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A REVIEW ON CYCLODEXTRINS AND ITS REGULATORY CONSIDERATIONS

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Abstract: A family of cyclic oligosaccharides known as cyclodextrins (CDs) is made up of α-(1, 4) connected glucopyranose subunits which was first identified and disclosed by the French scientist Villiers in 1891from starch being broken down by bacteria (*Bacillus amylobacter)*. They are of three types-α-CyD, β-CyD, γ-CyD and are prepared by using methods like Physical mixing, Kneading, Co-precipitation, Solvent evaporation, Freeze drying, Spray drying techniques, Microwave irradiation. Due to their capacity to modify the physical, chemical, and biological characteristics of their host molecules by forming inclusion complexes, CDs have been identified as promising candidates. Cyclodextrin can combine with a variety of active medicinal substances and creates an inclusion complex without changing the medication's biological characteristics. In the pharmaceutical business, they are a breakthrough excipient that improves the physiochemical characteristics of lipophilic medicines. Pharmaceutical scientists can overcome difficulties with drug administration for weakly water soluble medicines by using cyclodextrins, a unique structure with flexible physicochemical properties. Cyclodextrin are useful in enhancing water solubility of medicament and also used in various formulations like ophthalmic, nasal, etc. Here in this article, structure, factors affecting inclusion complex, physical and chemical properties, method of preparation, toxicological profile and regulatory status of the cyclodextrin have been discussed.

Keywords - Cyclodextrin, Inclusion complex, Oligosaccharide, Toxicology, Regulatory Status.

I. INTRODUCTION

Cyclodextrins are cyclic oligosaccharides shaped like buckets. (a-1-4)-linked α-D glucopyranose units are present in them. The outside of cyclodextrin is hydrophilic, while the inside is lipophilic. The pharmaceutical industry refers to them as "molecular cages" for obvious reasons [1]. Cyclic carbohydrates are created when the bacterial enzyme CD glycosyltransferase (*Bacillus macerans*) breaks down starch referred to as cyclodextrins [2]. Other names for cyclodextrins include schardinger dextrin, cycloamyloses, and cyclomaltoses. One issue that continues to impede the development of cyclodextrin formulations is regulatory acceptance of CD. Twenty CD products are marketed commercially among which two are sold in

the US market. Cyclodextrin is used to lessen gastrointestinal discomfort caused by medications, and it can turn liquid medications into amorphous or microcrystalline powder. It also helps to avoid interactions between pharmaceuticals and their excipients [3]. Cyclodextrin can greatly increase the water solubility of medications [4].

When it comes to increasing drug solubility and stability[5], masked tastes and odors[6], improving drug absorption[7], regulating drug release profiles[8], reducing local and systemic toxicity[9], and enhancing drug permeability across biological barriers[10], CDs have developed a high-quality platform over time. CDs containing formulations have been delivered through various delivery systems like oral, ocular, nasal, dermal and rectal[11-14]. From an application standpoint, CDs have several benefits, including non-toxicity, affordability, safety (approved by safety and health authorities), and accessibility [15].

II. HISTORY

The first person to identify and disclose cyclodextrins was the French scientist Villiers in 1891. He described them as the result of starch being broken down by bacteria (*Bacillus amylobacter*). Villiers has been named this substance was given the name "cellulosine" because to its cellulose-like characteristics, which include resistance to acid hydrolysis and non-reducing qualities [16]. Schmidt started researching the chemistry of CyDs in the first ten years of the 1900s. He found both beta- (β-CyD) and alpha-cyclodextrin (α-CyD) [17–19] and classified them as cyclic oligosaccharides. Freudenberg and associates had chemically determined during the 1950s that CyD molecules were repeating units of glucopyranose connected by a-(1,4) glycosidic linkages in a ring configuration. Additionally, they succeeded in synthesising the first pure CyD and separated gamma-cyclodextrin (γ-CyD) [19–25].

