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Review Article

CYCLODEXTRINS: VERSATILE CARRIER IN DRUG FORMULATIONS AND DELIVERY SYSTEMS

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ABSTRACT

The aim of this review is to summarize the wide range of applications of cyclodextrins (CDs) and their derivatives in different areas of drug delivery and pharmaceutical industry due to their complexation ability and other versatile characteristics. Cyclodextrins were first described by Villiers in 1891. He described Cyclodextrin as enzyme conversion product of starch. Schardinger laid the foundation of the cyclodextrin chemistry in 1903–1911. In the 1930s, Freudenberg suggested that larger cyclodextrins could exist. Freudenberg and co-workers showed that cyclodextrins were cyclic oligosaccharides formed by glucose units. Cramer and co-workers described their ability to form inclusion complexes. By the early 1950s the basic physicochemical characteristics of cyclodextrins had been discovered, including their ability to solubilize and stabilize drugs. The first cyclodextrin-related patent was issued in 1953 to Freudenberg, Cramer and Plieninger. Cyclodextrin also effects on drug solubility and dissolution, bioavailability, safety, stability, and drug release from formulation by forming the Cyclodextrin-drug complex. Various factors are responsible for complex formation. The article highlights important CDs applications in the design of various novel delivery systems like liposomes, microspheres, microcapsules, and nanoparticles. New cyclodextrin-based technologies are constantly being developed and, thus, 100 years after their discovery cyclodextrins are still regarded as novel excipients of unexplored potential.

Keywords: Cyclodextrins, Carrier, Novel delivery systems, Complexation.

INTRODUCTION

Cyclodextrins (CDs) are cylindrical oligosaccharides with a lipophilic central cavity and hydrophilic outer surface. In aqueous solutions, CDs are able to form inclusion complexes with many drugs by taking up some lipophilic part of the drug molecules in the cavity.[1] CDs are well known for their ability to form inclusion complex with various type of guest molecules, which fit partially or completely into the host CDs cavity as shown by the crystallographic results.[2] In many cases, the main interaction between CDs and guest molecules is Vander Waals force. [3] CDs are relatively inexpensive and are prepared by the action of bacteria on starch.[4] Complexation of guest molecule with CDs can alter guest solubility, increase stability against the effect of light, heat, and oxidation.[5] Complex often displays altered physicochemical properties compared to the guest molecule itself.[6.] CDs can also accelerate or decelerate many types of reactions taking place in aqueous solution.[7]

HISTORY

The history or development of an applied research field can be visualized on two levels:

- By the number of publications.
- By utilization of the research result in the form of products and technologies.[8]

Professor Jozef Szejtli (1933-2004) divided the chemical and industrial developments of CDs into three stages, the discovery period, the exploratory period, and the utilization period.[9]

Discovery period, 1891 to the mid 1930s: CDs are belonging to the category of carbohydrates and discovered just over 100 years ago. They are called 'Cellulosine', when first discovered by A. Villiers in 1891.[10] In 1904, Schardinger isolated a new organism capable of producing acetone and ethyl alcohol from sugar and starch-containing plant material. In 1911, he described that this strain also produces large amount of crystalline dextrin.[11] Freudenberg and his coworkers elucidated the cyclic structure of dextrins only in second half of the 1930s.[8]

1. **Exploratory period, mid 1930s to 1970*:*** In 1938 Freudenberg and his coworkers showed the ring structure of CDs with a central cavity.[9] In 1942 the structure of CDs were determined by X-ray crystallography.[11] Frudenberg, Cramer, and Plieninger obtained a patent in 1953. In this they covered practically important aspects of the application of CDs in drug formulation.[8] During this period the enzymatic production of CDs was also being investigated. Cramer describes all the basic structural and physicochemical characteristics of CDs including their chemical structure, cavity size, solubility, reactivity, complexing abilities, and their effect on the chemical stability of guest molecules.[9] The first fundamental review on CDs was published in 1957 by French. It was followed in 1965 by a monograph by Thoma and in 1968 by Caesar.[8]

