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Review Article

CYCLODEXTRIN A GIFT TO PHARMACEUTICAL WORLD REVIEW

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ABSTRACT
The macrocyclic cyclodextrins (enzymatic conversion products of starch) were discovered in 1891, and the structures were elucidated in the mid-1930s. Their industrial significance become obvious in the 1970s, and by now thousands of tons of the three cyclodextrins (α-, β-, and γCD) and of their chemical derivatives and inclusion complexes are produced industrially. The paper highlights important CD applications in drug solubility and dissolution, bioavailability, safety, and stability, their use as excipients in drug formulation, design of various novel delivery systems like liposome, microspheres, microcapsules, and nanoparticles. Recently Thorsteinn et. al. filled a patent on nano ophthalmic composition which is an aqueous suspension comprising drug, cyclodextrin and water[1]. The size of the solid particles being from about 10 nm to about 1 mm, the drug/cyclodextrin particles being capable of dissolving in aqueous tear fluid within 24 hours of application to the eye surface. Eunsook Cho et.al used sulfobutylether ß-cyclodextrin in formulation of nasal drug delivery of ondansetron HCl. The addition of 10% SBCD to aqueous solution containing 10% PEG 300 and 0.01% Benalkonium chloride could be a good candidate for ondansetron nasal delivery systems because of its safety profile, stable storage in refrigerator and solubilizing effect. The article also focuses on various factors influencing inclusion complex formation because an understanding of the same is necessary for proper handling of these versatile materials. Some important considerations in selecting CDs in drug formulation such as their commercial availability, regulatory status, and patent status are also summarized. Apart from these various properties of different cyclodextrin are also discuss in these paper.[2]

Keywords: Cyclodextrin, α – CD, β – CD, γ - CD

INTRODUCTION

Cyclodextrin comprise a family of three well-known industrially produced major, and several rare, minor cyclic oligosaccharides. The three major CDs are crystalline, homogeneous, non hygroscopic substances, which are torus-like macro-rings built up from glucopyranose units. The α-cyclodextrin (Schardinger's α-dextrin, cyclomaltohexaose, cyclohexaglucan, cyclohexaamylose, αCD, ACD, C6A) comprises six glucopyranose units, βCD (Schardinger's β-dextrin, cyclomaltoheptaose, cycloheptaglucan, cycloheptaamylose, βCD, BCD, C7A) comprises seven such units and γCD (Schardinger's γ-dextrin, cyclomaltooctaose, cyclooctaglucan, cyclooctaamylose, γ CD, GCD, C8A) comprises eight such units[1,9,10,11].

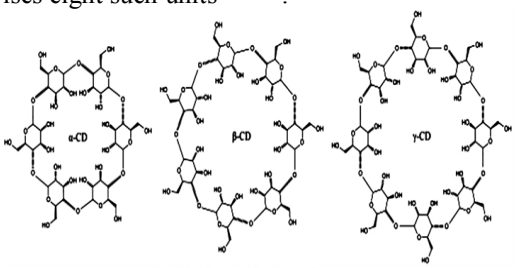

Fig. 1 - Structre of Cyclodextrin

TABLE 1: PROPERTIES OF CYCLODEXTRINS[13,14,15]

Cyclodextrin	α -CD	β-CD	γ-CD
Number of Glucopyranose units	6	7	8
Molecular Weight	972	1135	1297
Solubility in water (g/100 mL)	14.5	1.85	23.2
pKa	12.33	12.2	12.08
Height (nm)	0.79	0.79	0.79
Cavity Volume (nm^3)	0.174	0.262	0.472
Cavity Volume (mL) Per 1 mol Per 1 g	 104 0.1	 157 0.14	 256