III. STRUCTURE

Various bacilli (*Bacillus macerans* and *B. circulans*) produce cycloglycosyl transferase amylases, which break down starch to make CDs, which are cyclic oligosaccharides. Depending on the precise response circumstances, three primary CD types- α-CD, β-CD, and γ–CD—are produced; each has six to eight dextrose units, respectively [26]. CDs are ring molecules that are toroidal rather than cylindrical and lack free rotation at the level of bonds between glucopyranose units or formed like a cone. The active molecule is placed within a hollow, tapered cavity measuring 0.79 nm in depth within CDs. Whereas the secondary groups are on the wider side, the primary hydroxyl groups are on the narrower side [15]. By replacing certain functional groups on the CD rim, its properties can be altered replacing CD's hydroxyl group chemically and enzymatically. The solubility can be increased via processes involving a range of substitution groups, such as hydroxypropyl, methyl, carboxyalkyl, thio, tosyl, amino, maltosyl, glucosyl, and sulfobutyl ether groups to β-CD. The polar (hydrophilic) component of CDs aids in the solubility of the medication and CDs in aqueous solution, whereas the non-polar (lipophilic) internal cavity of CDs causes solubility of non-polar solutes. Owing to these unique qualities, CDs have garnered significant attention as a solubilizing option and have been able to overcome the biopharmaceutical shortcomings of a number of medications in recent years[15,26-28]. In most organic solvents, CDs are insoluble, however they are widely soluble in some polar, aprotic solvents [29]. As a result of the guest molecule's greater affinity for the

solvent than for water, inclusion complexes do not form in non-aqueous solvents even though CDs are more soluble in some organic solvents than in water[29]. Acidic substances like sulfuric and hydrochloric acids can hydrolyze CDs, though the rate at which this happens varies with temperature and acid concentration. CDs are stable against bases [29].Low molecular lipophilic drug molecules and polymers can be partially accommodated in the hydrophobic cavity of CDs[30]. Lipophilic drug or hydrophilic drug-CD complexes are created when medicinal molecule that is lipophilic in the core cavity. Thus, the lipophilic guest molecule is shielded from the aqueous environment by the lipophilic cavity, and the solubilizing action is provided by the CD's outer polar surface [31].

