International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

A Systematic Review on Cyclodextrin: A Versatile Tool for Enhanced Formulations and Diverse Applications

Ankit Choudhary[1], Anup Jyoti Roy[2], Kundan Dutta[3], Jon Jyoti Sahariah[4], Hans Raj Bhat[5]

[1,3,4,5]Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh, Assam, India, 786004
[2]Girijananda Chowdhury Institute of Pharmaceutical Sciences, Girijananda Chowdhury University, Guwahati, Assam, India, 781017

Abstract

Cyclodextrins (CDs) are cyclic oligosaccharides that have gained significant attention in various industries due to their unique structural properties and versatile applications. This study aims to provide a comprehensive overview of the types, formulation techniques, and wide-ranging applications of cyclodextrins. It explores the formulation techniques used to incorporate cyclodextrins into different matrices. *Cyclodextrin Complex Formation, Cyclodextrin-Based Nanostructures* involves the encapsulation of guest molecules within the hydrophobic cavity of cyclodextrins. The study presents a broad range of applications where cyclodextrins have demonstrated their utility. The pharmaceutical industry extensively employs cyclodextrins as excipients to enhance drug solubility, stability, bioavailability, and taste masking. Additionally, CDs find applications in the food and beverage industry for flavor encapsulation, preservation, and controlled release of bioactive compounds. They also play a vital role in various fields, including agriculture, cosmetics, environmental remediation, and separation sciences.

Keywords

Cyclodextrin, Complxation, Nanostructures, Mucoadhesive, Bioconvesion, Cosmetic

1. Introduction

Cyclodextrins are non-reducing and oligosaccharides which are composed of glucopyranose units. The α-, β-, and γ-cyclodextrins which contains 6, 7 and 8 units respectively are widely knows. Cyclodextrins have inner cavities which are lipophilic in nature and hydrophilic outer surfaces which make them capable for the interaction with a larger group of guest molecules and ultimately form noncovalent inclusion complexes with the molecules. [1] The cyclodextrins can also alter of different physico-chemical properties of guest molecules; hence they eventually have considerable pharmaceutical potential. [3]. Recently the smallest cyclodextrins which are synthetized, contains 3 and 4 glucopyranose units, while on the other hand the big oligosaccharides which have more than 8 units been also known to be synthesised and are applied for complexation and also as chiral selectors for enantiomeric pharmaceuticals. Cyclodextrin rings can be chemically modified, linked with substituents also other

cyclodextrin rings can be used to build up larger nanostructures. The type and the application of these nanostructures are continuously increasing. Besides the drug complexation, cyclodextrins can form complexes with natural, biological important molecules like phospholipids, cholesterol or other lipophilic molecules. It causes various effects, especially at cellular level or on biological barriers. On the other hand, a cholesterol complexation property of hydroxypropyl-β-cyclodextrin is applied in the treatment of many diseases and was approved as an effect drug. This mini-review gives a summary on the basic complexation, drug delivery and biological properties of cyclodextrins and the cyclodextrin-based nano-scale drug delivery systems. [1]

2. Types of Cyclodextrin

Cyclodextrin Complex Formation

Cyclodextrins are widely used excipients in pharmaceutical formulations also the interest in cyclodextrin research and application is very significant. Cyclodextrins are commonly used to enhance the bioavailability and solubility of poorly water-soluble drugs by complex formation. The drugs having low solubility, high permeability (Class 2 of Biopharmaceutics Classification System) and low solubility, low permeability (Class 4 of Biopharmaceutics Classification System); These drugs belong to the Class 2 (low solubility, high permeability) or Class 4 (low solubility, low permeability) through the cyclodextrins application both their solubility and permeability can be improved [4]. But in this case the improvement possibilities for these properties of Class 4 drugs by the molecule are limited. By increasing the cyclodextrin concentration in a solution, the concentration of dissolved drug can also be increased. [5]

Cyclodextrin-Based Nanostructures

1. Cyclodextrin Associates, Polypseudorotaxanes and Polyrotaxanes

Besides the association of lipophilic drug molecules and drug-cyclodextrin complexes, the aggregation of cyclodextrin molecules is also a known phenomenon [6]. α-, β-, and γ- cyclodextrins form aggregates in concentrated (mM) solutions and bind together via a network of hydrogen bonds as well as via intermediary, bridging water molecules. This phenomenon is known as cyclodextrin aggregation. These wormlike, self-assembled aggregates of cyclodextrins might be called “poly-CD”. The optimal configuration for the neighbouring cyclodextrin ring is the “head-to-head/tail-to-tail” orientation. [7]Mixing of the concentrated aqueous solution of α-cyclodextrin with the polymer polyethylene-glycol (PEG) [8] or β-cyclodextrin with poly(propylene glycol) [9] causes the cooperative threading of the cyclodextrin molecules along a single polymeric chain. These mixtures become turbid and a precipitate is formed, but the process is reversible. The assembly is called polypseudorotaxane [10]. Pegylated molecules maintain their ability to form polypseudorotaxane. Pegylated insulin forms polypseudorotaxanes with alpha- and gamma-CDs, by inserting one or two PEG chains in the CD’s cavity respectively [11] and coumarin linked PEG chains form polypseudorotaxanes with alpha-CDs arranging in supramolecular micelles [12]. If the two ends of the polymer chain are linked to two bulky end groups and the cyclodextrin rings are prevented from dethreading, the structure is called polyrotaxane [13]. It is a mechanically interlocked molecule, like a molecular necklace, where no covalent bonds can be found between the cyclodextrin rings, but the cyclodextrins remain on their axles. Several types of cyclodextrins and water soluble and insoluble polymers were used for the formation of polyrotaxanes and different strategies were established for their synthesis, which was extensively reviewed earlier [14]. Polyrotaxanes are widely used in the formation of drug delivery systems. Both the

CD ring and the polymer chain can be functionalized for the improved efficiency or cellular internalization. Recently α-CD ring was modified with α-D-mannose for the improved mannose receptor mediated endocytosis [15]. Folate-terminated polyrotaxanes were developed by modifying PEG chains and target mitochondrium [16]. Polyrotaxane-based theranostics were also fabricated.