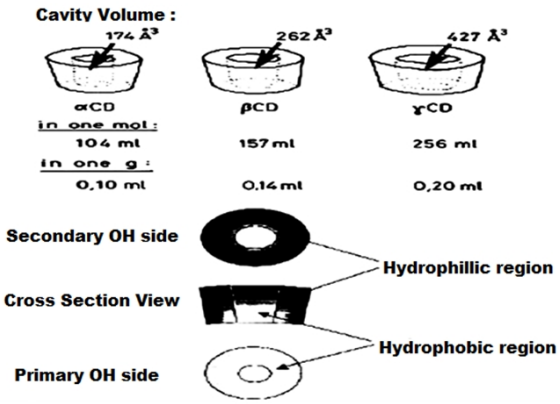

Fig.2 - Cavity Volume and internal characteristics

Cyclodextrin Derivatives

The aim of derivatizations may be -

- To improve the solubility of the CD derivative (and its complexes);
- To improve the fitting and/or the association between the CD and its guest, with concomitant stabilization of the guest, reducing its reactivity and mobility;
- To attach specific (catalytic) groups to the binding site (e.g., in enzyme modeling); or
- To form insoluble, immobilized CD-containing structures, polymers (e.g., for chromatographic purposes.

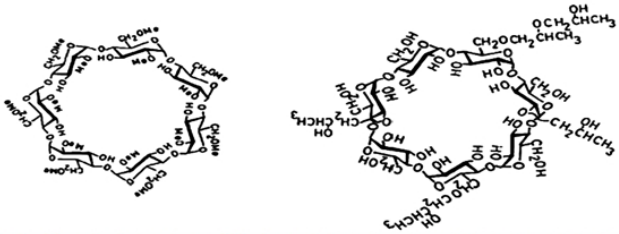

Fig.3 - Chemical strusture of Hydroxy β Cyclodextrin and Methylated β Cyclodextrin

Derivatives of Cyclodextrin[19,20,21]

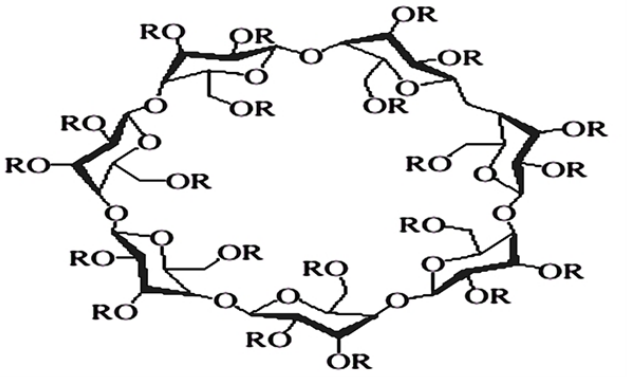

Fig . 4 - Basic ring of cyclodextrin

Cyclodextrin	R = H or
β -Cyclodextrin	–H
2-Hydroxypropyl-β –cyclodextrin	-CH2CHOHCH3
Sulfobutylether β -cyclodextrin sodium salt	2)4SO3 - Na +
Randomly methylated β –cyclodextrin	- CH_3
Branched β –cyclodextrin	Glucosyl or maltosyl group

Table 2: The effects of the Molecular structure and Physicochemical properties on formation of Drug/Cyclodextrin complexes[22,23]

Property	Consequences
Size of the cyclodextrin cavity	The size of the cyclodextrin cavity will influence the complex formation. For instance, the α-cyclodextrin cavity is too small for naphthalene and only the γ-cyclodextrin cavity can accommodate anthracene α-Cyclodextrin can be used for small molecules or side chains of larger molecules (e.g. prostaglandins), β-cyclodextrin is very useful for complexing molecules containing a phenyl group, a group encompassing many drugs, and γ-cyclodextrin can be used for complexation of larger molecules such as macrolide antibiotics
Molar substitution	Chemically modified cyclodextrins of lower molar substitution are frequently better complexing agents than the same derivatives with higher molar substitution
The intrinsic solubility of the drug	The lower the intrinsic drug solubility, the greater the relative solubility enhancement obtained via cyclodextrin complexation. Drugs that possess aqueous solubility in the µg/ml range generally demonstrate much greater relative enhancement than drugs possessing solubility in the mg/ml range.
Hydrophilic drugs possessing low intrinsic solubility in water	Zwitter ionic drugs, and other polar drugs of limited aqueous solubility, generally demonstrate low complexing abilities. The basis for such poor enhanced solubility is that the low aqueous solubility of the drug is frequently due to high crystal energy rather than their lipophilicity. Once in solution, the hydrated drug molecules often have little tendency to be included into the hydrophobic cyclodextrin cavity. However, many ionisable drugs are capable of forming cyclodextrin complexes, and, although the ionized form tends to form complexes less rapidly than the unionized form, it is frequently possible to enhance aqueous solubilisation of ionisable drugs by appropriate pH adjustments.
Ion pairing	Compared with neutral cyclodextrins, enhanced complexation is frequently observed when the drug and cyclodextrin molecules have opposite charge, while decreased complexation is observed when the drug and cyclodextrin carry the same type of charge.