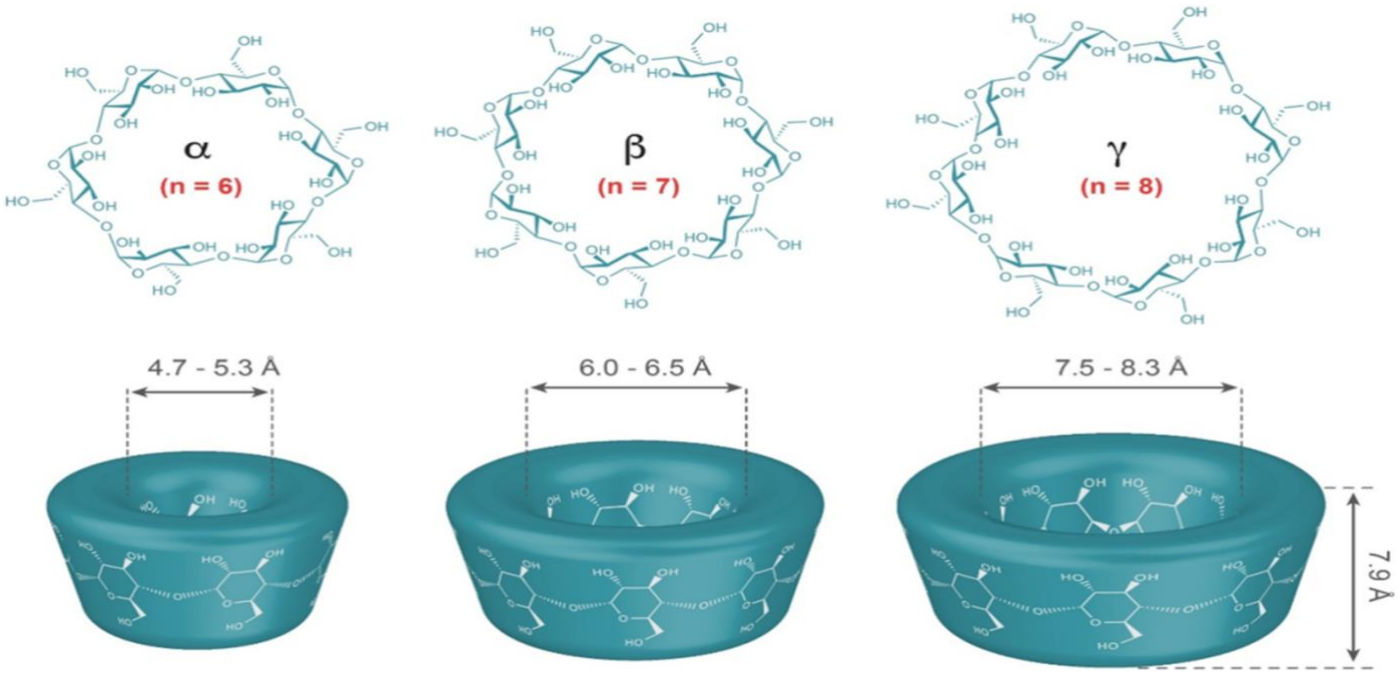

Figure 1:Schematic representations of three primary cyclodextrins, namely α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin, have that show their dimensions and comprise six, seven, and eight glucose units in their structures, respectively.

IV. PHYSICAL AND CHEMICAL PROPERTIES OF CYCLODEXTRIN

1. Cavity size

While choosing the right cyclodextrin for an inclusion complex, cavity size is an important factor to consider. Drug inclusion will not be appropriate if the size of the API is too large in relation to the size of the cavity. Compounds of low molecular weight or aliphatic side chain complex with α cyclodextrin, as indicated by the dimensions. Larger molecules like steroids and macromolecules combine with γ cyclodextrin to form complexes, while heterocyclic compounds do the same [33].

2. Aqueous Solubility

Despite being hydrophilic in nature, the natural cyclodextrins α, β, and γ along with their complexes have limited solubility. This is especially the case for β cyclodextrin, as strong intramolecular hydrogen bonds between secondary hydroxy groups reduce their ability to form hydrogen bonds with nearby water molecules. To combat this, a number of chemically modified derivatives have been developed, such as

sulfobutyl ether βCD sodium salt (SBEβCD), randomly methylated βCD (RMβCD), and hydroxypropylated βCD and γCD (HPβCD and HPγCD). [5,34,35].

3. Enzyme Stability

Compared to its linear counterparts, cyclodextrin's cyclic structure offers it resilience against both enzymatic and non-enzymatic hydrolysis. In the presence of β-amylase, which hydrolyzes starch from the non-reducing end of the glucose polymer, they remain stable; however, α-amylase gradually breaks them down. Salivary α-amylase cannot break down β or α CD, but salivary and the pancreatic α-amylase breaks down γ CD quickly. In g.i.t, natural CDs and their derivatives are susceptible to bacterial digestion [36].

4. Stability

At low pH levels in aqueous solution, cyclodextrin is susceptible to hydrolytic cleavage, which results in ring opening and the formation of different linear oligosaccharides and glucose units. When bases are present, they remain stable [33,37].

V. INCLUSION COMPLEX

Structures known as inclusion complexes are made up of two or more molecules, where one of the molecules is the "host" molecule and the other is a "guest" molecular structure. The host cavity contains molecules, or portions of molecules, that are hydrophobic and can fit into the host cavity when water is present.

