

REVIEW ARTICLE

Cyclodextrins: Structural Features, Complexation Mechanisms, Pharmaceutical Applications, and Emerging Trends

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ABSTRACT

Cyclodextrins are cyclic oligosaccharides composed of six to eight glucose units produced through the enzymatic degradation of starch. Their unique truncated-cone structure, featuring a hydrophilic outer surface and a hydrophobic inner cavity, enables the formation of inclusion complexes with diverse guest molecules. This property makes CDs valuable excipients that enhance the solubility, stability, and bioavailability of poorly water-soluble drugs. The synthesis of CDs involves solvent and non-solvent processes, along with chemical modifications such as methylation, hydroxypropylation, and sulfation, which improve aqueous solubility and functional versatility. Recent advancements in amphiphilic, hydrophobic, and stimuli-responsive CDs have broadened their application in targeted and controlled drug delivery systems. Owing to their excellent biocompatibility, biodegradability, and regulatory acceptance, CDs continue to attract interest, although toxicity may vary with dose and route of administration. Furthermore, computational approaches, including molecular docking, molecular dynamics, and QSAR modelling, facilitate the design of optimised CD-based systems and support innovations in nanotechnology-driven formulation development.

Keywords: CDs, Complexation mechanisms, Drug delivery, Bioavailability enhancement, Computational modelling, pharmaceutical applications.

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INTRODUCTION

Starch, one of the most abundant natural polysaccharides, can be enzymatically converted into unique cyclic molecules known as cyclodextrin (CDs). These compounds possess a distinctive cage-like architecture featuring a stable, hollow cavity with a hydrophobic (water-repelling) interior. Owing to this structural characteristic, CDs act as molecular containers capable of encapsulating and stabilising a wide range of guest molecules, making them highly valuable in various scientific and industrial applications(1). To convert starch into CDs, the enzyme CD glycosyltransferase is essential. Although attempts have been made to create these molecules chemically, the process is too complex and inefficient for mass production. The most prevalent varieties are α -, β -, and γ -CDs, which are composed of 6, 7, and 8 glucose units, respectively, with 1–4 bonds connecting them. Researchers have also identified larger rings, with evidence of cyclodextrins (CDs) containing up to 16 glucose units. Smaller quantities of less prevalent varieties, such as κ -CDs (which have 12 glucose units) and δ -CDs (which contain 9 glucose units), have also been effectively separated and investigated. Despite this variety, α -, β -, and γ -CDs continue to be the most important in industry since they are the most widely used in commercial applications today (2). The extraordinary capacity of CDs to form inclusion complexes with a wide range of chemicals has become increasingly important in practice. This complexation can significantly increase the solubility of previously poorly soluble compounds and improve the bioavailability of medications that are often difficult to absorb. Furthermore, once trapped within the CD cavity, sensitive molecules, including unsaturated chemicals, are protected from oxidation, even when exposed to pure oxygen. These

complexes are very helpful in industrial and medicinal applications because they dissolve in water and allow for the slow release of some of the contained "guest" molecules when the complex dissociates (3).

History

When Villiers published his discovery in 1891, the term "CDs" was first used. Using *Bacillus amylobacter*, which was likely not a pure culture but also contained heat-resistant *Bacillus macerans* spores, he was able to extract around 3 grammes of crystalline material from 1,000 grammes of starch. After studying the material's composition and finding that it was $(C_6H_{12}O_2)_2 \cdot 3H_2O$, he classified it as "cellulosine". Because it lacked reducing properties and resembled cellulose in its resistance to acid hydrolysis, Villiers gave the substance its name. Interestingly, he also witnessed the formation of two distinct crystalline forms, which are today recognised as the predecessors of α - and β -CD. Twelve years or so later, Schardinger continued the research by examining bacterial strains thought to cause foodborne illness and to survive cooking. In his tests, he discovered that using one of these microorganisms to digest starch yielded trace amounts of two crystalline chemicals that appeared to be the same as the "cellulosines" that Villiers had previously reported. Schardinger persisted in investigating these peculiar crystalline dextrans in the hopes of gaining a better understanding of the production and degradation of starch. He determined that *Bacillus macerans* was the causative microbe and observed that these dextrans have a special quality: they produced distinctive iodine complexes when exposed to an iodine-iodide solution, a trait that was subsequently connected to CDs. According to Schardinger, a greater percentage of amorphous dextrans and around 25–30% of starch might be converted into crystalline dextrans. Among the crystalline products, α -dextrin was the most prevalent type. He used the distinctive responses of the two primary types— α - and β -dextrans—with iodine to distinguish between them. While the β -dextrin-iodine complex always displayed a reddish-brown colour, whether wet or dry, the α -dextrin-iodine complex was blue while wet and changed to a grey-green when dry. With these meticulous observations and tests, Schardinger successfully laid the groundwork for the chemistry of CD (4).

General properties

CDs (or CDs) are regarded as safe and environmentally benign substances due to their natural breakdown and compatibility with biological systems (5). CDs are a class of cyclic oligosaccharides that include numerous less frequent minor forms in addition to three common varieties that are commonly manufactured on an industrial basis. The main CDs are homogeneous, crystalline, non-hygroscopic substances made of repeating glucopyranose units that resemble toruses. Six glucopyranose units are present in α -CD, which is sometimes referred to as Schardinger's α -dextrin, cyclomaltohexaose, or cyclohexaamylose. Seven units make up β -CD, also known as Schardinger's β -dextrin, cyclomaltoheptaose, or cycloheptaamylose, whereas eight units make up γ -CD, also known as Schardinger's γ -dextrin, cyclomaltooctaose, or cyclooctaamylose (6). Figure 1 shows the structure and conformation of natural CDs (7).

Non-toxic sugar-based polymers known as CDs (or CDs) have become popular for their ability to remain stable in both water and certain organic solvents (4). Even in alkaline conditions, CDs maintain their remarkable stability; their natural forms generally have pKa values in the range of 12.1 to 13.5 (8). CDs are susceptible to acid hydrolysis at low pH values, which breaks their ring structure and produces glucose molecules and other linear oligosaccharides (9). Hollo and Szejti found that the acid hydrolysis of amylose slows down in the presence of complexing agents. The addition of toluene significantly decreased the rate of β -CD hydrolysis, as reported in similar studies. However, complex formation stops at high temperatures (around 80–100°C), and any complexes that form at lower temperatures have a tendency to disintegrate; therefore, there was little to no change in hydrolysis with or without toluene (3). Human salivary and pancreatic α -amylases (1,4- α -D-glucan glucanohydrolase, EC 3.2.1.1) effectively break down γ -CD. When conducted at 37°C with 0.1 M NaCl, these enzymatic reactions exhibit optimal activity at around pH 5, which is significantly lower than the ideal pH of approximately 6.9 that is shown for the identical enzymes when operating on starch (10). Non-reducing, ring-shaped oligosaccharides, CDs are composed of many α -D-glucopyranose units connected by α -1,4-glycosidic linkages. They are hydrophilic on the outside and have a distinctive, round, truncated cone-like form. This cone has a hollow, hydrophobic cavity that is about 7.9 Å deep. This cavity is perfect for holding hydrophobic guest molecules of the right size (6,11,12). CDs' D-glucose units often take on the 4C_1 chair structure; however, the 1C_4 form is less frequently used (13,14). This specific arrangement lowers the overall angular strain of the CD ring. By positioning the larger oxygen-containing groups, such as hydroxyl and glycosidic groups, on the equatorial plane, the CD molecule's structural stability is further enhanced (15).

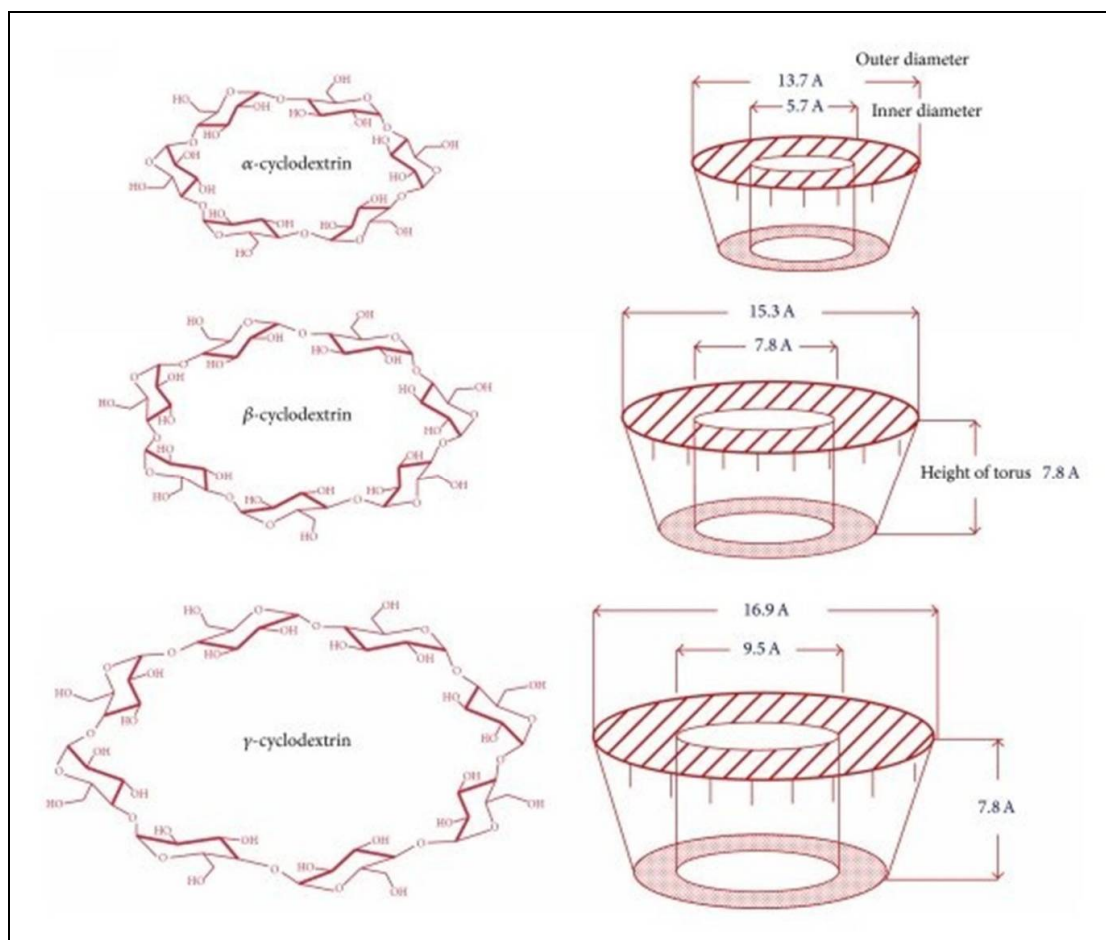


Figure 1: Structural representation and dimensional comparison of α-, β-, and γ-CDs showing their toroidal (truncated cone) geometry.

The chair conformation of the D-glucose units, which results in a truncated cone shape rather than a totally symmetrical cylinder, also affects the overall structure of CDs (16,17). This conical shape modifies the orientation of the hydroxyl groups, with the C6–OH groups facing the narrower rim and the C2 and C3–OH groups facing the wider rim. As a result, the CD's exterior is covered with hydroxyl groups, which enable it to form hydrogen bonds with surrounding water molecules and provide the material with considerable water solubility (8). In contrast to their polar exterior, CDs contain a hydrophobic inner chamber. Its hydrophobic characteristics are attributed to the non-polar groups lining the interior, such as C3, the aliphatic-like C5–CH groups, and the ether-like O4 glycosidic connections (18). The hydrophobic inner chamber of CDs can completely or partially enclose small chemical molecules (19). CDs are very useful in many different sectors, such as medicines, food processing, textiles, cosmetics, and many more, due to their remarkable ability to encapsulate molecules.

