 Novel Drug Delivery:

The realm of drug delivery has witnessed intriguing innovations with the utilization of cyclodextrins and their derivatives. These compounds have played a central role in crafting novel drug delivery systems characterized by supramolecular architectures like micelles, nanosponges, nanoparticles, and nanovesicles. Among these, lipid nanocarriers, often combined with modified CDs, have emerged as prominent nanomaterials. Offering biodegradability and biocompatibility, these systems bring forth versatile advantages, including targeted delivery, stability, and co-drug loading (both hydrophobic and hydrophilic). Moreover, they exhibit superior efficacy and pharmacokinetics [67].

Comprehensive studies on lipid nanosystems, incorporating both parent and derivatized CDs, underscore the potential of this approach in enhancing the bioavailability of diverse pharmaceutical formulations. This expanding application holds promise across various disorders such as diabetes, hypertension, cancer, and numerous other ailments. The integration of cyclodextrins into these novel drug delivery platforms showcases their adaptability and potential to elevate therapeutic outcomes. [68]

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5.7 Food and Flavor Industry Applications:

5.7.1 Solubility Enhancement in Food Ingredients:

CDs excel in improving the solubility of poorly water-soluble food ingredients, enhancing their dispersibility and overall stability in formulations. This property is particularly beneficial for incorporating certain flavors and functional compounds into food products. [69]

5.7.2 Encapsulation of Flavors:

CDs are widely employed for encapsulating volatile flavor compounds, protecting them from degradation due to factors such as light, oxygen, and heat. This encapsulation technique helps maintain the integrity of flavors during food processing and storage.

5.7.3 Controlled Release of Aroma Compounds:

The ability of CDs to form inclusion complexes allows for controlled release of aroma compounds in food products. This controlled release enhances flavor perception and contributes to an improved sensory experience.

5.7.4 Reduction of Undesirable Tastes and Odors:

CDs have been employed to mask or reduce undesirable tastes and odors in food products. Their encapsulation properties help in minimizing the perception of off-flavors and improving overall sensory acceptability.

5.7.5 Stabilization of Food Additives:

CDs contribute to the stabilization of food additives, preventing their degradation and enhancing their shelf life. This is particularly crucial for maintaining the quality and efficacy of sensitive additives in various food formulations. [15] [70]

Characterization Techniques to validate the molecular structure and interactions in Cyclodextrin:

Spectroscopic methods play a pivotal role in characterizing cyclodextrins, offering insights into their molecular structures and interactions. Nuclear Magnetic Resonance (NMR) spectroscopy is commonly employed to elucidate the structure and conformation of cyclodextrins, especially in the context of inclusion complexes formed with guest molecules. Fourier Transform Infrared Spectroscopy (FTIR) is utilized to identify functional groups, providing information on the chemical structure and interactions of cyclodextrins. UV-Visible spectroscopy is instrumental in studying inclusion complexes, shedding light on binding affinity and stoichiometry.

Chromatographic techniques, such as High-Performance Liquid Chromatography (HPLC) and Gas Chromatography (GC), are widely used for cyclodextrin analysis. HPLC is effective in separating and quantifying cyclodextrins, offering insights into their purity and concentration. GC, on the other hand, is suitable for the analysis of volatile cyclodextrin derivatives, particularly in the study of the release of encapsulated volatile compounds.

Microscopic and imaging techniques contribute to the visualization of cyclodextrin structures. Scanning Electron Microscopy (SEM) provides detailed images of cyclodextrin particles, revealing morphology and surface characteristics. Atomic Force Microscopy (AFM) offers topographical information at the nanoscale, aiding in a comprehensive understanding of cyclodextrin structures.

Analytical methods for quantification encompass various approaches. Spectrophotometric methods utilize light absorption or emission to determine cyclodextrin concentrations in solutions. Chromatographic methods, including both HPLC and GC, are employed for the precise quantification of cyclodextrins in complex mixtures. These analytical techniques are crucial for optimizing cyclodextrin concentrations in diverse applications, ensuring accurate and reliable results. [71]

Current Challenges in Cyclodextrin Research:

Cyclodextrins, with their diverse applications in drug delivery, encapsulation, and other fields, are not without challenges in current research. One notable challenge involves the optimization of anchoring techniques to ensure stability and longevity of the cyclodextrin complexes. Achieving efficient and reproducible anchoring on various substrates while maintaining the structural integrity of cyclodextrins poses a significant hurdle.