2. Formation of Cyclodextrin Conjugates, Polymers, and Nano sponges

In addition to intermolecular forces, it is also possible to modify the cyclodextrins by functional groups and build up larger structures by covalent bonds. The 2,3,6-hydroxyl groups of the cyclodextrin ring are reactive and can be modified by the ways mentioned below. The hydroxyl groups show different reactivity, the 2,6-OH is the most reactive [17].The modification of the hydroxyl groups can help the extensive usability of cyclodextrins in the pharmaceutical development. The basic methods for the synthesis of modified cyclodextrins are deprotonation, dehydration and condensation. In the case of deprotonation, the reaction of acidic hydroxyl group with a strong base produces an anion which needs to the SN2-type polymerizations. The most common cross-linker, epichlorohydrin, also reacts with the CD-ring by this mode. The dehydration method creates polyethers and polyesters. A typical reaction of cyclodextrins happens with diol or diacid in sulphuric acid solution. The third type is the condensation which means the reaction of cyclodextrins directly with a bi-functional linker such as diisocyanate [18].

3. Mucoadhesive Drug Carriers

Grafted cyclodextrins can ensure improved mucoadhesion of the complex to the absorption areas. rafted cyclodextrins can ensure improved mucoadhesion of the complex to the absorption areas. This modification is useful in sublingual, gastroretentive, or vaginal applications. The best known materials that have mucoadhesive properties are polyethylene-glycol, chitosan, alginate, or molecules having thiol groups [19]. Thiolated cyclodextrins are the smallest mucoadhesive drug carriers, it can be formulated from α–cyclodextrin, β-cyclodextrin, or γ-cyclodextrin [20]. Cysteamine conjugated β–cyclodextrin can be a new promising excipient for oral drug delivery. Itshows a significant buccal mucoadhesion, and increases the solubility of a model drug, miconazole nitrate [21].

3. Structure

Due to their cyclic structure, they are more resistant to enzymatic degradation and non-enzymatic hydrolysis than the linear dextrins, and possess better complexing properties and solubilizing potential [22,23]. Cyclodextrins are cyclic oligosaccharides containing six or more D-(+)-glucopyranose units linked by α-1,4- glycosidic bonds [24]. Cyclodextrins exist in various forms depending on the number of D-(+)-glucopyranose units. α-CD includes six units, β-CD contains seven D-(+)- glucopyranose units, γ-CD has eight, δ-CD has nine and εCD has ten [25]. Larger CDs are also known; for example, ζCD has 11 glucopyranose units, η-CD has 12 and θ-CD has 13 [26]. However, they demonstrate very small yields and poorer complexing properties than natural cyclodextrins [27]. Even the large-ring CDs characterized by more than eight glucopyranose units have less complexation capacity, are more expensive than α-CD, β-CD and γ-CD and are not so significant pharmaceutically [28]. Moreover, the larger cyclodextrins have a smaller cavity than γ-CD because they are collapsed, rather than bearing a regular cylinder-shaped structure [29]

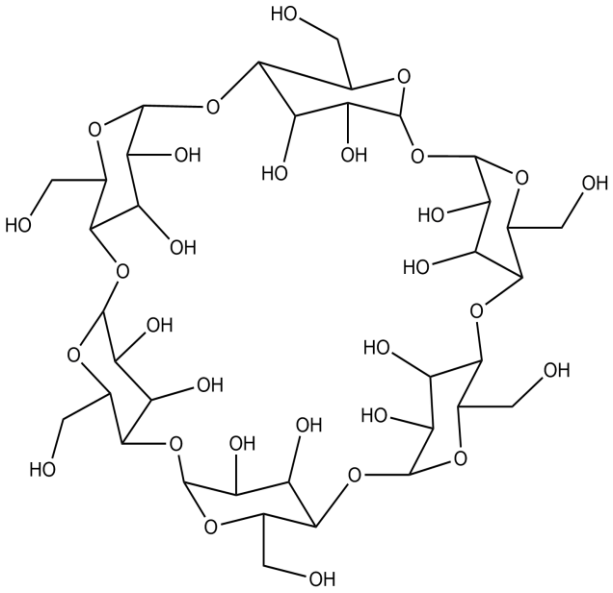

Figure 1: Structure of α-Cyclodextrin

4. Synthesis

By treating starch with enzymes, cyclodextrins are created.[30][31] Along with -amylase, cyclodextrin glycosyltransferase (CGTase) is frequently used. First, starch is heated or made liquified by -amylase, and then CGTase is added to complete the enzymatic conversion. The product of the conversion is a mixture of the three primary types of cyclic molecules, in ratios that are strictly dependent on the enzyme used: each CGTase has its own unique ::: synthesis ratio. CGTases produce mixes of cyclodextrins.[32] The different water solubilities of the three different types of cyclodextrins are used in their purification; the less water-soluble -CD, which is only 18.5 g/l or 16.3 mM (at 25C), can be easily recovered through crystallisation, while the more water-soluble - and -CDs, which are 145 and 232 g/l respectively, are typically purified using pricy and time-consuming chromatography techniques. A "complexing agent" can be introduced as an alternative during the enzymatic conversion process; these agents (often organic solvents like toluene, acetone, or ethanol) form a complex with the desired cyclodextrin and then precipitate. By converting starch into precipitated cyclodextrin, the complex formation increases the amount of this substance in the final mixture of products. Wacker Chemie AG employs specialised enzymes that can specifically create alpha-, beta-, or gamma-cyclodextrin. Since only alpha- and gamma-cyclodextrin can be ingested without a daily intake cap, this is very useful for the food business.

