β-CYCLODEXTRIN AND ITS DERIVATIVES

PREPARATION, CHEMISTRY AND APPLICATIONS

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β-Cyclodextrin and Its Derivatives: Preparation, Chemistry, and Applications

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CONTENTS

FOREWORD

Beta-Cyclodextrin, a naturally occurring cyclic oligosaccharides, has emerged as one of the most versatile and widely studied macrocyclic molecules for host-guest chemistry. It's unique structure—a hydrophobic cavity and a hydrophilic exterior enables the formation of inclusion complexes with wide range of guest molecules. Over the past few decades, this remarkable compound and its derivatives have captured attention of researchers across disciplines-from chemistry and materials science to environmental engineering and pharmaceuticals.

This book, **"Beta-Cyclodextrins and its derivatives: Preparation, Chemistry, and Applications"**, provides a comprehensive and multidisciplinary exploration of β-Cyclodextrin and its analogues, highlighting their synthesis, functional properties, and groundbreaking applications across diverse industries. It meticulously covers these advancements, beginning with the fundamentals then systematically delves into the specialized applications ranging from pollutant remediation and agriculture to anticorrosion technologies, biomedical uses, drug delivery systems, and cancer therapy.

The key strength of this book lies in its interdisciplinary approach, bridging chemistry, materials science, pharmaceuticals, and environmental engineering. This book acts as an invaluable source of reference to graduate students, researchers, as well as industry professions working various fields such as chemistry, biotechnology, materials science, environmental sciences.

The book offers a commendable scholarly rigor from the authors and editor in consolidating decades of research while inspiring the future breakthroughs by provoking the readers to further explore the potential of this remarkable molecule-β-cyclodextrin.

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PREFACE

In the fields of chemistry, pharmaceuticals, food science, materials engineering, and environmental technology, cyclodextrins—in particular, beta-cyclodextrin (β-CD) and its derivatives—have become highly relevant. They can form inclusion complexes with a variety of guest molecules thanks to their special structural characteristics, which include a hydrophilic exterior and a hydrophobic cavity, improving solubility, stability, and bioavailability. Modifying β-CD to customize its properties for specific uses has been the focus of much research over the past few decades, which has resulted in advancements in drug delivery, catalysis, nanotechnology, and other fields. The goal of this book, β-Cyclodextrin and Its Derivatives: Preparation, Chemistry, and Applications, is to give researchers, academics, and professionals interested in the science and applications of β-CD a thorough and updated resource.

The book methodically discusses:

Methods for Synthesis and Modification: Comprehensive procedures for creating β-CD and its chemically altered derivatives, such as ethers, esters, and polymerized forms. Structural and Chemical Properties: An investigation of the kinetics, thermodynamics, and molecular interactions that control host-guest complexation. Numerous Applications: Real-world applications in advanced materials (*e.g.*, sensors, nanocarriers), food and flavour stabilization, pharmaceuticals (*e.g.*, drug encapsulation, controlled release), and environmental remediation (*e.g.*, pollutant removal), etc. Chapters in the book offer both theoretical insights and helpful advice by fusing basic ideas with current developments. To close the gap between lab research and industrial application, special attention is paid to green chemistry techniques, synthesis scalability, and regulatory considerations.

For engineers, chemists, formulation scientists, and graduate students looking to capitalize on the potential of β-cyclodextrin derivatives, this book is meant to be a reference. In this ever-evolving field, we hope it stimulates more creativity and interdisciplinary cooperation.

Our appreciation goes out to the many researchers whose groundbreaking research has influenced our knowledge of cyclodextrins, as well as to the reviewers and contributors who have added their knowledge to this book.

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CHAPTER 1

Cyclodextrins and β-Cyclodextrin: Fundamentals, Classifications, Origin, Synthesis, Properties, and Greenness

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Abstract: Cyclodextrins (CDs) are compounds well-known for improving the water-solubility of hydrophobic drugs in the field of drug delivery. They are produced by the enzymatic degradation of starch and have an extreme capacity to hold poorly water-soluble compounds in the cavity. CDs can be defined as natural and synthetically derived. Since the 1930s, discoveries have been evolving with new derivatives of synthetic CDs. The α, β, and γ-CDs are naturally available, and synthetic CDs are derived from some bacterial and microbial cultures of starch. Their molecular shape, size, and loading capacities make them an ideal candidate in the medical field. Of the three native forms of cyclodextrins, β-CDs are the most utilized and researched owing to their cost-effectiveness relative to the other two, their high complexation efficiency, and the dimensions of their cavity, which effectively accommodate a substantial quantity of molecules. The limited aqueous solubility of native β-CD is a drawback, prompting the development of CD derivatives with different substituents, including methyl, carboxymethyl, hydroxypropyl, and sulfobutyl. However, Modifications in their structure improve their properties further. Chemical properties of some derivatives have also improved through some chemical reactions like substitution, oxidation, esterification, *etc*. A detailed chemistry is explained here that involves the improvement of the chemical properties of different derivatives of CDs. In the pharmaceutical industries, β-CD is most widely used due to its chemical properties and water-solubility.

Keywords: Cyclodextrins, Chemical and structural properties, Solubility.

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Kamlesh Kumari, Ayushi Prajapat, Prashant Singh & Chandrabhan Verma (Eds.)

INTRODUCTION

When starch is broken down by enzymes, stable macromolecules known as cyclodextrins (or CDs) are created. These compounds have water solubility and biocompatibility, distinguished by a hydrophilic exterior and a lipophilic interior. Because of the chair structure of the glucopyranose units, they have a form more akin to a truncated cone or torus than a whole cylinder. Cyclodextrins can be classified into natural and derived types [1].

What are Cyclodextrins

Industrially, the enzyme cyclodextrin glucosyltransferase is used to enzymatically generate cyclodextrins from modified starch, making the process economically feasible with an estimated annual production of 150 tons. However, natural CDs have limited solubility. Colonic bacteria, which are non-toxic and not ingested in the upper part of the gastrointestinal tract, fully digest the finished product [2]. Examples of natural CDs are the well-known cyclic oligosaccharides α, β, and γ, which consist of 6, 7, and 8 glucopyranose units, respectively (Fig. **1**). These compounds are homogenous, crystalline, and non-hygroscopic in nature. The main reason for β-cyclodextrin's popularity is its lower price, high availability, optimal cavity size, good drug complexation as well as loading characteristics, and ease of use [1].

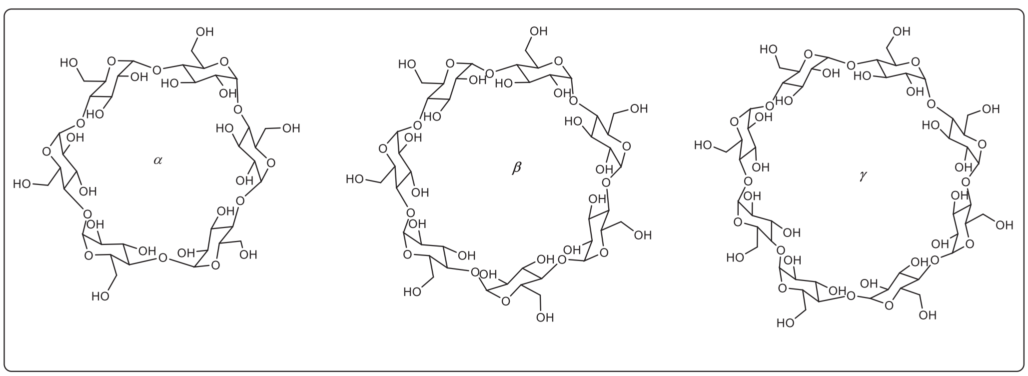

Fig. (1). Chemical structure of different cyclodextrins (CDs).

Historical Background

CDs are often referred to as "Schardinger dextrins" or cycloamyloses. They are water-soluble, non-reducing macrocyclic polymers made up of α 1, 4-glycosidic linkages connecting glucose molecules [3]. The three most prevalent cyclodextrins, α, β, and γ, each have six, seven, and eight glucose units [4]. The ring-shaped structure features a cavity diameter of roughly 6 Å for β-cyclodextrin and 8 Å for γ-cyclodextrin [5]. It was in 1891 when cyclodextrins were discovered, when French pharmacist Antoine Villiers identified α- and β-cyclodextrins as byproducts of potato starch digestion by the bacterium "Bacillus Amylobacter" [6]. After 1.5 decades, a microbiologist, Franz Schardinger from Austria, while researching microorganisms involved in food spoilage, isolated "Bacillus Macerans," which consistently produced two distinct crystalline substances from starch media. He named these substances α- and β-dextrin due to their properties resembling known partial starch degradation products, though their chemical structure was not yet understood [6, 7].

In the early 1930s, Freudenberg and colleagues, building on insights from researchers like Karrer and Miekeley, determined that these crystalline Schardinger dextrins consisted of maltose units linked solely by α-1,4-glycosidic bonds. Later in 1936, they developed a method for isolating homogeneous fractions and proposed the cyclic structure of these dextrins. Then, in two years, 1948-1950, γ-cyclodextrin was discovered, and its structure was elucidated [8]. In the early 1950s, two researchers, the French and Cramer teams, focused on the enzymatic production of cyclodextrins, aiming to fractionate them and characterize their properties. French's team identified larger cyclodextrins, while Cramer's group investigated their inclusion complex-forming abilities [6]. Freudenberg, Cramer, and Plieninger obtained a patent in 1953 that covered key aspects of cyclodextrin applications in drug formulations, showcasing how cyclodextrin complexation could protect sensitive substances from oxidation, enhance solubility, and minimize the loss of volatile compounds. French published the first thorough assessment of CDs in 1957. Thoma and Stewart's monographs followed in 1965, and Caesar's in 1968 [9]. Over the next 25 years, research expanded, revealing promising results from toxicological studies. By the late 1960s, laboratory-scale methods for the preparation of CDs, along with their structures and properties, were known to researchers. Cyclodextrins emerged as intriguing and promising molecules, highlighting their industrial potential [9].

CLASSIFICATION OF CYCLODEXTRINS: Α, Β, AND Γ

The natural, unsubstituted α-, β-, and γ-CD, as well as their complexes, are water-soluble in nature. As a result, aqueous pharmaceutical applications, such as parenteral formulations, are more likely to employ compounds that are more soluble, including sulfobutylether βCD sodium salt and 2-hydroxypropyl-β-CD. Although α-CDs and γ-CDs are also present in low concentrations in these products, the superior solubility of these derivatives makes them more suitable for use [10]. European Pharmacopoeia and the United States Pharmacopeia have monographs for α-, β-, and γ-CD, together with two β-CD derivatives. CDs are

CHAPTER 2

β-Cyclodextrin and its Derivatives in Heavy Metals and Pollutant Removal Applications

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Abstract: Cyclodextrins (CDs) and their derivatives, including polymers, hydrogels, and nanoparticles, possess unique properties that have cemented the way for the development of pioneering and greener strategies for environmental remediation. Host-guest behavior of beta-cyclodextrin results in the formation of inclusion complexes, which aid in the removal of heavy metal ions from water. These intrinsic structural and chemical properties, biocompatible and bioabsorbent character, and the ability to interact selectively with a wide range of molecules, forming inclusion complexes and higher order supramolecular structures, make these materials highly attractive for removing persistent and emerging pollutants. This chapter exclusively deals with heavy metal ions removal from water and discusses the variety of modifications of β-Cyclodextrin (β-CD) which have proven to be useful in the removal of pollutants from water. This chapter provides a critical and timely compilation of the key contributions and advances in environmental remediation technologies based on natural/modified CDs, with selected examples of adsorbents and target matrices and adsorbed compounds.

