Chapter

Cyclodextrins: An Overview of Fundamentals, Types, and Applications

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Abstract

Cyclodextrins are one of the most interesting pharmaceutical excipients with substantial theoretical and applied impacts in pharmaceutical industry. Even though the chemical foundation of these macrocyclic molecules was laid more than 100 years ago by Villiers and Schardinger, it was not until recently that cyclodextrins have been regarded as a subject of numerous potential pharmaceutical applications including inclusion complexation. This particular chapter discusses the fundamental concepts of cyclodextrin chemistry, structure, properties, and host-guest interaction with a special focus on molecular dynamics. Further in this regard, applications of cyclodextrins and numerous drug delivery approaches including novel lipid-based nanosystems are also highlighted.

Keywords: cyclodextrins, properties, solubility, drug molecules, inclusion complexes

1. Introduction

In general, cyclodextrins (CDs) comprise sugar molecules, which are combined together in the form of rings. The sugar molecules that specifically constitute cyclodextrins are "Glucopyranosides," that is, glucose molecules arranged in pyranose configuration. The first indication to a substance that is eventually identified as cyclodextrin was reported in 1891 after Villiers isolated a crystalline substance while working on enzymatic digestion of starch. After Villiers, Schardinger studied these crystalline substances and described the essentials of cyclodextrin molecules known to us in detail [1].

Chemically, cyclodextrin molecules are cyclic oligosaccharides consisting of alpha-1➔4 linked D-glucopyranose units. Depending upon the number of glucopyranosides, cyclodextrin molecules can be categorized as alpha α (6), beta β (7), and gamma γ (8) cyclodextrins, respectively (**Figure 1**) [2].

As complicated as they sound, the CDs are comparatively easy to constitute. Like discussed above, cyclodextrins are typically obtained by treating starch with a variety of enzymes notably amylase or glucosyl transferases. Similar to the enzymes, sources of starch can also be variable resulting in particular ratio of α, β, and γ cyclodextrins [4].

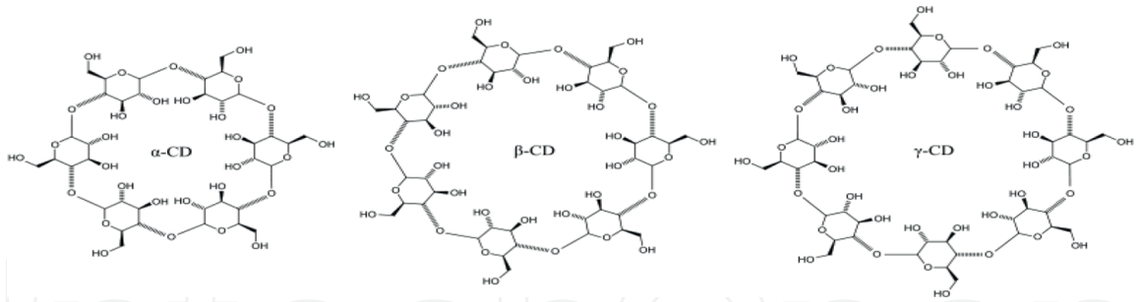

Figure 1.
Chemical structure of the α-, β-, and γ-cyclodextrins [3].

Furthermore, the CD molecules are large, but owing to stoichiometric constraints, it is not possible to acquire smaller CD molecules having less than six glucopyranosides residues. In contrast, those with higher glucose residues have been reported though concerns such as poor yield, and limited complexing ability renders them unacceptable for pharmaceutical use [5].

1.1 Structure and properties of cyclodextrin

In terms of structure, CDs have basket or truncated cone-like structure in which diameter of the inner cavity is a function of the glucopyranose units as shown in **Figure 2** [8]. The spherical arrangement of glucose units with secondary OH groups on wider end of the rim and primary OH groups on narrower end of the rim imparts it basket-like shape since the ability of primary OH groups to freely rotate decreases the diameter of the cavity at one end. Moreover, H-atoms bonded to CH group as well as OH groups form the external and hydrophilic exterior surface. In comparison to rims, internal cavity presents the hydrophobic microenvironment as it is surrounded with carbon and ether oxygen [9].