Phase-Solubility Diagram

Higuchi and Connors have classified complexes based on their effect on substrate solubility and it is indicated by the phase-solubility profiles. A-type phase-solubility profiles are obtained when the solubility of the substrate (i.e. drug) increases with increasing ligand (cyclodextrin) concentration. When the complex is first order with respect to ligand and first or higher order with respect to substrate then AL-type phase-solubility profile is obtained. If the complex is first order with respect to the substrate, but second or higher order with respect to the ligand then AP-type phase solubility profile is obtained. It is difficult to interpret the AN-type phase-solubility profile. The negative deviation from linearity may be associated with cyclodextrin induced changes in the dielectric constant of the aqueous complexation media, changes in complex solubility or self-association of cyclodextrin molecules. B-type phase-solubility profiles indicate formation of complexes with limited solubility in the aqueous complexation medium.[24]

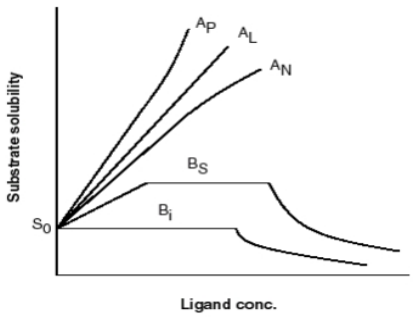

Fig. 5 - Phase Solubility Diagram

In general, the water-soluble cyclodextrin derivatives form A-type phase solubility profiles, whereas the less soluble natural cyclodextrin forms B-type profiles. Most of the drug/cyclodextrin complexes are thought to be inclusion complexes, but cyclodextrins are also known to form non-inclusion complexes and the complex aggregates are capable of dissolving drugs through micelle-like structures[25]. The phase-solubility profiles only describe how the increasing cyclodextrin concentration influences the drug solubility.

The most common type of cyclodextrin complexes is the 1:1 drug/cyclodextrin (D/CD) complex where one drug molecule (D) forms a complex with one cyclodextrin molecule (CD) and is given in eq. 1.

$$D + CD \xleftrightarrow{K_{1:1}} D/CD$$

Eq. 1

The value of K1:1 is most often between 50 and 2000 M-1 with a mean value of 129, 490 and 355 M-1 for α-, β- and γ-cyclodextrin respectively [26,27]. Under such conditions, for an AL-type phase-solubility diagram with slope less than unity, the stability constant (K1:1) of the complex can be calculated from the slope and the intrinsic solubility of the drug in aqueous complexation media (i.e., drug solubility when no CD is present) and is given in eq. 2.

$$K_{1:1} = \frac{Slope}{S_0 (1 - Slope)}$$

Eq.2

For 1:1 drug/CD complexes the complexation efficiency (CE) can be calculated from the slope of the phase-solubility diagram (eq. 3) by

$$CE = \frac{[D/CD]}{[CD]} = S_0 \cdot K_{1:1} = \frac{Slope}{S_0 (1 - Slope)}$$

Eq. 3

The most common stoichometry of higher order D/CD complexes is the 1:2 D/CD complex resulting in Ap-type phase solubility diagram. Consecutive complexation is assumed where 1:2 complexes (eq. 4) is formed when one additional cyclodextrin molecule forms a complex with an existing 1:1 complex.

