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Evaluation and notability of cyclodextrin-A review

M Jude Jenita
Department of Chemistry, Government College of Engineering, Bodinayakannur, Theni, Tamil Nadu, India

Abstract
Cyclodextrins (CDs) are a type of cyclic oligosaccharide made up of glucopyranose subunits which is an effective chelating agent at the molecular level that are connected together (1, 4).Their supramolecular structure resembles that of cryptands, calixarenes, cyclophanes, spherands, and crown ethers.Since they are large in size and contain a large number of hydrogen donors and acceptors, they do not pass-through lipophilic membranes in general. DSC, FTIR, XRD, and SEM studies confirms the production of inclusion complexes. The breakthrough in their applications, as well as the features of the various CDs is reviewed in this paper. Small amounts of CDs can be mixed with the target substance to be stabilized to produce their beneficial effects. They can form stable inclusion complexes with sensitive lipophilic nutrients as well as flavour and taste components. The toxicity of CDs has also been studied, with findings indicating that they are harmless when consumed orally. A review of current legislation was also done, with the results indicating that CDs are becoming more accepted as food additives in general. As a result of customer demand for healthy and functional items, CDs have better scope to lead the future.

Keywords: Cyclodextrins, Inclusion complex, drug delivery, applications, nano, food, cosmetic

Introduction

The physical and chemical features of the guests are positively affected by encapsulation in the hydrophobic cavity of CDs during the formation of inclusion complexes. α-, β-, and γ-CDs are the three major natural CDs that vary in their ring size and solubility. When compared to α- and β-CDs, γ-CDs tend to have huge internal cavity and high solubility, which could produce better characteristics. As a result, many scientists are interested to explore more on γ-CDs. Takada M. *et al*. 2003, [1, 2, 3, 4] and few other authors' have attempted to adjust the properties of glucosyltransferase (CGT) in order to boost γ-CD formation. Through inclusion complexation, cyclodextrins are utilised to improve the solubility of water insoluble medicines. Natural cyclodextrins have been widely employed in this application. CDs can be made by degrading starch enzymatically with the enzyme glucosyltransferase (CGTase) [5]. Many microbes, including Bacillus maverans, generate CGTase. The "lock and key" connections between enzymes and substrates can be traced back to the fundamental principles of host–guest chemistry. Upon interaction of CDs with drug tends to produce medicinal values and in turn forms supra molecular in nature [6]. According to French *et al*., CDs are cyclic oligosaccharides made up of numerous D-(+)-glucopyranose units organised in a saddle.Freudenberg and his colleagues found the cyclic structure of α- and β- dextrin. They're built up of glucose units that are joined by (α-1,4). CDs with fewer than 6 glucopyranose units cannot be produced due to steric hindrances [7]. Analytical applications, of CDs appear to be endless to quote of few CDs finds wide range of application in medical domine, Pharmaceutical industry, food processing, textiles, and many more.

Structure

Cyclodextrins are a collection of structurally related natural compounds that are generated when cellulose is digested by microorganisms. These cyclic oligosaccharides have a lipophilic inner chamber and a hydrophilic outer surface and are made up of (α-1, 4)-linked α-D-glucopyranose units. The cyclodextrins have the shape of a truncated cone rather than perfect cylinders due to the chair conformation of the glucopyranose units. The hydroxyl functions of the sugar residues are orientated to the outside of the cone, with the primary hydroxyl groups at the narrow edge and the secondary hydroxyl groups at the wider edge [8].The glucose residues' skeletal carbons and ethereal oxygen line the centre cavity, making it lipophilic. The polarity of the cavity is assumed to be similar to that of an ethanolic aqueous solution. α-, β-, and γ-cyclodextrin have six, seven, and eight natural glucopyranose units, respectively. Natural cyclodextrins, particularly β-cyclodextrin, have low water solubility, which means that complexes generated when lipophiles interact with them can have low solubility, resulting in solid cyclodextrin complexes precipitating from water and other aqueous solutions.In reality, natural cyclodextrins have a substantially lower water solubility than equivalent acyclic saccharides [9]. This is assumed to be due to the crystal state's relatively strong intermolecular hydrogen bonding. CDs have hydrophobic voids and hydrophilic surfaces and are joined by α-1.4- glycosidic linkage. Chemical reactions can be used to build polymers with various shapes and functions thanks to the unique structure of CDs.