Keywords: Amino-β-CD, β-Cyclodextrin, Carboxyl-β-CD, Cross-linked β-CD, Heavy metals, Pollutant, Thiol-β-CD.

INTRODUCTION

Heavy metal pollution and organic contaminants are major environmental threats due to their toxicity, persistence, and ability to bioaccumulate in ecosystems and human bodies. Heavy metals like lead (Pb), cadmium (Cd), mercury (Hg), and arsenic (As) are released into the environment because of the contribution of industrial activities, such as mining, manufacturing, agriculture, and urbanization [1]. These metals are non-biodegradable and create severe health threats, including respiratory disorders, neurological damage, and cancer. Moreover, orga-

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Kamlesh Kumari, Ayushi Prajapat, Prashant Singh & Chandrabhan Verma (Eds.)

nic pollutants, such as pharmaceuticals, pesticides, herbicides, and polycyclic aromatic hydrocarbons (PAHs), come into the environment through agricultural runoff, wastewater discharge, and industrial waste [2]. These compounds frequently reveal long-term perseverance in ecosystems, leading to contamination of water bodies, soil, and food chains. For example, persistent organic pollutants (POPs), such as DDT, PCBs, and dioxins, are detrimental to wildlife and humans even at low concentrations [3].

The removal of anthropogenically derived pollutants, such as inorganic, organic, and pharmaceutical active compounds, is still struggling with different technological, economic, and social issues. These comprise limited availability of environmental data, compound specificity, poor resource management, and a lack of regulatory stringency to address the diversity of contaminants. Existing remediation techniques, for instance, ion exchange, chemical precipitation, and activated carbon adsorption, have limitations in terms of selectivity, cost, and efficiency. Thus, pioneering materials that can selectively remove these pollutants while being environmentally friendly are in high demand.

β-cyclodextrin (β-CD) is a ring-like structure (cyclic oligosaccharide) having seven glucose units linked by α-1,4-glycosidic bonds. This exclusive architecture design gives β-CD a hydrophilic outer surface and a hydrophobic inner cavity, allowing it to form inclusion complexes with diverse hydrophobic molecules. This host-guest interaction is based on non-covalent forces, such as hydrogen bonding, Van der Waals forces, and hydrophobic interactions (Fig. **1**) [4]. The ability of β-CD to encapsulate guest molecules makes it a versatile material for environmental applications. Its hydrophobic cavity can lock and immobilize organic pollutants, such as pesticides and pharmaceutical residues, as well as complex with certain metal ions [5]. β-CD is biodegradable, biocompatible, and non-toxic, making it a sustainable substitute to synthetic adsorbents.

However, unmodified β-CD has limitations in terms of its affinity for metal ions and some hydrophilic pollutants. To enhance its performance, β-CD can be chemically modified or functionalized, creating derivatives that have a higher affinity for specific contaminants. These modifications can increase its efficiency in adsorbing heavy metals and organic pollutants, even in complex environmental matrices (Fig. **2**). The significance of β-CD derivatives in environmental remediation lies in their ability to selectively and efficiently remove both heavy metals and organic pollutants from contaminated environments [6]. Modifications of β-CD can introduce functional groups, such as amine, carboxyl, and sulfonic acid groups, which enhance the binding affinity for specific pollutants. For instance, carboxylated β-CD derivatives can chelate heavy metal ions, while hydrophobic modifications can improve the capture of nonpolar organic pollutants [7].

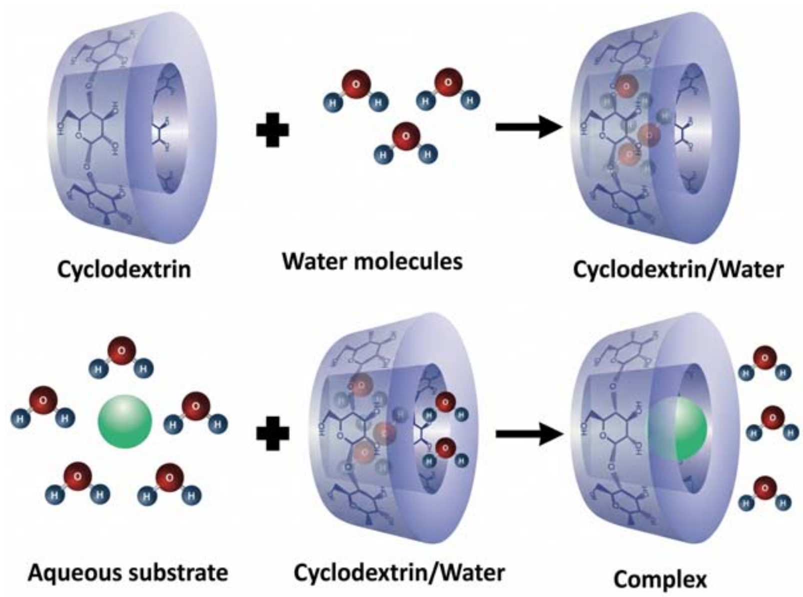

Fig. (1). β-CD Complex formation by encapsulation of the guest molecule.

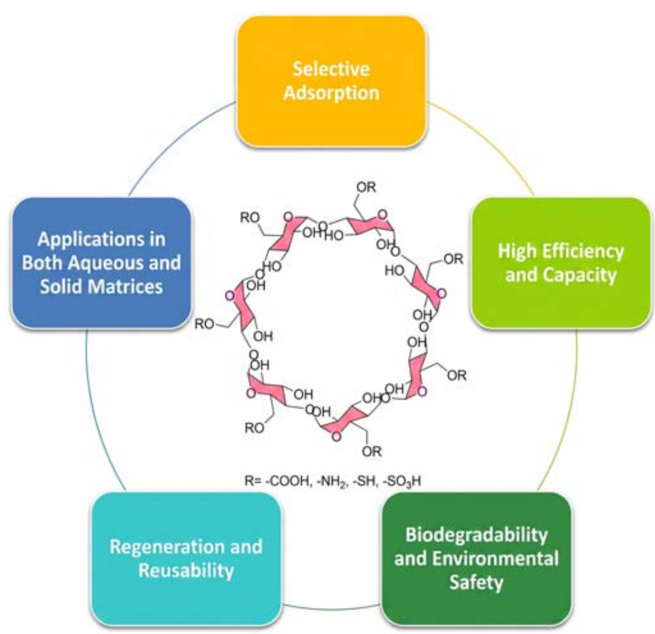

Fig. (2). Key advantages of using β-CD derivatives for pollutant removal [8].

CHAPTER 3

β-Cyclodextrin and its Derivatives in Anticorrosive Applications

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Abstract: In recent years, there has been increased interest in the synthesis of β-Cyclodextrin (β-CD) and its functionalised derivatives with novel, biocompatible, biodegradable, and widespread applications. β-CD is a cyclic oligosaccharide having a cone-like cavity in the structure with a hydrophilic outer external surface and a hydrophobic internal cavity. Through host-guest interactions, this cage structure has the capacity to create inclusion complexes with different molecules. β-CD is found to have a wide variety of applications, including targeted drug delivery, wastewater remediation, corrosion inhibition, environmental protection, cosmetics, nanotechnology, and textile production. In this book chapter, the structure, properties, and applications of β-CD and its derivatives as corrosion inhibitors are thoroughly discussed. This book chapter aims to fill the gap between the basics of β-CD and its derivatives and the real-world applications.

Keywords: Anticorrosive applications, β-Cyclodextrin (β-CD), Corrosion inhibition, External surface hydrophilic, Hydrophobic cavity.

INTRODUCTION

A major issue that has the potential to do significant harm to both society and property is corrosion. According to studies, corrosion-related damages amount to $2.5 trillion, or around 3.4% of the world's gross domestic product [1]. This huge economic loss due to corrosion can be reduced significantly by appropriate corrosion protection materials. The most popular approach is to use a corrosion inhibitor, which is inexpensive and simple to apply [2, 3]. Corrosion inhibitors are inorganic and organic water-soluble compounds that efficiently inhibit corrosion. Currently used inhibitors suffer from various drawbacks, such as toxicity, non-biodegradable, non-eco-friendly, and poor thermal stability in an acidic environment, causing their limited use due to strict environmental regulations.

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Kamlesh Kumari, Ayushi Prajapat, Prashant Singh & Chandrabhan Verma (Eds.)

The increasing ecological awareness, therefore, shifted the trend towards the use of green corrosion inhibitors such as macrocycles, polymeric substances, inorganic salts, and organic compounds that contain heteroatoms like oxygen, nitrogen, sulphur, and phosphorus [4 - 12].

The presence of chelation points, benzene rings, a higher number of atoms of hetero and conjugations with π bonds are among the intriguing characteristics of macrocyclic molecules and their analogs that make them an excellent choice for efficient corrosion inhibition. These are large planar systems: Porphyrin rings, cyclodextrins, calixarenes, phthalocyanines, and crown ethers [13 - 15]. These inhibitors can prevent metals from corroding destructively in aqueous systems, such as neutral, bacterial, or microbial solutions, saline solutions (3.5 percent NaCl or simulated sea water), acidic solutions (0.1–1 Molar H_3PO_4, H_2SO_4, HCl, and H_2S).

One of the most sought macrocyclic compounds as a corrosion inhibitor is β-Cyclodextrin (β-CD). β-CD and its derivatives are found to be effective, sustainable, low-cost, environmentally friendly, excellent water-soluble, and versatile corrosion inhibitors and hence are an innovative material for corrosion protection. The presence of surface-active hydroxyl functional groups and the tendency to form inclusion complexes aid β-CD in exhibiting high corrosion inhibition efficiency. On metal surfaces, β-CD and its derivatives are chemically and/or physically adsorbed to create a stronger protective thin layer that effectively prevents corrosion while preserving the material's mechanical and electrical qualities [16, 17]. A comprehensive discussion on the structure, properties, and plausible mechanism of corrosion inhibition is presented in the following section.

β-CD molecules are natural sugar macromolecules involving seven D-(+)-glucopyranosides-glucose molecules forming a basket-like or truncated cone-like structure with a wider end at one side anda narrower end at the other [18]. Due to their unique basket-like or truncated cone-like shape, CDs are perfect structures for host-guest-type interactions that can encapsulate other molecules in aqueous solutions to form nonpolar complexes. The hydrophobic and basic character of the cavity arises from nonbonding electrons of the pair of ether-type oxygen bridges facing the interior of the cavity. The hydrophobic cavity interacts with the guest molecules to form inclusion complexes. A deeper comprehension of the corrosion inhibition mechanism is facilitated by the interaction between the guest and host molecules through van der Waals interactions, hydrophobic interaction forces, and chemical and physical adsorption [19 - 22].

There are several corrosion inhibition β-CD derivatives, such as polymeric-based, superamolecular-based (host-guest), organic molecule-based, graphene oxide, and other nanomaterial-based derivatives, which are obtained by modifications through the external hydrophilic hydroxyl functional groups. These derivatives differ in their chemical composition, physical attributes, molecular frameworks, functional groups with polarity, and other features, leading to different corrosion inhibition properties. As a result, their high inhibitory efficacy is promoted by an exterior hydrophilic surface that contains active hydroxyl functional groups. In high-impact industries like metal processing and metallurgical, oil-gas extraction and processing, and chemical and petrochemical manufacture, these compounds are essential for protecting metallic materials from harmful corrosion [23].

CORROSION INHIBITION MECHANISM

The inhibition mechanism is understood through a range of analytical techniques, including electrochemical characterization techniques like Weight Loss (WL) measurements, Electrochemical Impedance Spectroscopy (EIS), Potentio-Dynamic Polarization (PDP), surface characterization techniques like energy dispersive spectroscopy in combination with Scanning Electron Microscopy (SEM), and spectroscopic techniques like Fourier Transform Infrared Spectroscopy (FTIR) and X-ray photoelectron spectroscopy (XPS). The characterisation techniques shed light on the corrosion mechanism. It has been discovered that β-CD-based corrosion-preventing agents cover a significant portion of a metal surface and create a stable coating. The most advantageous adsorption mechanisms for inhibitors and protective film development are chemical and physical (Fig. **1**).