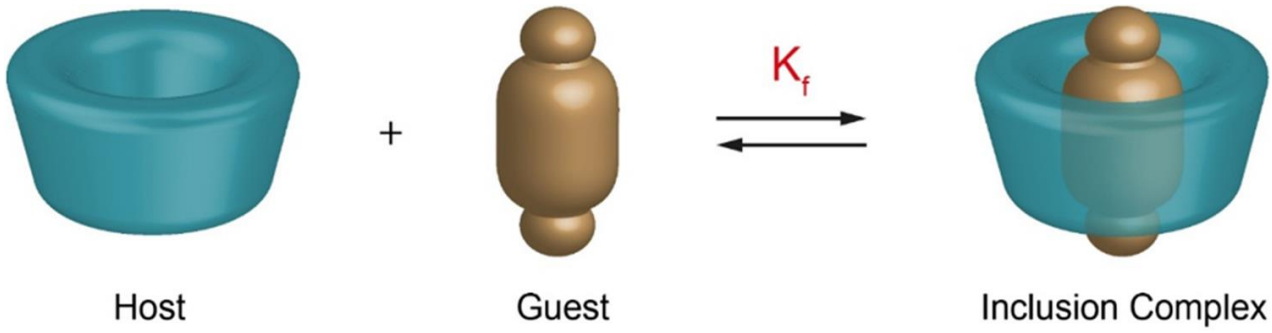

Figure 2: Diagrammatic representation of how a cyclodextrin (host) and a guest form an inclusion complex

Cyclodextrins can form inclusion complexes with pharmaceuticals in aqueous solutions by absorbing the drug molecule or the lipophilic moiety of the molecule into the core cavity where water molecules occupy the polar cyclodextrin cavity. Since the water molecules are energetically unflavored, they can be easily substituted by a guest molecule that is less polar than water.

VI. FACTORS AFFECTING INCLUSION COMPLEX FORMATION

1. Type of cyclodextrin

The kind of CD can significantly affect how well it develops and functions. The cavity's size should be suitable for incorporating a drug molecule of a specific size. Compared to neutral CDs, complexation can be enhanced when the drug and cyclodextrin have different charges, but it can decrease when they have the same charges [38–44].

2. Temperature

The strength of the drug/CD complex's apparent stability constant generally decreases with increasing temperature. This was attributed to a potential decrease in drug/CD contact forces, such as Van der Waals's hydrophobic forces with temperature rise [44, 45].

3. Method of preparation

The drug's and CD's physical and chemical characteristics dictate how effective the procedure is. Spray and freeze drying were shown to be the most effective procedures for drug complexation in the majority of cases [46–51].

4. Molar Substitution

The same type of derivative with low molar substitution works better as a complexing agent when compared to CD derivates with high molar substitution.

5. pH and Ionization

It has been noted that variations in ionization and pH lead to variations in the way that drugs and CD interact [52].

VII. METHODS FOR PREPARATION OF INCLUSION COMPLEX

There exist multiple methodologies utilised in the development of inclusion complexes, each with unique benefits and drawbacks. The physiochemical characteristics of the medication, the resources that are accessible, the quantity needed, and the cost all play a role in the inclusion complicated method selection.

The procedure should be optimised in order to obtain the best results. Techniques that are frequently employed include:

- Physical mixing
- Kneading
- Co-precipitation
- Solvent evaporation
- Freeze drying
- Spray drying techniques
- Microwave irradiation

1. **Physical Mixing**

The medicine and CDs are combined in a laboratory via mechanical trituration to form an inclusion complex. This mixture is then run through a suitable sieve, the choice of which depends on the desired final product particle size.

2. **Kneading**

This approach involves making a slurry of CDs with the least quantity of water or hydroalcoholic solution, adding the medicine, and properly kneading it for the necessary amount of time. The mixture is next dried and, if necessary, put through the proper sieve [53].

3. **Co-precipitation**

A sufficient quantity of the medicine dissolves in the alcoholic solution, and then it is added to the CD solution drop by drop while being constantly stirred. The prepared precipitate is separated using vacuum filtration and then let to dry at room temperature.

4. **Solvent Evaporation**

Two mutually miscible solvents are used to create a separate drug and CD solution. The CD solution is then gradually added to the drug solution while being constantly stirred. After the mixture has been stirred for a full day, the solvent is removed with a vacuum, and the finished product is extracted.

5. **Freeze Drying**

The freeze-drying approach involves dissolving the CDs and API in water or a water-cosolvent mixture and letting it sit at room temperature for 48 hours while stirring. The final product is recovered when the solution is mainly frozen and lyophilized.

6. **Spray Drying Techniques**

The medication and CDs are dissolved in water, and the resulting mixture is then dried with a spray dryer. To operate well, this approach needs the right conditions, including the right temperature and sample feeding rate. Used exclusively with thermostable compounds [54].