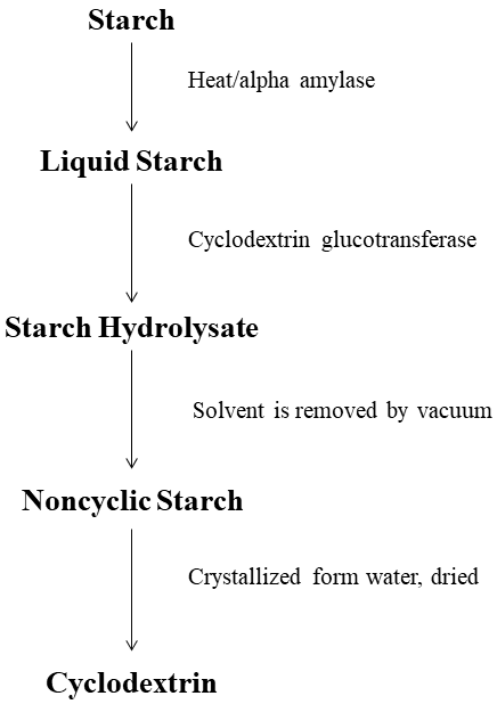

Figure 2: Formation of Cyclodextrin from Starch

Creation of the Inclusion Complexes

CD molecules are characterized by a hydrophilic exterior and a nonpolar, lipophilic central cavity, which can incorporate a variety of molecules, which are poorly soluble in aqueous solution [33]. The interaction between the CD cavity and the hydrophobic part of the drug is the basis of drug – cyclodextrin complexation [34]. Cyclodextrins can create inclusion complexes with organic compounds, which are incorporated into the cavity, resulting in dramatic physical, biological and chemical changes to the drug [35]

One of the most important properties of CDs is its ability to form inclusion complexes through the non-covalent interaction between the cavity and a drug molecule [36]. Inclusion complexes may be created in liquid and solid phases and can be formed with different organic compounds [37]. As long as they are of an appropriate size, organic, inorganic, or even organometallic molecules of cationic, anionic, neutral or radical character can be integrated [38]. Complexes can also be formed with drugs which do not readily complex with other pharmaceutical excipients (e.g., poorly water-soluble drugs of BCS class II and IV) [39]. In addition, the CDs influence other properties of the bound drug molecule; for example, they can suppress the bitterness of pharmaceuticals such as antihistaminic drugs [40]

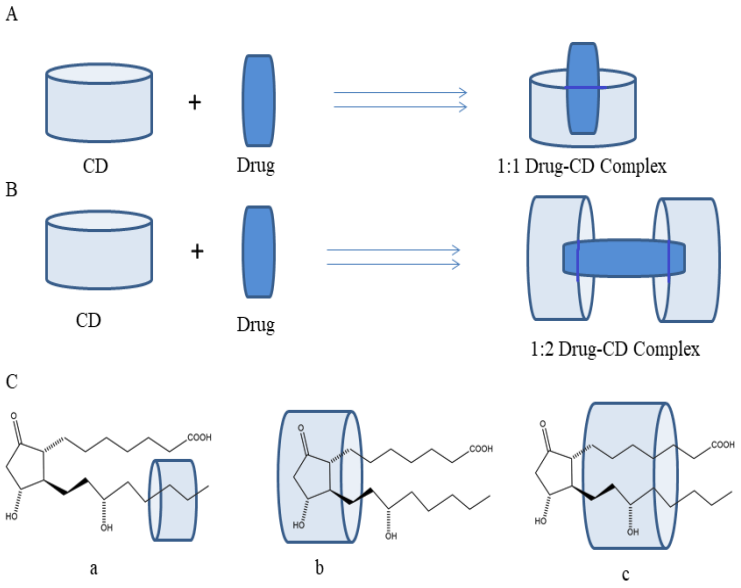

Figure 3: Formation of inclusion complex

Complexation with CDs influences not only the degree of physico-chemical stabilization but also its release kinetics, pharmacodynamic and pharmacokinetic properties [41]. During the formation of the inclusion complex, no covalent bonds are broken or formed. In aqueous solutions, the drug molecule carried in the cavity exists in a dynamic equilibrium with the free drug molecules held in solution [42]. This process is a stoichiometric one, with only one molecule being held within the cavity . Different molecular ratios can be employed when creating complexes between CD molecule and drug molecule. Assuming a 1:1 ratio, one molecule of the drug (D) and one molecule of CD (CD) forms a complex (D/CD). Two parameters play critical roles in the drug release mechanism: the complexation constant (K) and the lifetime of the complex [43].

Drugs can be complexed with both native CDs and modified, ionic CD complexes [44]. For example, the stability and absorption of oral insulin has been improved by complexation with β-CD [45].

CD complexation has widened the availability of insoluble substances as drugs by improving drug release time, dissolution rate, chemical stability and absorption efficiency [46]. These changes influence the oral bioavailability of the drugs and increase their biological activity, which may allow the dosage to be reduced. CDs can convert the physicochemical properties of molecules incorporated in their internal cavity [47]. The cavity includes glycosidic oxygen bridges and hydrogen atoms [48]. The size of the cavity and affinity to specific types of compounds are governed by the degree of polymerization: for example, α-CD has a smaller cavity than the other two primary cyclodextrins. In addition, δ-CD, characterized by larger construction of nine glucopyranose units, has a poorer ability to form complexes than the parent CDs [49].

Regarding the stability of the complexes, the nature of the drug-cyclodextrin interaction is influenced by several types of bonds, such as electrostatic, van der Waal, hydrophobic and hydrogen bonds. The balance between them also influences the stability of the created complexes [50]. However, not every drug can generate stable complexes. Substances, which are very highly soluble in water, may interact with the outer, hydrophilic, surface of the CD . The size of the molecule is also a very important factor [51]. A co-solvent can be used to create inclusion complexes by increasing the stability of the complexes and allowing the guest molecule to be partially dissolved before entry to the cavity ; the co-solvent may

also dissolve excess amounts of guest molecules which are not integrated into the cavity [52]. However, co-solvents may also impair the process of solubilisation, depend on their concentration [53].

5. Methods of Creating Complexes

Solid complexes can be created in various ways, with the physicochemical properties of the complexes depending on the mode of preparation. Four such methods are a physical mixture, kneading, freeze-drying and co-evaporation; however, other techniques such as co-precipitation, heating, damp mixing, extrusion and dry mixing, paste complexation and slurry complexation can also be used [54].

Physical Mixture Method

The required amounts of cyclodextrin and drug are mixed together by trituration in a mortar. After grinding with a pestle, a small volume of ethanol/water mixture is added to wet the contents of the mortar and obtain a paste, which is then passed through an appropriate sieve. The resulting mixture can be stored in airtight containers until further evaluation [55].