Numerous active chemical groups, π-bonds, and a broad structure are characteristics of modified β-CD. Additional functional groups, aromatic π-systems, and electron-rich nitrogen atoms facilitate the chemical interaction between the corrosion inhibitor and the metal surface. The physical adsorption occurs through electrostatic interactions between the opposite charges on the metal and the inhibitor molecules. This adsorption is stable only at relatively low temperatures because the heat of adsorption is low. When heteroatoms (O, S, N, *etc*.) in active polar functional groups donate their lone pairs of electrons to the metal's unoccupied d-orbitals (Zn, Al, Fe, Cu, *etc*.) in order to create a coordinate covalent bond, chemical adsorption takes place. For nitrogen-based β-CD derivatives, physical adsorption is achieved by electrostatic interactions between the inhibitor's protonated nitrogen atoms and the negatively charged metal surface, while chemical adsorption occurs when β-CD derivatives and metal ions go through a chemical reaction through electron pair transfer from the nitrogen atom on the inhibitor to the vacant d-orbitals of the metal that forms stiff covalent

CHAPTER 4

β-Cyclodextrin and Its Derivatives in Analytical Applications

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Abstract: Owing to their biocompatibility, biodegradability, and relatively low-cost production, cyclodextrins and their derivatives have been of great interest to scientists and researchers in both academia and industry for over a century. Cyclodextrin derivatives are widely used in several industries, such as the medical, pharmaceutical, cosmetics, food, and textile industries. This chapter overviewed recent contributions related to the synthesis of Cyclodextrin (CD)-based derivatives, and their analytical applications, especially Chromatography, Spectroscopy, Electrochemistry, and Sensor technologies. The goals of this paper are to establish the basic principles of molecular recognition-based CD-assisted analytical methods, to highlight recent advances, and to demonstrate the benefits and limits of their application in this field.

Keywords: Chromatography, Electrochemistry, Hydroxypropyl-β-cyclodextrin, Methyl-β-cyclodextrin, Spectroscopy, Sulfobutyl ether-β-cyclodextrin, Sensor technologies.

INTRODUCTION

Cyclodextrins (CD) are naturally occurring cavity compounds and are employed in several varied fields of analytical chemistry, owing to their tendency to form reversible inclusion complexes and bind to analytes selectively. This characteristic demonstrates how these nanocavities can serve analysts in sample preparation, enantio-separation, sensitivity/selectivity improvement, creating single-molecule sensors, and automating DNA sequencing [1]. As research progresses, the applications of CD are expected to expand further, particularly in fields demanding advanced precision and detection capabilities. There are two types of CDs accessible: native CDs and modified CDs. The most common native CDs used for pharmaceutical applications are α-CD, β-CD, and γ-CD, consisting of 6, 7, and 8 glucose units, respectively, although larger CDs are known [2, 3].

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Kamlesh Kumari, Ayushi Prajapat, Prashant Singh & Chandrabhan Verma (Eds.)

β-Cyclodextrin (β-CD) is a truncated cone-like structure with a hydrophobic cavity and a hydrophilic exterior having seven glucose units linked by α-1,4-glycosidic bonds [4]. A hydrophobic cavity is formed due to the orientation of the glycoside oxygen and hydrogen atoms toward the cavity, in a cyclic structure. The unique combination of these features allows β-CD to form inclusion complexes with a variety of guest molecules. These guest molecules, when trapped within the hydrophobic cavity, can experience altered chemical properties, such as enhanced solubility or stability. These inclusion complexes can significantly modify the physicochemical characteristics of guest molecules, resulting in enhanced selectivity, sensitivity, and precision in analytical techniques [5]. The aptitude for the formation of inclusion complexes (Fig. **1**) underlies the widespread use of β-CD in various fields, particularly analytical chemistry [6, 7]. Cyclodextrins and their derivatives are effective analytical agents for a diverse range of investigations.

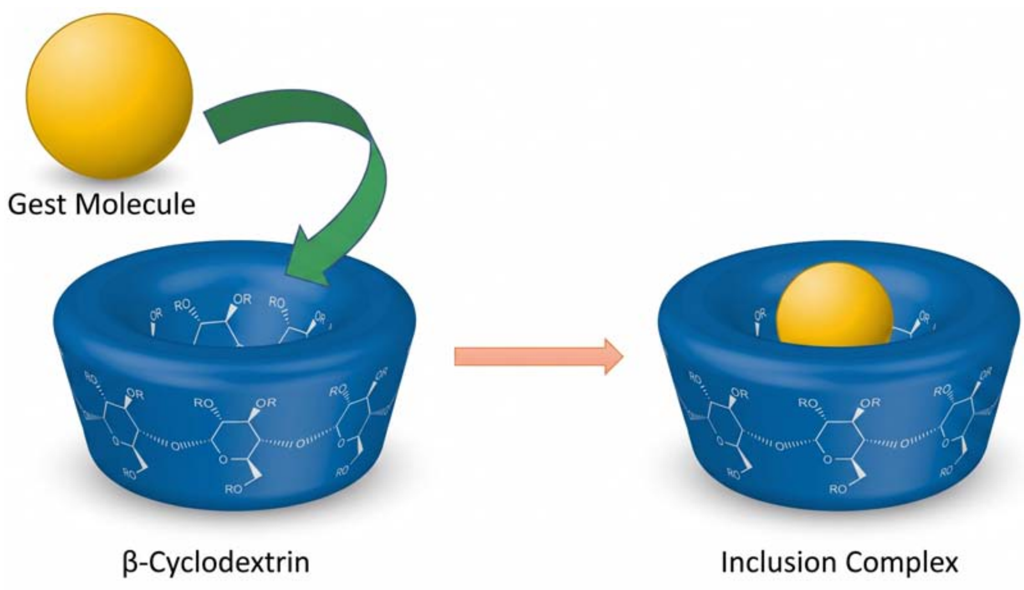

Fig. (1). Inclusion complex formation of β-cyclodextrin.

β-Cyclodextrin is an inexpensive, extensively accessible, biocompatible, and biodegradable material and is esteemed for encapsulation properties. β-Cyclodextrin has applications in various fields such as pharmacy [8], personal care products, biomedicine, food, molecular recognition, and supramolecular chemistry [9 - 12]. Cyclodextrin is also an enormously adaptable molecule for polymer science [13]. It is mainly esteemed for easy functionalisation, including attachment of initiator moieties as well as unsymmetrical modification [14].

In analytical applications, β-CD is favoured for its ability to:

- **Enhanced selectivity:** The ability to form complexes with specific analytes allows β-CD to reduce interference from other components in complex samples [15].
- **Improved sensitivity:** By stabilizing and solubilizing otherwise poorly detectable analytes, β-CD increases the reliability of detection methods [16].
- **Reduction of matrix effects:** β-CD helps to shield analytes from interfering substances within a sample matrix, improving the accuracy of quantitative analyses [17].

Considering the facts discussed, this chapter will provide an in-depth analysis of β-CD and its derivatives in the context of analytical applications. It will explore the various modifications and derivatives of β-CD, their properties, and their specific applications in techniques such as:

- Chromatography
- Spectroscopy
- Electrochemistry
- Sensor technologies

Additionally, the chapter will consider challenges, limitations, and regulatory aspects of using β-CD derivatives in different industries, and will highlight emerging trends in β-CD research.

β-CYCLODEXTRIN DERIVATIVES

The native CDs have been modified to improve their solubility and ability to facilitate complex formation. CDs can be customized by replacing diverse functional groups on the primary and/or the secondary face of the molecule. This substitution could happen to any glucosyl residue, and the ligands need not be attached to the identical glucose unit. By alteration in the functional groups, there is a change in the chemical and physical properties of cyclodextrins, which shows various applications such as enzyme mimicry [18, 19] and for the catalysis of the reactions of molecules held within the cavity [20]. Cyclodextrins (CDs) are utilized across various fields, including pharmaceuticals, food science, and analytical separation methods.

To produce CD derivatives, diverse functional groups are appended to the hydroxyl sites, specifically at positions 2, 3, and 6, within the glucose molecules. Notable examples of these functionalized cyclodextrins encompass hydroxypropyl, methyl, carboxymethyl, and sulfobutyl ether β-cyclodextrins

CHAPTER 5

β-Cyclodextrin and its Derivatives in Bio-, Thermo-, and Chemo-sensing Applications

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Abstract: Cyclodextrin (CD), consisting of cyclic glucopyranose oligomers with a basket-like shape, features an internal hydrophobic cavity and exterior hydrophilic sites, enabling it to act as a neutral carrier by producing inclusion complexes consisting of a broad array of guest compounds, including various chemicals as well as biomolecules of interest. The interaction and complex formation ability occur by means of noncovalent bonds, particularly Hydrophobic interactions, and hydrogen bonding. These noncovalent interactions enable cyclodextrin derivatives to create stable inclusion complexes with guest molecules, without altering their chemical structures. The supramolecular chemistry of β-CD facilitates the creation of complex formation between guest and host with several biologically important organic and neutral molecules. This complexation phenomenon endows β-CD with sensing capabilities through the selective creation of host-guest complexes. In the chapter, the details about the derivatives of β-CD, properties responsible for sensing ability, will be discussed. Apart from bio, chemical, and thermo-responsive sensors, various other sensors in detail, like fluorosensors, immunosensors, chiral sensors, and potentiometric sensors, will be further described. The chapter will elaborate on their wide applications in the medical, diagnostic, and pharmaceutical industries. Future aspects of β-CD in upcoming 3D/4D printing technology, tumor/cancer treatment, as a nano delivery system with antibiotic agent for antimicrobial resistant strains will also be enlightened.

Keywords: Acetylcholinesterase sensor, β-Cyclodextrin, Conducting polymers, Chiral sensor, Electrochemical sensors, Multiwalled carbon nanotubes, Potentiometric sensors, Single-walled carbon nanotubes.

INTRODUCTION

Supramolecular chemistry presents the macrocyclic host cyclodextrin (CD), which, owing to its hydrophobic cavity's strong association with hydrophobic

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guest molecules, forms host-guest complexes with noncovalent interactions. CDs are basically very useful functional excipients with hollow, truncated cone-shaped cyclic oligosaccharides. Beta-CDs (β-CDs), produced through enzymes from starch, possess a distinctive structure having a hydrophilic outer surface besides the hydrophobic cavity, enabling interaction with different moieties and improving their characteristics. CDs are formed due to the degradation of starch, corn, and potato by enzymes, most notably CD glycosyl transferases and α–amylase, generating a distinct ratio of three CDs. Their capacity to form complexes of host-guest *via* H_2 bonding, hydrophobic interactions, or alternative procedures renders them dynamic tools across various industries, facilitating a wide range of applications [1, 2].

This distinct chemical structure enables them to entrap poorly water-soluble substances, including antioxidants, pharmaceuticals, antimicrobials, antibiotics, nanoparticles (NPs), forming inclusion complexes resulting in improved stability, solubility, controlled release, dissolution, absorption, bioavailability, and permeability. CDs are biomolecules, sugar by class, glucopyranosides-glucose molecules with pyranose (six-membered) ring structure, linked together in rings by -1,4 glycosidic linkages of varying diameters. Six, seven, or eight glucopyranosides combine to make CD of different forms like α-, β-, and γ-.

Among them, β-CDs have gained wide applications in distinct domains like the pharmaceutical industry, pharmaceutical delivery, photodynamic therapy, detection for early warning of contamination in the environment, biosensors, chemosensors, and thermo-responsive CD inclusion complexes. They also have potential applications in new technologies, like 3D/4D printing.