7. **Microwave Irradiation**

A uniform blend of medication and CDs is made using the least amount of water and an organic solvent in the right ratio. The mixture is then microwaved for 60–90 seconds at 60°C. After the produced product was filtered via Whatman filter paper and vacuum-dried, it was cleaned of residue using a solvent mixture (water and organic solvent).

Table 1: Comparison of various techniques for creating inclusion complex

METHOD	ADVANTAGES	DISADVANTAGES
PHYSICAL MIXING	Simple, most common and economical	Not as effective as other methods
KNEADING	Equipment commonly available and simple method	Less effective
CO-PRECIPITATION	None compared to others	Low yield and risk of using organic solvent
SOLVENT EVAPORATION	Simple and economic	Limited commercially utility
SPRAY DRYING	Common technique and scalable	Not for highly volatile and heat labile molecules and low yield
FREEZE DRYING	Gold standard method as compared to other	Expensive and long processing time
MICROWAVE IIRADIATION	Minimum solvent required, shorter reaction time and high product yield	Not for volatile and thermolabile molecules

VIII. TOXICOLOGY OF CYCLODEXTRIN

The size of cyclodextrin molecules (ranging in molecular weight from 1000 to > 2000 Da) and their abundance of hydrogen givers and receivers cause them to be poorly absorbed by biological membranes. Natural α- and β-CD cannot be hydrolyzed by human salivary or pancreatic amylase, while γ-CD can. At low to moderate oral dosages, hydrophilic cyclodextrins are not harmful [55,56]. For topical and oral formulations, natural cyclodextrins and their derivatives are acceptable; for intravenous preparations, only α-cyclodextrin and its hydrophilic derivatives of β- and γ-CD are suitable. The production of noticeable clusters by γ-Cyclodextrin in aqueous solutions makes them unsuitable for in relation to the intravenous formulations [36]. βcyclodextrin is not used in intravenous preparations due to its tendency to produce nephrotoxicity. Hydrophobic CD derivatives have been found to have harmful effects because methylated cyclodextrins can be absorbed to some extent from the gastrointestinal tract to the systemic circulation when given by parenteral means [56]. The potential for toxicity has now limited the use of methylated β-cyclodextrin in oral administration systems.

IX. REGULATORY STATUS

1. As more products get better, the regulatory landscape is also evolving. Both α-CD and β-CD are documented in the US Pharmacopeia/National Formulary (USP/NF), European Pharmacopoeia (Ph.Eur) and Japanese Pharmaceutical Codex (JPC). While γ-CD is referenced in the JPC, it will soon be included to the Ph.Eur. and USP/NF as well.

2. The HPβCD monograph is available in ph.Eur., and a draft has been distributed for USP/NF. Though attempts to include further derivatives are ongoing, they have not yet been reported. The FDA has included both HPβCD and SBEβCD on its list of inactive pharmacological ingredients.
3. The maximum dose that is supplied without producing any obvious negative effects is known as the NOEL (no-observable-effect-level), and it is determined through animal toxicity tests, which are the basis for regulatory status in the food business. Using the aggregate NOEL from the most sensitive species divided by a safety factor, the appropriate daily intake (ADI) for humans is calculated.
4. The Joint (FAO/WHO) Expert Committee on Food Additives (JECFA) has approved an acceptable daily intake (ADI) of 5 mg/kg for β-CD in food products. However, the established ADI for α- and γ-cyclodextrin is not advised due to their favorable toxicological profiles.
5. The FDA lists α-CD, β-CD, and γ-CD flavor stabilizers as GRAS, or "generally recognized as safe."

X. CONCLUSION

The proposed review of cyclodextrin examines its value as a functional excipient that is helpful, well-received, and frequently utilized in the pharmaceutical sector. Through the formation of inclusion complexes, cyclodextrin's bioadaptability and multifunctional qualities enable it to reduce the negative qualities of pharmacological molecules in a variety of delivery methods. In most cases, cyclodextrins can be used safely in a variety of applications. They are appropriate for use in food- and pharmaceutical-related applications since they are lowly poisonous and biocompatible.

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