Cyclodextrin in drug medication

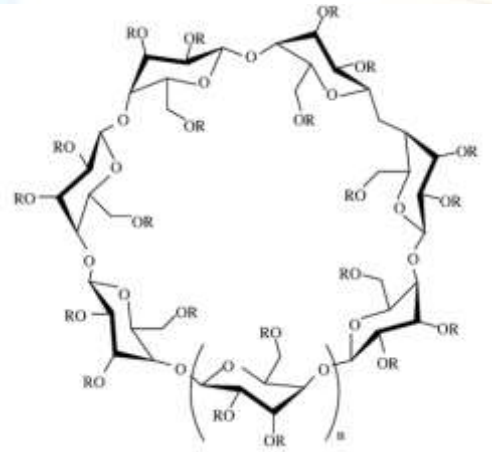
Zuxriddinov Biloliddin

Year 1, Medical school, Central Asian University, Tashkent, Uzbekistan

Abstract. Cyclodextrin molecules (CDs) are useful excipients in pharmacology in this day and age. The main interest in CDs was gained due to their ability to interact with hydrophobic molecules, increasing solubility in water. The high solubility is the result of complexation through non-covalent bonding, as well as the formation of aggregates. This review intends to give general knowledge about CDs' shape and structure. Discuss the effect of both host (CDs and their derivatives) and guest (drugs) molecules on complex formation. Further part covers the application of CD-based drugs to pharmacology. As a result of this review, the author believes that CDs will be modified to deliver complex molecules to treat crucial diseases in the near future.

Key words. Cyclodextrin, hydrophobic molecules, solubility, aggregates.

1. Introduction. In this day and age, the terms medicine or drug are very familiar to everyone. A drug is any chemical substance that is consumed to defend an organism from disorders, speed up healing or prevent possible complications. However, there is a drawback when the drug is insoluble in water and can't reach its destination. This review covers a type of molecule named 'Cyclodextrin', which was discovered as a solution. They are sugar-based, basket-shaped cyclic molecules (Figure 1), as shown in Figure 2 **[1]**. Hydrophobic molecules (i.e., drugs) spontaneously go into the cavity of CD molecules in aqueous surroundings, because they don't interact with water molecules. Hydrophilic parts of CD interact with water, which allows hydrophobic molecules to dissolve in water and be easily transported to their destination.



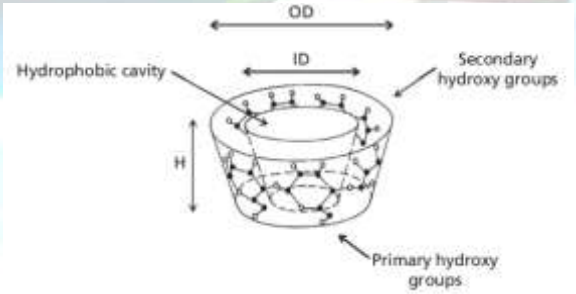


Figure 1. General structure of CD **[2]** **Figure 2.** 3d shape of CD **[1]**

CDs were first described by M.A. Villiers in 1891. He detected something new while investigating a bacterial digest from starch and called it "Cellulosine". Then, he isolated αCD and βCD. Subsequently, in the years 1903-1911, F. Schardinger performed studies in which he described two types of dextrins, α and β, resulting in CDs were later named

Schardinger sugars for a long period of time. Steadily, they reached the food industry, cosmetology, pharmacy, etc. It was not until 1953 that a German scientist patented the first ever CD-related study. This study covered a description of αCD, βCD and γCD, as well as the chemical properties for the formation of a host-guest complex. To date, more than 35 types of CDs have been described.

2. Shape and its effect on solubility.

2.1. Shape.

The structure of saccharides - subunits of CD molecules - helps to understand the structure of CDs. Preferably, saccharides exist in chair conformation, which is Z Z-shaped structure (Figure 3). This feature results in a "trunked" shape instead of a cylinder structure (Figure 4). In CD molecules, glycosidic bonds are situated in the equatorial plane to stabilize the molecule; thus, C6 is exteriorly directed towards the narrow aperture and C2, C3 are exteriorly directed towards the wide aperture. This allocation of hydroxyl groups is to form hydrogen bonding with solvent, making the exterior of CDs hydrophilic **[3]**.

On the other hand, in the inner part of CDs, there are more non-polar groups (glycosidic bond, aliphatic groups, etc.). Therefore, it is more hydrophobic and preferable for small organic molecules.

As stated above, there are many CDs, and there are some parameters that vary from one to another. First, "n" – difference in subunits between the CD and the smallest CD (n=0), which contains 6 subunits (Figure 1). For example, a CD with n=2 has 8 subunits (2+6). The next parameters are "ID" – inner diameter of CD; "OD" – outer diameter of CD; "H" – height of CD (Figure 2). For instance, ID = 5.7 A; OD = 13.7 A; H=7.8 A is for αCD **[4]**.