Solubility Properties

Generally, CDs are soluble in water but insoluble in most organic solvents; at higher temperatures, their solubility increases. The one that dissolves the least in water is β-CD. Because of their tight alignment, the C2 and C3 hydroxyl groups of adjacent α-D-glucopyranosyl units in β-CD maximise their interactions with one another while decreasing their availability to interact with water. The α-CD ring, on the other hand, is under higher strain, which causes its hydroxyl groups to be farther apart and allows greater interaction with water, thereby improving solubility. Because the γ-CD ring is the least strained, its hydroxyl groups interact more easily with water and less with each other. In general, (CDs) become more soluble in water when the internal hydrogen bonds between their hydroxyl groups are disrupted. Table 1 shows the solubility of CDs in water.

Table 1: Solubility of CDs in water (g /100ml)

Temperature	Alpha	Beta	Gamma
25 °C	12.8	1.8	25.6
45 °C	29.0	4.5	58.5
60 °C	66.2	9.1	129.2

In general, CDs are insoluble in most organic solvents. But in some polar aprotic solvents, β -CD can dissolve even more easily than in water. Additionally, their solubility in water and water-miscible organic solvent combinations is modest. The solubility of CDs in these mixes usually decreases as the amount of organic solvent increases (2) Table 2 shows the solubility of CDs in organic solvents.

Table 2: Solubility of CD in organic solvents

Solvent	Solubility, %
Dimethyl sulfoxide	>41
Dimethylformamide	28.3
N-Methyl pyrrolidone	14.8
Ethylene glycol	7.0
Pyridine	3.5
Propylene glycol	0.5
Tetrahydrofuran	0
Methyl isobutyl ketone	0
Methyl isopropyl ketone	0
Acetone	0
Alcohols	0

Excipients and CD Solubility

Drug/CD complexes cohabit alongside a range of excipients in pharmaceutical formulations, such as polymers, antioxidants, antimicrobials, and surfactants. These excipients have the potential to either enhance or hinder CDs' capacity to solubilise medications. For example, medication molecules may compete with preservatives such as propylparaben and methylparaben for the CD cavities, which might cause the pharmaceuticals to be displaced and lose their solubility (20,21). Furthermore, preservatives may lose some of their antibacterial activity when they combine with CDs to create complexes. To guarantee both efficient antibacterial protection and general safety, formulation scientists must carefully modify the preservative levels in goods using CD (22). By stabilising and solubilising drug/CD nanoparticles, a variety of additives that are often used in pharmaceutical formulations, including organic acids or bases, organic salts (counterions), cosolvents, metal ions, and water-soluble polymers, can increase the complexation efficiency of CDs. To further increase drug solubility, recent research has also demonstrated that CDs and drug/CD complexes can self-assemble into bigger aggregates in aqueous solutions (23–25). Depending on their nature and physicochemical properties, excipients in pharmaceutical formulations containing CDs can either enhance or diminish CDs' capacity to solubilise medications. Therefore, research—like phase-solubility experiments conducted in a medium that closely resembles the finished product should be used to identify the exact quantity of CD needed for a formulation. It's also important to consider any secondary drug's potential for competitive complexation (26).

Hydration States and Crystalline Forms of CDs

CDs often crystallise from water as hydrates, though the exact water content of these hydrates may differ. For instance, α -CD is generally found as a hexahydrate (α -CD·6H₂O) and can exist in two major crystalline forms, I and II. Additionally, a third crystalline form, α -CD·7.57H₂O, may be formed when crystallised from an aqueous solution containing barium chloride (BaCl₂). β -CD is most commonly found in two forms: undecahydrate (β -CD·11H₂O) and dodecahydrate (β -CD·12H₂O). However, the actual amount of water present is largely governed by environmental conditions like relative humidity; therefore, these water-to-host ratios are simply estimations. Similarly, although γ -CD is commonly referred to as an octahydrate, it really crystallises with seven to eighteen water molecules. Additionally, δ -CD has been isolated in a crystalline form with roughly 13.75 water molecules per δ -CD molecule. In conclusion, CDs'

hydration state is not constant; rather, it fluctuates with humidity levels in the surrounding environment and the conditions under which they crystallise (18).

Industrial Production Methods of CDs: Solvent and Non-Solvent Processes

In general, there are two primary methods for producing CDs. An organic complexing agent preferentially precipitates a certain form of CD in the "solvent process," directing the enzyme reaction to primarily create that type. The CGTase enzyme and the reaction conditions alone define the quantities of the various CDs produced by the "non-solvent process," which, in contrast, uses no complexing agents. There are currently no proven manufacturing techniques that effectively employ whole-cell biotransformation.

Solvent Method

A typical solvent process flowsheet is depicted in Figure 2a. An organic solvent, usually toluene, ethanol, or acetone, acts as a complexing agent in the solvent-based procedures used to create the majority of CDs on an industrial scale. Starch liquefaction, usually at concentrations of 20–30%, is the first step in the process. Heat-stable α -amylase, acids such as HCl, mechanical disruption, or thermostable CGTases can all be used to induce this liquefaction; however, certain α -amylases need calcium ions to function. Before moving on to the next stage, α -amylase must be rendered inactive by heat. Jet-cooking is typically used in industry to liquefy starch. To start the CD manufacturing process, CGTase and the organic complexing agent are introduced to the liquefied starch solution once it has cooled to the ideal temperature for the enzymatic reaction. The required kind of CD is created enzymatically by building a complex with the organic complexing agent, which precipitates out. This CD-agent complex is extracted from the reaction mixture by centrifugation or filtering when the conversion is finished. Unreacted starch, linear dextrans, glucose, maltose, CGTase, residual complexing agent, miscellaneous byproducts, and water are all present in the residual solution. To recover any excess complexing agent, the filtrate is distilled, and the precipitated complex is washed. The CD is then released from the CD complex by heating it while it is floating in water. After that, the complexing agent is eliminated, generally by steam distillation; however, liquid-liquid extraction is required for some agents that cannot be distilled. Activated carbon is often used to eliminate contaminants from the CD solution after it has been initially concentrated by vacuum distillation. The CD precipitates during crystallisation, after which it is filtered, cleaned, and dried. The CDs are mostly separated from the reaction mixture by this downstream procedure, but the various CD types are not distinguished from one another. Therefore, the type of enzyme and complexing agent utilised has a significant impact on the selectivity of CD production and recovery.

Non-Solvent Method

A typical non-solvent process flowsheet is displayed in Figure 2b. Created to produce β -CD, the non-solvent approach is now widely employed in industry, especially in Japan. β -CD is easily purified by crystallisation because of its poor solubility. On the other hand, α - and γ -CD purification has historically included intricate and expensive chromatography, which has led to low yields and a variety of byproducts. Recent years have seen the introduction of more affordable techniques, which could potentially have positive environmental effects. Unlike CDs generated using solvent-based techniques, those synthesised without an organic complexing agent are free to be employed in the food business. Similar to the solvent procedure, the non-solvent method starts with starch liquefaction and enzymatic conversion to produce β -CD, but no complexing agent is used. After the enzymatic process is complete, glucoamylase is introduced, the pH is decreased, and CGTase is rendered inactive. Any leftover starch and non-cyclic dextrans that can obstruct purification are broken down by this enzyme into glucose and maltose. After employing activated carbon to clarify the solution, it is filtered and concentrated at a lower pressure until it contains around 60% dissolved solids (w/v). Deionisation is sometimes carried out before the activated carbon treatment. The β -CD that precipitates after crystallisation and recrystallisation is collected, cleaned, centrifuged, and dried. With the addition of glucose, maltose, and α - and γ -CD, the leftover mixture is condensed into a syrup that may be used as a food additive. Lower enzymatic reaction yields, a more complex purification process with an ineffective crystallisation step, higher energy requirements, and the production of multiple by-products are some of the significant disadvantages of the traditional non-solvent method when compared to the solvent-based process (27).

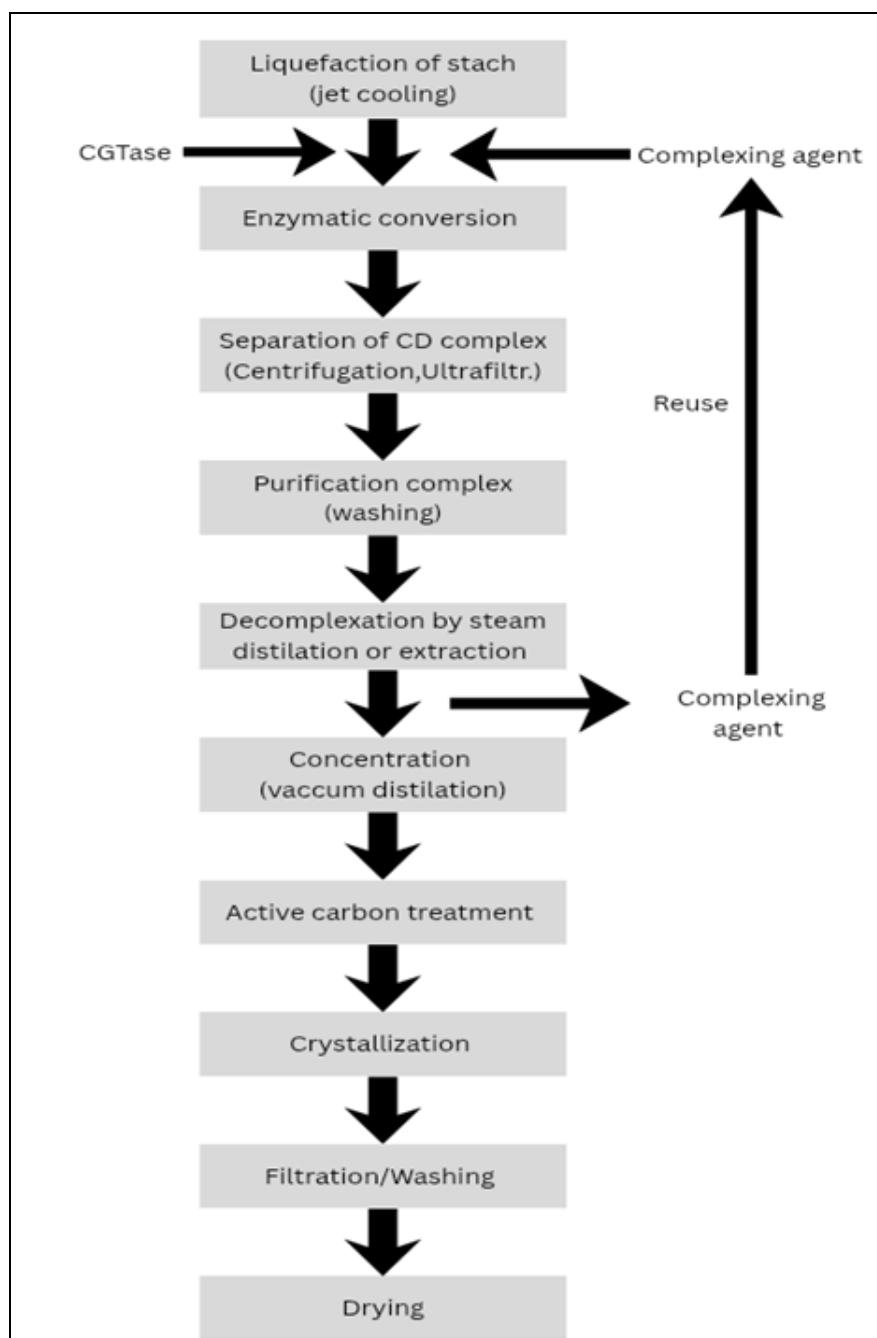


Figure 2: (a) Typical flowsheet of a solvent process. Data is taken from((27)