Drug delivery has been successfully achieved through various routes, such as oral, nasal, and subcutaneous (s.c.) injection, using CD-based vehicles. These vehicles enhance drug stability by preventing degradation, augmenting absorption, and prolonging circulation times, hence increasing efficacy. CDs are in high demand in the pharmaceutical sector due to their adaptable prospect as a nanocarrier. They enhance the reliability, solubility, distribution, and compatibility of modified molecules in biological systems, making them ideal for creating nano/microcarriers that reliably administer antidiabetic substances, viz., insulin, α-lipoic acid, glucagon-like peptide-1agonists (GLP-1 agonists), and bilirubin, for regulating blood glucose levels [3].

Moreover, β-CDs have the ability to control/slow down the delivery of the guest molecules, augmenting their role as therapeutic agents. With respect to the drug manufacturing sector, their hydrophilic nature is particularly valuable, as it raises the solubility of drugs with low water solubility.

An increase in the concentration of CDs leads to higher cytotoxicity, which is impacted by their modifications. β-CD leads to hemolysis through the removal of cholesterol from RBC membranes. In drug formulations, CD derivatives are employed to increase solubility and support better absorption [4]. *E.g.*, 2-hydroxypropyl-β-CD (HP- β-CD) is incorporated in diclofenac sodium eye drops and oral itraconazole solutions to enhance the rate of absorption. Methylated-β-CD (M- β-CD) is utilized in eye drops of chloramphenicol to improve therapeutic strength [5]. β-CD is considered the most versatile CD derivative because of its cost-saving, optimal size of the hydrophilic cavity, biodegradability, accessibility, and noncytotoxicity. While generally recognized as safe (GRAS), CDs may cause adverse effects depending on their type and dosage. In elevated oral doses >1 g/kg/day, their osmotic activity surpasses that of polysaccharides, possibly leading to gastrointestinal complications like diarrhea or cecal enlargement. At concentrations of 20%, randomly methylated β-CD (RM-β-CD) is said to cause nasal irritation or harm. In ocular instillation, α-CD and methylated β-CD may result in corneal toxicity and irritation, but β-CD, HP- β-CD, and sulfobutylether β-CD (SB-β-CD) are less likely to cause such effects. No irritation reported so far through rectal route administration of CDs.

β-CD is the most extensively utilized CD on the basis of affordability, accessibility, biocompatibility, and its capability of forming inclusion complexes with an enormous range of chemicals through host-guest interaction. The exceptional encapsulating quality has the property of altering or increasing the guest molecule's biological, chemical, and or physical behavior monitoring, which makes CDs as sensors for monitoring bio, synthetic, and semi-synthetic molecules in the form of contaminants, antioxidants, and the fabrication of immuno-sensors. Leveraging the unique properties of β-CD allows researchers to drive the creation of next-generation treatments that respond to the evolving challenges of modern healthcare.

DERIVATIVES OF β-CD

Hydroxypropyl-β-CD: This derivative is a selective and sensitive biosensor for monitoring (+)-Catechin, an important flavonoid with protective effects against cancer and cardiovascular diseases [6].

β-CD capped gold NPs (β-CD AuNP): This derivative acts as an electrochemical catechol biosensor and ibuprofen effect inhibitor applying a tyrosinase-based nanosensor [7].

CHAPTER 6

β-Cyclodextrin and Its Derivatives in Catalytic Applications

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Abstract: Beta-cyclodextrin (β-CD) is a unique natural catalyst containing a ring structure of seven glucose units, and it is considered one of the most versatile as well as eco-friendly catalysts for organic synthesis and chemical transformation. This chapter discusses the unique structural characteristics of β-CD and its derivatives that lead to the catalytic properties of β-CD, including toroid structure, hydrophobic cavities, and hydrophilic exteriors. We highlight the potential usages of β-CD-based catalysts for multi-component reactions, oxidation reactions, hydrolysis reactions, *etc.* The benefits of β-CD catalysts are detailed in the chapter as they can function in aqueous media, accelerate reaction kinetics, increase reaction rates, and improve product efficacy. Recent developments in β-CD modification strategies to fine-tune catalytic activity and substrate specificity are discussed. This review highlights the crucial role that β-CD and its derivatives have as versatile tools in contemporary organic synthesis and chemical process development.

Keywords: Beta-cyclodextrin (β-CD), Beta-cyclodextrin derivatives, Green catalysis, Multi-component reactions, Supramolecular catalysis.

INTRODUCTION

Cyclodextrins are non-reducing cyclic oligosaccharides that have emerged as a versatile class of molecules with great impact in many disciplines of chemistry and biochemistry. The compounds are products of enzymatic degradation of starch [1], which were first described by Villiers in 1891 and then more accurately classified by Schardinger at the beginning of the 20th century. Of the three naturally available cyclodextrins, β-cyclodextrin (β-CD), composed of subunits

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Kamlesh Kumari, Ayushi Prajapat, Prashant Singh & Chandrabhan Verma (Eds.)

derived from glucose linked *via* specific α-1,4 chemical bonds, has attracted special interest owing to its well-suited cavity dimension for multiple applications [2].

β-cyclodextrin (β-CD) has a unique molecular structure that forms a conic or bucket-like structure. Its outer surface has hydroxyls that attract water, while its inner cavity forms a safe haven that repels water. This duality enables β-CDs to encapsulate a range of molecules within their cavity to create what chemists refer to as inclusion complexes. A feature that was initially identified by Cramer back in the 1950s, which set the stage for the very widespread application of β-CD in supramolecular chemistry [3]. Due to its ability to encapsulate lipophilic molecules in aqueous solutions, β-CD has been employed extensively in pharmaceuticals, food technology, and cosmetics [4].

Research involving β-cyclodextrin and its derivatives has come to be widely studied, both in their role as a catalyst as well as a support for catalytic processes. This progress bridges both homogeneous and heterogeneous catalytic approaches, offering unique advantages in selectivity, efficiency, and environmental sustainability [5]. The catalytic power of β-CD is due to its pseudo enzyme-like nature, which provides a spatial restriction for a chemical reaction that can enhance the reaction rate and selectivity [6].

β-CD has a broad spectrum of catalytic applications. β-CD and its derivatives play a crucial role as catalysts or catalyst supports in a wide range of organic reactions, such as oxidative and reductive reactions and carbon-carbon bond formation [7]. β-CD has also used in biocatalysis for improving the activity and stability of enzymes, and the solubility of hydrophobic substrates [8]. Environmental applications have become more popular, as β-CD-containing materials have been utilized for pollutant degradation and in water treatment processes [9].

β-CD was adapted to enlarge its spectrum of catalytic applications. A large number of derivatives have been synthesized by the chemical modification of the hydroxyl groups of β-CD. These alternative forms provide better solubility, more robust catalytic activity, and higher substrate-specificity [10]. These modifications include simple alkylations and acylations as well as the addition of metal-binding sites and catalytic moieties [11].

Diving deeper into this curious realm of research shows that β-cyclodextrin and its derivatives represent a separate class of catalysts, combining the selectivity that enzymes offer with the robustness of synthetic catalysts. This work improves our understanding of supramolecular catalysis and will further pave the way towards developing more efficient and sustainable catalytic processes in all areas of chemistry.

This chapter covers a comprehensive overview of the applications of β-cyclodextrin and its derivatives in catalysis. The main text discusses many catalytic achievements of β-cyclodextrin and its derivatives, with a special emphasis on their roles in organic syntheses. Additionally, we will discuss the benefits and drawbacks of utilizing these compounds as catalysts, and finish with outlooks from the field going forward in this dynamic field.

CATALYTIC APPLICATIONS

This section will explore the catalytic applications of β-Cyclodextrin (β-CD) and its derivatives. The discussion is divided into two parts:

Native β-Cyclodextrins: We will first examine the catalytic properties and applications of unmodified β-CDs.

β-Cyclodextrin Derivatives: The second part will focus on the various derivatives of β-CDs and their catalytic uses.

Native β-Cyclodextrins

β-Cyclodextrins (β-CDs) are naturally occurring cyclic oligosaccharides. In summary, they contain seven glucose subunits connected by α-1,4 glycosidic bonds in a characteristic toroidal structure. This elaborate structure yields a molecule with opposite properties: a hydrophilic outer section and a hydrophobic inner cavity [4]. This dual character allows β-CDs to serve as versatile molecular hosts and catalysts in diverse chemical transformations. This part will discuss the catalyzing features of unmodified β-CDs mainly in the area of organic synthesis.

The following studies highlight the diverse applications of the unmodified β-cyclodextrin in multicomponent reactions, showcasing its versatility and effectiveness in modern organic synthesis:

In 2024, Garg and their co-workers [12] developed a new approach to the convenient preparation of Hantzsch condensed N-aminopolyhydroquinoline derivatives using β-cyclodextrin catalysis. Through mild reaction conditions, the protocol allowed the combination of substituted aromatic aldehydes, dimedone, and hydrazine hydrate (Scheme **1**). The results showed that the best condition was 5% β-cyclodextrin in acetonitrile, giving 96% yield in 6 h, significantly more efficient than conventional synthetic routes. The stability of the catalyst was a particularly commendable feature of the work, with the β-cyclodextrin showing no loss in catalytic performance after many reaction cycles and minimal degradation in product yield. Together with the mild reaction conditions, this

CHAPTER 7

β-Cyclodextrin and Its Derivatives in Processing Applications

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Abstract: The CD, a family of cyclic oligosaccharides produced from the enzymatic degradation of starch, represents one of the most versatile classes of supramolecular hosts in modern science. The distinct architecture features a hydrophilic exterior, rendering them water-soluble, and a lipophilic or hydrophobic internal cavity. The naturally occurring CD, β-cyclodextrin (β-CD), composed of seven glucose units, is the most widely studied and utilized due to its cavity size, accessibility, and affordability. First discovered by A. Villiers in 1891 and later characterized by Franz Schardinger, β-cyclodextrin has transitioned from a chemical curiosity to an indispensable component in numerous industries, including pharmaceuticals, food technology, cosmetics, environmental engineering, and agriculture. Its ability to modify the physicochemical properties of guest molecules, such as enhancing solubility, improving stability, controlling release, and masking flavors, underpins its widespread importance. This chapter provides an in-depth exploration of β-cyclodextrin, focusing on its fundamental chemistry, preparation, and the critical role of its derivatives in overcoming the limitations of the native molecule to expand its application in human life. This work is based on an extensive analysis of the scientific literature concerning the history, synthesis, properties, and applications of β-cyclodextrin. The study delves into the core chemistry of β-CD, including its molecular weight (1135 g/mol), unique structural dimensions (cavity diameter of 6.0-6.5 Å), and the non-covalent forces (Van der Waals forces, hydrogen bonding) that drive the formation of inclusion complexes. A significant portion of the analysis is dedicated to addressing a primary limitation of native β-CD, its relatively low water solubility (1.85 g/100mL at 25°C). This limitation has spurred the development of numerous chemically modified derivatives. The chapter includes synthesis mechanisms, properties, and specific advantages of key derivatives, including hydroxypropyl-β-cyclodextrin, methyl-β-cyclodextrin, Sulphobutylether-β-cyclodextrin, and Carboxymethyl-β-cyclodextrin. The analysis highlights how strategic derivatisation, such as hydroxypropylation or methylation, significantly enhances aqueous solubility, improves complexation efficiency, and reduces toxicity, thereby broadening the scope of practical applications. The β-cyclodextrin and its derivatives stand out as remarkably versatile and impactful functional molecules. Their ability to form stable inclusion complexes through host-guest chemistry allows for the intelligent modification of a vast range of chemical compounds. The advanced derivatives have unlocked new possibilities in high-technology fields, most notably in sophisticated

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Kamlesh Kumari, Ayushi Prajapat, Prashant Singh & Chandrabhan Verma (Eds.)

drug delivery systems. From enhancing the efficacy of life-saving medicines to improving the quality of everyday consumer products and helping to remediate the environment, β-CD influence is profound and continues to grow as new derivatives and applications are explored.