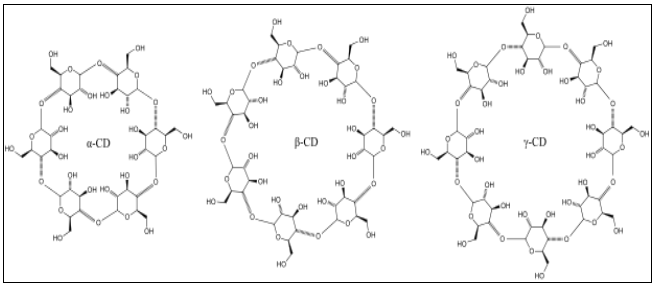

Fig 1: Chemical structure of the three main types of Cyclodextrins.

Inclusioncomplexs

CDs can develop apolar-apolar contacts as a result of their structure, enclosing other a polar molecules that may undergo structural modifications and functioning as molecular capsules. X-ray diffraction demonstrated the formation of an inclusion complex between α-CD and iodine that revealed the idea of one new molecule which resulted to build a novel chemistry termed as adduct, inclusion complex. Native cyclodextrins, cyclodextrin derivatives, and inclusion complexes have received a lot of attention because of the unique structure and selectivity of the cyclodextrin cavity, and are widely used in medicine, food, the environment, cosmetics, chemical analysis, separation technology, catalysts, and other fields [10]. If the guestmolecule is minimal, it will readily slip through the cavity, resulting in a weak or non-existent connection. It is also feasible to make complexes with molecules much larger than the cavity, although only a few groups or side chains can fit inside the CD cavity. The polarity of the "guest" molecule has an impact on the inclusion complex's stability. The type of media used for complexation, on the other hand, has a considerable impact on stability. Furthermore, while some systems (Figure 2) use a 1:1 ratio between the substrate and the CD molecule, 1:2 and 2:1 complex forms are also possible.

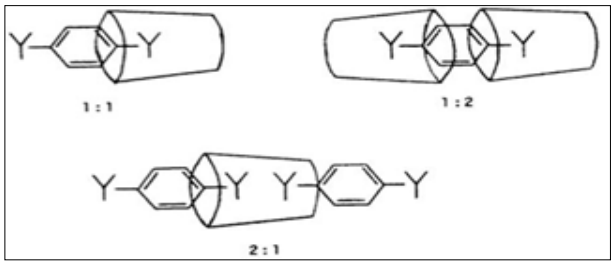

Fig 2: Complexes of α-CD and 1,4-disubstituted benzene

Depending on the nature of the "guest" molecule, the rigid structure of CDs "host" translates into a well-defined and differentiated inclusion complex. CDs are attractive host molecules because they are non-toxic and offer a wide range of functionalities [11]. Finally, the inclusion complex's stability reduces as the temperature rises. The temperature dependency of the equilibrium constant can be used to calculate enthalpy and entropy changes.

Characterization Techniques of Inclusion Complex

1. Scanning Electron Microscopy: It specifies crystallization or amorphous state of the active drug and the complex.

2. Infra-Red (IR) spectroscopy: It specifies the stretching vibration of the group involved in the formation of hydrogen bonds with the cyclodextrin-active drug complex causes absorbance bands to shift to a lower frequency, increase the intensity, and widen the band [12].

3. pH-Potentiometric Titration:

When an active medication possesses a prototropic function, binding to Cyclodextrin increases the pka value of an acidic drug molecule while decreasing the pka value of a basic drug molecule.

Method of drug delivery system

A pharmaceutical formulator must be aware of the benefits and drawbacks of each excipient utilized in a product's formulation. Excipients are chosen depending on the medication's physicochemical qualities (such as solubility and stability), the route of distribution (such as tablet, parenteral solution, and so on), and the intended pharmacokinetics (e.g., instant release, sustained release etc.).

1. Oral drug delivery

The influence of cyclodextrins on oral drug absorption can be explained using the Biopharmaceutics Classification System (Table 1) [13]. With a 90 percent absolute bioavailability, Class I medications are relatively water soluble. These medicines move fast through the aqueous diffusion layer and are lipophilic enough to partition into the gastrointestinal mucosa before passing. In general, hydrophilic cyclodextrins have little effect on the bioavailability of Class I medications.Class II medicines have low water solubility, limiting oral absorption to a slow rate of dissolution. CDs in combination with solution quickly pass through cellular membranes, resulting in a 90 percent absolute bioavailability. Resulting medicines' are water-soluble cyclodextrin complexes will improve mucosal surface diffusion, enhancing oral bioavailability.