As cited earlier, there are three kinds of cyclodextrin, that is, Alpha α, Beta β, and Gamma γ also known as first or parent generation CDs. Due to the presence of sugar backbone in their framework, they can also be identified as cycloamyloses or dextrins [10, 11]. As far as the physicochemical properties are concerned, all the cyclodextrin molecules are large, hydrophilic, stable in basic media, hydrolyzable in acidic media,

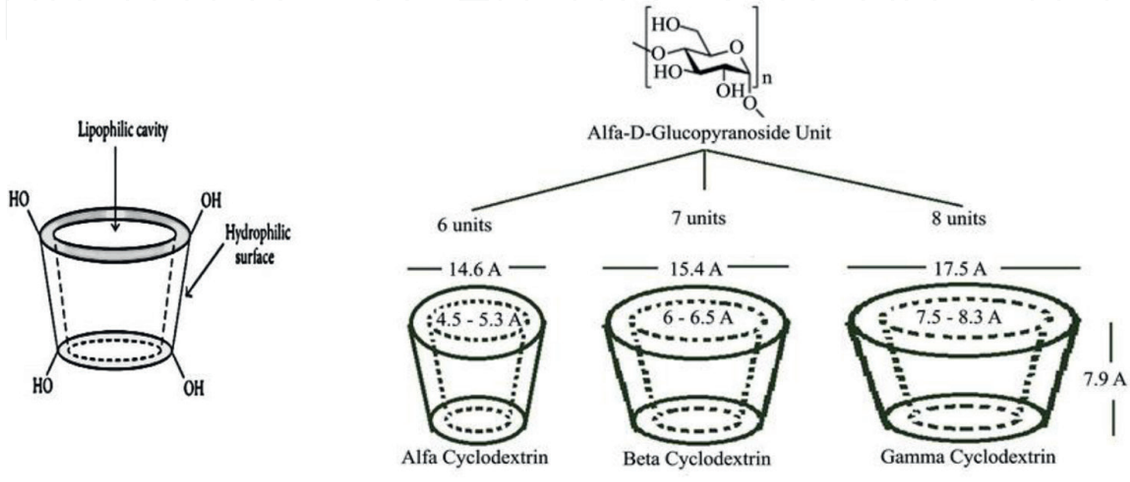

Figure 2.
Schematic diagram of shape and dimensions of parent cyclodextrin [6, 7].

Property	Alpha	Beta	Gamma
Glucose subunits	Hexa	Hepta	Octa
Synonyms	Cyclo-hexaamylose (alfadex)	Cyclo-heptaamylose (betadex)	Cyclo-octaamylose (gammadex)
Height	7.9	7.9	7.9
Cavity diameter	4.5-5.3	6-6.5	7.5-8.3
External diameter	I4.6	15.4	17.5
Solubility	14.5	1.85	23.2
Molecular weight	972	1135	1297

Table 1.
Important characteristics of parent cyclodextrin [7].

and similar in their ability to modify the physical, chemical, and biological features of drugs by yielding inclusion complexes (**Table 1**) [12].

The aqueous solubility of natural CDs and their complexes are known to be restricted, especially in case of β-CD, despite the fact that they are hydrophilic. This is owed to comparatively strong molecular bonding in CDs in their crystal state. Furthermore, significant number of intermolecular hydrogen bonds between secondary OH groups in the β-CD structure makes it stiff and inhibits the overall hydration. Interestingly, substituting any OH-group even by, for example, methyoxy group, can dramatically enhance the solubility. Nonetheless being less bulky, parent cyclodextrins exhibit lower molecular weight relative to their derivatives [13].