Freeze-drying Method

Appropriate quantities of each component (drug and cyclodextrin) are added in water and stirred until complete dissolution. The solutions are then frozen to ensure complete solidification and then freeze-dried for storage [56,57].

6. Modification

The effective methods for selective cyclodextrin modification are then compiled for the creation of novel chiral selectors for various chromatography and electromigration analytical techniques. The modification techniques presented here are well suited to the needs of scientists working on chiral separation using cyclodextrin chemistry [57].

Through modification, the natural cyclodextrins are effective templates for the generation of a wide range of molecular hosts. This makes it possible to tailor a cyclodextrin host to a particular guest, to meet specific requirements in the host-guest complex, and opens the way to diverse new areas of supramolecular chemistry. Metallocyclodextrins, rotaxanes and catenanes, as well as surface monolayers of modified cyclodextrins, are readily obtained. The native cyclodextrins serve as scaffolds, on which functional groups and other substituents can be assembled, with controlled geometry. This results in substantially improved molecular recognition and procedures for chemical separation, including enantiomer discrimination, through guest binding. Access to the gamut of functional groups greatly expands the utility of cyclodextrins in chemical synthesis and provides catalysts which mimic the entire range of enzymic activity. Modifications to the cyclodextrins also lead to a wide range of photochemistry of cyclodextrin complexes, through which the enhancement of guest reactivity occurs; in addition, light harvesting molecular devices and photochemical frequency switches may be constructed. In solution, modified cyclodextrins have been used to construct molecular reactors, as well as molecular, temperature and pH sensors. At surfaces, they form semipermeable membranes and sensor electrodes. Such exciting fields of chemistry, made possible only through modifications to the natural cyclodextrins [58].

Cyclodextrin (CD) can be chemically modified into desired and sophisticated functional molecules. However, poly-modification often produces complicated mixtures, resulting in a low yield of the desired product. As the most promising procedure to solve such problems and to achieve poly-modification of the CD molecule.

There are two primary factors needed to be considered in the chemistry of cyclodextrins for their modify cation: the nucleophilicity of the hydroxyl groups and the ability of cyclodextrins to form complexes with the reagents used [59]. All modify cations of cyclodextrins take place at the hydroxyl groups. Since hydroxyl groups are nucleophilic in nature, the initial reaction, which directs the regioselectivity and the extent of modify cation (mono, di, tri, etc.) of all subsequent reactions, is an electrophilic attack on these positions.

The best method to provide cyclodextrins of any size, shape, and most importantly containing any functional groups is to selectively convert the hydroxyl groups to other desired functionalities. The modify cation of cyclodextrins offers chemists both enormous opportunities and challenges. Hydroxyl groups present at the 2-, 3-, and 6-positions compete for the reagent used, which makes selective modify cation extremely difficult. Of the three types of hydroxyl groups present in CD rims, the most basic (and often most nucleophilic) are those at the 6-position, the most acidic are those at the 2-position, and the most inaccessible are those at the 3-position [60].

Thus, under normal circumstances, the 6-position is easily attacked by an electrophilic reagent. The less reactive reagents will attack the hydroxyl groups more selectively. Thus, more reactive reagents will not only react with hydroxyl groups at the 6-positions but also with those on the secondary side; whereas, less reactive reagents will react more selectively with the 6-position hydroxyl groups. For instance, the less reactive reagent tert- butyldimethylsilyl chloride (TBDMSCl) will react selectively with hydroxyl groups at the 6-positions, while the more reactive reagent trimethylsilyl chloride (TMSCl) will indiscriminately react with all hydroxyl groups in CD rings [61].

7. Application of Cyclodextrin

Drug delivery

More than 30 different licenced medications contain cyclodextrins as a component. Cyclodextrins combine with hydrophobic substances to create complexes because they have a hydrophobic inside and a hydrophilic outside. The U.S. FDA has approved alpha-, beta-, and gamma-cyclodextrin as generally safe. Drugs including hydrocortisone, prostaglandin, nitro-glycerine, itraconazole, and chloramphenicol have all been delivered using these. These medications have solubility and stability thanks to the cyclodextrin. When combined with hydrophobic molecules, cyclodextrin compounds have the ability to permeate body tissues and, under certain circumstances, release biologically active substances. Most often, the loss of hydrogen or ionic connections between the host and guest molecules results from the pH of aqueous solutions changing, which is the basis for the method of controlled breakdown of such complexes. Heat or the action of enzymes that can cleave the -1,4 links between glucose monomers are further methods for disrupting the complexes. Drug mucosal penetration was also demonstrated to be improved by cyclodextrins [62].

Based on cancer treatment

As a result of a variety of pharmaceutical uses, cyclodextrins—one of the safe excipients—are able to create host-guest complexes with fitting molecules due to the special nature of their structure. On the other hand, targeted or responsive materials are appealing therapeutic platforms for the development of next-generation precision medications. Meanwhile, cyclodextrin-based polymers or assemblies can condense DNA and RNA in result to be used as genetic therapeutic agents. Armed with a better understanding of various pharmaceutical mechanisms, especially for cancer treatment, researchers have

made lots of works about cyclodextrin-based drug delivery systems in materials chemistry and pharmaceutical science.

Chromatography

For the creation of stationary phase medium for HPLC separations, cyclodextrins are utilised [65].

Application in food industry

Since CDs are hygroscopic substances, they are largely utilised in foods to encapsulate interesting chemicals and promote water retention [66]. Their use can improve a number of technological benefits, including easier-to-standardize, more uniform formulations. There are many uses for CDs that have been mentioned, including enhancing organoleptic quality (eliminating all or part of undesirable smells or odours), extending food shelf life, component sequestration, and pickering emulsions, among others.