Table 1: Analysis of inclusion complexes for species

Drug	Cyclodextrin	Formulation	Species
Class I			
Piroxicam	βCD	Tablet, capsule and oral suspension	Human, rat, rabbit
Class II			
Carbamazepine	DMβCD	Oral powder and solution, tablet	Rabbit, dog, rat
Digoxin	γCD	Tablet	Dog
Spironolactone	βCD, γCD, DMβCD, SBEβCD, HPβCD	Oral solution and powder	Rat, dog
Tolbutamide	βCD, HPβCD	Suspension, oral powder	Rabbit, dog
Class III			
Acyclovir	βCD	Oral suspension	Rat
Diphenhydramine	HCl DMβCD, HPβCD	Solution	Rat
Class IV			
Cyclosporin A	DMβCD	Oral suspension	Rat

Despite the fact that Class III medications are water soluble, their size and/or hydration make them difficult to pass through cellular membranes. As a result, generating hydrophilic drug/cyclodextrin complexes will diminish the capacity of dissolved drug molecules to partition from the aqueous exterior into the gastrointestinal mucosa, rather than increasing drug bioavailability in the mouth. Water-insoluble Class IV medicines have a hard difficulty passing

through lipophilic cellular membranes. Cyclodextrins can improve the water solubility of some major lipophilic substances, resulting in increased drug availability at the mucosal surface. This usually results in increased oral bioavailability [14]. Table 1 shows several cyclodextrins in oral formulations that have been studied *in vivo* in people and/or animals, as well as the effect of cyclodextrin complexation on absolute bioavailability when compared to a cyclodextrin-free formulation.

2. Nasal drug delivery

Cyclodextrins are commonly utilised in nasal preparations to boost the water solubility of lipophilic medicines. Lipophilic cyclodextrins, on the other hand, can interact with biological membranes and act as penetration intensifiers, particularly in the delivery of peptides through the nose [15].Methylated cyclodextrins, in particular, have been shown to be effective absorption enhancers in numerous investigations, which is one of the reasons they are the most investigated cyclodextrine. By incorporating methylation cyclodextrins in the formulation, the nasal bioavailability of insulin in rats was raised from around 0% to 100% [16]. However, human investigations later found substantially reduced insulin bioavailability following nasal administration, and it is well known that nasal medication delivery has large interspecies variability.

3. Inject able drug delivery system

Water, organic solvents, and surfactants are widely used in injectable formulations of lipophilic water-insoluble medicines. In some situations, making a water-soluble prod rug of a lipophilic water-insoluble drug can help to reduce these negative effects. Because cyclodextrins are rapidly excreted in the urine, they can aid in the clearance of lipophilic water-insoluble medicines by the kidneys [17]. Finally, when compared to organic solvents and surfactant formulations, hydrophilic cyclodextrin derivatives such as 2-hydroxypropyl—cyclodextrin and sulfobutylether—cyclodextrin are relatively non-toxic., Hence this drug delivery system have no effect on the intrinsic pharmacokinetics of drugs, they are increasingly being used in *in vitro* and *in vivo* screening of new pharmacologically active molecules.

4. Dermal drug delivery

Drug distribution across aqueous diffusion layers (also known as aqueous diffusion barriers) is improved by cyclodextrins, but not through lipophilic barriers like the stratum corneum. Cyclodextrins can be used to increase penetration if the medication is released from an aqueous-based vehicle or if the pace of dermal drug delivery is determined by an aqueous diffusion layer on the skin's outer surface.If drug penetration through the lipophilic stratum corneum is the most important rate determining factor, cyclodextrins will not be able to improve drug delivery [18]. Cyclodextrins do not improve medication distribution from non-aqueous carriers in general.

Cyclodextrine Complexation with Anticancer Drugs

Chemotherapy for cancer has a limited therapeutic effect, especially in the case of recurring and metastatic disease [19]. A potential anticancer agent has low bioavailability, a short half-life *in vivo*, intestinal and liver cytochrome P450 (CYP3A4) and P-glycoprotein (P-gp) affinity, poor intestinal permeabilities, and severe dose-dependent side effects.

Table 2: Complexation of various anticancer drugs with cyclodextrin and their derivatives.