1.2 Derivatives of the CDs

Given the lower aqueous solubility, numerous scientists tried to prepare and evaluated a variety of derivatives of the CDs of medicinal interest. The CDs derivatives can be produced by polymerizing or substituting the methyl, carboxymethyl, ethyl, hydroxyethyl, sulfabutyl, or even saccharides. Bonding various functional groups causes chemical alterations into the main and secondary OH groups of the parent CD molecules [13, 14]. These derivatizations are carried out to achieve the following goals:

- To improve the solubility.
- To enhance the host-guest association or fitting.
- To stabilize the guest and lessen its reactivity and movement.

Remarkably, till date, a myriad of CD derivatives have successfully been produced and analyzed, yet only a small number including methylated, hydroxy alkylated, and ether substituted derivatives have been employed in studies involving novel pharmaceutical applications [15].

1. Methylated derivatives can be prepared by randomly methylating any secondary OH group in C2, C3, or C6 locations or by selectively methylating all secondary OH groups of C2 position and primary OH groups of C6. In relation to the natural CDs, methylated ones exhibit altered physical, chemical, and structural characteristics. Solubility of methylated CD is also substantially greater; how-

ever, the solubility is inversely proportional to the temperature as it diminishes when temperature rises.

2. Similarly, hydroxyl alkyl derivatives also offer higher aqueous solubility and are one of the most extensively used derivative group. Preparation of hydroxy alkyl derivatives typically entails non-selective condensation of hydroxy alkyl agents in basic medium.

3. In contrast, ether derivatives reduce the solubility when OH groups are substituted by alkyl groups through ester or ether bond(s) [16, 17].

2. Effect of CDs on formulation properties

The most prominent attribute of the CDs is inclusion complexation, that is, the capability to allow a therapeutic agent or more characteristically just the hydrophobic portion of medicinal moiety into their internal cavity [18].

2.1 Mechanism of inclusion complexation

When water molecules are removed from the lipophillic cavity of cyclodextrins (which is in an energetically unfavorable environment due to the nature of the polar-polar interaction), the number of formed hydrogen bonds increases, and the repulsive interaction between guest and aqueous environment decreases, whereas the hydrophobic interaction increases as the guest molecule or lipophilic group with size, shape, and polarity compatible with the CD structure exerts itself in central cavity. As a result, a complex (**Figure 3**) is formed in an aqueous solution [19, 20].

When a complex is formed, covalent bonds are neither formed nor broken, and the drug molecules of complex as well as those of solution are in equilibrium. The capacity of guest to interact well with the host molecules to create a stable complex determines the binding strength of thus formed complex. Other factors involved in affecting this host-guest complexation mechanism are:

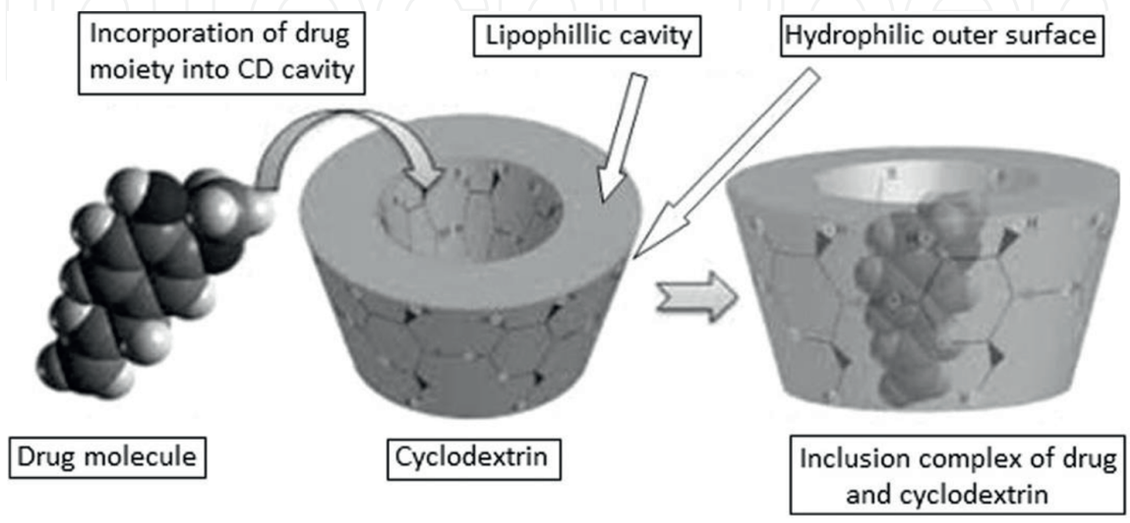

Figure 3.
Schematic illustration of the drug-CD inclusion complexation [3].