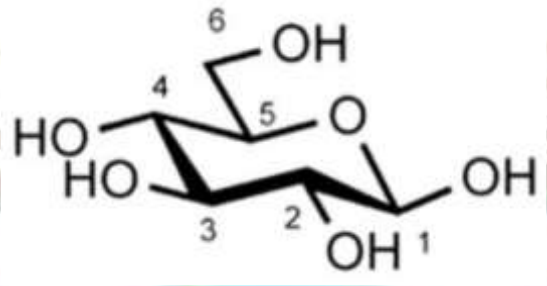


Figure 3. Glucose in chair conformation **[8]**.

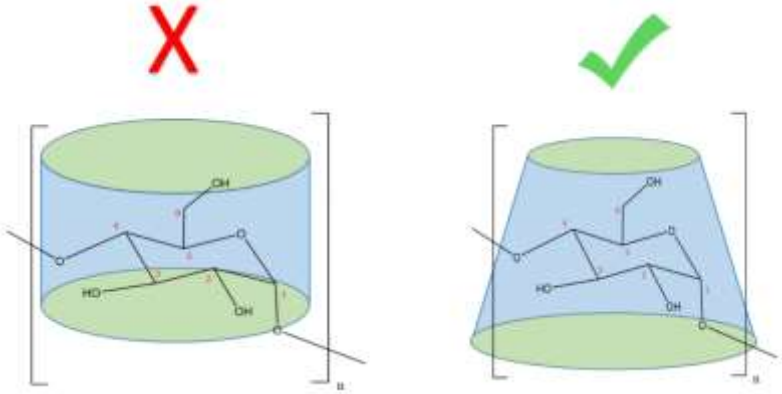


Figure 4. cylinder structure and conical structure **[7]**.

2.2. Solubility.

As stated earlier, CDs interact with their surroundings using hydroxyl groups, forming hydrogen bonds. Therefore, solubility depends on the number of donor and acceptor groups. For instance, the maximum solubility of αCD (n=0) is 12.8 mg/100mL, whereas the maximum solubility of γCD (n=2) is 25.6 mg/mL at room temperature. Additionally, maximum solubility depends on the rigidity of CDs. Specifically, on hydroxyl groups in C2 and C3 because they can form hydrogen bonds between each other (intramolecular) instead of surrounding molecules (intermolecular). For instance, maximum stability of βCD (n=1) is 1.8 mg/100mL due to the rigidity of the structure **[5]**. Lastly, solubility depends on temperature and is directly proportional to temperature (Table 1) **[6]**.

Table 1. Water solubility(g/100mL) of CDs and its dependence on temperature **[6]**.

Temperature	αCD	βCD	γCD
25 ºC	12.8	1.8	25.6
45 ºC	29.0	4.5	58.5
60 ºC	66.2.	9.1	129.2

In reality, this hydrogen bonding was not enough, and the maximum solubility of CDs was comparably low in industry. Thereafter, improvements in solubility were made by modifying hydroxyl groups. For example, if the hydroxyl group in βCD is modified to hydroxypropyl (HP-βCD - used to treat alveolar echinococcosis), solubility increases 65 times.

3. Complexation and its use in pharmacology.

3.1. Complexation.

There are many types of complexes between CD (host) and drug (guest), which differ in the ratio of host-guest molecules. The ratio depends on parameters of the host, size of the guest, kinetic, and thermodynamic parameters, etc. In a standard situation, the ratio is 1:1 (Figure 5).

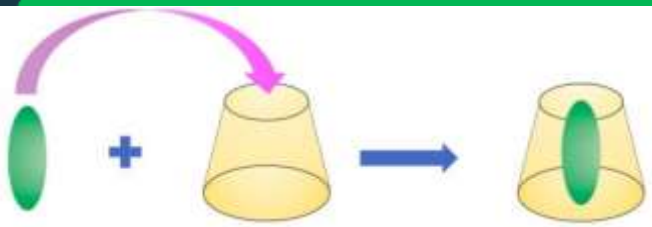


Figure 5. Standard complex formation between host and guest **[7]**.

3.1.1 Self-assembly of CDs.

There are two types of complex formation according to the organization of CDs. First, Cage-like patterns - isolated complex with guest molecules, consisting of "Herring bone" and "Brick-wall" structures. Second, Channel-like patterns - extended tubes or stacking channels, including "Head to Head" and "Head to Tail" structures (Figure 6) **[9]**. These phenomena, also known as aggregation, are essential due to the following reason. Aggregation is only observed at a certain concentration, accepted as 3-12 mM for native CDs, and there are two types of drugs. The first group of molecules increases complexation when aggregation happens (i.e., carotenoids **[10]**), and the second group of molecules decreases the strength of complex formation when aggregation happens (i.e., glipizide **[11]**). Overall, hypotheses can predict the trend for specific groups of molecules. However, each case must be studied individually, as some cases are exceptions to this hypothesis **[9]**.