Improving Sensorial Qualities

a. *Colour:* Food colour is the first quality parameter assessed by customers, so it is a key parameter of food quality. CDs can be applied to modulate food colour by increasing solubility and chemical stability of colouring compounds (natural ones and colouring components produced during food processing). They can provoke the inhibition of pro-browning polyphenol-oxidase reactions by complexing with several substrates or cofactors (e.g., chlorogenic acid, polyphenols, cinnamic acid, Cu^{2+}) [67]. Several studies have proven the utility of CDs in food science. For instance, a study found that curcumin and lycopene, two natural colours, can combine with CDs to improve their solubility and lessen the degree of oxidation as compared to the compounds alone. Another investigation using chopped ginger root demonstrated that the sample could be enzymatic browning stabilised for four weeks at 5°C while being vacuum packed by adding 1-4% of CDs. Another investigation using maltosyl-β-CDs in apple and pear juices revealed a similar inhibitory effect. The technique involves stopping ascorbic acid oxidation through an antioxidant effect, which preserves the colour and nutritional value of the food. To enhance the colour of the finished product α-, β-, and γ-CDs (the only CDs approved for use in the food sector by the EU and the US Food and Drug Administration) are frequently employed in the production of various juices.
b. *Flavor:* Despite their long history in food, flavouring chemicals have a number of drawbacks, including high volatility and sensitivity to light and heat. The CDs-based encapsulation of food odours, which is a common and easy way to preserve the stability, can help with some of these problems [68]. This factor is very important since the substances responsible for flavour usually involve numerous compounds, so it is interesting that all these molecules become part of the complex without seeing their organoleptic properties altered. This method can be also used in oils to achieve a manipulability powder that can be added to food [69].
c. *Taste:* One of the things that can cause a food product to be rejected is bitterness. There are, however, certain exceptions to this rule because some items, like coffee, beer, or wine, are anticipated to have a certain level of bitterness. Since complexed compounds cannot interact with taste receptors in the oral cavity, the bitter taste of some drugs may be completely or partially eradicated by using the proper CDs. As only dissolved chemicals have flavour; this kind of taste is not perceives. This technique has been used to analyse the bitter and astringent substances found in

foods and beverages, including nicotine in cigarette smoke, naringin in citrus juice, and chlorogenic acid and polyphenols in coffee [70].

d. *Improving shelf life:* The reactions of oxidation, light-induced reactions, heat-promoted decomposition, self-decomposition, and loss through volatility or sublimation are only a few of the substances present in meals that CDs can guard against. Physically and chemically, the stability of flavours, vitamins, colours, and unsaturated fats is improved by encapsulating CDs with lipophilic food components. As a result, the product's shelf life will be extended [69].
e. *Pharmaceutical Application*: Numerous medicinal applications make use of CDs. Among other uses, CDs have been described in medication formulation to improve bioavailability, solubility, stability, decrease haemolysis, prevent admixture incompatibilities, and act as excipients. It's intriguing to make medications more soluble because the chemical will have better therapeutic efficacy and fewer doses will be required [70]. Many anticancer CDs-based medications are now being scientifically tested. Due to their ability to interface with cellular membranes, CDs have also been utilised to transfer proteins, oligonucleotides, and oligosaccharides, enhancing cellular uptake. Delivering gene-therapeutic drugs using plasmids, viral vectors, and antisense constructs is another use [71]. It has been shown that CDs prolong the half-life of carbamates by protecting them in vitro. Pharmaceutical uses can benefit from its capacity to sequester specific molecules. Neuroactive steroids, which are powerful GABAA receptor modulators, can be trapped by CDs. In the preparation of antifungal econazole derivatives, they can be utilised to construct pickering emulsions that can be applied topically [72].
f. *Cosmetics and Personal Care:* CDs can be used to make cosmetics. Its use has many benefits, including stabilising compounds, obtaining more agreeable odours and flavours, enhancing the action of the compound by changing a liquid constituent to a solid form, lowering vapour pressure, altering the solubility in water, and enhancing the thermal stability of oils, among others [73]. Since they permit a controlled release of scents from the host-guest complex, producing more dubious scents, they are employed to reduce the volatility of perfumes, air fresheners, and detergents [74]. Paper towels, tissues, underarm shields, liquid and solid fabric softeners, toothpaste, and skin creams are some products that utilise them. As a result, CDs are a reliable formulation support since they may enhance the performance of the finished product and address any issues that might develop during its formation. Numerous researches have been conducted to examine various CD aesthetic uses. For instance, an in vitro study has demonstrated that CDs are an effective means of delivering ferulic acid, a substance with well-known antioxidant and photoprotective effects, enhancing its photo-stability, which may be a useful characteristic for cosmetic formulations [75].
g. *Packing and textile Industry:* The textile sector has focused its research on developing sustainable and practical textiles. The ability of the -CDs to form complexes with various types of chemicals, which results in a new wide variety of textile products and applications with advanced features, such as antibacterial or photoprotective, can play a crucial role in this field. The addition of CDs to textiles may also function to transport scents, absorb malodors (sweat, smoke), or improve the materials' capacity to hold colours, reducing the amount lost in wastewater as a result [76]. Additionally, they may be flame retardant. Medical tissues with CDs are used to release chemical compounds having advantageous qualities, such as antibacterial, anti-allergic, antifungal, anti-inflammatory, and insect protection, either topically or internally [75].

h. *Bioconversion and Fermentation:* Because the substrate or product in the catalyst can be toxic or inflammatory, bioconversion and fermentation processes are typically constrained. Given that the majority of organic substrates is lipophilic and hence has low water solubility and the catalyst is typically more active, the medium is also very significant. As a result, the biocatalyst can only access a small portion of the substrate [77]. CDs are used to increase the effectiveness of various chemicals synthesis. For instance, CDs improved the spiramycin production process. The rate at which spironolactone is deacetylated is likewise accelerated by modified -CDs [76].

8. Side Effect

When CDs were first found, they were thought to be toxic compounds, hence their use in complex creation was seen as anecdotal evidence. Numerous studies on the toxicity of CDs are based on their uses in medicine. Despite the fact that each medication's safety should have been evaluated throughout development and should be listed on the data sheet, this does not always happen in practise. However, taking a lot of CDs can have negative effects. Despite having a relatively limited oral availability, excessive dosages can cause reversible diarrhoea and caecum hypertrophy. The permeability of the tissues and, as a result, the bioavailability of the injected active compounds, may also change depending on the dose. Nephrotoxic effects have been noted in animal cases of high systematic exposures. There is currently no proof that these effects exist in humans [77].

9. Conclusion

Cyclodextrin provides a wide variety of applications in pharmaceutical, cosmetic and other fields. The cyclodextrin can alter different physico-chemical properties of guest molecules; hence they eventually have considerable pharmaceutical potential in targeted drug delivery, controlled release and masking odor and taste.