1. Steric factor—which is based on the proportion of the CD to drug size and/or on specific functional group of active component. If the active component is too big, it will not fit inside the cavity adequately. Moreover, the dimensions of these molecules also important in this aspect on the basis of dimension smaller compounds or those having aliphatic chain will form complex with the alpha cyclodextrin and those having higher molecular weight, for example, steroids will be accommodated by gamma cyclodextrin. On the other hand, heterocyclic as well as aromatic compounds will form complex with the β-CDs [21].

2. Besides the steric, thermodynamic interaction among various CD components, the host molecule is another important determinant. In order for complexation to take place, a favorable driving force that can draw the host molecule into the CD cavity is necessary. This thermodynamic force is attributable to the unique toroid or cone-like structure of the CDs [3].

3. Structure of substitution added to derivate CDs.

4. Places, where substitution are made within the molecule.

5. Finally, the degree of substitution

2.2 Types of complexes

It is crucial to measure the stability or dissociation constant of complexes, since they are an indicator of how a compound's physicochemical characteristics change after inclusion. The phase solubility method proposed by Connors and Higuchi [22] is most extensively used analytical procedure in this regard as shown in **Figure 4**, which is known as phase solubility profile.

Connors and Higuchi categorized complexes by examining the influence of solubilizer or ligand concentration on drug or substrate solubility. If by increasing the solubilizer or ligand concentration, there is a rise in substrate solubility, then the solubility profile is said to be A-type. Three additional profiles, that is, A_P, A_L, and A_N make up A-type profile. The A_L profile shows that solubility increases linearly with

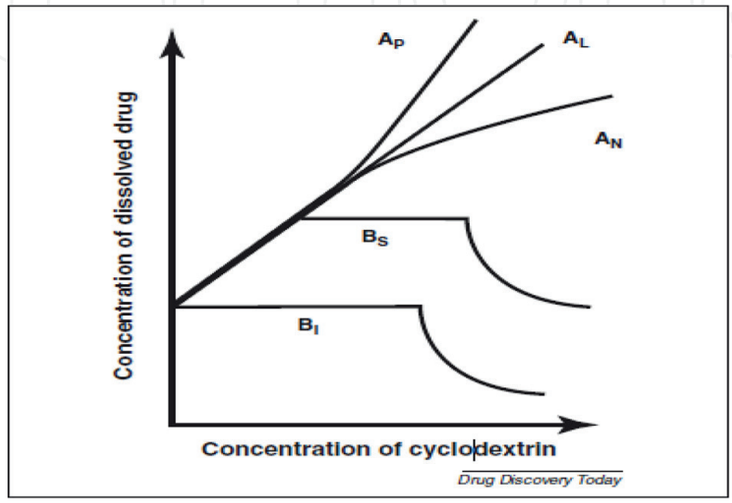

Figure 4.
A and B-type phase solubility profile and their subtypes [23].

ligand concentration or solubilizer concentration. A_P type shows an isotherm with significant deviation but in a positive way implying proportionality but only at higher quantities. On the other hand, A_N profile also exhibits deviation but is a negative way implying no proportionality even at higher amounts. All three trends together show that complexes formed are water-soluble. Type B profile on the other hand indicates that the complex has restricted solubility. They are typically seen with parent CDs especially with the β-CD. They are also of two types, that is, B_S and B_T [24].

Although inclusion complexes are expected to make up the majority of CD complexes but non-inclusion complexes (complex aggregate) that can dissolve drug through micelle formation can also form [3].