Keywords: Cyclodextrin derivatives, Drug delivery, Inclusion complex, Solubility enhancement.

INTRODUCTION

The CD family of oligosaccharides consists of a microcyclic ring of glucose subunits. In CD, glucose subunits are joined by α-1, 4 bonds, glycosidic bonds by enzymatic conversion. The CD is used in food, pharmaceutical, drug delivery, chemical industry, and agricultural and environmental engineering. The cyclodextrin is composed of five or more α-D-glucopyranoside units linked by α-1, 4 bonds in fragmented starch. In general, CD six to eight glucose monomers occur in the ring. The structure of the CD is cone-like, and it is of three types according to the glucose monomer units present in the ring. The six glucose monomer units present in the ring are called α-cyclodextrin. The glucose monomer units present in the seven rings are called β-cyclodextrin; if the glucose monomer units are present in eight rings, they are called γ-cyclodextrin. The largest CD contains thirty-two units united by 1, 4-anhydroglucopyranoside bonds [1]. The cyclodextrin ingredients have been used in more than thirty different approved medicines; they are also used for the delivery of a variety of drugs, including chloramphenicol, prostaglandin, hydrocortisone, nitroglycerin, and itraconazole. The CD discovered by French scientist A. Villiers in 1891 was obtained from starch post-degradation, called 'cellulosine'. Cyclodextrin occurs naturally and is chemically modified. The naturally occurring CD, which contains seven glucose subunits, is linked with α-1, 4 end-to-end linkages. The β-cyclodextrin has a tapered shape at one face; it shows seven primary alcohols and fourteen alcohol groups. The β-cyclodextrin is capable of removing inorganic, organic, and heavy metal impurities from wastewater as compared to conventional water purification methods. The cyclodextrin derivatives are used in the pharmaceutical industry to modify and release drugs. In the cosmetic industry, they are used for controlled release of fragrance from inclusion products such as detergents, perfumes, and room fresheners, in the personal care products, including toothpastes, toiletries, skin cream, and dusting powder. The food industry, a generally larger industry, uses β-cyclodextrin to remove cholesterol from eggs, milk, and butter. It is also used for flavor protection and flavor delivery. In the agro-industry, it is used in the formation of complexes with pesticides, herbicides, and insecticides. In environmental science, it is used in the removal of organic pollutants and heavy metals from water and soil. Drugs like antioxidants and other water-soluble drugs are not easily entrapped by CD in their cavities through inclusion. Its complex results are a significant improvement in the stability and solubility of drugs.

OBJECTIVES

- To study β-cyclodextrin and its derivatives
- To study the importance of β-cyclodextrin
- To analyze the preparation and chemistry of β-cyclodextrin
- To focus on CD and its application in human life

ANALYSIS

On the basis of affordability, accessibility, and capability, β-cyclodextrin is widely studied and commonly used. It complexes an extensive range of chemicals; the important distinctive character of β-cyclodextrin is to produce inclusion complexes with many chemicals by a host-guest interaction process. β-cyclodextrin has a molecular weight of 1135g/mol, and the melting point of β-cyclodextrin is 501°C. The β-cyclodextrin cavity has a diameter of 6-6.5A° and a volume of 262 $Å^3$; the height of its tori is 7.9 Å. The water solubility of β-cyclodextrin is 185g/100ml at 25°C.

CYCLODEXTRIN

In history, CD was first seen in a 1891 publication, and the patent was granted in 1953. In recent days, it has been used in more than thirty different pharmaceutical products. In 1891, a French scientist, A. Villiers, for the first time discovered CD in a product obtained from starch post-degradation called 'cellulosine'. In 1903, the chemistry of CD was established by Austrian microbiologist Franz Schardinger. He discovered two compounds (A and B), which were crystalline and similar to cellulose obtained from potato starch through bacterial degradation. He replaced the name 'cellulosine' with alpha (α-) dextrin, beta (β-), and Gamma (γ-) dextrin, which were later known as α -cyclodextrin, β-cyclodextrin, and γ –cyclodextrin or Schardinger sugars. The γ-cyclodextrin was later identified and known as a larger CD in 1935 by Freudenberg. The CD is a cyclic oligosaccharide formed by glucose units. Cramer and co-workers described their ability to form inclusion complexes. The first patent related to CD was granted to Freudenberg, Cramer, and Plieninger in 1953. The basic physicochemical characteristics of Cyclodextrin were discovered in the 1950s, such as their ability to solubilize and stabilize drugs [2]. CD is suitable for pharmaceutical applications, the first Cyclodextrin-containing pharmaceutical marketed in Japan, later in the European market, and in the United States market in 1997. The cyclodextrin is today regarded as a novel excipient with unexplored potential. The cyclodextrin has a

CHAPTER 8

β-Cyclodextrin and Its Derivatives in Biomedical Applications

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Abstract: Beta-cyclodextrin (β-CD), a cyclic oligosaccharide derived from starch, has garnered significant attention in biomedical sciences due to its unique molecular structure and ability to form inclusion complexes with a variety of molecules. This property allows β-CD to enhance the solubility, stability, and bioavailability of otherwise poorly soluble drugs, making it a versatile tool in drug delivery systems. Moreover, various derivatives of β-CD, such as hydroxypropyl β-CD and sulfobutyl ether β-CD, have been developed to improve its solubility, reduce toxicity, and increase its potential in a wider range of biomedical applications. This chapter delves into the structural characteristics of β-CD and its derivatives, with a focus on their role in drug delivery, gene therapy, imaging, and diagnostics. It also highlights the use of β-CD in antimicrobial, antiviral, and cancer therapies, where it has demonstrated potential to improve therapeutic efficacy and reduce side effects. While the biocompatibility and low toxicity of β-CD make it a promising candidate for various applications, challenges remain in optimizing its use in clinical settings. Future directions in β-CD research are also discussed, emphasizing the need for innovative approaches to overcome current limitations and expand its applicability in modern medicine.

Keywords: Biomedicine, β-Cyclodextrin, Cancer, Drug delivery, Inclusion complex.

INTRODUCTION

β-Cyclodextrin (β-CD) is an oligosaccharide obtained from starch consisting of seven units of D-(+)-glucopyranose joined by an α-1,4 bond [1]. β-CD is commonly utilized, due to its accessibility and optimal cavity size, for drug encapsulation purposes. Additionally, it exhibits complexation properties that are valuable for a diverse array of pharmaceutical compounds [2]. β-CD is a type of sugar that does not reduce and consists of an oligosaccharide structure, with

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Kamlesh Kumari, Ayushi Prajapat, Prashant Singh & Chandrabhan Verma (Eds.)

inclusion characteristics such as surface area and porous structure, as well as distinctive host-guest properties [3]. The most common β-CD derivatives are hydroxypropyl-β-CD and sulfobutylether-β-CD [4]. Immense attention has been gained by hydrophilic cyclodextrins such as Hydroxypropyl-β-CD (HP-β-CD), sulfobutylether β-CD (SBE-β-CD), and branched β-CD among other compounds due to their lower toxicity and high solubility in aqueous solution, ensuring parenteral use [5]. HP-β-CD is a modified form of β-CD obtained by reacting it with propylene oxide, in an alkaline solution. HP-β-CD can be safely administered orally or parenterally as a pharmaceutical without causing any undesired effects. HP-β-CD has proven effective in enhancing the characteristics of flavonoids showing promise for creating formulations [6]. β-CD is mostly used due to its ready availability and appropriate cavity size. Furthermore, it possesses pharmaceutically beneficial complexation properties for a variety of drugs. β-CD-epichlorohydrin polymer is a high molecular weight compound, which effectively operates as a drug carrier to boost solubility and oral bioavailability of drugs by increasing their therapeutic efficiency [2]. β-CD is recognized to increase the soluble nature of incorporated drugs and also function as a permeability enhancer for different macromolecular drugs [7].

The significance of β-CD in biomedical research can be illustrated through several examples. Perbutanoyl β-CD (TB-β-CD) has been investigated for its application in regulating the release of aqueous pharmaceuticals such as captopril (Cap). It has a well-known ability to retard drugs that are soluble in water and differentiate from other derivatives, which have short or long chains, owing to its muco-adhesive properties and hydrophobic nature. The combination of poly β-CD with charged adamant derivatives (Ada) serves as an innovative and effective non-viral carrier for gene delivery purposes. A porphyrin β-CD conjugate proved useful in delivering PTx medication. The effectiveness of carboplatin (Carb) and 5-fluorouracil (5-FU) on MCF 7 and MDA MB 231 breast cancer cell lines was enhanced by pretreating with methyl β-CD (Me-β-CD). The findings indicate that pre-treatment with Me-β-CD boosts the sensitivity of breast cancer cells to amounts of Carb or 5-FU by enhancing the buildup of these medications [8]. HP-β-CDs have the ability to form a gel, which helps in enabling the extended release of water-soluble drugs. Furthermore, sulfobutyl ether β-CD (SBE-β-CD) possesses the capability to modulate solubility and functions as an osmotic pumping agent for osmotic pump tablets. These tablets feature controlled porosity, allowing for the regulation of the release rate of water-soluble drugs, whether high or low [9]. The polyanionic cyclic oligosaccharide SBE-β-CD is made up of glucopyranose units arranged in a ring-like torus. Many advantageous characteristics endow SBE-β-CD, including enhanced stability, biocompatibility, and a solubility that is >50 times greater than that of β-CD, validating its use as a smart polymer for drug delivery applications [10]. β-CD, as a drug carrier, can perform activities such as solubilization, stabilization, and transportation of hydrophobic drugs in addition to a reduction in the undesired side effects related to corresponding drugs without β-CD [11].

Derivatives of β-CD are crucial for the advancement of more effective antiviral medicines. HP-β-CDs can remove cholesterol molecules from the outer covering of HIV and simian immunodeficiency virus (SIV), disrupting their infectivity. Sulfo undecyl thioether-β-CD was recently reported for activity against both HSV-1 and the acyclovir-resistant HSV-2 strain [12]. To establish a new function for HP-β-CD as a sugar-based Aβ inhibitor, its inhibitory efficacy against Aβ1–42 aggregation and Aβ-induced toxicity was examined recently. HP-β-CD is a prominent sugar utilized in medication administration, genetic vectors, environmental protection, and the treatment of Niemann-Pick disease type C1 (NPC1). Experimental results demonstrated that HP-β-CD molecules were not only harmless to cells but also significantly prevented Aβ fibrillization and decreased Aβ-induced toxicity, in a concentration-dependent manner [13]. The functional groups in an acid-degradable polyrotaxane based on β-CD and containing N-acetyl-D-galactosamine moieties increased its binding affinity to asialoglycoprotein receptors. When treating NPC1, using supramolecular structures like polyrotaxanes with threaded HP-β-CD can be helpful. Twenty-three cyclodextrin-based formulations were included in a list of recently approved formulations released by the Food and Drug Administration (FDA). The majority (9) of these new formulations are based on HP-β-CD; however, the list also encompasses native, SBE-, and methylated β-CDs, as well as HP-γ-CD. All formulations for currently available modes of administration, excluding nasal, utilize HP-β-CD. For instance, diclofenac exhibits near insolubility at pH levels below 7; nevertheless, its solubility in water can increase fivefold when complexed with HP-β-CD [14].

