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THE CYCLODEXTRINS: A REVIEW

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Abstract

Cyclodextrins are useful functional excipients that have enjoyed widespread attention and use. The basis for this popularity from a pharmaceutical standpoint is the ability of these materials to interact with poorly water-soluble drugs and drug candidates resulting in an increase in their apparent water solubility. The cyclodextrins have a wide range of applications in different areas of drug delivery and pharmaceutical industry due to their complexation ability and other versatile characteristics. The purpose of this review is to discuss and summarize some of the findings and applications of cyclodextrin (CD) and their derivatives in different areas of drug delivery. This article also highlights the chemistry, molecular structure, methods of complexation and focuses on its use for parenteral, oral, ophthalmic and nasal drug delivery.

INTRODUCTION:

Solubility problems are a genuine challenge for formulators since about 40% of marketed drugs are classified as "practically insoluble," according to Takagi (T. Takagi, *et al* 2006). There are less chances of improvement in it during the coming decades as most of the drugs in development show increasingly poor solubility, one third of drugs in development are poorly soluble; and two thirds of synthesized drugs have low solubility (Duchhene D *et al* 2005). Many techniques had been developed to overcome these solubility problems such as, hydrotropy, alteration of pH of the drug microenvironment, solid dispersion, inclusion of complex by using cyclodextrins, micro emulsion, solid solution, eutectic mixture and selective adsorption on insoluble carriers, evaporative precipitation into aqueous solution, use of surfactants, etc. Cyclodextrins are natural cyclic oligosaccharides that were discovered 100 years ago but only recently did highly purified cyclodextrins become available as pharmaceutical excipients. In the pharmaceutical industry cyclodextrins have mainly been used as complexing agents to increase aqueous solubility of poorly soluble drugs, and to increase their bioavailability and stability. In addition, cyclodextrins can be used to reduce gastrointestinal drug irritation, convert liquid drugs into microcrystalline or amorphous powder, and prevent drug–drug and drug–excipient interactions.

Types of Cyclodextrins

α -cyclodextrin: six membered sugar ring molecule

β -cyclodextrin: seven membered sugar ring molecule

γ -cyclodextrin: eight membered sugar ring molecule

A drug delivery system is expected to deliver the required amount of drug to the targeted site for the necessary period of time, both efficiently and precisely. Different carrier materials are being constantly developed to overcome the undesirable properties of drug molecules. In pharmaceutical technology, cyclodextrins are one of the most versatile aids. These are of a wide range of delivery devices from the most classical dosage forms to the newest drug carriers. Cyclodextrins offer an

additional tool for the formulator to overcome some of the formulation and delivery limitations of some drugs. The history, chemistry, complexation methods, applications of cyclodextrin (CD) in different areas of drug delivery, particularly in parenteral, oral, ophthalmic, nasal, dermal and rectal drug delivery systems are explained in detail.

Synthesis of Cyclodextrins

The production of cyclodextrins is relatively simple and involves treatment of ordinary starch with a set of easily available enzymes. Commonly cyclodextrin glycosyltransferase (CGTases) is employed along with α-amylase. First starch is liquefied either by heat treatment or using α-amylase, then CGTase is added for the enzymatic conversion. CGTases can synthesize all forms of cyclodextrins, thus the product of the conversion results in a mixture of the three main types of cyclic molecules, in ratios that are strictly dependent on the enzyme used: each CGTase has its own characteristic α:β:γ synthesis ratio. Purification of the three types of cyclodextrins takes advantage of the different water solubility of the molecules: β-CD which is very poorly water soluble can be easily retrieved through crystallization while the more soluble α- and γ-CDs (145 and 232 g/l respectively) are usually purified by means of expensive and time consuming chromatography techniques. As an alternative a "complexing agent" can be added during the enzymatic conversion step: such agents (usually organic solvents like toluene, acetone or ethanol) form a complex with the desired cyclodextrin which subsequently precipitates. The complex formation drives the conversion of starch towards the synthesis of the precipitated cyclodextrin, thus enriching its content in the final mixture of the products (Biwer A *et al* 2002).