REFERENCES

1. J. Szejtli. “Introduction and General Overview of Cyclodextrin Chemistry”, *Chemical Review,* 1998, 98(5), 1743–1754.
2. D. Ikuta, Y. Hirata, S. Wakamori, H. Shimada, Y. Tomabechi, Y. Kawasaki, K. Ikeuchi, T. Hagimori, S. Matsumoto and H. Yamada. “Conformationally supple glucose monomers enable synthesis of the smallest cyclodextrins”, *Science*, 2019, 364(6441), 674–677.
3. T. Loftsson. “Cyclodextrins and the biopharmaceutics classification system of drugs”, *Journal of inclusion phenomena and macrocyclic chemistry*, 2002, 44, 63–67.
4. T. Higuchi and K. A. Connors. “Phase solubility techniques”, *Advanced Analytical Chemistry of Instrumentation*, 1965, 4,117-212.
5. A. W. Coleman, I. Nicolis, N. Keller and J. P. Dalbiez. “Aggregation of cyclodextrins: An explanation of the abnormal solubility of-cyclodextrin”, *Journal of inclusion phenomena and macrocyclic chemistry*, 1992, 13, 139–143.
6. A. Becheri, P. Lo Nostro, B. W. Ninham and P. Baglioni. “The curious world of polypseudorotaxanes: Cyclodextrins as probes of water structure”, *the journal of physical chemistry B*, 2003, 107, 3979–3987.
7. A. Harada and M. Kamachi. “Complex formation between poly (ethylene glycol) and α-cyclodextrin”, *Macromolecules*, 1990, 23, 2821–2823.

8. A. Harada and M. Kamachi. "Complex formation between cyclodextrin and poly (propylene glycol)", *Journal of the Chemical Society, Chemical Communications*, 1990, 24, 1322–1323.
9. T. Higashi, F. Hirayama, S. Misumi, K. Motoyama, H. Arima and K. Uekama. "Polypseudorotaxane Formation of Randomly-Pegylated Insulin with Cyclodextrins: Slow Release and Resistance to Enzymatic Degradation", *Chemical Pharmaceutical Bulletin*, 2009, 57, 541–544.
10. J. Chang, Y. Li, G. Wang, B. He and Z. Gu, "Fabrication of novel coumarin derivative functionalized polypseudorotaxane micelles for drug delivery", *Nanoscale*, 2013, 5, 813–820.
11. A. Harada. "Cyclodextrin-Based Molecular Machines", *Accounts of Chemical Research*, 2001, 34(6), 456–464.
12. S. A. Nepogodiev, J. F. Stoddart. "Cyclodextrin-Based Catenanes and Rotaxanes", *Chemical Reviews*, 1998, 98(5), 1959–1976, 1998.
13. K. Shibaguchi, A. Tamura, M. Terauchi, M. Matsumura, H. Miura and N. Yui. "Mannosylated Polyrotaxanes for Increasing Cellular Uptake Efficiency in Macrophages through Receptor-Mediated Endocytosis", *Molecules*, 2019, 24(3), 439.
14. H. Wang, H. Yin, F. Yan, M. Sun, L. Du, W. Peng, Q. Li, Y. Feng and Y. Zhou. "Folate-mediated mitochondrial targeting with doxorubicinpolyrotaxane nanoparticles overcomes multidrug resistance", *Oncotarget*, 2015, 6(5), 2827.
15. G. Yu, Z. Yang, X. Fu, B. C. Yung, J. Yang, Z. Mao, L. Shao, B. Hua, Y. Liu, F. Zhang, Q. Fan, S. Wang, O. Jacobson, A. Jin, C. Gao, X. Tang, F. Huang and X. Chan. Polyrotaxane-based supramolecular theranostics. *Nature Communications*, 2018, 9, 766.
16. P. Dandekar, R. Jain, M. Keil, B. Loretz, L. Muijs, M. Schneider, D. Auerbach, G. Jung, C. M. Lehr and G. Wenz. "Cellular delivery of polynucleotides by cationic cyclodextrin polyrotaxanes", *Journal of Controlled Release*, 2012, 164(3), 387–393.
17. R. W. Krause, B. B. Mamba, F. M. Bambo and T. J. Malefetse. "Cyclodextrin polymers: Synthesis and application in water treatment", *Cyclodextrins: Chemistry Physics, Transworld Research Network: Kerala, India*, 1st Ed, 2010, 168–194.
18. S. Mansuri, P. Kesharwani, K. Jain, R. K. Tekade and N. K. Jain. "Mucoadhesion: A promising approach in drug delivery system", *Reactive and Functional Polymers*, 2016, 100, 151–172.
19. M. Ijaz, M. Prantl, N. Lupo, F. Laffleur, A. M. Hussain, B. Matuszczak and A. Bernkop-Schnürch. "Development of pre-activated α-cyclodextrin as a mucoadhesive excipient for intra-vesical drug delivery", *International journal of Pharmaceutics*, 2017, 534(1), 339–347.
20. M. Ijaz, B. Matuszczak, D. Rahmat, A. Mahmood, S. Bonengel, S. Hussain, C. W. Huck and A. Bernkop-Schnürch. "Synthesis and characterization of thiolated β-cyclodextrin as a novel mucoadhesive excipient for intra-oral drug delivery", *Carbohydrate Polymers*, 2015, 132, 187–195.
21. T. Loftsson and M. E. Brewster, "Pharmaceutical applications of cyclodextrins: basic science and product development", *Journal of Pharmacy and Pharmacology*, 2010, 62(11), 1607-1621.
22. P. Jansook, N. Ogawa and T. Loftsson. "Cyclodextrins: structure, physicochemical properties and pharmaceutical applications", *International journal of pharmaceutics*, 2018, 535(1-2), 272-284.
23. J. Li and X. J. Loh. "Cyclodextrin-based supramolecular architectures: syntheses, structures, and applications for drug and gene delivery", Advanced Drug Delivery Reviews, 2008, 65(9).
24. A. Vyas, S. Saraf and S. Saraf. "Cyclodextrin based novel drug delivery systems", *Journal of inclusion phenomena and macrocyclic chemistry*, 2008, 62(1), 23-42.