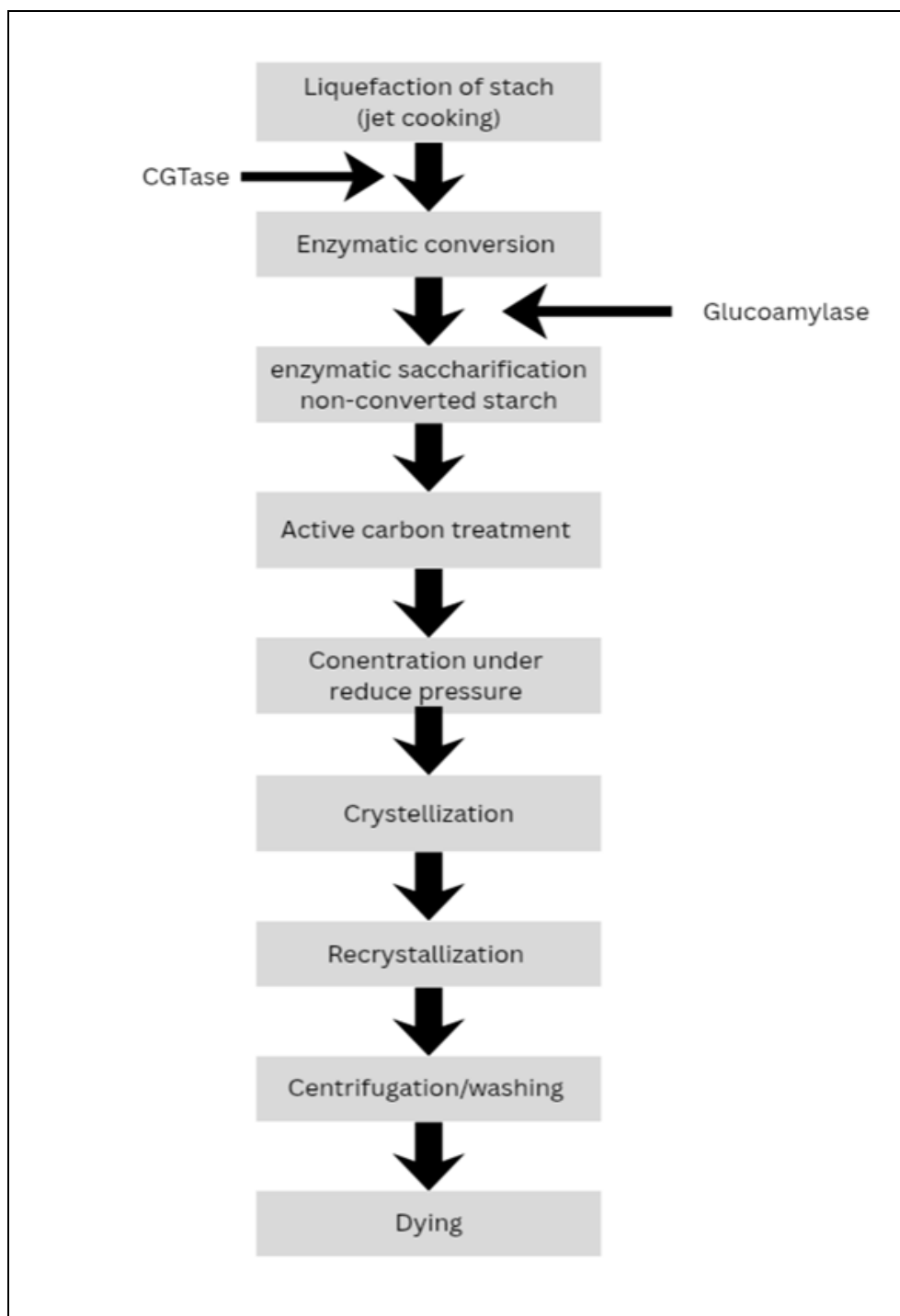


Figure 2 (b). Typical flowsheet of a non-solvent process. Data is taken from (27).

Purification and Industrial Refinement of CDs

Purification, on the other hand, separates the CDs from the bulk of the reaction mixture in the solvent-based process, but it does not separate the various types of CDs; any unwanted CD forms that are formed during the reaction, which may also be partially complexed, remain as impurities in the final product; further purification steps are necessary to obtain a single type of CD. In general, three main processes are used for CD isolation and purification. Several methods can be used to purify CDs. In contrast to using complexing agents during the enzymatic process, one technique uses organic solvents to precipitate. A different strategy uses chromatography or adsorption methods, such as affinity chromatography, ion exchange, molecular sieves, or adsorption onto artificial polymers. Filtration and membrane techniques are also used. Because of its poor water solubility, β -CD is one of the CDs that is comparatively

straightforward to purify. However, because α - and γ -CD are so soluble in water, it is more difficult to separate them. Chromatographic techniques using ion exchangers or molecular sieves are frequently used in industrial processes to address this, along with organic solvent extraction and, more recently, affinity adsorption (27). Several techniques may be taken to purify isolated α -dextrin. To guarantee high purity, it can first be precisely precipitated from an aqueous solution using cyclohexane, then recrystallised from 60% 1-propanol, and lastly recrystallised from water. Because these impurities can cause cloudiness or opalescence in the finished product, it is imperative to avoid contamination from greasy materials or mineral particles that are frequently found in commercial filter pads and charcoal. It is advised to filter the aqueous solution through a thin fritted-glass filter to get rid of any leftover particles before the final crystallisation. β -dextrin can be further purified by dissolving it in water at room temperature to a concentration of around 2% and allowing it to stand for a long time. This makes it possible for complexes and insoluble contaminants to group. To get a refined product, the solution is filtered through a fine fritted-glass filter, concentrated to around a tenth of its initial volume, and then allowed to crystallise. With the primary distinction being that toluene may be utilised as the particular precipitating agent, the purification procedure for γ -dextrin is comparable to that of α -dextrin. Repeat the recrystallisation process from 60% 1-propanol until there is no more β -dextrin visible in the mother liquors, which may be verified by letting a little sample crystallise on a microscope slide. β -dextrin crystallises efficiently in combination and is easily recognised by its characteristic crystal form (28). Ion exchangers are also used in industrial settings to extract shorter oligosaccharides from α - and γ -CDs. This technique permits the CDs to easily flow through, while the oligosaccharides are kept back on the column (27). Adsorption methods can be used to remove CDs as part of an integrated process or after enzymatic conversion. By attaching themselves to porous polymers, including styrene-divinylbenzene copolymers, CDs are extracted from byproducts. High yields are made possible by eluting and crystallising the CDs after they have been adsorbed. For the purification of α -CD, affinity adsorption is especially helpful. Here, stearic acid covalently bonded to chitosan beads functions as a highly selective adsorbent that can 100% selectively retain just α -CD. The type and concentration of the ligand, the temperature and composition of the mobile phase, the carrier material and its porosity, and other variables all affect the adsorption capacity (27). Biotechnological developments have greatly enhanced the synthesis of CD since the 1970s. Compared to previous techniques, genetic engineering has made it possible to isolate different CD glucosyltransferases (CGTases) that are more selective and active, favouring the formation of primarily α -, β -, or γ -CDs. Highly pure α -, β -, and γ -CDs are now easily accessible for application as food and pharmaceutical excipients thanks to the combination of modified CGTases with further technical and procedural advancements. These days, these CDs are made on an industrial scale; 10,000 tonnes of β -CD are generated annually, and food-grade β -CD is reasonably priced at less than \$5 per kilogram (29,30).

Derivative

Native CDs have undergone chemical modification to improve their solubility and ability to form inclusion complexes. Attaching different functional groups to the hydroxyl groups at positions 2, 3, and 6 of the glucose units within the CD structure accomplishes this (31). Methylation of CDs results in the substitution of methyl groups for their hydroxyl groups, producing derivatives like methyl- β -CD (M- β -CD). This modification increases the hydrophobicity of the CD, which enhances its solubility in organic solvents and increases its ability to solubilise hydrophobic guest molecules. Dimethyl- β -CD (DIMEB), which has two methyl groups instead of hydroxyl groups on each glucose unit, is less toxic and more hydrophobic than native β -CD. DIMEB is particularly helpful for drug administration and encapsulation because it effectively forms inclusion complexes that improve the solubility and bioavailability of poorly soluble medications. Hydroxypropylation is the process of incorporating hydroxypropyl groups into the CD molecule. Hydroxypropyl- β -CD (HP- β -CD), which is much more water-soluble and biocompatible than native CDs, is a typical example. This enhancement strengthens its ability to form inclusion complexes with a variety of drugs and increases its solubility, supporting applications such as controlled release and targeted drug delivery. Similarly, the process of adding acyl groups to CDs to alter their solubility and lipophilicity is known as acylation. These acylated compounds can be specifically designed for therapeutic delivery applications with improved drug stabilisation and more controlled release properties.

Phosphorylation and sulfation enhance the hydrophilicity and biological system interactions of CD by introducing charged groups to its backbone. CDs can be functionalised with a variety of groups, such as amino, carboxylic, or thiol groups, to change their properties for specific applications. These altered derivatives increase CD's effectiveness in areas including drug delivery, chiral separation, and targeted treatment. These modifications have greatly expanded the applications of CDs, making them valuable tools in cutting-edge biomedical fields, including tissue engineering, gene and drug delivery, and nanotechnology (5,32).

Types of CD

Amphiphilic CDs

Amphiphilic CDs have been developed to improve their ability to interact with biological systems and bind molecules in watery environments. These modified CDs can more effectively interact with a range of biological targets because they include both hydrophilic and hydrophobic components. Depending on the type of functional groups attached to the CD structure, these amphiphilic derivatives may be roughly classified into three types: neutral, positively charged, and negatively charged forms.

Neutral Amphiphilic CDs

Neutral amphiphilic CDs, which have both hydrophilic and hydrophobic properties, may be created by attaching certain molecules to the secondary hydroxyl groups of the CD structure. CD molecules feature two fatty acid chains, which are typically two to fourteen carbon atoms long, as a result of this modification. These amphiphilic CDs can improve the solubility and delivery of cholesterol-based drugs through strong interactions. Researchers have synthesised a new compound known as amphiphilic hepta (6-alkylthio-6-deoxy)- β -CD 2-oligo (ethylene glycol). After per-brominated CDs were altered by a nucleophilic substitution method, ethylene carbonate was added to form this. In addition to these multi-component amphiphilic CDs, simpler single-component variants have also been successfully produced. To further enhance the functioning of CD amphiphiles, researchers have included responsive linkages and targeted moieties. For instance, because hydrophobic groups may be connected by disulfide bonds that either break or regenerate in response to redox conditions, they are suitable for controlled drug release. The addition of molecules such as galactosyl or mannosyl units to the oligo (ethylene glycol) chains increases the potential of CD-based drug delivery systems by enabling specific cell type identification and targeting.

Cationic amphiphilic CDs

The ability of cationic amphiphilic CDs to form supramolecular assemblies with unique surface properties and positive charge makes them valuable for the development of soft materials and gene delivery systems. The ability of these materials to effectively transport and transmit genetic material has garnered significant interest in recent years. One of the simpler methods to produce cationic β -CD amphiphiles, which produce easily accessible O-alkyl ether derivatives, is to add amide groups to the CD core and link alkyl chains to the 2 and 3 sites. As an alternative, cationic amphiphiles can be produced by adding a terminal amino group to the oligo (ethylene oxide) chain of amphiphilic CDs. In recent times, researchers have produced many amphiphilic β -CD polycations by replacing the primary hydroxyl groups with functional groups such as amino acids. By varying the length and type of alkyl chains linked at positions two and three, these molecules' surface charge density and hydrophilic-hydrophobic balance may be carefully controlled. Cationic CD amphiphiles can be modified for specific biological or therapeutic applications because of their structural flexibility.