Production of Cyclodextrins

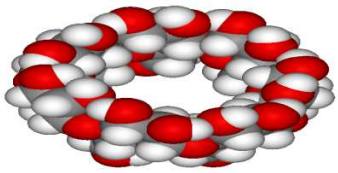
Treatment of starch with amylase from *Bacillus macerans* gives a crude mixture of cyclodextrin, The mixture was difficult to purify and it frequently contained several other linear and branched dextrins together with small amounts of proteins and other impurities. The biotechnological advances that occurred in the 1970s lead to dramatic improvements in their production. Genetic

engineering made different types of CGTases available that were both more active and more specific towards production of or cyclodextrin than the previously used enzymes. These enzymes together with other technological innovations made highly purified and cyclodextrin available that could be used as pharmaceutical excipients. In 1970, cyclodextrin was only available as a rare fine chemical at a price of about US$ 2000 per kg. Today the annuam cyclodextrin production is close to 10,000 tonnes and the bulk price has lowered to about US$ 5 per kg (CA Stanier *et al* 2001).

History of cyclodextrins

In 1891 a French scientist, A. Villiers, had isolated bacterial digest from starch (A. Villiers *et al* 1891, T. Loftsson *et al* 2007). The substance was a dextrin and Villiers named it as “cellulosine”. Later an Austrian microbiologist, Franz Schardinger, described two crystalline compounds α-dextrin and β-dextrin which he had isolated from a bacterial digest of potato starch. Schardinger identified β-dextrin as Villiers' “cellulosine” (Duan M, Zhao N *et al* 2005). Now these compounds are commonly called cyclodextrins (i.e. α-Cyclodextrin (α-CD) and β-cyclodextrin (β-CD)) or less commonly cyclomaltodextrins. Presently only α-CD, β-CD and γ-CD, as well as some of their derivatives have advanced to the market.

Fig-1: 3-D-Strcture of β-CD (b-cyclo dextrin).



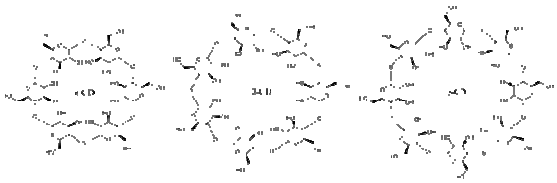
Cyclodextrins (CDs) have been recognized as useful pharmaceutical excipients. Due to their exhaustive studies, intensive basic research and industrial production, they can be used widely in pharmaceutical industry. Their molecular structures impart them with a unique property like hydrophilic exterior and a hydrophobic central cavity. This enables them to form non-covalent inclusion complexes by entrapping the drug into their central cavities. These non-covalent inclusion complexes offer a variety of physicochemical advantages over un manipulated drugs. They dramatically modify the physical, chemical and biological properties of parent drug and/or CDs.

Cyclodextrins are safe when administered through various routes. The formation of inclusion complexes of a drug with non-toxic agent is a promising approach used to improve the dissolution properties of drug.

Chemistry and Properties of Cyclodextrins

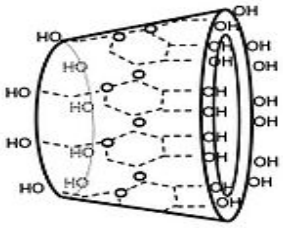
More than 1500 different CD derivatives have been described in the literature. Cyclodextrins are cyclic oligosaccharides containing at least six D-(+) glucopyranose units attached by α-(1, 4) glucosidic bonds as shown in Fig. 2.

Fig-2: The chemical structure of the three different types of cyclodextrin molecules.



Due to the chair formation of the glucopyranose units, cyclodextrin molecules are shaped like cones with secondary hydroxyl groups extending from the wider edge and the primary groups from the narrow edge. This gives cyclodextrin molecules a hydrophilic outer surface, whereas the lipophilicity of their central cavity is comparable to an aqueous ethanolic solution. The naturally occurring cyclodextrins are α, β and γ types containing 6, 7 and 8 glucopyranose units respectively. They have limited aqueous solubility due to the strong intermolecular hydrogen bonding in the crystal state. Substitution of the H-bond forming -OH group has improved their solubility (Hakkarainen B, *et al* 2005). The various derivatives that have gained pharmaceutical interest include hydroxyl propyl derivatives of β, γ and methylated β-cyclodextrins, sulfo butyl ether β-cyclodextrin etc.