25. E. Cho and S. Jung, S. "Supramolecular complexation of carbohydrates for the bioavailability enhancement of poorly soluble drugs", *Molecules*, 2015, 20(10), 19620-19646.
26. H. M. C. Marqudes. "A review on cyclodexdtrin encapsulation of essential oils and volatiles", *Flavour Fragrance journal*, 2010, 25, 313-326.
27. T. Loftsson and M. E. Brewster. "Pharmaceutical applications of cyclodextrins: basic science and product development", *Journal of pharmacy and pharmacology*, 2010, 62, 1607-1621.
28. G. Astray, C. Gonzales-Barreiro, J. C. Mejuto, R. Rial-Otero and J. Simal-Gándara, J. "A review on the use of cyclodextrins in food", Food Hydrocolloids, 2009, 23(7), 1631-1640.
29. J. Szejtli. "Introduction and General Overview of Cyclodextrin Chemistry", *Chemical Reviews*, 1998, 98(5), 1743–1754.
30. A. Biwer, G. Antranikian and E. Heinzle. "Enzymatic production of cyclodextrins", *Applied Microbiology and Biotechnology*, 2002, 59(6), 609–617.
31. M. G. Farahat. "Enhancement of β-cyclodextrin Production and Fabrication of Edible Antimicrobial Films Incorporated with Clove Essential Oil/β-cyclodextrin Inclusion Complex", *Microbiology and Biotechnology Letters*, 2020, 48(1), 12–23.
32. J. Zhou and H. Ritter. "Cyclodextrin functionalized polymers as drug delivery systems", *Polymer Chemistry*, 2010, 1, 1552-1559.
33. T. Loftsson, D. Duchêne, "Cyclodextrins and their pharmaceutical applications", *International journal of pharmaceutics*, 2007, 329(1-2), 1-11.
34. V. T. Karathanos, I. Mourtzinos, K. Yannakopoulou and N. K. Andrikopoulos. "Study of the solubility, antioxidant activity and structure of inclusion complex of vanillin with β-cyclodextrin", *Food Chemistry*, 2007, 101(2), 652-658.
35. V. J. Stella and Q. He. "Cyclodextrins", *Toxicologic Pathology*, 2008, 36(1), 30-42.
36. C. Nicolescu, A. Arama, A. Nedelcu and C. M. Monciu. "Phase solubility studies of the inclusion complexes of repaglinide with βcyclodextrin and β-cyclodextrin derivatives", *Farmacia*, 2010, 58(5), 620-628.
37. C. Muankaew and T. Loftsson. "Cyclodextrin-Based Formulations: A Non-Invasive Platform for Targeted Drug Delivery", *Basic & Clinical Pharmacology & Toxicology*, 2018, 122(1), 46-55.
38. A. García, D. Leonardi, M. O. Salazar and M. C. Lamas. "Modified βcyclodextrin inclusion complex to improve the physicochemical properties of albendazole complete in vitro evaluation and characterization", *PLoS One*, 2014, 9(2), 2014.
39. N. Ono, Y. Miyamoto, T. Ishiguro, K. Motoyama, F. Hirayama, D. Iohara, H. Seo, S. Tsuruta, H. Arima and K. Uekama. "Reduction of bitterness of antihistaminic drugs by complexation with βcyclodextrins", *Journal of Pharmaceutical Sciences*, 2011, 100(5), 1935-1943.
40. D. R. de Araujo, S. S. Tsuneda, C. M. Cereda, G. F. Del, F. Carvalho, P. S. Preté, S. A. Fernandes, F. Yokaichiya, M. K. Franco, I. Mazzaro, L. F. Fraceto, A. de F. A. Braga, E. de Paula. "Development and pharmacological evaluation of ropivacaine-2- hydroxypropyl-beta-cyclodextrin inclusion complex", *European journal of pharmaceutical sciences*, 2008, 33(1), 60-71.
41. T. Loftsson and M. E. Brewster. "Pharmaceutical applications of cyclodextrins: effects on drug permeation through biological membranes", *Journal of Pharmacy and Pharmacology, 2011*, 63(9), 1119-1135.
42. S. Shimpi, B. Chauhan and P. Shimpi. "Cyclodextrins: application in different routes of drug administration", *Acta Pharmaceutica*, 2005, 55(2), 139-156.

