

β -Cyclodextrins and Its Applications

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Abstract: Amidst the escalating energy crisis, the quest to harness renewable energy sources has become a topic of prevalent discussion in society. Lithium-ion batteries, as a forefront contender among new energy technologies, have garnered substantial attention from the scientific community. Enhancing the electrochemical performance of lithium-ion batteries is imperative for broadening their applications. Since its discovery in 1891, β -cyclodextrin has been employed in various fields such as pharmaceuticals, food, and textiles. Recent studies have illuminated the role of β -cyclodextrin in lithium-ion batteries, including its use as electrode binders and electrolytes, resulting in a marked improvement in battery efficiency. This paper will delve into the history of β -cyclodextrin, its chemical structure, principal reactions, and its dual applications in lithium-ion batteries and pharmaceuticals. Furthermore, it will explore how the unique structure of β -cyclodextrin influences its properties, thereby elucidating its suitability for use in lithium-ion batteries.

Keywords: β -cyclodextrins, lithium batteries, electrode binders, pharmacy

1. Introduction

In 1891, during experiments that targeted the enzymatic breakdown and reduction of carbohydrates, Villers noticed the unexpected emergence of crystalline structures possessing unique characteristics. This observation ultimately facilitated the discovery of cyclodextrins (CDs) [1]. Between 1903 and 1911, Schardinger characterized the structures of α -cyclodextrin (α -CD) and β -cyclodextrin (β -CD) and confirmed their identities [2]. In 1936, Freudenberg determined that the basic unit of these compounds is glucose [3]. In 1942, French defined CDs as cyclic oligosaccharides derived from starch polysaccharides, comprising nonreducing D-glucose polymers connected by α -D-1,4 glycosidic bonds [1]. In 1948, Freudenberg identified γ -cyclodextrin (γ -CD) and hypothesized the potential existence of CDs composed of either 9 or 10 units [4,5].

CDs and their derivatives are utilized in a wide range of industries, such as pharmaceuticals, food, cosmetics, and textiles, showcasing their diverse applications [2]. Among the natural CDs produced on an industrial scale, β -CD is particularly noteworthy. Its unique properties, such as hydrogen bonding capabilities and a macrocyclic structure, have made it highly valuable, leading to its widespread utilization [4-6]. There are two significant milestones in the history of CDs: firstly, the initiation of their production and commercialization; secondly, the pivotal toxicology study that demonstrated β -CD to be a non-toxic substance, thereby establishing a solid foundation for its safe use [1].

In this work, the structural and physicochemical aspects of β -CD are introduced, highlighting its significance in pharmaceuticals and lithium-ion batteries (LIBs).

2. General characteristics of β -Cyclodextrins

2.1. Origin and nature of CDs

During his 1891 experiments, Villers observed the accidental formation of crystalline structures that exhibited unique properties; this led to the discovery of CDs [1]. Between 1903 and 1911, Schardinger characterized the structures of α -CD and β -CD, confirming their molecular identities [2]. In 1936, Freudenberg determined that the fundamental unit of these compounds is glucose [3]. In 1942, French described CDs as cyclic oligosaccharides sourced from starch. These compounds are made up of nonreducing D-glucose polymers containing 6, 7, or 8 glucose units, which are linked through α -D-1,4-glycosidic connections [1]. Freudenberg identified γ -CD in 1948 and proposed the possibility of CDs containing 9 or 10 glucose units [4,5,7].

Researchers later discovered that CDs could be produced through the enzymatic action of cyclodextrin glycosyltransferase (CGTase) on starch. This enzyme catalyzes the conversion of starch into cyclodextrins by cleaving and restructuring the starch molecules into cyclic structures [6,8]. Subsequent studies have focused on the origin, structural characteristics, and production methods of CGTase, which have significantly improved the yield of CDs. Through processes such as disproportionation, hydrolysis, coupling, and cyclization, various CDs are synthesized, as shown in Figure 1.