APPLICATIONS IN DRUG DELIVERY SYSTEMS

A drug delivery system is supposed to provide a drug at the designated site with an anticipated concentration for an expected time in an effective and definite manner. Carriers are being developed in order to mitigate the problematic characteristics of the drug molecules [15]. Despite the extensive utilization of cyclodextrins in diverse scientific fields, little is known regarding their precise biochemical mechanism in this regard [16]. Encapsulation of drugs occurs with natural lipophilic compounds if their size and molecular structure are appropriate for the host-guest interaction. The complex formation with cyclodextrins is mostly exploited to increase the solubility of weakly water-soluble medicines. Phase-solubility diagrams may be used to define interactions of cyclodextrins with natural compounds, such as vitamins, cholesterol, and lipid membrane

CHAPTER 9

β-Cyclodextrin and Its Derivatives in Drug Delivery Applications

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Abstract: The drug delivery systems have evolved over the years, which is quite evident from the development of advanced treatment systems from traditional herbal medicines. Cyclodextrins and their major types have shown their resourcefulness in almost every type of medicine, like injections, oral drugs, capsules, and drug transport systems. Among all the types of cyclodextrins, β-cyclodextrin and its derivatives are prominent in the encapsulation of hydrophobic drugs as they can build inclusion compounds and clathrates with complementary guest molecules, which is required for the precise release and targeting of the drugs. This chapter highlights the importance of β-Cyclodextrin and its derivatives in the development of tailored medicines and existing drug delivery systems, along with the challenges in their applicability.

Keywords: β-Cyclodextrin, Controlled release, Drug delivery systems, Pharmaceutical designs, Targeted drug Delivery.

INTRODUCTION

During ancient times, medicinal plants, spices, herbs, and plasters were used for therapies, but after the evolution of pharmacy, allopathic drugs, injections, inhalers, capsules, tablets, *etc*., were formulated for more accurate dosage, speedy drug absorption, and to provide stability to the medicines for a longer term [1, 2]. The recent advancements in drug delivery technology have transformed therapeutic effectiveness due to the integration of biotechnology and nanotechnology in personalized medicines [3, 4]. These therapies are personalized according to patient requirements, work on the specific body spots, and minimize the possible side effects [5]. However, there is a downside to synthesizing these nanoparticles, as they are not stable for a long time and can form aggregates, which hinder their commercial use. To overcome these challenges, researchers are

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Kamlesh Kumari, Ayushi Prajapat, Prashant Singh & Chandrabhan Verma (Eds.)

working on combining different secondary ligands, polymers, proteins, surfactants, cyclodextrins, *etc*., in tailored medications [6].

Cyclodextrins are the cyclical oligosaccharides with an aquaphobic inner side and a hydrophilic exterior that increase the permanency and bioavailability of highly reactive drugs due to the formation of clathrates and inclusion complexes with various guest molecules. Due to this ability of cyclodextrin rings, they play a major role in pharmaceutical advancements [7, 8]. In all the cyclodextrin-based molecules, β-cyclodextrin and its derivatives are attracting attention for their outstanding physicochemical properties and adaptability for carrying numerous aquaphobic drugs in their cavity, which improves drug-controlled release. They are also considered to be safer by drug regulatory bodies, so their demand is increasing in tailored medications in the form of oral medicines, injections, nano-composite modifying drugs, and topical drug-delivery systems [8 - 10].

This chapter highlights the status of β-Cyclodextrin and its derivatives in the expansion of customized medications, their applicability in drug delivery systems, chemical modifications to increase their adaptability, safety, and toxicity considerations, and future trends in these medications.

CYCLODEXTRINS AND THEIR TYPES

Cyclodextrins are the cyclical oligosaccharides made up of glucose sub-units, consisting of aquaphobic inner side cavities and hydrophilic peripheries that are synthesized from starch through enzymatic conversion followed by purification [6]. The common types of cyclodextrin molecules are α-cyclodextrins (made up of 6 glucose units), β-cyclodextrins (made up of 7 glucose units), and γ-cyclodextrins (made up of 8 glucose units), as shown in Fig. (**1a**). Their unique structure (toroidal-like structure) can form clathrates and inclusion complexes with various guest molecules, as depicted in Fig. (**1b**), which makes the highly reactive drugs more durable and soluble in the human body with a controlled release [7, 8].

Due to this capacity of cyclodextrin rings, they play a major role in various industries like pharmaceutical advancements, food industries, and environmental biotechnology [11]. In the pharmaceutical industry, cyclodextrins are used for improving drug safety, solubility, and thermal and photo stability up to a specific time, which diminishes the side effects of medicines like exasperation and awful taste by the precise release. They also minimize the drug-drug interactions in the body [12]. In the food and beverages industry, they are useful as food additives, stabilizers, and adulterants that improve the flavour and texture of the processed food. Cyclodextrins are often recognized for environmental purposes where they eliminate water pollutants due to toxic compound encapsulation in their cavities [13].

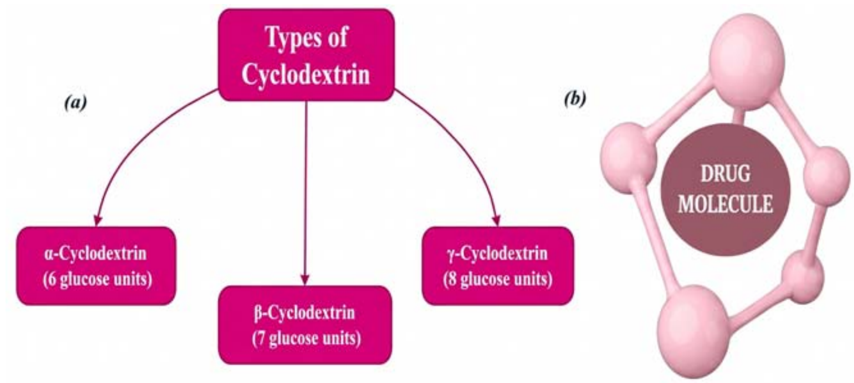

Fig. (1). (a) Cyclodextrins and their types. **(b)** Representation of the inclusion complex of cyclodextrin with drugs.

β-CYCLODEXTRIN FOR DRUG DELIVERY

β-Cyclodextrin and its derivatives like Taxol, Ondansetron, Risperidone, *etc*., are broadly used in pharmacological industries due to their flexible cyclic structure that can lodge the incoming aquaphobic molecules in their inner voids connected by α-1,4-glycosidic bonds, to make the inclusion complexes and clathrate complex systems [9, 10]. Enhances the solubility of partially soluble drug systems, thermal and photo-stability of limited effectiveness medications, protects drugs from degradation, and is helpful in gene therapy. They are also helpful in targeted drug delivery due to the controlled release of drug particles [14]. β-Cyclodextrin-based compounds are made up of natural products, and henceforth they are non-toxic, bio-compatible, and decomposable, due to which they are functional in the therapeutic applications [15].

Derivatives of β-Cyclodextrin and their Modifications

β-Cyclodextrin, the most important natural hepta-saccharide resulting from 7 glucose units by alpha-1,4 links, is used in various pharmaceutical products. The most common derivatives of β-Cyclodextrin are sulfobutylether derivatives, hydroxypropyl derivatives, and randomly methylated β-Cyclodextrin [14]. The derivatives of β-cyclodextrin are considered advantageous to synthesize inclusion multiplexes as they are functional, modifiable, and more cost-effective than other cyclodextrin derivatives [16]. The synthesis of β-Cyclodextrin and its derivatives depends on various factors like the types of solvent used, the reagents, reaction time-period, pH condition, moisture, photo-sensitivity, pressure, and thermal conditions [17]. The characterization of these compounds is done by Fourier

CHAPTER 10

β-Cyclodextrin and Its Derivatives in Cancer Therapy Applications

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Abstract: The unique physicochemical properties of CDs are of particular interest in the field of drug delivery and pharmaceutics. The chapter emphasizes the benefits of employing β-CD catalysts, as they are an excellent excipient to increase drug apparent stability, solubility, and bioavailability. They are also a useful tool for new drug delivery systems because of their special capacity to function as molecular containers by ensnaring a wide variety of molecules in their interior cavity, which are guests. One possible tactic for creating sophisticated and multipurpose CD-based delivery systems is to combine CDs with other technologies and materials. To improve in vivo anticancer therapies, the authors also discuss the multivalent functions of CD-based delivery systems, such as the inclusion of stimuli-responsive elements, surface functionalization, active target ligands, or extra connections with other delivery systems.

Keywords: Anticancer therapeutics, Beta-cyclodextrin derivatives, Beta-cyclodextrin (β-CD), Cancer therapy, Drug delivery systems.

INTRODUCTION

One of the deadliest diseases in the world is still cancer, according to the most recent data. Worldwide, more than 9 million deaths are reported per year, Fact Sheets *et al*. It is expected that 1.8 million new cases of cancer will occur in the United States, mostly observed in breast, prostate, lung, liver, and cervical cancer origins [1]. Even though chemotherapy is the most prevalent cancer treatment, anticancer medications are less effective due to poor pharmacokinetic characteristics. Solubility is one of the crucial factors in achieving the appropriate concentration of the drug in the bloodstream to provide the necessary pharmacological reaction [2].

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Kamlesh Kumari, Ayushi Prajapat, Prashant Singh & Chandrabhan Verma (Eds.)

Over time, various CD nanocomposites were created that specifically targeted cancer cells using photodynamic, photothermal, chemotherapeutic, and hyperthermia techniques. Their amphiphilic character and cup-like shape enable higher drug accumulation, stability, and solubility. Cyclodextrins are water-soluble because of a large number of hydroxyl groups. The carbohydrate oligomers are composed of 7 glucose unit ring structures, with a hydrophilic exterior and hydrophobic interior. Scientists can do many chemical modifications to improve the pharmaceutical application of cyclodextrin in cancer therapy. On the other hand, Gene therapy, cell treatment, immunotherapy, chemotherapy, and nanomedicine therapy have all made substantial use of cyclodextrin; all these points are included in the review of cyclodextrin-based chemotherapeutic anticancer drugs given by Bingren Tian *et al*. [3] (2020) (Fig. **1**).

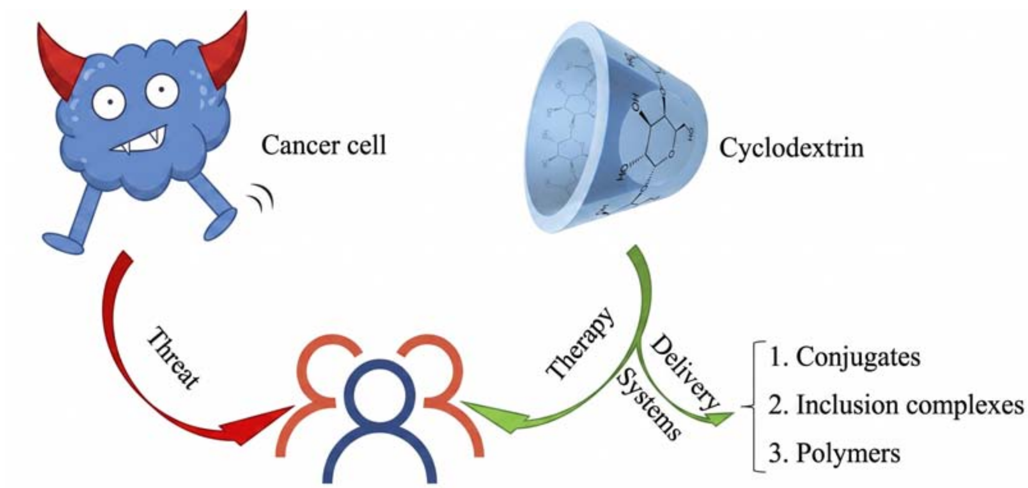

Fig. (1). Cyclodextrin-based drug delivery systems. (Adapted from Bingren Tian *et al*., 2020).