2. **Utilization period, 1970- onwards:** After adequate studies proved that any toxicity attributed to CDs originated from complex impurities, an inadequate form of administration, or extreme dosing, the number of CD-related publication displayed an explosion size increase. The first International Symposium on CDs was organized in 1981. According to CD News, the total number of CD-related publications was over 26000 by the end of 2003.[8]

CHEMICAL STRUCTURE AND PROPERTIES

CDs consist of (α-1, 4)-linked α-D-glucopyranose unit with a lipophilic central cavity. Due to the chair formation of the glucopyranose unit, CDs molecules are shaped like cones with secondary hydroxyl groups extending from the wider edge and the primary groups from the narrow edge.[12] The most common CDs are α-CD, β-CD, and γ-CD, which consist of six, seven, and eight glucopyranose units.[13] 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.[14] Modification of the hydroxyl group results in disruption of the hydrogen bonding occurring around the ring of CD molecule, which allows more interactions of these groups with water molecules.[15] Figure 1 represents the structure of cyclodextrin molecule.

The melting point of CDs are between 240 -265^0 C, consistent with their stable crystal lattice and structure.[13] CDs glass transition occurs at about 225 to 250^0 C. The glass transition temperature varies with the degree of substitution. Thermal decomposition of CDs occurs at 308^{0}C.[16] The polarity of the CDs cavity has been estimated similar to that of an aqueous ethanol solution.[17] The natural α-CD and β-CD, unlike γ-CD cannot be hydrolyzed by human salivary and pancreatic amylases, though all three are subjected to fermentation by the intestinal micro flora. The natural CDs and its derivatives are used in oral and topical formulations, but only α-CD and the hydrophilic derivatives of β- and γ-CDs can be used in parentral formulations.[12]

SYNTHESIS AND PRODUCTION

CDs are formed during the enzymatic degradation of starch.[18] CDs are formed by the action of cyclodextrin glucotransferase (CGTases) (EC 2.4.1.19). CGTases catalyze the formation of CDs from starch and related α-1-4 linked glucose polymer via a transglycosylation reaction. Several species of the *Bacillus* are the major sources of CGTases, in addition to some species of *Klebsiella*, *Thermococcus, Micrococcus*, and others.[19] Starch is liquefied by two processes by heat treatment or using α-amylase then, for enzymatic conversion CGTases is added. This conversion product gives three main types of cyclic molecule structure.[10]

TYPES OF CYCLODEXTRINS [15, 20]

More than 1500 CDs derivatives have been reported in the literatures. However, the most common parent CDs are α-, β-, and γ-CDs containing 6, 7, and 8 glucopyranose units respectively. Some of them are listed in Table 1. The various derivatives that gained pharmaceutical interest include:

- Natural CDs: α-, β-, and γ-CDs
- Hydroxyalkylated CDs: HP-β-CD and HP-γ-CD
- Methylated CDs: RAMEB (randomly methylated β-CD)
- Acetylated CDs: Acetyl γ-CD
- SBE-β-CD (Sulpho butyl ether β-CDs)
- Branched CDs: maltosyl and glucosyl β-CD
- Reactive CDs: chlorotriazinyl-β-CD

CDs are also categorized as:

- Hydrophilic CDs: HPCDs, DHP-β-CDs
- Hydrophobic CDs: Acetyl γ-CDs
- Ionizable CDs: SBE-β-CD

ADVANTAGES OF CYCLODEXTRINS AND DERIVATIVES [18, 20]

CDs have various advantages, such as:

1. Protection of guest molecules against:
   - Decomposition reactions induced by light or heat
   - Oxidation or hydrolysis
   - Loss by evaporation
   - Chemical reactions with other organic compounds
2. Solubilization of the guest molecules in water
   - Increase of solubility
   - Increase of rate of solubilization
   - Avoidance of organic solvents
   - Change of viscosity
   - Enhancement of dissolution
3. Elimination of
   - Undesired odors or tastes
   - Hygroscopicity
   - Toxicity
4. Improvement of handling
   - Of liquids or oily substances or powders
   - Increase in the stability of emulsions

DRUG AVAILABILITY FROM CD CONTAINING PRODUCTS [9]

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. 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.