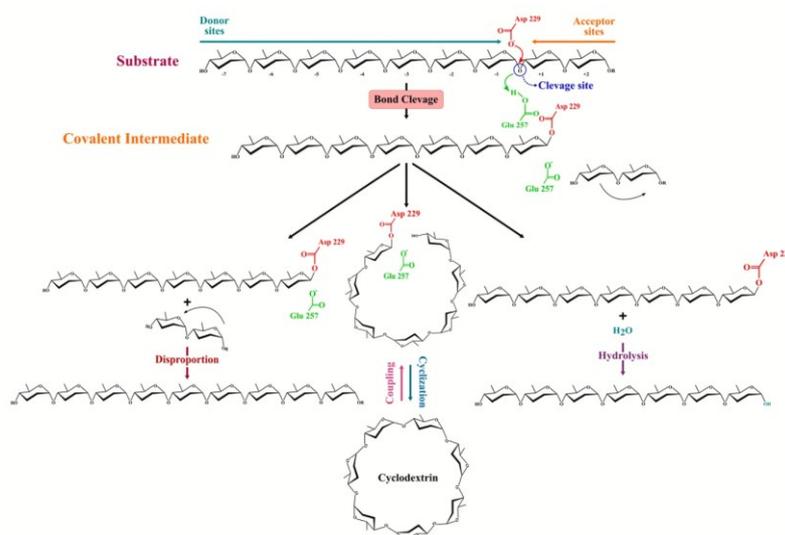
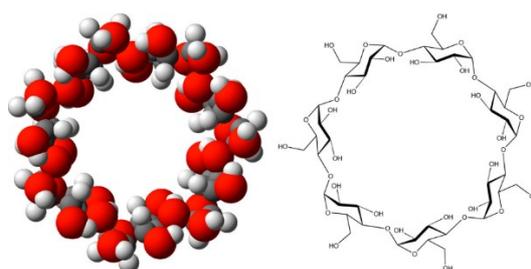


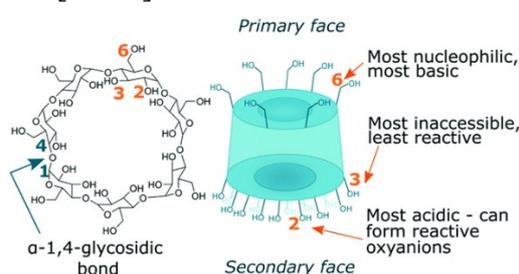
Figure 1: Overview of trans glycosylation reactions catalyzed by CGTase [6]

2.2. Structure and shape

According to Freudenberg et al., β -CD is a cyclic oligosaccharide composed of seven D-(+)-glucose units linked by α -1,4-glycosidic bonds. Its structure resembles a truncated cone, hollow in the center with a broader upper section and a narrower lower section, as illustrated in Figure 2. This unique shape allows β -CD to encapsulate various molecules, contributing to its functionality in different applications [9,10]. β -CD contains three primary functional groups: hydroxyl, ether, and acetal, among which the hydroxyl group is the most reactive. Due to ether bonds, β -CD can be degraded by strong acids.


 Figure 2: The Stuart molecular model (left) and structure (right) of β -CD [1]

There are three hydroxyl environments with distinct reactivity. The hydroxyl groups at the C6 position exhibit the highest reactivity, whereas those at the C3 position demonstrate the lowest reactivity, as depicted in Figure 3 [11-13].


 Figure 3: Structure of β -CD with highlighted three hydroxyl groups and their reactivity [14]

2.3. Solubility

The solubility profiles of the three CDs exhibit notable variations, as shown in Table 1. These dissimilarities can be attributed to the presence of secondary hydroxyl groups on one side of the cyclodextrin torus. These hydroxyl groups form hydrogen bonds with the secondary hydroxyl groups of adjacent glucose units, forming a complete secondary band. This configuration imparts rigidity to the cyclodextrin's structure. Consequently, β -CD displays the lowest solubility among the three naturally occurring CDs [15]. In the case of α -CD, there is distortion in one glucuronide sugar unit, leading to only four complete hydrogen bonds instead of the expected six. As a result, the hydrogen bonding bands within α -CD are incomplete. On the other hand, γ -CD possesses a non-coplanar and more flexible structure, which enhances its solubility compared to the other cyclodextrins [16].