Anionic Amphiphilic CDs

Negatively charged groups, such as carboxyl or sulphate moieties, are added to the CD structure to produce anionic amphiphilic CDs. These groups may be positioned on the molecule's main or secondary surfaces. Carboxyl-functionalized amphiphilic CDs are created by joining alkyl chains at the 6-position and adding carboxymethyl groups at the 2 and 3-positions. Similarly, sulphated amphiphilic CDs are produced by adding sulphate groups to the 6-hydroxyl sites of CDs that have previously undergone esterification at the second and third positions. These structural modifications provide the resulting CDs with both hydrophobic and negatively charged regions, which enhances their ability to interact with positively charged molecules and raises their potential for drug delivery and other biological applications.

Hydrophobic CDs

Hydrophobic CDs are created by incorporating nonpolar groups into the CD structure, allowing them to act as effective drug release vehicles. Hepta(2,3,6-tri-O-ethyl) and hepta(2,3,6-tri-O-butyryl) CDs are examples of alkylated or acylated derivatives that are typically synthesised to accomplish this. A common technique for acetylating CDs is to use 2-methoxypropene as the acetylating reagent. This yields hydrophobic CD derivatives that easily dissolve in organic solvents such as acetone, ethanol, methylene chloride, or tetrahydrofuran (THF). The disintegration rate of these acetylated CDs, whose hydrolysis behaviour depends on factors including pH and molecular structure, may be fine-tuned by adjusting the acetal type and degree of substitution by careful regulation of reaction kinetics. Toxicological evaluations carried out both in vitro and in vivo have shown the remarkable biocompatibility of acetylated CDs, making their nanoparticles suitable for safe local or systemic drug delivery. Additionally, when combined with adamantly-terminated polyethylene glycol (Ada-PEG), acetylated CDs can self-assemble into layered or cylindrical nanostructures, depending on their composition ratio. This suggests that the modified CDs

retain their ability to form inclusion complexes while offering greater flexibility for complicated drug delivery applications (33).

CDs Stimuli-Responsive Derivatives

Stimuli-responsive, or "smart," CDs are an intriguing advancement in host-guest chemistry that may change their behaviour in response to external stimuli such as pH, temperature, light, redox conditions, or enzyme activity. Because they provide precise control over the timing and position of guest molecule encapsulation and release, these intelligent systems show considerable potential for use in biosensing, diagnostics, targeted drug administration, and adaptive materials. For instance, pH-responsive CDs are supplemented with functional groups that ionise at specific pH values, such as carboxylic acids or tertiary amines. For example, carboxymethylated CDs can show pH-dependent complexation, which makes them ideal for drug release in the acidic environments seen in tumours or inflammatory tissues. Temperature-responsive CDs are often combined with polymers that have a fixed lower critical solution temperature (LCST), such as poly(*N*-isopropylacrylamide) (PNIPAM). Below the LCST, the system remains hydrated and swollen; however, as the temperature rises above this point, the polymer collapses, releasing the trapped guest molecules. These techniques are ideal for pulsatile drug delivery and thermoresponsive gels.

On the other hand, photochromic groups like azobenzene or coumarin change light-responsive CDs. When exposed to light, these groups alter their interactions with CDs, enabling precise optical control over the capture and release of guest molecules. Redox-responsive CDs are made via ferrocene groups or disulfide bridges. When the disulfide bonds break in settings rich in reducing agents, like glutathione, which is often found inside cells, the trapped guest molecules are liberated. This approach is very useful in nanomedicine for cancer. Similar to this, medication release under pathological circumstances is made possible by enzyme-responsive CDs, which are attached to substrates that are specially recognised by overexpressed enzymes like glycosidases or proteases. For instance, targeted medication delivery to tumours is made possible by CD-peptide conjugates that are broken down by matrix metalloproteinases (MMPs) (34).

Thermal Behaviour

The three most prevalent naturally occurring CDs have been the main subject of several prior investigations (35,36). In general, native CDs' TG and DTA profiles may be separated into three different areas. Depending on the particular CD, the first step, which takes place between room temperature and around 120°C, reflects water loss with a mass decrease of roughly 9–14%. The TG curve displays a steady plateau with no discernible change in mass throughout the subsequent phase, which occurs between 120°C and 250°C. Nonetheless, the DTA curve shows faint endothermic peaks, one for α -CD at around 142°C and another for β -CD at about 210°C, which suggest potential structural changes in the molecules (37–39). CDs undergo significant thermal deterioration over 250°C, which can result in a significant mass loss of up to 78% of the original sample. Melting and decomposition take place concurrently in the solid state, where this process begins (36).

Biocompatibility And Safety

All parent CDs are 'generally recognised as safe' (GRAS; European Medicines Agency, CDs used as excipients, (EMA/CHMP/495747/2013)). CDs have more osmotic action than polysaccharides because of their comparatively tiny molecular size. They might cause adverse effects including diarrhoea or cecum enlargement, when taken orally in high dosages over 1 g/kg/day. Only at 20% concentrations has RM- β -CD been shown to cause tissue damage and nasal discomfort. When used in the eyes, α -CD and methylation β -CD have been linked to irritation and epithelial toxicity, respectively, whereas β -CD, HP- β -CD, and SB- β -CD did not exhibit any negative effects. Furthermore, there have been no reports of discomfort after rectal CD administration (5). Despite their relatively modest cytotoxicity, natural CDs can become more poisonous as concentration rises and can change based on chemical changes. For instance, it has been discovered that rabbits' corneal epithelium is harmed by solutions that include 4% α -CD or 5% RM- β -CD. Their haemolytic potential is a more serious issue; β -CD, for example, extracts cholesterol from red blood cell membranes, seriously damaging them. Interestingly, because HP- β -CD may form compounds with cholesterol *in vivo*, it is also used therapeutically (40). Dimethyl- β -CD exhibits the highest capacity to remove cholesterol among the methylated forms of β -CD, but it also has the most haemolytic activity (41). The haemolytic action of α - and γ -CDs is probably related to their capacity to combine with phospholipids and other elements of the cell membrane to form inclusion complexes (42).

Self-Aggregation

The tendency of CD molecules to self-associate in aqueous solutions, resulting in aggregation formation, has long been known (25). To the best of our knowledge, the idea that α - and γ -CDs can self-associate in aqueous solutions to form dimers and perhaps bigger aggregates or nanoparticles was initially put out by

Miyajima and associates. These results were validated by further research, which showed that all three of the natural CDs— α , β , and γ —can form nanoscale aggregates. These aggregates usually have a diameter of 20 to 200 nm, and as the CD concentration increases, so does their size (43). Aqueous γ -CD solutions may look hazy or opalescent due to nanosized CD clumps or clusters. These solutions become transparent when filtered over a 0.45 μm membrane, but after a period of storage, the opalescence returns (44). It's interesting to note that cloudy γ -CD solutions do not lose concentration when filtered. It seems that during filtration, the γ -CD aggregates momentarily disintegrate but eventually reassemble in the filtrate. Similar to this, aggregates made of CDs and other low-molecular-weight saccharides are difficult to detect because they are temporary and readily dissociate when the aqueous solutions are handled. For example, using several ^1H NMR (proton nuclear magnetic resonance) methods, Valente and colleagues were unable to detect any aggregates in aqueous solutions of α -, β -, or γ -CD (45). While there is still much to learn about this subject, several findings are generally acknowledged. One is that when CD concentrations rise, CD aggregates get bigger (46). Furthermore, at concentrations (3–12 mM) much below their water solubility limits, aggregates of native CDs can form. There have been reports of critical aggregation values of 25 mg/mL (26 mM) for α -CD, 8 mg/mL (7 mM) for β -CD, and 9 mg/mL (7 mM) for γ -CD, below which aggregation does not occur (47). CD aggregation may also be impacted by the presence of guest molecules. For example, β -CD has a critical aggregation concentration of 4.2% (w/v) in a pure aqueous solution (48). According to Rodrigues Sá Couto and associates (2019), the presence of carbamazepine, a drug frequently recommended for epilepsy, (49) In the solution, β -CD's critical aggregation concentration drops to 2.5% (w/v) (48).

Inclusion Complex

The formation of inclusion complexes is the fundamental property of CD supramolecular chemistry. CDs can stabilise and solubilise substances that would otherwise have poor solubility by allowing guest molecules to reside inside their hydrophobic cavities. In the pharmaceutical business, where CDs are frequently utilised to improve the solubility, stability, and general performance of active pharmaceutical ingredients (APIs), this exceptional property has found widespread use (50). Because CDs may accommodate the complete drug molecule or, more frequently, only its lipophilic part within their central cavity, they can form inclusion complexes with a variety of medicines in aqueous solutions. Covalent bonds are neither formed nor broken during the complex formation process, and the drug molecules inside the complex maintain a quick equilibrium with the free molecules in the solution. Although the complex forms swiftly at first, it takes longer to achieve the final equilibrium. In order to maximise interactions with the weak van der Waals forces present; a drug molecule undergoes minor structural changes as it enters the CD chamber. The displacement of enthalpy-rich water molecules from the cavity, electrostatic and van der Waals interactions, hydrophobic effects, hydrogen bonding, the release of conformational strain, and charge-transfer interactions are some of the forces that propel the formation of CD-drug inclusion complexes. Steric compatibility is the most crucial of several criteria that determine a CD's capacity to host a medicinal molecule. The size of the CD cavity in relation to the drug molecule or its main functional groups determines this. If the drug is too large to fit inside the CD cavity, complex formation is limited. The three natural CDs differ in the quantity of glucose units that make up their structure and in the breadth of their internal cavity, even though they are all the same height. These structural differences affect the kind of guest molecules they can host. While α -CD usually forms inclusion complexes with smaller molecules or those with aliphatic chains, β -CD is more adapted to accept aromatic or heterocyclic compounds. However, γ -CD's larger cavity allows it to encapsulate large molecules like steroids or macrocyclic medicines. The establishment of a stable combination requires not only size compatibility but also the thermodynamic equilibrium between the medicinal molecule and the CD. For inclusion to occur, an energetically favourable interaction must push the guest molecule into the CD cavity. The most stable three-dimensional form of CD is a torus, with hydroxyl groups exposed to the environment by the wider and narrower rims and the centre cavity remaining primarily hydrophobic. The thermodynamic foundation for the formation of stable drug-CD inclusion complexes is provided by this unique structural arrangement, which also accounts for the exceptional physicochemical behaviour of CDs. Several energetically advantageous interactions drive the complex creation process:

1. Polar water molecules are released from the nonpolar interior of the CD cavity;
2. More hydrogen bonds are formed as the displaced water molecules mix back into the bulk solution.
3. The hydrophobic drug molecule and the aqueous environment have fewer unfavourable interactions, and
4. The hydrophobic interactions are enhanced as the guest molecule embeds itself within the CD's apolar cavity.

Once they form a complex, the physicochemical properties of an unbound CD and a free medication are significantly different. Several analytical methods can be used to determine these changes in the drug's characteristics. Assessing changes in solubility, chemical reactivity, UV/VIS absorption, fluorescence, and NMR chemical shifts are examples of frequently used techniques. Changes in potentiometric readings, pKa values, permeability across artificial membranes, chemical stability, and drug retention can also offer important information on complex formation (51).