Examining this fascinating area of research shows that β-cyclodextrin and its derivatives combine the lastingness of synthetic catalysts with the selectivity of enzymes to produce a unique catalyst category. This study advances our understanding of supramolecular catalysis and provides opportunities for developing more efficient and sustainable catalytic processes in a variety of chemical fields.

B-CYCLODEXTRIN DERIVATIVE IN CANCER THERAPY APPLICATIONS

Numerous chemical changes can be made to further enhance CDs' special physicochemical characteristics. By creating an Inclusion Complex (IC), CDs improve the stability and bioavailability of active medicinal compounds through host-guest interactions [4]. A number of hydrophobic anticancer medications have been combined with CDs as inclusion complexes to increase their systemic circulation and bioavailability. Although CD-drug inclusion complexes alone can help address several issues with anticancer drug administration in Free form.

In this regard, Zhang Y. *et al*. [5] (2022) As a result, through host-guest interaction, an ultrasmall gold nanoparticle-based nanocomposite AuNP@CD-AD-PEG2000-PLL(DTPA-Gd) was created for tumor-targeted MRI CA. The scheme is shown in Fig. (**2**). Next, Bioimaging techniques that use nanomaterials to identify different tumor-targeted diagnoses. The T1-weighted transverse Before sample injection, MR images of the tumor-bearing animals were obtained. (Fig. **3**) The mice were then transversely T1-weighted and given tail-vein injections of samples. Two hours after injection, MR pictures of the tumor-bearing mice were obtained. As shown in Fig. (**3A**), there was no discernible difference between the tumor site and normal tissue for the Magnevist group. But the distinction became quite important. with relation to the AuNP@CD-AD-PEG2000-PLL(DTPA-Gd)-FA and AuNP@CD-AD-PEG2000-PLL(DTPA-Gd) groups. For simplicity in comprehending the alteration of MR signals, the light intensity variations in the tumor region were quantitatively evaluated using ImageJ software. As shown in Fig. (**3B**) showed less brightness change after being treated with Magnevist and AuNP@CD-AD-PEG2000-PLL(DTPA-Gd), increasing by 1.4 and 1.8 times, respectively, compared to the precontrast image. However, the AuNP@CD-AD-PEG2000-PLL(DTPA-Gd)-FA-treated tumor was 2.4 times larger than the precontrast picture. These findings demonstrated that the tumor could readily absorb ultrasmall AuNPs using the EPR effect, and that cell absorption efficiency increased dramatically following targeting ligand conjugation.

CHAPTER 11

β-Cyclodextrin and Its Derivatives in Enzymatic Applications

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Abstract: β-Cyclodextrins (β-CDs) are known for their versatility in various applications, particularly in the food and beverage industries. β-CDs are uniquely capable of forming inclusion complexes with different enzymes and biomolecules, especially with amylases and lipases. Moreover, the ability of β-CDs to increase aqueous solubility of different drugs and enzyme agents through attachment in their hydrophobic inner cavity (*e.g*., for lipophilic compounds) and outer hydrophilic structural nature promotes their use to decrease cost when used in combination with known enzymes. They also demonstrate the ability to increase enzymatic activity or inhibit the same, often in a dose-dependent manner, allowing control in reactions such as starch degradation or in enzymatic browning reactions of fruit. Another major application of β-CDs is also as a medium for immobilization of enzymes, increasing their thermal stability and altering their optimal reaction conditions. In addition to industrial processes, their use allows for more efficient drug delivery and controlled drug release in disease treatments, while also supporting the reuse of enzymes throughout multiple processing cycles. Based on the previous and ongoing experimental studies involving β-CDs, the inclusion complexation mechanism may provide potential solutions in several enzymatic reactions, including in biomedical, industrial, and food-related aspects.

Keywords: Degradation, Enzyme immobilization, Inclusion complexes, Industrial enzymes, Inhibition, Stabilization.

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Kamlesh Kumari, Ayushi Prajapat, Prashant Singh & Chandrabhan Verma (Eds.)

INTRODUCTION

Cyclodextrins are a large group of oligosaccharides forming a macrocyclic structure with a cavity, resembling a truncated cone in which different compounds can confine themselves within, as shown in Fig. (**1**). They are produced from the enzymatic degradation of starch obtained from potatoes, corn, rice, and other sources, with a strong initial resemblance to cellulose which was described by Antoine Villiers in 1891. The activity of cyclodextrin glycosyltransferase (CGTase) on starch results in the formation of cyclodextrins by cleavage of starch at two locations, followed by joining of the cleaved chain to form cyclic oligosaccharides, which are further characterized into α-, β-, and γ- types based on increasing degree of polymerization [1].

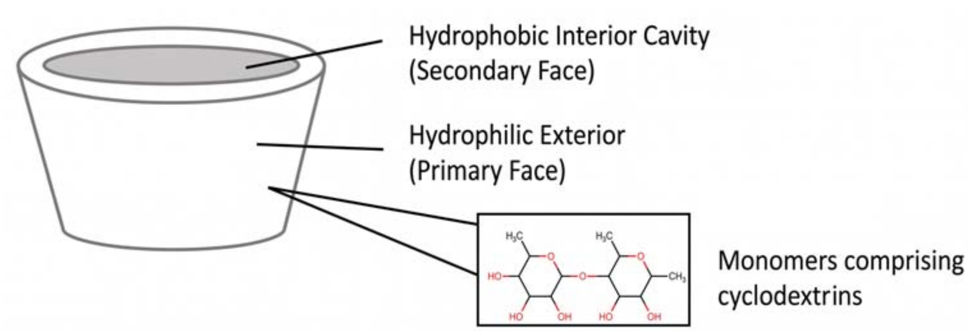

Fig. (1). 3-D Structure of β-cyclodextrin.

β-Cyclodextrins (β-CDs) are a category of cyclodextrins well known for their structures that feature a macrocyclic portion that resembles a pocket or cavity, where smaller molecules are often able to confer or enhance functionality in the role of 'guests' as they form an inclusion complex with the host [2]. Cyclodextrins have a characteristic hydrophilic outer surface and a hydrophobic cavity, known to be a phase transfer additive in water-oil interface reactions [3]. The compound 2-hydroxypropyl-β-cyclodextrin is used to solubilize hydrophobic inhibitors and inhibit the catalytic enzyme activity based on the bridging of the substrate to the enzyme active site and the compound without substrate sequestration [4].

β-CYCLODEXTRINS AND MEDICINAL PRODUCT SYNTHESIS

The flavonoids icariin and icaritin are from traditional Chinese medicine, well known for their anti-cancer activity. The aglycone of icariin, icaritin, is produced through acid hydrolysis of glycosides, where multiple byproducts and low icaritin yields pose challenges to this production method. Icariin/β-CD inclusion complex formation has shown to improve icariin solubility without protecting the glycosidic bond from snailase (an enzyme mixture of the crop and enteron of snails containing cellulase, pectinase, and other biomolecule-degrading enzymes), and enzymatic hydrolysis to icaritin was achieved with 99.3% purity [5].

Naringenin (4',5,7-trihydroxy-flavanone-7-rhamnoglucoside-glucopyranoside) is a phenolic flavonoid that is found in citrus fruits, such as grapefruit, and is known for its anti-cancer, anti-oxidant, anti-inflammatory, and other significant pharmacological properties, including delay of tumorigenesis in the mammary glands [6]. While naringin can be enzymatically converted into naringenin using naringinase, the reaction is currently limited by a low conversion rate. Although experiments have been conducted using naringinase immobilized in calcium alginate beads, it has been speculated that the enzymatic conversion rate was not altered, partially due to the naringin being water-insoluble, thus limiting contact with the enzyme. β-CDs have been used to increase the solubility of naringin in water and hence their rate of enzymatic hydrolysis through incorporation into the inclusion complexes along with snailase [7].

Modification of β-CD by polymerization followed by carboxymethylation affects its ability as an enzyme stabilizer. However, polymerized β-CD showed moderate ability as a single enzyme protectant, especially in supercooled conditions. However, the presence of trehalose enhanced the enzymatic stability in both combinations with β-CD and polymerized β-CD when undergoing freeze-drying and thermal treatment, although in the former combination, trehalose was the sole protectant, whereas in the latter system, both additives protected the enzyme. It is also considered that electrostatic charges may influence protein stability; for example, when the enzyme is negatively charged, the native structure is affected by the polyanionic polymerized and carboxymethylated β-CD, in contrast to both β-CD and polymerized β-CD being neutrally charged and enzymatic supramolecular interactions contributing to greater protein stability [8].

B-CYCLODEXTRIN IN INTERACTIONS WITH INDUSTRIAL ENZYMES

Cyclodextrins are often tested for inhibition of specific enzymatic activity or promoting the binding based on increased water solubility, where inclusion complexation is a common mechanism, as shown in Fig. (**2**). For instance, upon the addition of cyclodextrins at 1:2 ratio with proteases (from bursa of Fabricius) and respective 4:1 ratio reactions with lipase and amylase enzymes (from kombucha), the enzymatic activity was preserved and it was found that cyclodextrins could be key in increasing shelf life of food products [9].

CHAPTER 12

β-Cyclodextrin and Its Derivatives in Textile Applications

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Abstract: Beta-cyclodextrin is a cyclic oligosaccharide with a singular-doughnut-shaped conical structure. It is synthesized through the enzymatic degradation of starch present in potatoes, corn, and rice. It has attracted significant attention in the textile industry owing to its unique shape, which allows for modifying the properties of textiles. This chapter focuses on the structural and chemical properties of beta-cyclodextrin. It also highlights various derivatives of beta-cyclodextrin currently employed to enhance the features of fabrics. Beta-cyclodextrin derivatives are employed for varying applications, as they alter the performance of textiles and textile-based goods. The applications include creating water resistance, odor control, durability in fabrics, and drug delivery. Beta-cyclodextrin-modified fabrics are used in industries based on functional finishing of fabric, UV-protection, and dyeing. This chapter summarizes the recent advancements and sets a new perspective for their future applications.

Keywords: Cyclodextrin, Carboxymethyl-β-cyclodextrin (CM-β-CD), Hydroxypropyl-β-cyclodextrin (HP-β-CD), Methyl-β-cyclodextrin (M-β-CD), Sulfobutylether-β-cyclodextrin (SBE-β-CD), Textile.

INTRODUCTION

The large-scale production of β-CD is both cost-effective and environmentally benign, making it hold incredible significance in the textile industry. Attaching β-CD to the fabric surface is essential for enhancing the performance and functionality of the textiles. The derivatives are effectively harnessed for various textile applications, including potent antibacterial activity, controlled fragrance release, robust UV protection, superior water resistance, enhanced antimicrobial resistance, excellent heat resistance, and effective insect repellency.

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Kamlesh Kumari, Ayushi Prajapat, Prashant Singh & Chandrabhan Verma (Eds.)

β-CD effectively enhances textile properties through innovative cross-linking and binding techniques, allowing textiles to attain superior performance and functionality. The excellent complexation abilities help in attaining low solubility in water. This property makes β-CD valuable in industries for improving the stability and bioavailability of active compounds. Textile research is firmly moving toward functionalizing textile systems, and β-CD is a pivotal component of these advancements. Permanently fixing β-CD on the surfaces of textile fibers introduces pioneering properties within the textiles or on their surface. Cyclodextrin's inclusion compound development facilitates the development of textile fabrics with novel finishes, including deodorant, aroma, antimicrobial, insect repellent, and mite repellent applications. This presents numerous opportunities for creating innovative textile products with improved properties and functionalities, positioning β-CD as a versatile and promising material for the textile industry. β-CD can form complexes with surfactants in aqueous solutions, enabling the removal of a significant portion of absorbed surfactants. This, in turn, enhances the outcomes of subsequent textile processing steps [1].