Table 1: Properties of cyclodextrins [1,17]

Properties	α - cyclodextrin	β - cyclodextrin	γ - cyclodextrin
D- (+)-glucose monomers	6	7	8
Aqueous solubility (g/L)	129.5	18.4	249.2
Cavity diameter (nm)	0.57	0.78	0.95
Empirical formula	$C_{36}H_{60}O_{30}$	$C_{42}H_{70}O_{35}$	$C_{48}H_{80}O_{40}$

2.4. Host guest interactions

Host-guest interactions are essential for the functionality of β -CD, primarily due to its unique structure comprising a hydrophobic inner cavity and a hydrophilic outer surface. This configuration allows β -CD to engage with a diverse array of substances, such as organic and inorganic compounds, noble gases, and others, through various supramolecular forces, including hydrophobic

interactions and molecular complementarity [18]. The stability of complexes formed with cyclodextrin or its derivatives is notably affected by the guest molecule's size and shape, which must align with the dimensions of the cyclodextrin cavity [19]. Guest molecules may be encapsulated, displacing the water molecules originally occupying the hydrophobic central cavity to form supramolecular structures [20]. During the formation of these complexes, the hydrophobic regions of the guest interact with the internal walls of the cyclodextrin cavity, while the hydrophilic exterior interfaces with the surrounding solvent. This dual interaction not only enhances the solubility of the resulting complex but also promotes the effective encapsulation and stabilization of hydrophobic guest molecules, as illustrated in Figure 4 [21].

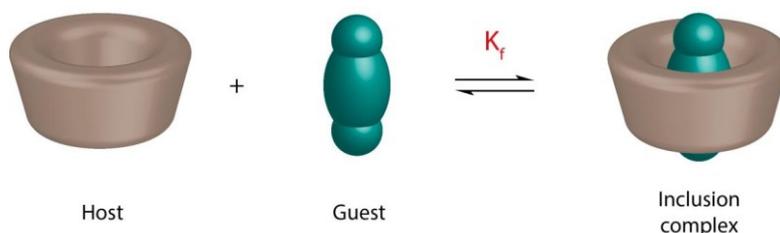


Figure 4: Schematic illustration of the formation of inclusion complex [22]

In 1956, Cramer highlighted that CDs can also form non-inclusive complexes with solubilizing properties. He noted that the hydroxyl groups of CDs can form hydrogen bonds with other molecules. Additionally, these groups can aggregate to solubilize lipophilic molecules typically insoluble in water [23].

2.5. Thermal behaviour

Regarding thermal effects, experimental data from Hădărugă et al. indicate that β -CD demonstrates the least thermal stability, as shown in Figure 5 [24,25]. This underscores the necessity for chemical modification to synthesize more thermally stable β -CD derivatives.

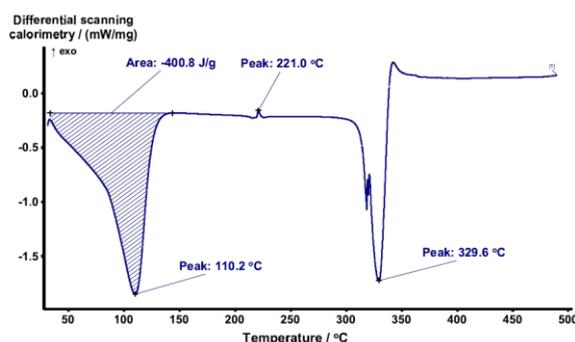


Figure 5: Differential scanning calorimetry analysis of β -CD [24]

3. Functionalization of β -CDs

Due to the larger cavity diameter of β -CD compared to α -CD, its production cost is lower than that of γ -CD [18]. Consequently, β -CD remains favored in industrial production. To overcome solubility challenges, chemical modification of β -CD offers opportunities for synthesizing derivatives.

Three methods are commonly employed for modification: cross-linking CD to polymers, using CD as a monomer for polymerization, and attaching functional groups to CD [26]. The first two methods are frequently utilized to synthesize cyclodextrin polymers (CDPs), while the third method is typically employed for derivative synthesis.

Advanced techniques such as RAFT, ROP, ATRP, FRP, click reactions, and condensation reactions facilitate the creation of diverse cyclodextrin-based polymers with enhanced properties. Three kinds of CDPs can be produced: CD-cored star polymers, CD-threaded polymers, and CD-capped polymers, as depicted in Figure 6 [26,27]. By selecting appropriate substituents and modifying the chemical structure of CD molecules, the resulting CD derivatives can reduce the number of hydroxyl groups, diminish the tendency for self-assembly in water, and significantly enhance water solubility [28]. For instance, β -CD derivatives are used to improve the solubility of steroidal drugs in water [29]. Chemically synthesized CD derivatives, such as acetylation, methylation, hydroxypropylation, and sulfobutyl ethers, exhibit higher decomposition temperatures and stability compared to native CDs [25].