The value of k1:2 frequently lies between 10–500 μ-1 and is lower than that of k1; 1(50–2000 μ-1)

$$D/CD + CD \xleftrightarrow{K_{1:2}} D/CD_2$$

Eq. 4

The various methods that are used to prepare D/CD complexes include solution method, co-precipitation method, neutralisation method, slurry method, kneading method, grinding method etc[28] and water is essential for the successful complex formation. In solution, the cyclodextrin complexes are prepared by addition of excess amount of drug to an aqueous cyclodextrin solution. The suspension formed is equilibrated at desired temperature and then centrifuged to form clear D/CD complex solution. For preparation of solid complexes water is removed from the aqueous D/CD complex by evaporation or sublimation. For a variety of reasons, such as isotonicity of parenteral formulations and formulation bulk of solid dosage forms, it is important to include as little cyclodextrin as possible in a pharmaceutical formulation. The complexation efficiency can be enhanced by various methods.[29]

Table 4: Methods that can be applied to enhance the Complexation efficiency[24,25,28,29]

Effect	Consequences
Drug ionization	Unionized drugs usually form more stable complexes than their ionic counterparts; however, ionization of a drug increases its apparent intrinsic solubility, resulting in enhanced complexation.
Salt formation	It is sometimes possible to enhance the apparent intrinsic solubility of a drug through salt formation.
The acid/base ternary complexes	It has been shown that certain organic hydroxy acids (such as citric acid) and certain organic bases are able to enhance the complexation efficiency by formation of ternary drug/cyclodextrin/acid or base complexes.
Polymer complexes	Water-soluble polymers form a ternary complex with drug/cyclodextrin complexes, increasing the observed stability constant of the drug/cyclodextrin complex. This observed increase in the value of the constant increases the complexation efficiency.
Solubilisation of cyclodextrin aggregates	Organic cations and anions are known to solubilise uncharged drug/cyclodextrin complexes that have limited aqueous solubility. This will enhance the complexation efficiency during preparation for example, solid drug/cyclodextrin complex powder.
Combination of two or more methods	Frequently, the complexation efficiency can be enhanced even further by combining two or more of the aforementioned methods, for example drug ionization and the polymer method, or solubilisation of the cyclodextrin aggregates by adding both polymers and cations or anions to the aqueous complexation medium.

APPLICATIONS

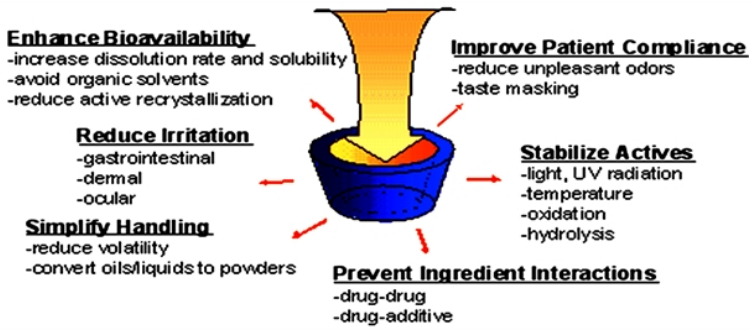

Fig.6 - Pharmaceutical Applications of Cyclodextrin

A] Bioavailability Enhancement

Drugs with poor bioavailability typically have low water solubility and/or tend to be highly crystalline. As shown, cyclodextrins are water soluble and form inclusion complexes with a polar molecules or functional groups in water insoluble compounds. The resulting complex hides most of the hydrophobic functionality in the interior cavity of the cyclodextrin while the hydrophilic hydroxyl groups on its external surface remain exposed to the environment[2].

B] Active Stabilization

For an active molecule to degrade upon exposure to radiation, heat, oxygen or water, chemical reactions must take place. When a molecule is constrained within the cyclodextrin cavity, it is difficult for reactant to diffuse into cavity and react with the protected guest[30].

C] Odour Or Taste Masking

Through encapsulation within the cyclodextrin cavity, molecules or specific functional groups that cause unpleasant tastes or odors are hidden from the sensory receptors. The resulting formulations have no or little taste or odor and are much more agreeable to the patient[33,34,35].