THE DIVERSE USES OF β-CD DERIVATIVES IN THE TEXTILE INDUSTRY

The textile and apparel industry is intricate and poses significant environmental challenges [2]. It has considerable social, economic, and ecological impacts; however, strategic interventions can help mitigate these effects. For instance, informed decision-making and systematic, thoughtful design can improve social and environmental outcomes [3]. Often overlooked for its eco-friendly practices, textile manufacturing releases harmful toxic substances that threaten the environment and human health. Consequently, there is an urgent need to improve the industry's sustainability. Sustainability covers the resources and processes utilized in manufacturing products, ensuring they are safe and beneficial for human health and the environment. All components involved in a product's life cycle must be derived from renewable and natural resources. β-CDs have emerged as a crucial component within the textile industry and are produced globally in thousands of tons annually through environmentally sustainable methods. Due to their natural provenance and biodegradability, β-CDs are appealing and environmentally friendly materials for the textile industry [4]. Additionally, the chemical oxygen demand of cyclodextrins in wastewater, measuring 1060 mg/g, is significantly lower than that of polyester and fatty alcohol polyglycol ether. β-CDs are essential for enhancing the processing and functionalization of textile materials. By strategically utilizing β-CDs in developing innovative, eco-friendly textile products, one can effectively tackle the sustainability challenges facing the textile industry [5]. β-CD derivatives can fabricate diverse textile products containing molecular encapsulation systems that immobilize fragrances, flame retardants, antimicrobial agents, and sequester malodorous compounds [6].

Dyeing Process

β-CDs play two roles in the dyeing process. Firstly, they can act as a dyeing aid, in which β-CD forms complexes with the dye molecules [7, 8]. Secondly, they can chemically modify the surface of the textile, which helps improve subsequent dyeing operations [9, 10]. Fig. (**1**) demonstrates two processes.

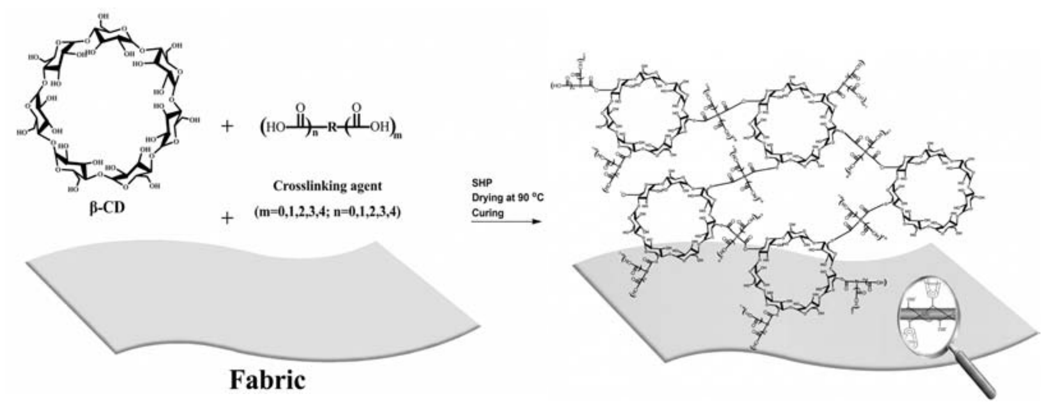

Fig. (1). Use of Beta-cyclodextrins in dyeing [11].

Due to their remarkable ability to form a range of inclusion complexes with dyes, β-CD alters the properties of dye molecules in a manner that profoundly influences the overall quality of the dyeing process. These alterations can enhance dye solubility, stability, and colorfastness. All these alterations ultimately improve the dye uptake and uniformity on fabrics. Therefore, β-CDs emerged as valuable auxiliaries in the textile dyeing industry. It continuously helps to achieve better and more consistent results in color application on various textile materials compared to conventional surfactants [12]. The results show that β-CD is an effective additive as it reduces the concentration of unbound dye molecules, slows the dye uptake, and promotes uniform color deposition. The β-CD-dye complex has a higher molecular weight than the unbound dye molecule. This hinders the diffusion of dye molecules on the fiber's surface, thereby enhancing color leveling [13]. Previous studies demonstrate the effectiveness of β-CDs in textile dyeing processes. For instance, Voncina *et al*. found that dyeing polyacrylonitrile fabrics with cationic dyes in the presence of β-CDs significantly enhances color intensity and improves dye exhaustion compared to quaternary ammonium compounds [14]. Cellulose acetate fibers face dyeing challenges due to their compact structure and hydrophobic nature, which limit dye diffusion. To improve this, Raslan *et al*. treated the fabric with monochlorotriazinyl-β-CD using a

CHAPTER 13

β-Cyclodextrin and Its Derivatives in Essential Oil Applications

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Abstract: Essential oils are secondary metabolic products collected from various parts of plants using different processes. They are Generally Regarded As Safe (GRAS) and mostly employed as flavoring ingredients in foods, pharmaceuticals, and cosmetics industries. Yet, consumer desire for goods derived from sustainable sources of energy, with minimal toxicity for animals as well as humans, and with natural allure, has prompted research into novel applications for essential oils. Cyclodextrins are naturally occurring oligosaccharides used to produce inclusion complexes with essential oils, resulting in increased chemical and physical stability of the oil by lowering volatility and susceptibility to light, oxidation, and heat. Furthermore, the combination of essential oils with cyclodextrins offers a variety of other benefits from a technical point of view, such as improving the handling of dried powders, concealing unpleasant tastes, and reducing storage and packaging costs. This chapter highlights the preparation strategies of inclusion complexes of β-cyclodextrin derivatives combined with essential oils and explores their potential applications in revolutionizing agricultural, food packaging, cosmetic, and pharmaceutical sectors.

Keywords: Agriculture, β-cyclodextrin, Cosmetics, Essential oils, Encapsulation, Food, Inclusion complexes, Pharmaceuticals.

INTRODUCTION

Essential oils (EOs) are the secondary metabolites of plants, exhibiting exceptional biological and pharmacological properties. Having an oily consistency, these plant products are volatile in nature and have a unique fragrance. EOs are a complex blend of various low molecular weight, bioactive compounds, including terpenes, terpenoids, tannins, and phenols, that contribute to their usefulness as antimicrobial or antioxidant agents in various industries [1]. Under natural conditions, these bioactive compounds or essential oil components

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Kamlesh Kumari, Ayushi Prajapat, Prashant Singh & Chandrabhan Verma (Eds.)

(EOCs) impart various benefits to plant growth, with a prominent role in signaling pathways, attracting pollinators, and providing protection from environmental stress or pests [2].

Comprising less than 5% of the vegetable dry matter of the plant, these volatile oils are usually observed to be colorless liquids at room temperature. They can be extracted from almost all parts of the plants, including seeds, flowers, twigs, fruits, or bark [3]. The secretory cells, glandular trichomes, and epidermal cells are the primary storage sites of EOs. As EOs are commonly obtained from aromatic plants, they are also known as aromatic plant essences. Because of their hydrophobic constituents, they are sparingly soluble in water and are highly soluble in organic solvents, with unique optical properties. EOs are a renewable source of active compounds with proven biological and medicinal activities [4]. With their inherent insecticidal, antimicrobial, antioxidant, and parasitic properties, EOs are being introduced to pharmaceutical, cosmetic, agricultural, and food industries [5].

Out of the 3000 well-known varieties of EOs, 300 forms are frequently utilized in different industries. The final composition of the EOs depends on the plant source, environmental conditions, the method of EO extraction, and the part of the plant targeted for the isolation of EOs. A wide range of EOCs have the potential to contribute to improved hygiene and health [6]. With their unique odoriferous properties, EOs constitute about 85-99% volatile compounds, and the remaining (1-15%) are non-volatile components. The volatile components constitute odoriferous compounds, particularly terpenes and terpenoids, along with other aromatic and aliphatic constituents. The other chemical forms of volatile components that are frequently observed include ketones, acids, alcohol, oxides, phenols, aldehydes, and amines [7].

The most abundant volatile constituents in EOs are terpenes, which are categorized as straight-chain or cyclic hydrocarbons. They exist in various forms encompassing acyclic, alicyclic, or aromatic hydrocarbons. Terpenes are produced in the cytoplasm of plant cells through mevalonic pathways, derived from a mixture of isoprene elements with a molecular formula of $(C_5H_8)_n$. The main terpenes are monoterpenes and sesquiterpenes, which comprise about 90% of Eos. Diterpenes and triterpenes are also present in small concentrations. Pinene, camphene, terpinene, *p*-cymene, and sabinene are the common examples of terpenes present in EOs [8]. Terpenoids, a modified form of terpenes, are aliphatic acid esters characterized by the presence of oxygen with diverse functional groups. Terpenoids can be biochemically modified *via* enzymes, where oxygen atoms are replaced by different oxidized methyl groups. Menthol, thymol, linalool, citronellal, and piperitone are well-known examples of terpenoids [9].

Other less frequent EOCs include phenylpropanoids and methylenedioxy compounds, *e.g*., myristicin and safrole [10].

Depending on the part of the plant source, EOs can be extracted by a variety of conventional and advanced methods. Distillation (water or steam distillation), maceration, and solvent extraction are the simple and commonly used procedures to extract EOs [7]. Distillation utilizes a specialized apparatus in which plant material is allowed to react with boiling water or steam, resulting in vaporization of volatile compounds [11]. In maceration, there is frequent agitation of the plant material with a suitable solvent at room temperature for about three or more days to separate EOs [12]. For delicate plant materials, including flowers, solvent extraction is an ideal process. In this process, the precursor plant materials are treated with organic solvents, with mild heating. The major disadvantages of these traditional methods include poor efficiency, loss of volatile components, longer extraction time, breakdown of unsaturated compounds, and accumulation of toxic solvent residues [13]. Considering the above disadvantages, certain advanced techniques have been introduced, which include supercritical fluid (SCF) extraction, Ultrasound-Assisted Extraction (UAE), and microwave-assisted extraction. These well-documented methods offer certain advantages over traditional approaches, such as improved yield, reduced extraction time, and cost effectiveness [14, 15].

Because of their well-documented antimicrobial and antioxidant activities, EOs are being employed extensively in almost all industries, particularly pharmaceutical, agricultural, and food industries [15 - 17]. With their ability to affect the central nervous system, EOs are helpful in improving mental and emotional health [18]. In the food industry, EOs are commonly utilized to improve the shelf life of perishable food or as flavoring agents to enhance the flavor of beverages, dietary supplements, and other foods [19]. Despite all the reported advantages of EOs, their low solubility and fast release limit their usefulness. They are highly sensitive to changes in environmental factors, including light, pH, and oxygen levels. EOs are more prone to deterioration by oxidative degradation, resulting in the formation of free radicals. When EOs are used as preservatives in food products, these free radicals compromise the quality of food, affecting the shelf life and sensory properties. Light sensitivity of EOs also needs to be considered [20].

Reduced bioavailability of EOs in hydrophilic conditions makes them difficult to incorporate into therapeutic products. Being highly volatile, proper protocols are needed to extract and process fragile and unstable EOs. Moreover, EOs can cause severe cytotoxicity in target eukaryotic cells. With a variety of bioactive components, EOs have the ability to target multiple parts of a cell, primarily

SUBJECT INDEX

Kamlesh Kumari, Ayushi Prajapat, Prashant Singh & Chandrabhan Verma (Eds.)

C

D

E

F

G

H

I

K

L

M

N

O

P

Q

R

S

T

Therapeutic agents 101, 201, 202, 220, 307
multiple 220
potential 307

U

V

W

X

Y

Z

Kamlesh Kumari

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Prashant Singh

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