S. No	Drug	Use	Cyclodextrin	Method	Outcome
1	9-Nitro camptothecin	Aden carcinoma	HP-*β*-CD	Colyophilization	Significant improvement in antitumor activity and reduction in toxicity
2	Methotrexate	Malignant Melanoma and Cutaneous Melanoma	*β*-CD HP *β*-CD	Neutralization	Enhancement of aqueous solubility and bioavailability
3	Lonidamine	Carcinoma of Prostate cancer	PM-*β*-CD	Physical mixture	Enhancement of solubility
5	Imatinib	Chronic lymphocytic leukemia	*β*-CD, RM *β*-CD	Freeze-drying	Enhancement of solubility

Cyclodextrine-Based Nano carrier of Anticancer Drugs

Nanotechnology and cellular/molecular biology advancements have aided advancements in cancer chemotherapy and gene therapy, with the hope of avoiding toxic doses of nonspecific drugs. Innovative delivery systems or administration schedules can lead to a low cost, very efficient therapy with minimal/less intricacy [20, 21]. Nanoparticles, which are 100–10,000 times smaller than human cells, have a unique interaction with bimolecular chemicals that could aid cancer diagnosis and treatment. The EPR effect, which is generated by increased vascular permeability and reduced lymphatic function in tumors [22, 23], is used by liposomes, macromolecular carriers, and nanoparticles to target treatment to the tumour.The majority of cytotoxic chemotherapy medicines travel all over the body, harming both normal and malignant cells [24]. Figure 3 depicts the influence of EPR on tumour targeting. EPR refers to the process through which a non-targeted high-molecular-weight medication or prod ruggather in tissues with increased vascular permeability, such as irritant regions and cancer. The EPR effect enables nanotechnology-based delivery methods to passively reach tumors' via leaky vasculature [25, 26]. The notion of dual approach, which includes combining two separate techniques in a single delivery system, is used to create cyclodextrin-based nanocarriers. This involves two aspects: first, the anticancer agent is complexed with appropriate cyclodextrin, and second, the complexed drug is encapsulated inside a carrier.

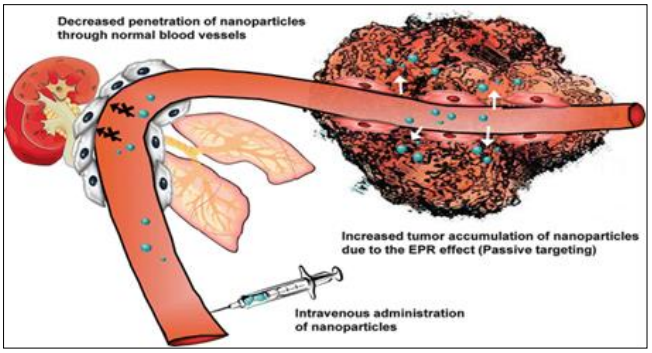

Fig 3: Role of EPR effect in Cancer Therapy

Encapsulating chemotherapeutic anticancer medications in newly created, multifunctionalized cyclodextrin-based carriers would be a huge step forward in this tough field. A higher dose of cyclodextrin could be harmful. CDs given to parents intravenously evaporate fast from the systemic circulation and are excreted in their entirety by the kidneys [27]. CDs are transmitted to the kidneys, liver, urinary bladder, and other physiological tissues when they are delivered. Antineoplastic medicines encapsulated in carrier vesicles were shown to have less drug-induced side effects and improved antitumor effectiveness.

Applications of Cyclodextrine in food Industry

CDs are hygroscopic, hence they are largely used in foods products for the encapsulation of chemicals of interest and the enhancement of water retention [28, 29]. CDs have been employed for a range of applications, including increasing organoleptic quality (full or partial elimination of unpleasant flavors/odors), extending food shelf life, component sequestration, and Pickering emulsions.

1. Improving Sensorial Qualities

1.1 Color

Food colour is a significant indicator of food quality since it is the first quality parameter that buyers assess [30]. By enhancing the solubility and chemical stability of colouring chemicals, CDs can be used to adjust food colour (natural ones and colouring components produced during food processing). By complexing with numerous substrates or cofactors (e.g., chlorogenic acid, polyphenols, cinnamic acid, Cu^{2+}), they can prevent pro-browning polyphenol-oxidase processes [31, 32]. α-, β-, and γ-CDs are often used to improve the colour of various juices.