Types of Complexes

Higuchi and Connors examined how changing a ligand or solubiliser's concentration affects a drug's solubility in order to classify various complex kinds. The phase-solubility profile is the name given to this connection, which is seen in Figure 3. An A-type phase-solubility profile is the curve that results when a drug's solubility rises as the concentration of CD (ligand) increases. Three subtypes may be distinguished from this A-type profile. As the ligand concentration increases, the AL profile indicates a straight-line increase in solubility. At larger concentrations, the solubiliser becomes more effective, as seen by the AP profile's positively curved departure from linearity. The AN profile, on the other hand, shows a negative departure from linearity, indicating that the solubiliser's efficiency declines with increasing concentration. Figure 3 shows the Phase solubility profile. All three of the curves in Figure 3 point to the creation of water-soluble complexes that are more soluble than the medication when it is not complexed. A 1:1 combination between the medication and the ligand is often indicated by a slope of less than one in an AL-type phase-solubility plot. On the other hand, a slope larger than one indicates that higher-order complexes are involved in the solubilisation process. The production of a 1:1 complex is usually presumed unless more evidence indicates otherwise, even if a slope below unity does not completely rule out the possibility of such higher-order complexes.

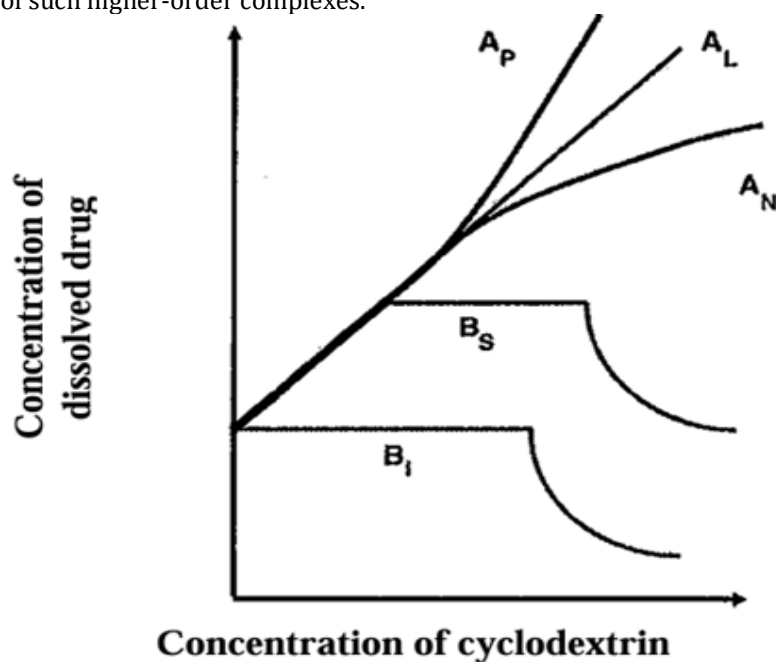


Figure 3: Phase solubility profile (52)

As seen in Figure 3, an AL-type phase-solubility profile is seen when the complex formation process follows first-order kinetics concerning both the ligand (complexing agent) and the substrate (drug). The resultant profile is categorised as AP-type if the complex formation stays first order concerning the drug but becomes second order or higher with respect to the ligand. In contrast, because of its non-linear behaviour, the AN-type phase-solubility profile is more complicated and sometimes difficult to understand. Less soluble natural CDs frequently display B-type phase-solubility profiles, whereas water-soluble CDs typically yield A-type profiles. A B-type phase-solubility profile, which is frequently seen with naturally occurring CDs, particularly β -CD, indicates the development of complexes with low water solubility. Bs and Bt are the two further classifications for these B-type complexes. CDs can form aggregate structures or non-inclusion complexes that improve drug solubility through micelle-like processes, even though the majority of drug-CD interactions result in inclusion complexes. It is crucial to remember that phase-solubility experiments only show how the drug's solubility changes with increasing CD concentration; they cannot verify if an inclusion complex has formed (51). CDs have been widely used

in a variety of industries, such as the food and chemical sectors, medicines, drug delivery systems, and cosmetics. Many commercial formulations, including pills, ocular drops, and ointments, already include them. An extensive study has been conducted on the usage of CDs to improve the performance and overcome the constraints of many chemicals in many sectors due to their shown ability to form inclusion complexes with bioactive molecules (53). Comparing the effects of the medication in both its complexed and uncomplexed forms is essential when researching the biological activity of substances complexed with CDs. To ensure that any detected changes are caused by the complexation itself and not by variations in drug amount, this comparison should be done using an equivalent drug dosage or an identical weight (54,55). Research into CD inclusion complexes, both in vitro and in vivo, can provide important information on their efficacy and therapeutic potential.

In Vivo Studies of Inclusion Complex

Anti-Inflammatory Activities of CD Inclusion Complexes

The most often researched CD (CD) for creating inclusion complexes (CD-IC) with anti-inflammatory pharmaceuticals is β -CD (β -CD) because of its affordability, high oral tolerance, and potent capacity to encapsulate these medications. Generally categorised as either corticosteroids or non-steroidal anti-inflammatory medicines (NSAIDs), anti-inflammatory pharmaceuticals are frequently used to treat inflammatory diseases. However, these medications frequently have serious adverse effects, such as cardiovascular problems, neutropenia, and gastrointestinal discomfort. By reducing the negative effects of these anti-inflammatory drugs and increasing their therapeutic effectiveness, CDs can improve treatment results overall (53).

Antinociceptive Activities of CD Inclusion Complexes

(-)-Linalool (LIN) is a monoterpene generated from plants that is mostly found in species belonging to the Lamiaceae and Lauraceae families. It has analgesic and anti-inflammatory qualities. However, LIN's weak chemical stability and poor solubility as a terpene limit its medicinal use. LIN was created as a combination with CD (CD) to improve its stability, pharmacological efficacy, and water solubility. The acetic acid-induced writhing, formalin, and hot plate tests were used to evaluate the antinociceptive potential of LIN and the LIN/CD complex at a dosage of 40 mg/kg. Significant pain-relieving benefits were shown in all experiments ($p < 0.01$ or < 0.001), with the LIN/CD combination showing more antinociceptive activity than LIN alone (56).

Anticancer Activities of CD Inclusion Complexes

To make the water-soluble γ -CD (γ -CD) more soluble and bioavailable, it was complexed with betulinic acid, a very promising anti-melanoma compound. The resulting complex was characterised using differential scanning calorimetry (DSC), X-ray diffraction, and scanning electron microscopy (SEM). Its antiproliferative activities were evaluated using the MTT test and cell cycle analysis. Additionally, the therapeutic potential of the compound was examined using a mouse melanoma model. A 100 mg/kg intraperitoneal dose was administered to the mice. The findings demonstrated a significant reduction in tumour weight and volume, indicating that complexation with γ -CD effectively enhanced the antiproliferative action of betulinic acid and inhibited tumour growth in vivo (57). Curcumin (CUR) has anti-cancer potential; however, its medicinal usage is limited by its poor bioavailability. CUR was created as a CD (CD) compound to enhance its administration for cancer chemoprevention. A dosage of 100 mg/kg of curcumin was administered to rats that had been injected with lung cancer cells to perform in vivo investigations. In comparison to free curcumin, the CUR/CD complex dramatically increased curcumin's bioavailability and therapeutic efficacy, showing higher efficacy both in vitro and in vivo (58).

In Vitro Studies of Inclusion Complex

Although CDs have been shown in several in vitro investigations to cause haemolysis, their toxicological effects in vivo are usually regarded as negligible. The effects of the free, uncomplexed drug, the direct activity of the CD-drug complex, and whether the inclusion complex dissociates under experimental conditions are just a few of the crucial factors that should be carefully considered when designing both in vitro and in vivo experiments (53).

Antimicrobial Activities of CD Inclusion Complexes

To assess their solubility and antibacterial efficacy against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Saccharomyces cerevisiae*, carvacrol, eugenol, linalool, and 2-pentanoylfuran were added to CD complexes. These substances were added to CDs, which greatly increased their antibacterial activity and solubility in aqueous media. Carvacrol had the lowest minimum inhibitory concentration (MIC) of 0.5 g/mL and the greatest antibacterial activity among them all. Eugenol and linalool both showed significant effectiveness against Gram-positive bacteria, with MIC values of 1.25 g/mL and 2.5 g/mL for *B. subtilis* and 2.5 g/mL for *S. aureus*, respectively. With a MIC of 1.25 g/mL, 2-pentanoylfuran

had the most favourable action against the yeast *S. cerevisiae* while having the smallest antibacterial effect (59).

Antichagasic Activity of CD Inclusion Complexes

Although benznidazole (BNZ) is a crucial treatment for Chagas disease, its high toxicity and low solubility restrict its clinical use. In order to overcome these obstacles, inclusion complexes (ICs) were created and characterised in ternary systems (TS) that incorporate BNZ, RMCD, and hydrophilic polymers as well as binary systems (BS) that comprise BNZ and randomly methylated CD (RMCD). The results showed that the drug's dissolution rate was considerably increased by the solid binary systems ($Q > 80\%$). The most promising method for creating a solid oral dosage form was the CD-IC made with the kneading process at a ratio of 1:0.17, which produced a dissolution rate of 77.8% in 60 minutes (60).

Analytical techniques for characterisation

It is difficult to create inclusion complexes and characterise the ensuing guest-CD solid systems since doing so necessitates integrating many analytical methods to fully comprehend the process(61). Characterising guest-CD inclusion complexes in solution usually involves identifying changes in the guest molecule's chemical or physical characteristics brought on by complex formation (62).

Table 3: analytical techniques and an example of their use. Data is taken from (63).

Techniques	An example where this technique is used
Scanning Electron Microscopy	Characterisation of host-guest inclusion complexes made of synephrine, phenylephrine hydrochloride, and α - and β -CDs.
Fourier-transform infrared spectroscopy (FTIR)	β -CD and 2-hydroxy-1-naphthoic acid produce a host-guest inclusion complex.
Powder X-ray diffraction (PXRD)	Characterisation of the host-guest inclusion complex that β -CD and fluconazole, an antifungal active pharmaceutical component, create.
Raman spectroscopy	Examine how limaprost interacts with α - and β -CD.
Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC)	β -CD and 2-nonanone produce a host-guest inclusion complex that is characterised.
Ultraviolet/visible spectroscopy (UV-vis)	Examine the thermodynamic characteristics and association constants of the host-guest inclusion complex made up of vitamins and β -CD.
Nuclear magnetic resonance (NMR) spectroscopy	Research on β -CD inclusion complexes with isoflavones (daidzin and daidzein)
Fluorescence	Characterisation of β -CD and benzoguanamine-formed host-guest inclusion.
Circular dichroism	The best choice of CD for drug complexation.
High-performance liquid chromatography (HPLC)	An HPLC technique for measuring norfloxacin in β -CD inclusion complexes was developed and validated.

Pharmacokinetics

Both humans and animals can consume CDs through food additives or pharmaceuticals taken orally. These can be free CDs or inclusion complexes that include flavours, medicines, or other guest compounds. The stomach's acidic environment rapidly breaks down these complexes since the supplied CD dosage is typically minimal, allowing the CD and the guest molecule to be absorbed by different routes. While just a small portion of intact CD is absorbed because of its huge molecular size and very hydrophilic surface, the absorption of the hydrophobic guest molecule is substantially increased. By solubilising the hydrophobic guest, keeping it in solution, and facilitating its passage to the lipophilic cell membrane, the CD essentially serves as a carrier. The CD stays in the aqueous environment after the guest molecule is delivered to the cell, which has a higher affinity for it. Thus, it is possible to summarise the general behaviour of β -CD following oral administration, regardless of whether it is ingested freely or in complexed form:

1. Rapid dissolution of the inclusion complex causes a dynamic equilibrium between complex creation and dissociation to be established swiftly.
2. The circulation quickly absorbs the guest molecule.
3. Through the intestinal wall, only a very small portion of the CD that is taken orally gets absorbed intact.
4. The intestinal microbiota in the colon breaks down the majority of the CD that is consumed.
5. Similar to starch, the main breakdown products—likely acyclic maltodextrins, maltose, and glucose—are subsequently metabolised, absorbed, and finally expelled as water and carbon dioxide.