43. G. Tóth, R. Mohácsi and A. Rácz. Equilibrium and structural characterization of ofloxacin–cyclodextrin complexation", *Journal of inclusion phenomena and macrocyclic chemistry*, 2013, 77 (1-4), 291-300.
44. E. F. Muhammad and R. Adnan. "Computational Investigation of the Monomer Insulin-β-CD Complex for the New Insulin Formulation", *Australian Journal of Basic and Applied Science*, 2015, 9(17), 7-13.
45. Q. Zhu and G. K. Scriba. "Advances in the use of cyclodextrins as chiral selectors in capillary electrokinetic chromatography: fundamentals and applications", *Chromatographia*, 2016, 79(21-22), 1403- 1435.
46. J. C. Miranda, T. E. A. Martins, F. Veiga and H. G. Ferraz. "Cyclodextrins and ternary complexes: technology to improve solubility of poorly soluble drugs", *Brazillian journal of pharmaceutical science*, 2011, 47(4), 665-681.
47. G. Astray, C. Gonzales-Barreiro, J. C. Mejuto, R. Rial-Otero and J. Simal-Gándara. "A review on the use of cyclodextrins in food", *Food Hydrocolloids*, 2009, 23(7), 1631-1640.
48. R. Zidovetzki and I. Levitan. "Use of cyclodextrins to manipulate plasma membrane cholesterol content: evidence, misconceptions and control strategies", *Biochimica et Biophysica Acta*, 2007, 1768(6), 1311-1324.
49. G. S. Jadhav and P. R. Vavia, "Physicochemical, in silico and in vivo evaluation of a danazol-β-cyclodextrin complex", *International journal of pharmaceutics*, 2008, 352(1-2), 5-16.
50. S. Charumanee, S. Okonogi, J. Sirithunyalug, P. Wolschann and H. Viernstein. "Effect of cyclodextrin types and co-solvent on solubility of a poorly water soluble drug", *Scientia Pharmaceutica*, 2016, 84(4), 694- 704.
51. T. Loftsson and M. E. Brewster. "Cyclodextrins as functional excipients: methods to enhance complexation efficiency", *Journal of pharmaceutical sciences*, 2012, 101(9), 3019-3032.
52. A. Ghosh, S. Biswas and T. Ghosh. "Preparation and Evaluation of Silymarin β-cyclodextrin Molecular Inclusion Complexes", *Journal of Young Pharmacists*, 2011, 3(3), 205-210.
53. H. M. Patel, B. N. Suhagia, S. A. Shah, I. S. Rathod and V. K. Parmar. "Preparation and characterization of etoricoxib-beta-cyclodextrin complexes prepared by the kneading method", *Acta Pharmaceutica*, 2007, 57(3), 351-359.
54. C. Garnero, A. Zoppi, D. Genovese and M. Longhi. "Studies on trimethoprim: hydroxypropyl-β-cyclodextrin: aggregate and complex formation", *Carbohydrate Research*, 2010, 345(17), 2550-2556.
55. C. W. Lee, S. J. Kim and Y. S. Youn. "Preparation of bitter taste masked cetirizine dihydrochloride/β-cyclodextrin inclusion complex by supercritical antisolvent (SAS) process", *Journal of Supercritical Fluids*, 2010, 55(1), 348-357.
56. S. Y. Lin, C. H. Hsu and M. T. Sheu. "Curve-fitting FTIR studies of loratadine/hydroxypropyl-β-cyclodextrin inclusion complex induced by co-grinding process", *Journal of Pharmaceutical and Biomedical Analysis*, 2010, 53(3), 799-803.
57. S. Li and W. C. Purdy. "Cyclodextrins and their applications in analytical chemistry", *Chemical Reviews*, 1992, 92(6), 1457-1470.
58. R. A. Khan, P. Forgo and K. J. Stine. "Methods for selective modifications of cyclodextrins", *Chemical Reviews*, 1998, 98, 1977–1996.

59. A. Hybl, R. E. Rundle and D. E. William. "The crystal and molecular structure of the cyclohexaamylose- potassium acetate complex", *Journal of American Chemical Society*, 1965, 87(13), 2779–2788.
60. F. Ramer, G. Mackensen and K. Kensse. "On ring compounds. XX. ORD-spectra and conformation of the glucose ring in cyclodextrins", *Chemische Berichte*, 1969, 102, 494–508.
61. A. Gu and N. Wheate. "Macrocycles as drug-enhancing excipients in pharmaceutical formulations", *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, 2021, 100(1), 1-15.
62. A. Motoyama, A. Suzuki, O. Shirota and R. Namba. "Direct determination of pindolol enantiomers in human serum by column-switching LC-MS/MS using a phenylcarbamate-β-cyclodextrin chiral column", *Journal of Pharmaceutical and Biomedical Analysis.* 2002, 28(1), 97–106.
63. L. Szente and J. Szejtli. "Cyclodextrins as food ingredients", *Trends Food Science Technology*, 2004, 15, 137–142.
64. A. J. Andreu-Sevilla, J. M. López-Nicolás and A. A. Carbonell-Barrachina. "García-Carmona F. "Comparative Effect of the Addition of α-, β-, or γ-Cyclodextrin on Main Sensory and Physico-Chemical Parameters", *Journal of Food Science*, 2011, 76, S347–S353.
65. C. dos Santos, P. Buera and F. Mazzobre. "Novel trends in cyclodextrins encapsulation. Applications in food science", *Current Opinion in Food Science*, 2017, 16, 106–113.
66. G. Astray, C. Gonzalez-Barreiro, J. C. Mejuto, R. Rial-Otero and J. Simal-Gándara. "A review on the use of cyclodextrins in foods", *Food Hydrocolloids*, 2009, 23(7), 1631–1640.
67. J. Szejtli and L. Szente. "Elimination of bitter, disgusting tastes of drugs and foods by cyclodextrins", *European Journal of Pharmaceutics and Biopharmaceutics*, 2005, 61(3), 115–125.
68. L. Szente and J. Szejtli. "Cyclodextrins as food ingredients", *Trends in Food Science and Technology*, 2004, 15(3), 137–142.
69. N. Sharma and A. Baldi "Exploring versatile applications of cyclodextrins: An overview", *Drug Delivery*, 2016, 23(3), 739–757.
70. M. Sing, R. Sharma and U. C. Banerjee "Biotechnological applications of cyclodextrins", *Biotechnology Advances*, vol. 20, issue 5-6, pp. 341–359, 2002.
71. L. Leclercq, V. Nardello-Rataj. "Pickering emulsions based on cyclodextrins: A smart solution for antifungal azole derivatives topical delivery", *European Journal of Pharmaceutical Sciences*, 2016, 82, 126–137.
72. H. J. Buschmann and E. Schollmeyer. "Applications of cyclodextrins in cosmetic products: A review", *Journal of Cosmetic Science*, 2002, 53(3), 185–191.
73. M. Centini, M. Maggiore, M. Casolaro, M. Andreassi, R. Maffei Facino and C. Anselmi. "Cyclodextrins as cosmetic delivery systems", *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, 2007, 57, 109–112.
74. A. Cid, G. Astray, J. Morales, J. C. Mejuto and J. Simal-Gándara. "Influence of b-Cyclodextrins upon the Degradation of Carbofuran Derivatives", *Journal of Pesticides and Biofertilizer*, 2018, 1, 1–4.
75. C. D. Radu, O. Parteni and L. Ochiuz. "Applications of cyclodextrins in medical textiles", *Journal of Controlled Release*, 2016, 224, 146–157.
76. P. Jarho, D. Vander Velde and V. J. Stella. "Cyclodextrin-catalyzed deacetylation of spironolactone is pH and cyclodextrin dependent", *Journal of Pharmaceutical Sciences*, 2000, 89(2), 241–249.

77. B. A. R. Lina and A. Bär. "Subchronic oral toxicity studies with α-cyclodextrin in rats", *Regulatory Toxicology and Pharmacology*, 2004, 39, 14–26.