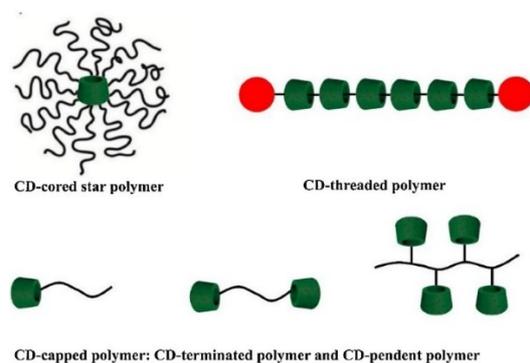


Figure 6: The architectures of three main categories of CD-based polymers [30]

4. Applications

4.1. LIBs

Lithium-ion batteries are now the dominant energy storage devices due to their lightweight structure, high energy density, and environmentally friendly features [31]. The choice of β -CD as a lithium-ion diffusion channel is driven by its hydrogen bonding properties and the appropriate size of its lumen diameter [32]. Significant research has focused on β -CD, especially its potential use in cyclodextrin-based binders. These studies emphasize its ability to improve the performance of lithium-ion batteries, positioning it as a strong contender for advancing energy storage technology.

4.1.1. Anode binders

Currently, graphite remains the only commercially available anode material for lithium-ion batteries, boasting a theoretical specific capacity of around 372 mA h g^{-1} . In contrast, silicon emerges as a highly promising alternative, offering an impressive specific capacity of 4200 mA h g^{-1} [33]. However, silicon's potential is hindered by significant challenges, including substantial volume changes during alloying and dealloying processes, which lead to capacity loss and mechanical degradation. Additionally, silicon exhibits low conductivity and diffusivity for lithium ions, complicating its use in battery applications [33,34].

To tackle these challenges, polymer binders are used to ensure the structural and mechanical integrity of electrodes [35]. Although polyvinylidene fluoride (PVDF) is commonly used as a binder, it exhibits drawbacks such as inadequate adhesion, limited mechanical strength, and low ionic and electronic conductivity [36].

Innovative binders with a three-dimensional network structure based on cross-linked cyclodextrin units offer an effective solution. This design creates a multidimensional hydrogen

bonding network that strengthens interaction with silicon, enhances adhesion, and accommodates the volume expansion of silicon particles, thereby improving cycling stability.

You Kyeong Jeong et al. introduced β -CDP that utilizes a hyperbranched structure to support multidimensional hydrogen bonding. This feature allows the binder to maintain consistent contact with silicon during continuous volume changes, aided by its self-healing properties [37]. Jiang et al. developed a cross-linked β -cyclodextrin-carboxymethyl cellulose (β -CD-CMC) binder, showcasing efficacy as an aqueous binder for silicon-based anodes. This binder effectively mitigates the volume changes experienced by silicon during battery operation [38].

4.1.2. Cathode binders

Zeng et al. introduced a novel multifunctional aqueous polycation binder, β -CDP, with quaternary ammonium cation, designed specifically for the sulfur cathode [39]. Originating from β -CD, this binder incorporates a quaternary ammonium cation into the β -CDP structure, effectively mitigating sulfur volume changes during polysulfide shuttling and the charging and discharging processes in lithium-sulfur batteries, as shown in Figure 7.

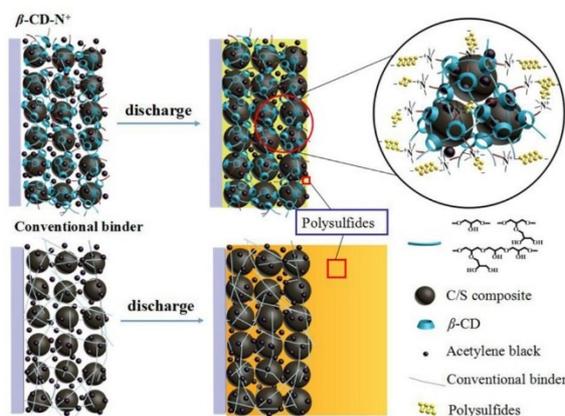


Figure 7: Schematic representations of cathode configurations with the new binder β -CDP- N^+ and the conventional binder

Jiulin Wang et al. discovered that treatment with hydrogen peroxide alters β -cyclodextrin into a soluble form, as shown in Figure 8 [40]. The resulting modification produces carbonyl- β -cyclodextrin (C- β -CD), which serves as a novel binder for sulfur composite cathodes. This binder demonstrates advantages such as environmental sustainability and broader electrochemical stability compared to polyvinylidene fluoride and polytetrafluoroethylene.