The primary distinction with regard to starch metabolism is the location of degradation: CDs are mostly metabolised in the colon, while starch is primarily metabolised in the small intestine. As a result, maximal metabolic activity happens around 1-2 hours after consuming starch and 7-8 hours after consuming CD. This trend suggests that γ -CD metabolises more quickly than β -CD, although α -CD metabolises more slowly.

Upon administering 50 g of α -CD (α -CD) to diabetics, there were no changes in urine glucose levels. Studies investigating the interaction of human colon microflora with α -CD and β -CD found that both types of CDs undergo extensive hydrolysis in the colon, and 24 of the 30 tested *Bacteroides* strains were able to break down CDs, as evidenced by their capacity to grow on CDs as their sole carbon source. Additional analysis of CGTase enzymes from two of these *Bacteroides* strains showed that the enzyme activity was mainly related to the cell surface and was induced after only 2–4 hours of growth on CDs. Under colon-typical circumstances (pH 6.8 and 37°C), these enzymes were shown to be stable and highly active. Significant CD degradation took place in 18 hours under these circumstances, with discernible breakdown starting as early as 1-2 hours. Anaerobic bacteria in the colon readily ferment the glucose and maltooligosaccharides produced by the breakdown of CDs to form short-chain fatty acids and intestinal gases, among other byproducts. There was a 10- to 100-fold rise in faecal *Bifidobacteria* levels after two weeks of consuming 10 g of β -CD daily in human adults, suggesting a prebiotic impact. Overall, research indicates that the digestive system absorbs a very small amount of CD that is taken orally undamaged. Instead, indigenous bacteria in the colon break down the majority of the CD that is eaten. Similar to starch, the resultant metabolites—mainly glucose, maltose, and acyclic maltodextrins—are subsequently quickly metabolised and absorbed before being expelled as carbon dioxide and water. The primary difference between CDs and starch metabolism is where they are broken down: CDs are broken down in the colon, whereas starch is metabolised in the small intestine. Therefore, maximal metabolic activity happens 6–8 hours after CD intake and 1-2 hours after starch ingestion. In contrast, γ -CD breaks down more quickly than β -CD, whereas α -CD metabolises more slowly (64).

CD-based supramolecular architectures

An assemblage of two or more molecular units held together and arranged by non-covalent intermolecular interactions is referred to as a supramolecule. The potential of CD (CD)-based polyrotaxanes and polypseudorotaxanes, which are structures created by threading multiple CD rings along a polymer chain, with or without bulky end groups, to create sophisticated supramolecular biomaterials like hydrogels and biodegradable polymers, has drawn a lot of attention in recent years. These innovative materials provide new possibilities for controlled drug delivery by employing techniques distinct from those of traditional systems. A supramolecular compound made of many α -CD rings threaded onto a PEO chain was developed by researchers in 1992. It was one of the first studies in this field since the molecule was stabilised by big end-caps that prevented the CDs from slipping off. Since that discovery, a lot of research has been done on the structural and functional properties of CD-based polyrotaxanes and polypseudorotaxanes, as well as their potential applications in the synthesis of biomaterials. It has been observed that CDs may selectively recognise and form complexes with certain polymer segments, resulting in supramolecular structures having both complexed and free portions. Research on these block-structured systems has impacted the development of new and more sophisticated biomaterials, particularly for targeted drug and gene delivery applications (65).

CD EFFECTS ON IMPORTANT DRUG PROPERTIES IN FORMULATION

CDs are crucial for improving the formulation of poorly water-soluble drugs because they increase their apparent solubility and dissolution. This can be achieved by methods such as inclusion complexation or solid dispersion. CDs can also be utilised as dissolving enhancers in tablet formulations, particularly for high-dose drugs like paracetamol that struggle to form a CD complex, or as hydrophilic carriers for drugs lacking the proper molecular properties for complexation. The apparent stability constants (K) of drug/CD complexes typically range from 0 to 100,000 M^{-1} , depending on the specific drug and CD involved. Among the several commercially available CDs, it has been demonstrated that methylated derivatives with lower degrees of molar substitution are the most effective in increasing solubility. The reduction in drug crystallinity that occurs during complexation or solid dispersion with CDs also promotes improved apparent solubility and faster rates of dissolution.

Effect on Drug Bioavailability

By increasing the solubility, dissolution, and occasionally permeability of poorly soluble medications, CDs can increase their bioavailability. By transporting the chemical to the surface of biological barriers, such as the skin, mucosa, or cornea, CDs help hydrophobic medications become more permeable. Once there, the medicine can partition into the membrane without causing any damage to its lipid layers. Because

using too much CD might actually decrease drug availability, it is important in these situations to utilise just enough to solubilise the drug in the aqueous medium.

At low concentrations of RM- β -CD, for instance, hydrocortisone in suspension exhibited increased flux with rising CD levels; however, at higher CD concentrations, when the drug was fully solubilised, further increases in CD decreased the flux. Adding polymers can further increase drug permeability from aqueous CD solutions; for example, carboxymethyl cellulose (CMC) improved the bioavailability of triclosan in toothpastes containing β -CD by forming a drug/CD/CMC complex with enhanced retention; CDs improved the solubility and absorption of the lipophilic drug itraconazole in both oral and intravenous formulations, increasing its bioavailability; for water-soluble drugs, CDs can directly act on mucosal membranes to increase permeability, improving absorption and overall bioavailability.

Effect on Drug Safety

CDs have been used to minimise the side effects and discomfort that some medications produce. CDs may improve medicinal efficacy and potency by making drugs more soluble, which reduces toxicity by enabling therapeutic benefits to be obtained at lower dosages. For example, ganciclovir's antiviral activity against clinical strains of the human cytomegalovirus was enhanced by β -CD, and the accompanying increase in medication potency helped lessen the harmful effects of the drug. Similarly, toxicities associated with the crystallisation of weakly water-soluble medicines in parenteral formulations can be mitigated by the creation of soluble drug-CD complexes. Phenytoin is a prominent example; in a BALB/c mouse model, its formulation with HP- β -CD resulted in noticeably less tissue irritation than an injectable formulation that is sold commercially.

Effect on Drug Stability

By shielding labile medications against oxidation, photodegradation, hydrolysis, and dehydration, CDs can increase their stability and prolong their shelf life. It is believed that CDs' capacity to prevent undesirable interactions between the medication and the formulation vehicle and to lower drug bioconversion at the absorption site is what causes this stabilising effect. CDs protect sensitive drug molecules from different degradation processes by encasing them at the molecular level and functioning as a molecular shield. It has been demonstrated that SBE- β -CD offers the best stabilisation among the various CDs for a large number of chemically unstable medications. The functional groups of the medication and the kind of vehicle determine how much stabilisation occurs. For instance, in 1,4-dihydropyrimidine derivatives, complexation with CDs reduced the stabilising effects of halogen and cyanogen groups as well as the photodegradation-promoting impact of nitro groups. Similarly, as compared to an emulsion carrier, HP- β -CD significantly decreased the photodegradation of 2-ethylhexyl p-dimethyl aminobenzoate in solution (66).

Effect on drug release

By raising the concentration of diffusible drug molecules inside the matrix, CDs can enhance drug release from polymeric systems. The use of CDs and other additives to improve the solubility of buprenorphine, a weakly water-soluble opioid painkiller, and alter its release from buccal patches composed of poly (acrylic acid), poly(isobutylene), and poly(isoprene) was studied by Guo and Cooklock in 1995. Compared to the bile salts sodium taurocholate and sodium glycodeoxycholate, they discovered that both α - and β -CD were more successful at solubilising buprenorphine base and its HCl salt, with β -CD offering the greatest solubility improvement. Similarly, Samy and Safwat (1994) showed that β -CD could alter the release rates of flurbiprofen, diclofenac sodium, and piroxicam from gels based on silica (Aerosil®) and cellulose. A 1:1 drug-to-CD ratio patch released 50% of the drug over 24 hours, more than twice the release from patches containing the drug alone at the same loading, according to in vitro studies (67).

Toxicity

CDs often exhibit minimal toxicity when taken orally, mostly due to their limited gastrointestinal absorption. Their favourable safety profile is a result of their reduced systemic exposure, which makes them extensively appropriate for usage in oral formulations, including tablets, capsules, and suspensions. α -CD, for example, is frequently used as a dietary fibre supplement (68), while derivatives of β -CD are employed as excipients in oral medications to increase the solubility of weakly water-soluble substances without having a major negative impact (69,70). However, when CDs are given via parenteral means, such as intramuscular (IM) or intravenous (IV) injection, their safety profile might significantly alter. Since CDs reach the systemic circulation directly in these situations, their effects on organs such as the kidneys are more significant. Excessive dosages or extended usage of β -CD and its derivatives have been associated with nephrotoxicity; certain animal studies have shown that buildup in the renal tubules can cause kidney damage. Because highly substituted derivatives like methyl- β -CD can interact with cell membranes and cause toxic consequences, this danger is particularly significant (71). Although inhalable CDs, including hydroxypropyl- β -CD (HP- β -CD), have also been investigated for pulmonary drug administration, it is

important to carefully assess their propensity to irritate or inflame the lungs (72). All things considered, the method of administration has a significant impact on the bioavailability, systemic exposure, and organ-specific toxicity of CDs, which in turn determines their safety.

The toxicity profile of γ -CD has also been studied. Very low acute toxicity was shown by the acute LD50, which was determined to be larger than 16,000 mg/kg in mice and over 8,000 mg/kg in rats when given orally. Rats fed up to 20 grams of δ -CD over a 90-day feeding trial did not exhibit any adverse effects. The LD50 values were equally high for the other routes of administration: intravenous administration surpassed 10,000 mg/kg in mice and more than 3,750 mg/kg in rats; intraperitoneal treatment in rats exceeded 4,600 mg/kg, and subcutaneous administration in rats was above 2,400 mg/kg. All of these results demonstrate that γ -CD has a good safety profile when taken through a variety of routes.

α -CD

The main features are the possibility of minor ocular irritation, the ability to bind to certain lipids, and the potential for mild discomfort when injected intramuscularly. Just 2-3% of it is absorbed in rats after oral treatment, and it is only broken down by the intestinal microbiota in the colon and caecum. It does not undergo any metabolism in the upper gastrointestinal tract. After rat oral ingestion, over 60% is eliminated as CO₂ (no CO₂ was found in germ-free rats), 26-33% is converted into metabolites, and 7-14% ends up in the urine and faeces. It has a half-life of around 25 minutes in rats and is mostly removed unaltered by the kidneys after intravenous injection. With an intravenous LD50 of 500-750 mg/kg and an oral LD50 in rats above 10,000 mg/kg, the chemical exhibits mild toxicity.

β -CD

This CD's primary features are its capacity to bind cholesterol and its lower irritability when administered intramuscularly compared to other CDs. It is not metabolised in the upper gastrointestinal tract after oral treatment, and only very small quantities (about 1% to 2%) are absorbed there. Rather, microorganisms in the colon and caecum break it down. This CD is the most well-researched in humans and is now the most commonly utilised in pharmaceutical formulations. High dosages, however, can be hazardous and are not advised since bacterial breakdown in the colon can result in gas production and diarrhoea. Its toxicity profile reveals an intravenous LD50 range from 450 to 790 mg/kg and an oral LD50 in rats above 5,000 mg/kg.