Fig-3: Cyclodextrins Toroid structure showing spatial arrangement.



The three natural CDs, α -, β - and γ -CDs (with 6, 7 or 8 glucose units respectively) differ in their ring size and solubility (Table-1).

Table-1: Characteristics of CDs.

Type of CD	Cavity Diameter Å	Molecular weight	Solubility (g/100 ml)
α - CD	4.7-5.3	972	14.5
β - CD	6.0-6.5	1135	1.85
γ - CD	7.5-8.3	1297	23.2
δ - CD	10.3-11.2	1459	8.19

Modification of the 2- or 3- hydroxyl group results in disruption of the hydrogen bonding occurring around the ring of the CD molecule. The disruption allows more interactions of these hydroxyl groups with water molecules, resulting in altered solubility (Robyt JF *et al* 1998). Complexation of molecules to cyclodextrins occurs through a non-covalent interaction between the molecule and the CD cavity. This is a dynamic process whereby the guest molecule continuously associates and dissociates from the host CD. Cyclodextrins are insoluble in most organic solvents; they are soluble in some polar, aprotic solvents. Although the solubility of cyclodextrins is higher in some organic solvents than in water, complexation may not occur readily in non-aqueous solvents because of the increased affinity of the guest for the solvent compared to its affinity for water.

Complexation and Mechanism of Drug Release from Cyclodextrin Complexes

The internal cavity is hydrophobic in nature which is a key feature of the cyclodextrins providing the ability to form complexes, which include a variety of guest molecules. Cyclodextrin inclusion is a stoichiometric molecular phenomenon in which usually only one molecule interacts with the cavity of the cyclodextrin molecule to become entrapped. A variety of non-covalent forces, such as *Vander Waals* forces, hydrophobic interactions and other forces are responsible for the formation of the stable complex. Inclusion complex formation can be regarded as 'encapsulation' of the drug molecule, or at least the labile part of the molecule. The encapsulation protects the drug moleculeagainst attack by various reactive molecules and in this way reduces the rate of hydrolysis, oxidation, stearic rearrangement, racemization and even enzymatic decomposition (Robyt JF *et al* 1996). In addition, cyclodextrins can decrease the photo degradation of various light sensitive drugs.

COMPLEXATION TECHNIQUES

Many techniques are used to form complexes with cyclodextrin, like grinding, kneading, co-precipitation, solid dispersion, neutralization, spray drying, freeze drying, melting, etc. The name itself describes the process of complex formation.

1. Physical blending / Grinding method: Inclusion complexes can be prepared by simply grinding/ triturating the drug with cyclodextrin in mortar, on small scale. Whereas on large scale, the preparation of complexes is based on extensive blending of the drug with cyclodextrin in a rapid mass granulator usually for 30 minutes.

2. **Kneading method:** Paste of cyclodextrin is prepared with small amount of water to which the drug is added without a solvent or in a small amount of ethanol. After grinding paste, solvent get evaporated and powder like complex is formed. On laboratory scale kneading can be achieved by using a morter and pestle (Faucci MT *et al* 2007)**.** On large scale the kneading can be done by utilizing the extruders and other machines. Parikh (Parikh *et al* 2005) reported the dissolution enhancement of Nimesulide using complexation method.

3. **Co-precipitation:** Cyclodextrin is dissolved in water and the guest is added while stirring the cyclodextrin solution. By heating, more cyclodextrin can be dissolved (20%) if the guest can tolerate the higher temperature. The cyclodextrin and guest solution must be cooled under stirring before a precipitate is formed. The precipitate can be collected by decanting, centrifugation or filtration and washed. Mehramizi (Mehramizi A *et al* 1997) had studied the solid-state characterization and dissolution characteristics of Gliclazide-Beta- cyclodextrin inclusion complexes.