Another challenge lies in the development of environmentally friendly and sustainable anchoring methods. The use of certain anchoring agents may have environmental implications, and researchers are actively exploring green chemistry approaches to

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minimize the ecological footprint of cyclodextrin applications.

Furthermore, the scalability of cyclodextrin processes is a current concern. Transitioning from laboratory-scale experiments to large-scale industrial applications requires addressing issues related to cost-effectiveness, reproducibility, and the feasibility of mass production. Overcoming these challenges will be crucial for the broader implementation of cyclodextrins in various industries.

7.1 Emerging Trends and Future Directions in Cyclodextrin Research:

As researchers address current challenges, several emerging trends and future directions are shaping the landscape of cyclodextrin research. One prominent trend involves the exploration of novel anchoring techniques that enhance the versatility and applicability of cyclodextrins. Innovations such as stimuli-responsive anchoring and dynamic covalent anchoring are gaining attention, enabling controlled release and tailored functionality of cyclodextrins.

The integration of cyclodextrins into advanced materials is another noteworthy trend. Researchers are exploring the incorporation of cyclodextrins into smart materials, coatings, and membranes with enhanced functionalities. This trend aligns with the growing demand for multifunctional materials in diverse fields, including medicine, environmental science, and nanotechnology.

Additionally, the application of cyclodextrins in personalized medicine is an emerging area of interest. Tailoring cyclodextrins to specific patient needs for drug delivery and therapeutic purposes represents a promising avenue for future research. This trend aligns with the broader shift toward precision medicine and targeted therapies.

In conclusion, the future of cyclodextrin research is characterized by a dynamic interplay between overcoming current challenges and exploring innovative trends. As researchers strive to optimize anchoring techniques, develop sustainable practices, and expand the applications of cyclodextrins, the field holds tremendous potential for transformative advancements in materials science, drug delivery, and beyond. [72]

Conclusion:

In conclusion, cyclodextrins (CDs) have emerged as indispensable tools in pharmaceutical and related industries, offering versatile solutions to enhance the physicochemical characteristics of various compounds. The historical trajectory of cyclodextrin chemistry, from initial skepticism to widespread acceptance, reflects a transformative journey marked by pivotal discoveries and applications.

The structural uniqueness of CDs, characterized by a torus-like shape with a hydrophobic cavity, facilitates the formation of inclusion complexes, contributing to solubility enhancement, dissolution improvement, stability, and controlled drug release. Methylated CDs, particularly notable for their efficacy in increasing solubility, play a crucial role in optimizing drug formulations.

The advent of cyclodextrins represents a cutting-edge approach, providing enhanced stability, versatility, and precise control over release kinetics. Immobilizing CDs onto surfaces ensures prolonged functionality and opens avenues for tailored material properties, demonstrating potential applications in targeted drug delivery and beyond.

Fundamental aspects of cyclodextrin chemistry, including their structural features, types, and inclusion complex formation mechanism, serve as the foundation for understanding their diverse applications. Anchoring methods, encompassing chemical bonding, physical adsorption, crosslinking, and polymer matrix incorporation, offer a spectrum of strategies to achieve stability and controlled release.

Physicochemical characteristics enhancement through CDs extends across solubility improvement, stability enhancement, drug safety optimization, and controlled drug release. CDs contribute significantly to various drug delivery systems, addressing challenges in oral, ocular, nasal, and novel drug delivery platforms. Their impact extends to the food and flavor industry, where CDs enhance the stability and dispersibility of food ingredients.

The continuous exploration, modification, and application of CDs underscore their ongoing significance in pharmaceutical research, drug development, and various industrial domains. The comprehensive understanding of CDs and their

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counterparts, facilitated by sophisticated characterization techniques, positions them as indispensable components in advancing therapeutic outcomes and addressing complex challenges in diverse fields.

9. Conflicts of interests

All 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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