19.3 γ -CD

The primary characteristics of this CD are that it causes no discomfort when injected intramuscularly and that, even at large daily dosages (10-20 g/kg), digestive enzymes quickly and completely break it down into glucose in the upper gastrointestinal system. Approximately 0.1% of the intact CD is absorbed after oral delivery, and essentially none of it is metabolised after intravenous treatment. It is thought to be the least harmful of the three naturally occurring CDs. Major producers aggressively market it as a food ingredient. It typically has a lesser complexation capacity than other CDs and their water-soluble derivatives, making it less capable of forming inclusion complexes. Furthermore, the complexes it creates frequently agglomerate and have low water solubility, producing somewhat opalescent solutions. According to toxicity studies, rats' oral LD50 is 8,000 mg/kg, whereas their intravenous LD50 is around 4,000 mg/kg (73).

Regulatory Status of CDs in Different Pharmacopoeias

From a regulatory perspective, major pharmacopoeias such as the European Pharmacopoeia (EP 6.0) and the U.S. Pharmacopoeia/National Formulary (USP/NF25) recognise α - and β -CDs (CDs). Furthermore, a monograph on CDs is included in the Handbook of Pharmaceutical Excipients, which classifies them as substances that improve the stability and solubility of medications. As previously said, the approval of goods by regulatory bodies in the US, Europe, and Japan indicates that the road for the commercial use of pharmaceutical formulations using CDs has been created. CDs may be present in formulations as a standalone form or as a component of a drug-CD combination. After being given, the temporary complex that developed between the CD and the active component breaks down in the body, releasing the medication and enabling it to have its intended therapeutic effect. As a result, rather than the transient CD-drug combination, regulatory approval concentrates on the active pharmaceutical component itself (74).

AI and Computational Modelling in CD Research

Gaining a comprehensive understanding of how CDs interact with guest molecules is essential to advancing the use of host-guest inclusion complexes. To investigate these interactions, researchers typically combine computer modelling and experimental techniques, which together provide insight into the properties and behaviour of the complexes (75). Recently, a number of computational methods have been developed to study how CD (CD) interacts with its guests. Quantitative structure-activity relationship (QSAR) modelling, quantum-chemical calculations, molecular docking, and molecular

dynamics (MD) simulations are often employed techniques. These methods allow researchers to study both static binding conformations and dynamic interaction processes by simulating the interactions of CDs and guest molecules under certain conditions. They also provide detailed information on binding sites, significant residues, and the types of pressures involved. By examining interactions at the atomic level, computational methods may assess the stability of host-guest complexes and help understand or validate experimental data. Additionally, they can predict the physicochemical and structural properties of CDs or guest molecules, which enables efficient screening of potential host-guest pairs (76). There are currently very few studies that specifically address the use of computational techniques to study CD-guest interactions. Lipkowitz 6 described how various molecular modelling techniques, including quantum mechanics, molecular dynamics (MD) simulations, and Monte Carlo simulations, have been used to study CD-guest complexes (77). An overview of the computational techniques used to investigate CD-drug-drug inclusion complexes, including quantum mechanics, molecular docking, molecular dynamics (MD) simulations, and QSAR modelling, has been provided by Abdolmaleki and colleagues (78). Although there are currently few comprehensive studies on this topic, CDs and natural compounds have recently been investigated utilising a variety of computational methodologies. Meanwhile, new applications of these computational techniques continue to gain traction.

Quantitative Structure–Activity Relationship.

Through computer modelling, QSAR allows scientists to statistically correlate a molecule's structural characteristics with its biological or physicochemical function. The fundamental tenet of this strategy is that substances with equivalent chemical structures typically have comparable biological effects and features. Scientists may effectively find possible active compounds, create novel molecules, forecast their activity levels, and learn more about the underlying processes of interactions by using QSAR models. This approach has gained popularity and become a useful tool in the field of food science since it relies on the chemical structure and does not require experimental testing (76).

Molecular Docking.

QSAR models often link a ligand's properties to its receptor, assuming that the receptor remains unchanged. However, in real molecular interactions, the receptor plays a crucial role. Molecular docking is a significant computational technique for modelling how tiny molecules interact with target proteins and calculating their binding affinities. Finding potential active ligands from large chemical databases is made feasible by molecular docking, which concentrates on receptor–ligand interactions. This greatly increases the efficiency and accuracy of locating potential target molecules (79). Molecular docking has been widely used in the investigation of the interactions between CDs and their guest molecules. It helps determine the key functional groups, binding sites, and orientations that allow the guest molecule to enter the CD cavity. It also helps forecast the best binding conformations and understand experimental findings related to CD-guest complexes (80).

Molecular Dynamics Simulations.

Molecular docking allows for the rapid simulation of a range of host-guest interactions, although speed sometimes comes at the expense of accuracy. Furthermore, because docking only provides static images, it is unable to accurately depict the dynamic nature of the contact process. Molecular dynamics (MD) simulations can overcome these limitations and give a more realistic view of the interactions between host and guest molecules by modelling atomic motion over time using classical Newtonian physics (76). By calculating the potential energy of molecules and atomic bonds within a system, molecular dynamics determines the positions, speeds, and motion patterns of individual particles. This enables the evaluation of various molecular properties and the optimisation of structural conformations. As a result, MD simulations have become a powerful and widely utilised tool in food chemistry and several other scientific domains (81).

Application

CDs Can Stabilise Supersaturated Solutions

An aqueous solution is considered supersaturated when the concentration of dissolved medication exceeds the drug's thermodynamic equilibrium solubility. Drug precipitation can occur quickly in an unstable supersaturated drug solution. Drug precipitation inhibitors are pharmaceutical excipients that prevent nucleation and crystal formation. These excipients include cocrystals, surfactants, hydroxypropyl methylcellulose, polyvinylpyrrolidone, and CDs (82–84). While several common pharmaceutical excipients can stabilise supersaturated solutions, CDs have been demonstrated to both increase the drug dissolution rate and stabilise the resulting supersaturated drug solution. The mechanism of inhibition may include changes in surface tension, an increase in adsorption to the crystal layer, thereby blocking crystal growth (85).

CD Complexation with Anticancer Drugs

Chemotherapy has a limited therapeutic benefit for cancer, especially when it comes to recurring and metastatic illness. Treatment of cancer has long been hampered by promising anticancer drug candidates' limited aqueous solubility (hydrophobicity), degradation in gastrointestinal fluids, low bioavailability, short in vivo stability (half-life), affinity for intestinal and liver cytochrome P450 (CYP3A4) and P-gp in the intestinal barrier, poor intestinal permeability, and strong dose-dependent side effects. Short blood circulation times and lack of selectivity, which result in several harmful side effects, are other serious concerns. A significant obstacle is the limited therapeutic index of some anticancer medications and the fact that these cytotoxic medications harm both healthy and normal tissue in addition to cancer cells. Another significant issue is multidrug resistance, which is brought on by an increase in efflux pumps like P-glycoprotein (P-gp) in the cell membrane that carry the majority of anticancer medications out of the cell. Therefore, it is necessary to create a delivery method that integrates convenience, safety, and efficacy. CDs are capable of overcoming some of the aforementioned side effects of anticancer medications. In order to improve the therapy's usefulness and acceptability, new technologies based on the combined approach of CD complexation and nanotechnology must be developed and put into practice due to the absence of effective treatment. The drug's physicochemical qualities increase when an inclusion complex is formed with harmless substances. In order to improve solubility and stability, boost bioavailability and dissolution, decrease toxicity, and alter physicochemical properties, the majority of anticancer medications have been complexed with CD and its derivatives. When doxorubicin is complexed with γ -CD and HP- γ -CD, the membrane was disrupted, increasing permeability across the blood-brain barrier (7).

CDs in Nanomaterials and Nanostructured Coatings

A new area of material science has been made possible by the incorporation of CDs into nanomaterials and nanostructured coatings. These nanoparticles, which are well-known for their incredibly small size and large surface area, inherently have exceptional mechanical strength, chemical reactivity, and a variety of special physical characteristics. These qualities are further increased by the addition of CDs, resulting in materials with improved performance and specialised functionality. Researchers may combine the molecular inclusion potential of CDs with the versatility of nanotechnology to generate innovative materials that are tailored for specific applications by including CDs into systems such as nanoparticles, nanofibers, and nanocomposites. CD-modified nanoparticles have emerged as a significant innovation in modern drug delivery methods. By attaching CDs to the surface of nanoparticles, researchers may significantly improve the stability and drug-loading efficiency of encapsulated medications. One well-known example is the use of gold nanoparticles functionalised with β -CD in targeted cancer treatment. The hydrophobic pocket of γ -CD can effectively encapsulate anticancer medications such as doxorubicin in these systems, preventing early degradation and ensuring precise delivery to tumour cells. This ingenious combination reduces unwanted side effects while simultaneously boosting the medication's therapeutic performance, making cancer treatment safer and more successful.

CDs in Environmental Remediation

CDs have also received a lot of interest in the field of environmental remediation because they provide practical solutions for pollution reduction and sustainable resource management. Because of their unique ability to form inclusion complexes with hydrophobic and nonpolar molecules, they may effectively gather and remove a range of organic contaminants from polluted water and soil, including pesticides, synthetic dyes, and polycyclic aromatic hydrocarbons (PAHs). Because of this remarkable property, CDs are helpful tools for creating cleaner, more sustainable environments. Many studies have been conducted on the ability of CDs, particularly β -CD, to eliminate organic pollutants from soil and water. Their unique hydrophobic cavities allow them to capture and isolate dangerous substances, reducing their impact on the environment and making removal easier. For example, CDs can form inclusion complexes that make polycyclic aromatic hydrocarbons (PAHs), hazardous pollutants created during incomplete combustion, more soluble. Microbes may break them down more quickly due to their increased solubility, which would significantly increase the effectiveness of bioremediation and speed up the cleanup of contaminated regions. Furthermore, CDs have demonstrated remarkable effectiveness in removing pesticide contaminants from agricultural soils and rivers. For instance, atrazine, a popular herbicide that contaminates water systems, has shown significant promise when encapsulated in α -CD. Similarly, grafting β -CD onto cellulose increases its binding efficiency and durability, resulting in a potent sorbent material that can remove pesticide residues from complex environmental samples. Through this inclusion complex development, CDs help remove atrazine from polluted regions, therefore minimising its detrimental impacts on ecosystems and human health. Additionally, this method helps safeguard essential water resources by removing the herbicide from the surface environment and stopping it from leaking into groundwater. (86)

Applications of CDs in Drug Delivery Systems

Oral drug delivery system

CDs have been employed as an excipient to move medications through an aqueous medium to the gastrointestinal tract's lipophilic absorption surface; in other words, complexation with CDs has been utilised to increase the pace at which weakly water-soluble medications dissolve. In this context, hydrophilic CDs have proven especially helpful. Additionally, CD-based rapid dissolving complexes have been developed for sublingual and buccal delivery. This kind of medication delivery method avoids systemic and hepatic first-pass metabolism while also rapidly increasing the systemic drug concentration (87).

Rectal drug delivery system

According to recent research, the rectal mucosa may be utilised as a delivery route for medications that taste bitter and nauseating, have a high first-pass metabolism, and break down in the pH of the gastrointestinal tract. It is the best way to provide medication to patients who are unconscious, as well as to young toddlers and babies. Nevertheless, the rectal mucosa provides a relatively small region for drug absorption, leading to an unpredictable release of medications. Many excipients have been used to address these issues, and CDs have proven to be particularly helpful (88).

Transdermal drug delivery system

A more advanced and dependable method of delivering medication via the skin for both local and systemic impact is the transdermal drug delivery system. CDs should have the following qualities to be utilised as excipients in transdermal medication delivery systems:

They should:

1. Be therapeutically inert;
2. Not interfere with the skin's natural defences against heat, humidity, radiation, and other potential insults;
3. Do not change the skin's pH;
4. Not interact with any skin component; and 5. not irritate the skin (67).