4. **Solid dispersion / co- evaporated dispersion**: In this method, drug and cyclodextrin are dissolved in ethanol and in water separately. Both the solutions are mixed and stirred to attain equilibrium. The resulting solution is evaporated to dryness preferably under vacuum.

5. **Neutralization method**: Drug and cyclodextrin are separately dissolved in 0.1 N sodium hydroxide, mixed and stirred for about half an hour, pH is recorded and 0.1 N HCl is added drop wise with stirring until pH reaches 7.5, where upon complexes precipitates. The residue is filtered and

washed until free from chlorine, It is dried at 2500C for 24 h. and stored in desiccators.

Duchhene (Duchhene D *et al* 2007) had studied the enhancement of solubility of Piroxicam by complexation with beta-cyclodextrin.

6. **Spray drying**: In this method, first monophasic solution of drug and cyclodextrin is prepared using a suitable solvent. The solution is then stirred to attain equilibrium following which the solvent is removed by spray drying. Vozone (Vozone CM, et al 2003) had developed complexation of budesonide in cyclodextrins and particle aerodynamic characterization of the complex solid form for dry powder Inhalation.

7. **Lyophilization/ Freeze drying technique:** To get a porous, amorphous powder with high degree of interaction between drug and cyclodextrin, lyophilization/freeze drying technique is considered as a suitable. Here, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug and cyclodextrin at reduced pressure. Thermolabile substances can be successfully made into complex form by this method.

8. **Melting**: Complexes can be prepared by simply melting the guest, mixed with finely powdered cyclodextrin. In such cases there should be a large excess of guest, and after cooling this excess is removed by careful washing with a weak complex, forming solvent or by vacuum sublimation (Pandya SJ *et al* 2008).

2. Applications of Cyclodextrins in Drug Delivery

Ophthalmic Drug Delivery

Locally applied drug formulations such as suspensions, oily drops, gels, ointments and solid inserts have been used, but most of these formulations give rise to unwanted side effects. (e.g. eye irritation and blurred vision) Cyclodextrins enhance drug permeability through biological membranes such as eye cornea and skin by disrupting the membrane, either by permeating into the membrane or by extracting or complexing with some lipophilic components such as cholesterol and phospholipids from the membrane (D. Duchene *et al* 1996). Cyclodextrins work as an anti irritant by formation of inclusion

complex and thereby masking the irritating drugs or by replacing the irritating additives from the formulation.

Nasal Drug Delivery

Nasal route is another effective way to bypass first-pass metabolism. Cyclodextrins are normally used in nasal formulations to increase the aqueous solubility of lipophilic drugs. The lipophilic cyclodextrins acts as penetration enhancers, especially in nasal delivery of peptides. The nasal bioavailability of insulin in rats was increased from about 0-100% by including methylated cyclodextrins in formulations (Mehramizi A *et al* 1991). Promising results from nasal delivery of Dihydro ergotamine (Marttin E *et al* 1997), Midazolam (Loftsson T *et al* 2001), Heparins (Yang T *et al* 2004) and Ondansetron (Cho E *et al* 2008) had been reported.

Transdermal Drug Delivery

The main barrier for dermal drug absorption through the skin is the outer most layer stratum corneum. Penetration enhancers like alcohols, fatty acids etc. are used to decrease its barrier properties. Cyclodextrins improves the solubility and stability of drugs in the topical preparations, enhances the transdermal absorption of drugs, sustains the drug release from the vehicle and avoids undesirable side effects associated with dermally applied drugs (Hashimoto H *et al* 1999). The cyclodextrins enhance drug delivery through aqueous diffusion barriers, but not through lipophilic barriers like stratum corneum. Cyclodextrins alleviate drug induced skin irritation by lowering the extent of free drug resulting from inclusion equilibrium (CA Stanier *et al* 2008).