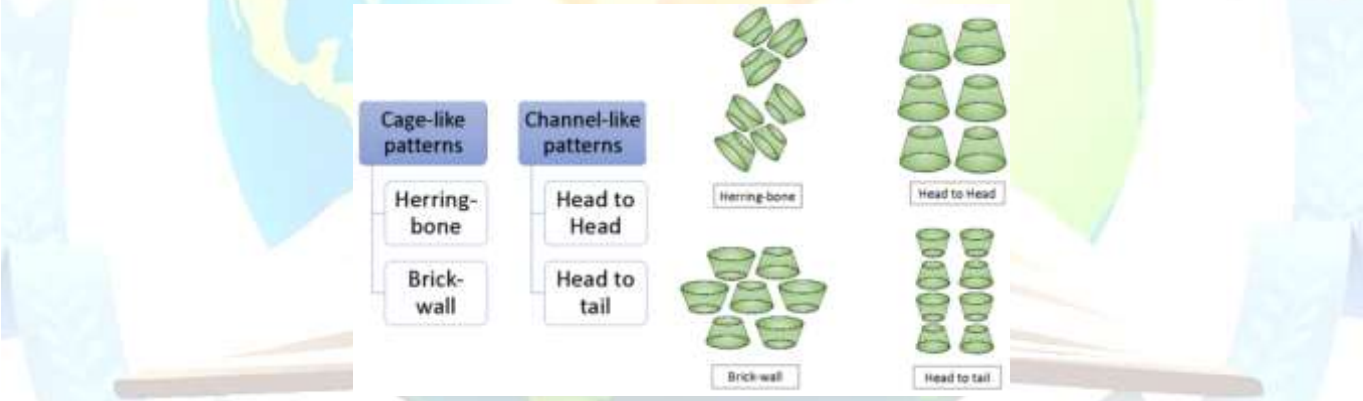


Figure 6. Standard systems of CD complexes **[9]**.

3.1.2 How guest molecules bond with CDs and what is driving interaction between them.

A few factors affect complexation, except size and shape, which have been discussed earlier. For instance, charge, intermolecular interactions (i.e., hydrogen bonding, van der Waals, dipole-dipole), etc.

The research paper states that the polarity of the inner cavity of natural CDs is similar to that of n-octanol **[12]**. Therefore, the strongest complexation is achieved when natural CDs bind with neutral molecules that possess van der Waals interactions. On the other hand, molecules containing a charge change their direction and position to increase stability by distributing the charge throughout the inner cavity. For instance, positively charged molecules (adamantane derivatives), when binding with CDs, have their ionic group

sticking out from the wider aperture. However, negatively charged molecules (adamantane derivatives) don't have a specific direction. They both show ionic charge sticking out towards wider and narrower apertures **[13]**. In addition, the trend for bond strength in the complex and the charge on the compound is totally different from complex to complex. For instance, imatinib (tyrosine kinase inhibitor) has the weakest complex with RAMEB (randomly methylated βCD) in the condition of +3. Whereas, when bound with βCD, imatinib had the strongest complex in the condition of +3 **[14]**. Subsequently, the trend for anionic compounds is unpredictable, too. For example, comparing p-nitrophenol and p-nitrophenolate, it says the complexation constant is 130 dm^3 mol^{-1} and 410 dm^3 mol^{-1}, respectively **[15]**. The complexation is nearly 3 times as strong in an anionic compound as in a neutral. This occurs because an anionic compound donates its negative charge to the inner cavity of CD, while that of a neutral molecule is relatively less.

When it comes to van der Waals forces, in some cases, their role in complexation is major. For instance, phospholipids - biomolecules that consist of a head (acylated phosphoric acid) and tail (acyl of fatty acid) - were examined to find whether the complex of αCD with the acyl group or the phosphoric group is more stable. This results in greater stability (of lower energy) of the complexation of αCD with the acyl group. In conclusion, van der Waals forces are major in this type of complexation because it is evident that the only force between the inner cavity and acyl group is van der Waals **[16]**.

The next type of bonding is hydrogen bonding. Generally speaking, hydrogen bonding is a minor parameter in complexation due to the rigidity of the inner cavity. As stated before, structure becomes rigid when it forms intermolecular hydrogen bonds rather than intramolecular hydrogen bonds. In conclusion, comparing hydrogen bonding to van der Waals forces, the hydrogen bonding should be omitted.