3. Applications of cyclodextrins

The exact potential of the CDs in the sector of pharmaceutical applications is because of their capability to affect several properties influencing the behavior and therapeutic outcomes of drugs. Cyclodextrins are typically employed to improve the solubility, permeability, stability as well as adverse effects including irritation. Generally, most of these applications are associated to their capability to form inclusion complexes.

3.1 Solubility and dissolution enhancement

The most extensive use of the CDs is to improve the solubility of drug in aqueous solutions. An increase in solubility also aids in improving bioavailability and hence therapeutic efficiency. Cyclodextrins have the capability to form the inclusion complexes, which increases the solubility and dissolution of drug molecules in the solid state [25]. Even though solubilization effects of all the CD molecules can be found throughout the literature, methylated CDs have the greatest potential of increasing the solubility as they decrease the crystallinity of drugs, which also increases the dissolution [26]. Although the influences of the CD complexation on it are extremely empirical, yet a number of historical findings permit several inferences:

- Firstly, the poorer the water solubility of the drug, the superior the solubility enhancement through the CD complexation.
- Secondly, derivatization of the CDs with reduced molar substitution offers the better solubilization than derivatives with more molar substitutions.
- Thirdly, solubilizing ability of the CDs is entirely dependent on the charge proximity to the cavity. Farther the proximity, better the ability.
- And lastly, it is feasible to increase complexation and consequently solubilization by incorporating various polymers of the group.

3.2 Permeability across biological membrane

Remarkably, permeability across the biological membranes can be affected by several factors, which include molecular weight, molecular structure in addition to the partition coefficient. CDs have no part in increasing the permeation of hydrophilic

drugs, but in CD complexation, free drug has the affinity to penetrate biological membrane [27]. At this point, delivery across biological membrane is entirely dependent on the drug formulation as well as the barrier. Delivery across barrier controlled by water diffusion layers can be affected by cyclodextrins, but those across lipophilic membranes are limited. The only exception to this barrier is inclusion of hydrophobic cyclodextrins that can effortlessly cross the mucosa [28].

3.3 Higher photo- and thermal stability

Another important signature of these excipients is their influence on the chemical stability of pharmaceuticals. Whenever any drug formulation has to be developed, stability parameters and the factors affecting the stability parameters should be kept in mind, and appropriate stability enhancers should be added as per the requirements. CDs are widely known for their capability to reduce the effect of temperature, light, and oxygen, thereby increasing the overall stability [29, 30]. Degradation of the product in the presence of light can lead to the several adverse effects. Higher photo stability was found when a complex of CD and vitamin E was formed. Apart from the protective effect of CD stability, studies are also important to discover the degree to which any formulation can be prevented from the excipient mediated degradation [31].

3.4 Improved drug safety

When CDs increase the solubility, dissolution, and bioavailability of the drugs [28], it means that drug will have the required residence time in the body and will not stay longer, thus reducing the risks of toxic effects [32]. A research was conducted on an anti-viral drug ganciclovir combined with CD, and it was found that toxic effects of the drug were reduced and efficacy was significantly improved. Similarly, irritation caused by both intravenous and ophthalmic products can also be reduced by CDs [33].

3.5 Control of drug release

CDs having ethyl group and acyl group have the potential to prolong drug release [34]. One alternative for controlling drug release is to utilize the epithelial surface of GIT in which per-Obutanoyl β-CD is known for its mucoadhesive property. HP-β-CDs are being utilized for their gel forming property, thus can extend the release of drug. In controlled drug delivery systems, osmotic pumps are widely utilized as they are unique and provide the uniform concentration of drug in the systemic circulation [35]. Advanced forms of extended delivery systems can be developed by joining the CD conjugates with respective release formulations. This effect was seen when ketoprofen having β-CD was combined with ketoprofen, and this formulation was added in CD conjugates, which provided a repeated release profile [36, 37].