IMPORTANT CONSIDERATION FOR CDs SELECTION IN DRUG FORMULATION

1. **Commercial availability[21]:** The natural CDs and hydroxypropyl, hydroxyl ethyl, sulphobutyl, and various methylated CDs derivatives are available in bulk quantities. Other CD derivatives are either synthesized in laboratory for the study or available on laboratory scale. For research and investigational purposes, various CDs, natural and modified, including some sugar branched derivatives like Glucosyl and Maltosyl-β-CDs can be obtained from "cyclodex" under the trade name "trappsol".
2. **Regulatory status:** The global regulatory status of CDs was discussed by Thomson.[21] In the US, standards for β-CD quality are defined in a National Formulary monograph and DMF's have been or will be submitted for the commercially available CDs. [22]
3. **Patent status:** Being known for several years, natural CDs would not ordinarily be considered as patentable subject matter, however, there are many unexpired patents claiming specific complexes of drug with natural CDs, particularly with β-CDs. The patent situation for CDs derivatives varies for known derivatives and complexes.[21]

CDs EFFECT ON DRUG PROPERTIES IN FORMULATIONS

Various drug properties are affected by cyclodextrin in formulations. Some of them are summarizes in Table 2, 3, 4 and 5.

➢ **Effect on Solubility and Dissolution**

CDs have been playing a very important role in formulation of poorly water-soluble drugs by improving apparent drug solubility and dissolution through inclusion complexation or solid dispersion, by acting as hydrophilic carriers for drugs with inadequate molecular characteristics for complexation, or as tablet dissolution enhancers for drugs with high dose,

with which use of a drug/CDs complex is difficult, eg. paracetamol.[21] CD-drug complex hides most of the hydrophobic functionality in the interior cavity of the CD while the hydrophilic hydroxyl groups on the external surface remain exposed to the environment. The net effect is that a water soluble CD-drug complex is formed.[10] (Table 2)

Although prediction of compound solubilization by CDs continues to be highly empirical, various historical observations permit several general statements. First, the lower the aqueous solubility of the pure drug, the greater the relative solubility enhancement obtained through CD complexation. Drugs that possess aqueous solubility in the micromole/liter range generally demonstrate much greater enhancement than drug possessing solubility in the range higher than micromole/liter. For example Paclitaxel has much larger enhancement factor than the Hydrocortisone and Pancratistatin.[13]

Out of various commercially available CDs, methylated CDs with a relatively low molar substitution appear to be the most powerful solubilizer. CDs, as a result of their ability to form *in-situ* inclusion complexes in dissolution medium, can enhance drug dissolution even when there is no complexation in the solid state.[12] SBE-β-CD was found to be an excellent solubilizer for several drugs and more effective than β-CD but not as effective as DM-β-CD.[23]

- **Effect on Bioavailability**

CDs enhance the bioavailability of insoluble drugs by increasing the drug solubility, dissolution, and /or drug permeability.[23] CDs 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 CDs while the hydrophilic hydroxyl groups on its external surface remain exposed to the environment.[24] In the case of water-soluble drugs, CDs increase drug permeability by direct action on mucosal membranes and enhance drug absorption and bioavailability.[21] In addition to improving solubility, CDs also prevent crystallization of active ingredients by complexing individual drug molecules so that they can no longer self assemble into a crystal lattice.[10]

It was reported that CDs, because of their ability to remove cholesterol, may increase membrane fluidity and induce membrane invagination through a loss of bending resistance and result in cell lysis. Labile drug stabilization by CDs and their ability to ameliorate drug irritation, and thus improve drug contact time at the absorption site in nasal, ocular, rectal and transdermal delivery are some other important factors that contribute to the CDs-improved bioavailability.[12]