Controlled and targeted drug delivery system

While the majority of early research on CDs focused on their ability to increase the pace at which pharmaceuticals are released from dosage forms, more recent research has also examined CDs as carriers in controlled-release drug delivery systems. Among the several CD derivatives, hydrophilic compounds have been used to increase the rate of drug release, while hydrophobic derivatives, such as alkylated and acylated derivatives, have been used to extend the rate. Recently, Kumar et al. [2003] created a bilayered melatonin tablet in which CDs were used to boost the drug's release rate in the fast-release half and cellulosic polymers were used to slow it down in the slow-release portion (89).

Gene and oligonucleotide delivery

Nonviral vectors for gene delivery were created in response to the toxicity and immunogenicity of viral vectors. In addition to vector systems based on plasmids or viruses, "naked" nucleotide derivatives have also been studied for potential application as therapeutic agents via various delivery methods. In an effort to identify the best carrier for the delivery of therapeutic nucleic acids, gene delivery scientists are now evaluating CD molecules. However, before using CDs in therapeutic settings, their limitations, such as CD-associated toxicity (e.g., DM- β -CD), must be taken into account (90).

The Use of CDs in Various Diseases

Niemann-Pick Disease Type C (NPC)

The accumulation of cholesterol and other lipids within cells, especially in the brain, is a hallmark of Niemann-Pick disease type C (NPC), a rare hereditary condition. Nerve cells sustain gradual and serious damage as a result of this aberrant buildup. The FDA and EMA have authorised hydroxypropyl- β -CD (HP- β -CD) as an orphan medication to treat this. According to preclinical research, HP- β -CD efficiently aids in the removal of extra cholesterol from neuronal cells, facilitating its movement and elimination from the brain and providing a potentially useful treatment option for NPC (91). According to preclinical research, mice given HP- β -CD intravenously showed no discernible therapeutic benefits, suggesting that this delivery method has limited effectiveness (92). Researchers came to the conclusion that HP- β -CD cannot pass across the blood-brain barrier, as a result, leading to the more intrusive delivery approach of intrathecal injection. In mice and cats with Niemann-Pick type C illness, HP- β -CD was found to slow down the course of neuronal damage when given intrathecally (93,94). Clinical studies have shown that HP- β -CD can assist individuals with Niemann-Pick type C illness in slowing down the disease's course, reducing neurological symptoms and improving their quality of life (95). Furthermore, individuals between the ages of 1.5 and 20 have been demonstrated to stabilise with long-term intrathecal HP- β -CD therapy. However, the illness stage at diagnosis has a significant impact on the therapy's overall efficacy (96).

Alzheimer's Disease

In Alzheimer's disease (AD), abnormal protein buildup, especially β -amyloid, leads to the formation of plaques in the brain that harm neurons and impair cognitive function. Elevated cholesterol is also considered a potential risk factor since it promotes the absorption of β -amyloid peptides by neurons. CD usage has demonstrated potential in lowering these detrimental accumulations. Preclinical research suggests that CDs may help prevent or reduce the buildup of amyloid plaque by promoting its clearance or inhibiting its formation. Additionally, CDs can enhance the stability and solubility of drugs used to treat Alzheimer's symptoms, such as acetylcholinesterase inhibitors. For instance, crocetin and γ -CD (γ -CD) combine to form an inclusion complex that may be administered across the blood-brain barrier as a potential therapy for AD. This substance not only makes the medication more soluble and bioavailable, but it also doesn't damage healthy brain cells. CDs also enhance the water solubility and antioxidant properties of compounds like resveratrol and oxyresveratrol by forming inclusion complexes. In particular, the oxyresveratrol- β -CD combination demonstrated strong antioxidant qualities and decreased histone deacetylase activity in rats with AD. Additionally, it has been demonstrated that this complex cures the cognitive and behavioural impairments associated with Alzheimer's disease.

Parkinson's Disease

Parkinson's disease is characterised by an abnormal accumulation of α -synuclein, a protein that, when present in excess and becomes toxic, degenerates dopaminergic neurones. Research suggests that CDs may protect neurons by preventing α -synuclein buildup. Moreover, the use of CDs such as β -CD and HP- β -CD in levodopa formulations permits controlled drug delivery, enhancing stability and bioavailability while decreasing fluctuations in therapeutic efficacy and potential side effects. Additionally, studies have shown that administering HP- β -CD subcutaneously twice a week for two weeks significantly reduced the loss of dopaminergic neurons in mice with experimentally induced Parkinson's disease.

Cystic Fibrosis

Thick, sticky mucus builds up in the lungs of people with cystic fibrosis, leading to recurrent infections and serious breathing issues. To improve the direct administration of inhaled antibiotics, including tobramycin, to the lungs, CDs are used. CDs make it possible to treat chronic bacterial infections that are frequently observed in people with cystic fibrosis more successfully by improving the solubility and stability of these medications. By improving tobramycin's distribution inside the lungs and lowering the frequency of doses needed, the formulation of tobramycin with CDs enhances the effectiveness and convenience of therapy. Furthermore, methyl- β -CD has been shown in studies by Gunasekara to assist in restoring the normal function of airway surfactants in people with cystic fibrosis (97).

FUTURE TREND OF CDs

Future CD applications have a lot of intriguing potential, including the creation of new derivatives and new uses for already-existing ones. Even though some drug-CD complexes have been commercialised, they have been linked to low-molecular-mass medications. Additionally, some studies suggest that CDs may be helpful for drug delivery using protein, peptide, and oligonucleotide dosage forms or for formulation enhancements. HPCD and other hydrophilic and lipophilic CD derivatives inhibit lyophilisation-related aggregation of interleukin-2 and agitation-associated aggregation of other proteins, including human growth hormone. CDs can also be used to stabilise insulin solutions against chemical and physical deterioration. The capacity of CDs to stabilise protein structure through interactions with accessible hydrophobic amino acid residues appears to be the foundation for these improvements. CDs are still regarded as novel excipients with special functions as drug delivery carriers and anti-aggregation agents, despite the fact that they are already found in around 56 pharmaceutical formulations. Research over the last ten years has demonstrated that CDs, particularly their inclusion complexes, can spontaneously form nanoparticles. In some cases, these nanoparticles can then further assemble into microparticles. When they come into contact with lipophilic medications, this behaviour becomes more noticeable. These findings have changed the focus of pharmaceutical research pertaining to CD and created new avenues for creating sophisticated formulations. In the fields of biomedicine and nanomedicine, CDs are frequently referred to as "dream molecules" due to their remarkable versatility. They are crucial in several cutting-edge applications, such as drug delivery using nanocarriers, the creation of innovative biosensors for biological target detection, and participation in molecular diagnostics and biorecognition. Additionally, their unique characteristics highlight their great potential in next-generation medical technology by making them helpful in tissue engineering, gene therapy, and medical imaging. CD surface modification or heat attachment can be very advantageous for medical devices such as bone implants, vascular grafts, prostheses, and catheters. Research examining these applications has noticeably increased as a result of this potential. Only a small number of therapeutic

nanosystems have been fully investigated, and most of this research is still in the early proof-of-concept stage. It is still very difficult to close the gap between these encouraging test results and their effective clinical use. CD-based drug delivery is a fast-evolving topic, with ongoing research aimed at creating novel uses, chemical changes, and enhanced formulations. It is anticipated that future developments will result in more individualised and accurate treatments by developing CD-incorporated customised drug delivery systems. Using molecular biology and nanotechnology, researchers are working to develop CD-based carriers that may target diseased regions directly, minimising adverse effects and improving therapy outcomes overall. Additionally, "smart" CD-based formulations that may respond to pH, temperature, light, or enzyme activity are the focus of study. These devices increase therapy efficacy and patient adherence by facilitating controlled and on-demand drug administration. CDs also hold considerable potential for the delivery of gene therapies like siRNA and mRNA by improving their stability and cellular absorption. Their use in non-viral gene delivery systems might be a breakthrough in the management of cancer, genetic disorders, and viral diseases. CDs are being studied for the treatment of neurological, cardiovascular, and respiratory conditions in addition to their well-known roles in increasing solubility and enabling controlled drug release. Their unique ability to interact with lipophilic substances makes them viable candidates for regulating cholesterol levels and aiding in the removal of pollutants. Despite these promising developments, very few drugs based on CD have reached the market. Thus, the primary goal of future research should be to translate laboratory results into clinical applications. This might be accomplished by ensuring safety, optimising large-scale production, and obtaining regulatory approval for innovative medicinal compositions (97).

CONCLUSION

One class of cyclic oligosaccharides that is both biocompatible and versatile is called CDs (CDs). They may create inclusion complexes with a range of guest molecules because of their unique molecular topologies. These complexes significantly improve the safety and therapeutic efficacy of poorly water-soluble drugs by increasing their bioavailability, stability, and solubility. Chemical modifications, including methylation, hydroxypropylation, sulfation, and acylation, which enable targeted administration, controlled release, and improved pharmacokinetic performance, have further expanded the usage of CDs. Amphiphilic and stimuli-responsive CD derivatives have opened up new avenues for gene transfer, smart drug delivery, and nanomedicine by fusing hydrophilic and hydrophobic characteristics with environmental sensitivity. Furthermore, by providing useful information on host-guest interactions, advances in computer modelling, such as molecular docking, molecular dynamics, and QSAR analysis, have enabled the logical design of CD-based formulations. Pharmacokinetic and toxicological assessments show that natural CDs and many of their derivatives are generally safe, biodegradable, and well-tolerated; nonetheless, concentration and delivery technique remain important. Their regulatory recognition by major pharmacopoeias demonstrates their importance as pharmaceutical excipients. All things considered, CDs have evolved from simple solubilising agents into adaptable platforms for improved drug administration, biomaterial synthesis, and diagnostics. It is anticipated that future studies combining biotechnological synthesis, molecular modelling, and artificial intelligence will further optimise CD-based systems for sustainable pharmaceutical applications and precision medicine.

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Declaration of generative AI and AI-assisted technologies in the manuscript preparation process:

During the preparation of this work, the author(s) used ChatGPT to avoid grammatical mistakes and correct statements. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

List of Abbreviations

AD	Alzheimer's Disease
AI	Artificial Intelligence
API	Active Pharmaceutical Ingredient
BNZ	Benznidazole
BS	Binary System

CD	Cyclodextrine
CGTase	CD Glycosyltransferase
CUR	Curcumin
DM- β -CD	Dimethyl-Beta-CD
DSC	Differential Scanning Calorimetry
DTA	Differential Thermal Analysis
EMA	European Medicines Agency
EP	European Pharmacopoeia
FDA	Food and Drug Administration
GRAS	Generally Recognised as Safe
HPCD	Hydroxypropyl-CD
HPLC	High-Performance Liquid Chromatography
HP- β -CD	Hydroxypropyl-Beta-CD
HP- γ -CD	Hydroxypropyl-Gamma-CD
IC	Inclusion Complex
LD50	Median Lethal Dose
MD	Molecular Dynamics
MIC	Minimum Inhibitory Concentration
NMR	Nuclear Magnetic Resonance
NPC	Niemann–Pick Disease Type C
PEO	Poly (ethylene oxide)
P-gp	P-glycoprotein
QSAR	Quantitative Structure–Activity Relationship
RM- β -CD	Randomly Methylated Beta-CD
SB- β -CD	Sulfobutyl Ether-Beta-CD
USP/NF	United States Pharmacopoeia/National Formulary
UV-Vis	Ultraviolet–Visible Spectroscopy
α -CD	Alpha-CD
β -CD	Beta-CD
γ -CD	Gamma-CD

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