4. Drug delivery approaches

4.1 Drug delivery by oral route

Drug delivery by oral route has traditionally been the most prevalent option for designing delivery systems. Drug release in oral delivery system may be controlled by dissolution, diffusion, pH, or osmosis [38]. The usage of CDs in an oral delivery

system is to increase the rate at which dissolution occurs—forming inclusion complexes with CD aids in increasing the solubility of drugs and hence transport of drugs across aqueous phase to lipid membrane in GIT [39]. The hydrophobic derivatives of CDs are mostly employed to accomplish this goal. In case of buccal and sublingual routes, rapid increase in drug concentration can also be achieved by complexation; however, in order to exhibit the therapeutic effect, drug must need to get released from the complex. For sublingual route, it is a little bit difficult since the amount of saliva as well as contact time is limited [40].

Cyclodextrins especially hydrophobic ones, that is, ethylated CDs, are also very important in achieving site-specific or sustained drug release. Additionally, cyclodextrins have productively been utilized in matrix tablets as well as osmotic pumps to control the drug release [41].

4.2 Ocular drug delivery

The primary treatment of an ocular aliment is mainly topical application of drug as aqueous solution. The current findings ascertain that cyclodextrin molecules are helpful components in ocular preparations, since they can enhance the solubility, stability, and consequently bioavailability of the ophthalmic formulations [42]. Among the CDs, hydrophilic cyclodextrins, mainly SB β-CD and HP β-CD, are reported to be most compatible and nontoxic [43]. It is well known that only a small amount an ophthalmic drug can actually reach systemic circulation, but increasing the availability of a drug at corneal surface through the CD complexation can easily enhance ocular bioavailability of hydrophobic drugs [44].

4.3 Nasal drug delivery

In order to have systemic absorption, drug must have optimum solubility in nasal fluids. Moreover, an optimum nasal formulation also must not have any effect on the defensive functions of cilia in respiratory tract. Both hydrophilic and hydrophobic CDs are the highly employed in this regard, as they can enhance the solubilization as well as the permeation, correspondingly. Besides, they are highly effective in small concentration and stereotypically inert from toxicological perspective [45, 46].

4.4 Transdermal drug delivery

Stratum cornea serves as the main barrier in the delivery of drugs through the skin. Various penetration enhancers are often employed to enhance the delivery across the barrier. Owing to the hydrophobic properties, cyclodextrins have the ability to deliver across water diffusion layer; however, if absorption is dependent on the lipophilic barrier solely, CDs are unable to deliver the drug dermally. Therefore, suitable selection of an aqueous vehicle is highly important [32, 47].

4.5 Novel drug delivery

Captivatingly, CD and its derivatives have been employed to develop the novel systems having supramolecular architectures such as micelles [48], nanosponges [49], nanoparticles [50], nanovesicles [51], etc., to build the functional platforms. Among these delivery systems, lipid nanocarriers are arguably the most common nanomaterials, which are used in association with modified CDs. Being biodegradable and

biocompatible, these systems offer versatile advantages including targeted delivery, stability, and co-drug loading (i.e., both hydrophobic and hydrophilic). In addition, they also exhibit superior efficacy and pharmacokinetics [52]. Conducive studies on the lipid nanosystems including parent and derivated CDs have proven the suitability of this approach to enhance the bioavailability of numerous pharmaceutical formulations; hence, continually increasing its implications in different disorder, for instance, diabetes [53], hypertension [54], cancer [55], and many other ailments.

5. Conclusions

It is evident from the data given here that cyclodextrins due to their distinctive cone-like structure and unique properties can provide an excellent option to address various issues regarding drug and its delivery. CDs have been introduced successfully in pharmaceutical industry because of their unique property of forming dynamic inclusion complexes, thus improving the solubility, dissolution, bioavailability, and release profile of numerous drugs. The effectiveness of different CDs in improving the therapeutic potential of drugs depends upon both the type of guest molecule and the CD as they can influence types of the complexes formed. According to Connor and Higuchi, complexes can be A-type, B-type, and even non-inclusion type, such as complex aggregation.

Apart from traditional drug delivery system, recent research on CD-based nanosystems has grown as the CDs are biocompatible and can nicely serve as the platform for the formulation and pharmacokinetic efficiency without raising the risks.

Conflict of interest

The authors declare no conflict of interest.

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