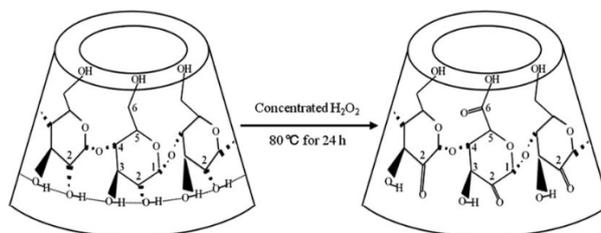


Figure 8: Schematic reaction of β -CD with H_2O_2

4.2. Pharmacy

CDs enhance the stability and solubility of pharmaceuticals through their cyclic dextrin structures, consequently increasing bioavailability [41]. Among the various CD-based pharmaceutical

formulations currently available on the market, β -CD and its derivatives boast the broadest spectrum of applications [42].

4.2.1. Change the physicochemical properties of the drug

Dinoprostone (PGE₂), which exhibits oxytocin-like effects, is employed for labor induction in childbirth; however, it is characterized by high instability. K Uekama et al. conducted studies indicating that the binding of PGE₂ to β -CD enhances the solid-state stability of the compound more effectively than when bound to α -CD. Based on these findings, a product named dinoprostone betadex was developed and subsequently approved for the Japanese market in 1976[42-44].

4.2.2. Controlled drug delivery

The study by Gao et al. highlights an innovative approach to drug delivery using poly(β -cyclodextrin) block copolymers and benzimidazole-poly(ϵ -caprolactone), as shown in Figure 9[45]. By leveraging the host-guest recognition properties of β -CD and benzimidazole, the developed copolymers enable the formation of micelles in aqueous environments, effectively encapsulating the anticancer drug doxorubicin. The high encapsulation efficiency of 74.77% is particularly noteworthy, as is the system's ability to control drug release based on pH and temperature conditions. This mechanism could significantly improve therapeutic outcomes in cancer treatment by allowing for targeted and controlled drug delivery.

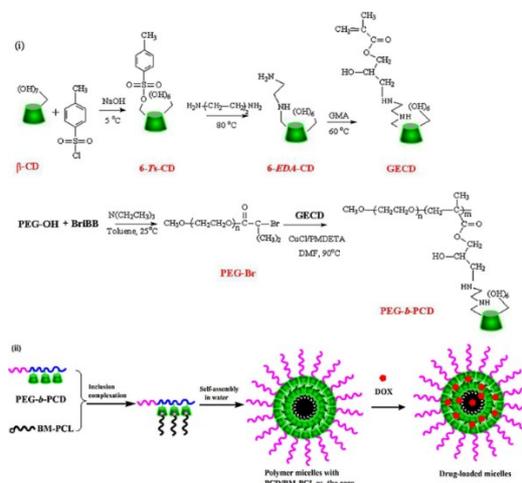


Figure 9: Synthetic process of poly(β -CD) diblock copolymer and the formation of complex micelles for drug loading

4.2.3. As drug

In 2004, John Dietschy and Steven Walkley discovered that 2-hydroxypropyl- β -cyclodextrin (HP β CD) could treat Niemann-Pick type C (NPC) [46]. In 2010, the National Institutes of Health launched the TRND program. By early 2011, one of the initial projects selected under TRND focused on developing HP β CD for the treatment of NPC1, which affects 95% of NPC cases. This initiative aims to advance therapeutic options for this rare genetic disorder, highlighting the potential of HP β CD in addressing critical health challenges. Currently, clinical trials have entered the third phase, which is expected to become one of the drugs for treatment [47].

5. Conclusion

β -CD distinguishes itself through its versatile host-guest interactions and cost-effective production, offering a broader range of applications compared to other cyclodextrins. The review focused on the properties of β -CD and its derivatives, emphasizing their crucial role in pharmaceuticals and LIBs, thereby underscoring the necessity for ongoing research to explore their potential in various industries.

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