Rectal Drug Delivery

Release of drugs from suppository bases is one of the important factors in the rectal absorption of the drugs, since the rectal fluid is small in volume and viscous compared to gastrointestinal fluid. Hydrophilic cyclodextrins enhance the release of poorly water-soluble drugs from oleaginous suppository bases because of the lesser interaction of the resultant complexes with the vehicles. The complexation of lipophilic drugs with hydrophilic cyclodextrins makes them insoluble in hydrophobic vehicles, the complex existing as well-dispersed fine particles in the vehicles. The methylated

cyclodextrins significantly enhance the rectal absorption of hydrophobic drugs, which are anti inflammatory agents, like Flurbiprofen (CA Stanier *et al* 1988), carmofur and biphenyl acetic acid from the oleaginous suppository.

Oral Drug Delivery

Immediate Release

Dissolution rate of the poorly water-soluble drugs is responsible for both the rate and extent of oral bioavailability of the drugs. The hydrophilic cyclodextrins are applied to enhance the oral bioavailability of steroids, cardiac glycosides, non steroidal anti inflammatory drugs, barbiturates, anti-epileptics, benzodiazepines, anti diabetics, vasodilators etc. (Szente R *et al* 1998, Uekama K *et al* 1987). The immediate release formulations of analgesics, antipyretics, coronary vasodilators etc., are very useful in emergency situations. The inclusion complexes with cyclodextrins improve solubility and wettability of the drugs. The stabilizing effect of cyclodextrins on labile drugs is also responsible for the improvement of oral bioavailability.

Prolonged release

Generally **s**low-release formulations are prepared to achieve zero-order or pH-independent release of drugs to provide a constant blood level for a long period of time. These formulations have benefits such as reduced dosing frequency, prolonged drug efficacy and absence of toxicity associated with the administration of a simple plain tablet. Hydrophobic cyclodextrins were the first slow-release carriers to be used in conjugation with Diltiazem (Hashimoto H *et al* 1991).

Modified Release

This involves the release of drug in a different physical state. The conventional formulation of Nifedipine, a typical calcium-channel antagonist, must be dosed either twice or thrice daily, because of the short elimination half-life due to the considerable first-pass metabolism. Due to poor aqueous solubility It shows low oral bioavailability and a decrease in dissolution rate during the storage due to the crystal growth . Wang (Z. Wang *et al* 1994) developed a double-layer tablet employing an amorphous Nifedipine powder prepared by spray drying with HP-β-CD and HCO-60®

(non-ionic detergent) as the fast release portion to attain initial rapid dissolution.

Delayed Release

An enteric preparation can be classified as time-controlled release, since the drug is preferentially released in the intestinal tract. Excipients having weak acidic groups are preferable because they are less soluble in water at low pH and soluble in neutral and alkaline regions due to the ionization of the acidic group. The absorption of Molsidomine from tablets containing CME-β-CD was studied in gastric acidity-controlled dogs in fasted and fed states. Under high gastric acidity, Molsidomine absorption was significantly retarded compared to that found under low gastric acidity conditions. The delayed absorption effect under high gastric acidity was more pronounced under fasted conditions (Higuchi T & Connors KA *et al* 1995).

Parenteral Drug Delivery

α-cyclodextrin and the hydrophilic derivatives of β- and γ-cyclodextrin can be used in parenteral formulations. The γ-cyclodextrin forms visible aggregates in aqueous solution and is not well suited for parenteral formulations (Szente R *et al* 1998). SBE4-β-CD or HP-β-CD was utilized for I.V. administration. Significant changes in the pharmacokinetics of a drug were studied by some researchers (Faucci *et al* 2000).

Drug Availability from Cyclodextrin-Containing Products

It has been widely believed that drug availability in cyclodextrin-containing formulations will be hampered by the slow release of drug molecules from the cyclodextrin cavities. However, it has been shown that the rates for formation and dissociation of drug/cyclodextrin complexes are very close to diffusion controlled limits with complexes being continually formed and broken down. Consequently, presence of water-soluble drug/cyclodextrin complexes right at the hydrated epithelial surface will frequently increase the availability of dissolved drug molecules, especially of lipophilic drugs with poor aqueous solubility. Studies have shown that cyclodextrin enhance oral bioavailability of FDA's Class II (poor aqueous solubility, high permeability) drugs but they can hamper bioavailability of Class I (high solubility, high

permeability) and Class III (high solubility, poor permeability) drugs.