1.2 Flavor

Flavoring compounds have a long history in food, despite the fact that their direct usage has a number of drawbacks, including high volatility and susceptibility to heat and light. Part of these annoyances can be alleviated by encapsulating food flavours on CDs, which is a common and straightforward way to preserve stability [33]. Each taste component in a multicomponent food system is effectively protected by CD encapsulation from whatever process it has been exposed to (freezing, thawing, and/or microwaving).This component is critical since flavoring ingredients normally contain a large number of compounds, therefore it's intriguing that all of these molecules can become part of the complex without their organoleptic properties changing [34].

2. Against Light-Induced Decomposition

CDs can also be used to preserve chemicals against deterioration caused by causes like light, heat, or oxidation. Furthermore, when the cavity of a CD is filled, other molecules are blocked from entering, ensuring that no undesired reactions occur. CDs have been used to safeguard vitamins and pharmaceutical goods with easily oxidizable double bonds [35, 36], for example (e.g., prostaglandins) Hydroxypropyl-β-CDs have been shown to protect peptides from hydrolysis and, as a result, loss of capacity.

Other Applications

1. Bioconversion and Fermentation

Bioconversion and fermentation processes are frequently hampered by the toxic or inflammatory effects of the substrate or product in the catalyst. Furthermore, because most organic substrates are lipophilic, which means they have low water solubility and the catalyst is usually more active, the medium is crucial. As a result, only a small fraction of the substrate is accessible to the biocatalyst [37, 38].To address these issues, a variety of strategies have been used. CDs have been utilised in several research to increase the efficiency of chemical manufacturing. CDs, for example, improved the efficiency of spiramycin synthesis.

2. Environment

The potential of these compounds to solubilize organic pollutants, improve and eliminate organic wastes and toxic metals from the environment plays a major role in the environmental area. CD studies and novel applications are predicted to expand in this field in the next years. Because they do not generate new pollution, β- CDs have been employed in the adsorption of pollutants [39]. Water treatment has been investigated using CDs nanosponge adsorbents. It is modified with adsorbent nanomaterials to achieve this (nanotubes made with carbon, titanium oxide, and silver nanoparticles). The results showed that these technologies are effective at eliminating pollutants from water.

Future Perspectives

CDs and their derivatives finds wide range of applications in a variety of industries (food, cosmetics, and medicines), especially in food industries, their use has grown in recent years. The capacity to produce host–guest complexes with a wide range of chemicals is the main reason for, these applications [40]. In addition, by using inclusion complex concept, sensory characteristics can be improved and microbial contaminations can be avoided. They may also be employed without harming human health due to their low toxicity, resulting in products that are not only healthier and more functional, but also less perishable. Reviewing cases of sold CDs-based food products revealed the significance of CDs technology in the food industry. Due to their low toxicity, ability to retain, orient, conceal, change chirality, and isolate guest molecules, CDs are an unusual sort of building block in creative molecular architecture. All of these features allow them to be used as extenders, chelating agents, and other multipurpose technological instruments in addition to excipients. In the last decade, their use in food, agriculture, medicinal items, and chromatographic procedures has skyrocketed. Due to their propensity to absorb whole molecules or parts of them into their cavity, CDs are also being used as encapsulation agents at the molecular level. They act as a key to a variety of future capsule formulation solutions. However, cost reduction and production efficiency are two major issues in order to carry out all of these procedures. There have been significant advancements in this area in recent years, indicating that their use is likely to grow. Furthermore, various investigations have shown that CD derivative formulations are more stable than those that are traditionally produced.

Conclusion

In the last decade, CDs finds application in food, agriculture, medicinal items, and chromatographic procedures has skyrocketed. Due to their unique design, CDs are a viable alternative for drug development, chiral separations, and as complexing agents Because of their propensity to absorb complete molecules or parts of them into their hollow, CDs are also used as molecular encapsulation agents. They could be the key to a wide range of future capsule formulation options. They are also predicted to be used in the future due to a variety of other benefits, such as enhanced solubility, stability against light, heat, and oxidizing environments, and lower volatility. However, cost reduction and production efficiency are two major issues in order to carry out all of these procedures. There have been significant advancements in this area in recent years, indicating their use is likely to grow. Furthermore, various investigations have shown that CD derivative formulations are more stable than those that are traditionally produced.

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