3.1.3 Equilibrium constant.

The reaction of complex formation is described by the following formula, and according to the equilibrium constant:

$mCD + nD \leftrightarrow CD_m \bullet D_n \quad Kc = \frac{[CDm \bullet Dn]}{[CD]^m[D]^n}$ (formation constant) Mainly, methods used to determine the equilibrium constant are based on titrating certain chemicals, analyzing concentration dependencies. The equilibrium constant is used to theoretical calculations reactivity of certain complexes. The trend is that the greater the equilibrium constant is, the stronger the complexation is, increasing the solubility of the drug. However, if complexation is strong enough, the drug wouldn't come out of the complex, decreasing the efficiency of the drug.

3.1.4 Drug release from the complex to the organism.

Generally speaking, a drug is released from the CD to tissues mainly due to the dilution. Additionally, the formation of a drug-protein complex and the competitive binding increase the rate of drug release. Several studies on humans and animals have confirmed that the equilibrium constant of complexation (KC) doesn't affect the drug release rate in

the majority of cases. However, a specific study has shown that KC must be greater than 105 M^{-1} to have an effect on the rate of drug release. While most of the CDs' KC range between 10 M^{-1} and 2000 M^{-1}, a rare exception is Sugammadex - derivative of γCD, specifically designed to bind rocuronium, a neuromuscular blocking agent - has KC = 1.8 * 107 M^{-1} for the complex sugammadex-rocuronium **[1]**.

3.2 Pharmacology.

3.2.1 General benefits of CD-based drugs.

Overall, CD-based drugs increase the solubility of the drugs as well as single-time dosage without affecting their bio efficiency. Considering that new drugs are more and more insoluble in water and that CDs are flexible to modify in order to fit with the host molecule. CDs and drugs are the best combination in pharmacology in this day and age.

3.2.2 Piroxam.

An example of a hydrophobic drug is Piroxam, an anti-inflammatory non-steroidal drug. Originally, its solubility in water is 0.02 mg/L, which is 8 times less than βCD-piroxam complex (pH=5, 37ºC) **[17]**. In addition, the usage of βCD-piroxam increased the absorption rate, reducing the probability of gastrointestinal irritation - one of the drawbacks of βCD-piroxam. In general, the ratio of reagents for synthesis is 1:2.5 for piroxam and βCD-piroxam, respectively. Synthesis proceeds in ammonium hydroxide solution due to its easy evaporation. After the reaction is complete, the solvent with ammonium hydroxide is evaporated to form white complex powder **[18]**.

4. Limitations and future directions.

In general, CDs are very useful tools in pharmacology, but there should be some drawbacks. First of all, the price of CDs is very high because the synthesis process includes purification CDs several times from natural starch. If the natural CD needs to be modified, the synthesis will include additional stages. The next limitation is the toxicity of CDs. Due to their strong ability to form complexes with organic molecules, they tend to disturb some natural processes. For instance, βCD can damage the kidneys by precipitating lipids and cholesterol. The last limitation is the size of the CD. The limitation for the size of the host molecule ranges from 5 Å to 8 Å for the majority of CDs. As a result, CDs are too big for tiny molecules and too small for large molecules.

In the future, the limitations stated above should be addressed. First of all, to reduce the price for CDs, the synthesis should be less complicated. Also, having some standard derivatives of CDs in constant large production will reduce the price, leading to a rise in demand. Secondly, the toxicology of CDs lacks new modifications that will decrease their effect on the processes in the human body. The next direction in development is synthesizing new derivatives of bigger size to allow large molecules such as DNA and RNA to be transported through the digestive system to tissues.

In conclusion, the author of this review sees a bright future of CDs in pharmacology due to their ability to be modified to perform different tasks. In addition, standard CDs are known to be renewable, strengthening their position in future pharmacology.

5. Conclusion.

Cyclodextrin was first found by M.A. Villiers in 1891 and has been further developed to this day. Nowadays, there are more than 10,000 derivatives of CDs, and all of them have their own unique shape and size for specific drugs or molecules. CD molecules are modern drug carriers, as new drugs are insoluble in water they need to be carried to show their bio effects. They are sugar based cyclic oligomers, resulting in high solubility in water, and to some extent, they are non-polar molecules, resulting in strong complexation with hydrophobic drugs and molecules. They tend to form complex assemblies to stabilize the complex. In addition, the complex is stabilized by van der Waals forces, hydrogen bonding, and other forces.

Many CDs have become a useful tool in pharmacology for insoluble but bioactive drugs. Their features are described by physicochemical constants, except for some features yet to be described for better theoretical prediction of CD based complexes. In addition, common CDs (i.e., αCD, βCD, γCD, RMβCD, HPβCD, and SBEβCD) are used to test new insoluble drugs due to strong complexation with various groups of molecules.

Disclosure of Interests. The author has no competing interests to declare that are relevant to the content of this article.

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