Cyclodextrins in Dispersed Systems

Both the parent cyclodextrins and their derivatives have been used in dispersed vehicle systems such as emulsions, microcapsules, microspheres, nanospheres, nanocapsules, liposomes and niosomes. Inclusion complexes of glycerides, fatty acids or fatty alcohols do possess surface activity and this property together with their ability to form aggregates frequently result in formation of dispersed systems. In other cases cyclodextrins have been uses to increase drug loading of polymeric microspheres or to increase drug availability from dispersed systems. Novel surface active cyclodextrin derivatives have also been synthesized and used as drug delivery systems. Applications of Cyclodextrins in Drug Delivery Oral Drug Delivery Immediate Release.

Table 2: Marketed Products Containing Cyclodextrin

Drug	Administration route	Trade name	Market
α-Cyclodextrin			
Alprostadil (PGE_1)	IV	Prostavastin	Europe, Japan, USA
Cefotiam hexetil HCl	Oral	Pansporin T	Japan
β-Cyclodextrin			
Benexate HCl	Oral	Ulgut, Lonmiel	Japan
Dexamethasone	Dermal	Glymesason	Japan
Iodine	Topical	Mena-Gargle	Japan
Nicotine	Sublingual	Nicorette	Europe
Nimesulide	Oral	Nimedex, Mesulid	Europe
Nitroglycerin	Sublingual	Nitropen	Japan
Omeprazol	Oral	Omebeta	Europe
PGE_2	Sublingual	Prostarmon E	Japan
Piroxicam	Oral	Brexin	Europe
Tiaprofenic acid	Oral	Surgamyl	Europe
2-Hydroxypropyl-β-cyclodextrin			
Cisapride	Rectal	Propulsid	Europe
Hydrocortisone	Buccal	Dexccort	Europe
Indomethacin	Eye drops	Indocid	Europe
Itraconazole	Oral, IV	Sporanox	Europe, USA
Mitomycin	IV	Mitozytrex	USA
Randomly methylated β-cyclodextrin			
17β-Estradiol	Nasal spray	Aerodiol	Europe
Chloramphenicol	Eye drops	Clorocil	Europe
Sulfobutylether β-cyclodextrin			
Voriconazole	IV	Vfend	Europe, USA
Ziprasidone maleate	IM	Geodon, Zeldox	Europe, USA
2-Hydroxypropyl-γ-cyclodextrin			
Diclofenac sodium	Eye drops	Voltaren	Europe

CONCLUSION

Cyclodextrins are useful functional excipients that have enjoyed widespread attention and use in the pharmaceutical industry. Studies in both humans and animals have shown that cyclodextrins can be used to improve the drug delivery from almost any type of drug formulations. Cyclodextrins are not only well-known solubilizers, but constitute very powerful

tool as permeation enhancers. There are a number of exciting possibilities for future applications of cyclodextrins, including new uses for existing derivatives, as well as the development of new derivatives. In future Cyclodextrins having properties of increasing solubility, bioavailability, stability etc may solve various problem associated with drug delivery through the complexation. It took cyclodextrins 100 years to evolve from interesting chemical oddities to enabling pharmaceutical excipients. In the pharmaceutical industry cyclodextrins have mainly been used as complexing agents to increase aqueous solubility of poorly soluble drugs, and to increase their bioavailability and stability. In the classical cyclodextrin chemistry, it is assumed that when a drug molecule forms a complex with cyclodextrin, then some given lipophilic moiety of the drug molecule enters into the hydrophobic cyclodextrin cavity. Studies in both humans and animals have shown that cyclodextrins can be used to improve drug delivery from almost any type of drug formulation. However, addition of cyclodextrins to existing formulations without further optimization will seldom result in acceptable outcome. Currently there are worldwide about 30 different pharmaceutical products containing drug cyclodextrin complexes on the market.

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