D] Compatibility Improvement

Often one would like to combine multiple ingredients or drug actives within a single formulation due to the potential for synergistic benefits. Encapsulating one of the incompatible ingredients within a cyclodextrin molecule stabilizes the formulation by physically separating the components in order to prevent chemical interaction[12].

E] Material Handling Benefits

Active ingredients that are oils/liquids or are volatile materials can be difficult to handle and formulate into stable solid dosage forms. Encapsulating these types of substances in a cyclodextrin converts them to a solid powder that has good flow properties and can be conveniently formulated into a tablet by conventional production processes and equipment[36,37].

F] Irritation Reduction

Active ingredients that irritate the stomach, skin or eye can be encapsulated within a cyclodextrin to reduce their irritancy. The formation of an inclusion complex reduces the local concentration of free active below the irritancy threshold.

Table 6: Approved and Marketed drug/CD formulations[26,28,36]

Drug/cyclodextrin	Trade name	Indication	Formulation	Company/country
PGE2/βCD	Prostarmon E	Induction of labor	Sublingual tablet	Ono, Japan
Piroxicam/βCD	Cicladol, Brexin	Anti-inflammatory, Analgesic	Tablet, sachet, and suppository	Masterpharma, Chiesi, Italy
Nitroglycerin/βCD	Nitropen	Coronary dilator	Sublingual tablet	Nippon Kayaku, Japan
Cefotiam-hexetil/αCD	Pansporin T	Antibiotics	Tablet	Takeda, Japan
Cephalosporin ME 1207)/βCD	Meiact	Antibiotics	Tablet	Meiji Seika, Japan
Diphenhydramine.HCl chlortheophylline+βCD	Stada-Travel	Travel sickness	Chewing tablet	Stada, Germany
Hydrocortisone/HPβCD	Dexacort	Mouth wash against aphta, gingivitis, etc.	Liquid	Island
Itraconazole/HPβCD	Sporanox	Esophageal Candidiasis	Liquid	Janssen, Belgium
Cloramphenicol/ methyl βCD	Clorocil	Eye drop,	Liquid	Oftalder, P`ortugal
Ziprasidone mesylate/ sulphobutyl βCD	Zeldox, Geodon	Antischizophrenic	Intramascular injection	Pfizer, USA
Nimesulide/βCD	Mesulid Fast Nimedex	Nonsteroid anti-inflammatory	Oral sachet	Novartis (LPB), Italy
Omeprazole/βCD	Omebeta	Proton pump Inhibitor	Tablet	Betapharm, Germany

Table 7: Reported work done on Cyclodextrin

Drug	Carrier	Method	Conclusion
Piroxicam	HPβCD	Freeze- drying	The in vitro release result demonstrated that matrix tablet containing the drug-HP βCD solid complex showed faster drug release compared to those containing a physical mixture or free drug.
Ampelopsin	βCD, HPβCD, PVP K30,	Co-evaporation	Increase in solubility in following order HPβCD=βCD>PVP K30> PEG 6000.
Benzocaine	βCD	Freeze-drying	Drug- βCD complex represent an effective novel formulation to enhance Benzocaine solubility in water, turning it promising for use outside its traditional application.
Indomethacin	βCD, HPβCD	Freeze- drying	Increase in solubility and hence enhance bioavailability.
Danazol	HP βCD	Co-evaporated	Absolute bioavailability of the coprecipitate complex and commercial formulation was 14.2% and 6.2%.
13-cis-retinoic	αCD, HPβCD	Freeze- drying	The result showed that HP βCD was a proper excipients for increasing solubility and stability of 13-cis-Retinoic acid.
Pilocarpine	αβCD, βCD	Spray-drying, Lyophilization	The use of cyclodextrin in ophthalmic preparatrion could be advantageous not only for lipophilic drugs but also for hydrophilic drugs.
7-rhamnogluside	HP Bcd	Co-evaporation	Antioxidant efficacy was in all cases higher for complexed drugs, with respect to the free ones; these results are of great interest for their potential usefulness in pharmaceutics.

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