- **Effect on Stability**

The feasibility of a pharmaceutical formulation can be limited by stability issues, especially for aqueous formulation of drugs that are prone to hydrolysis or oxidation.[25] CDs can improve the stability of several labile drugs against dehydration, hydrolysis, oxidation and photodecomposition and thus increase the shelf life of drugs by forming complex.[12] When a molecule is constrained within the CD cavity, it is difficult for reactant to diffuse into cavity and react with protected guest.[24] (Table 3)

SBE-β-CD showed greater stability enhancement than other CDs. The stabilizing effect of CDs depends on the nature and effect of the induced functional group on drug stability and vehicle.[12] The CDs were reported to have improved the photostability of trimeprazine[26] and promethazine.[27] CDs can also insulate a label compound from a potentially corrosive environment, eg. Doxorubicin stabilization in aqueous solution.[13] CDs also enhanced the shelf life of drugs, eg. Turmeric-oleoresin.[28] HP-β-CD significantly reduced the photo degradation of 2-ethyl hexyl p-dimethyl aminobenzonate in solution.[29] CDs were also reported to enhance the physical stability of viral factors for gene therapy and the formulation containing sucrose.[21]

The deliquescence of hygroscopic substances is also reduced by complexation with CDs. Physical changes like sedimentation and caking in suspension or recrystallization of drugs can also be prevented or reduced by complexation with CDs.[10] Since the hydrolysis of drug encapsulated in CDs is slower than that of free drugs, the stability of the drug/CD complex, plays a significant role in determining the extent of protection.[23] CD complex with tea tree oil is stable against light and oxygen.[18]

- **Effect on safety**

CDs have been used to ameliorate the irritation caused by drugs.[12] The increased drug efficacy and potency, caused by CD-increased drug solubility, may reduce drug toxicity by making the drug effective at lower doses.[23] β-CD enhanced the antiviral activity of ganciclovir and increase in the drug potency and reduced drug toxicity. The toxicities associated with crystallization of poorly water-soluble drugs in parentral formulations can

often be reduced by formation of soluble drug-CD complex.[30] CDs entrapment of drugs at the molecular level prevents their direct contact with biological membranes and thus reduces their side effects and local irritation with no drastic loss of therapeutic benefits.[31]

Inclusion complexation with HP-β-CD reduced the side effects of 2-ethylhexyl-p-dimethylaminobenzene by limiting the interaction of the UV filter with skin. [29] Inclusion complexation with CDs also reduces ocular drug irritation by limiting the free drug concentration on the precorneal area to a nonirritating level.[21] HP-β-CD alleviated the intrinsic irritancy effect observed on IV administration of CKD-732 hemi-oxalate against blood vessels.[32]

- **Material handling improvement**

Substances that are oils/liquids/volatile at room temperature can be difficult to handle and formulate into stable solid dosage forms. Complexation with CDs may convert such substances into microcrystalline or amorphous powder which can be conveniently handled and formulated into solid dosage forms.[10, 24]

- **Irritation reduction**

Active ingredients that irritate the stomach, skin or eye can be encapsulated within a CD to reduce their irritancy. Complex reduces the local concentration of free active below the irritancy threshold.[24] CD complex gradually dissociates which keeps the free drug concentration below the irritating level.[10]

- **Compatibility improvement**

Drugs are often incompatible with each other or with other inactive ingredients present in the formulation.[10] Encapsulating one of the incompatible ingredient with CDs stabilize the formulation by physically separating the components in order to prevent chemical interaction.[24]

- **Odor and taste masking**

Unpleasant odor and bitter taste of drugs can be masked by complexation with CDs. Molecules that cause unpleasant odors or taste can be hidden from the sensory receptors by encapsulating them within the CDs cavity. The resulting complex has no or little odor or taste and is much more acceptable to the patient.[10, 24] CDs-drug complex does not affect the drug activity while eliminating the unpleasant odors and bitter taste, eg. CD-chamomile complex reduced odor without affecting its anti-inflammatory activity.[2]

- **Effect on drug delivery through biological membrane**

The CD does not readily permeate the biological membranes due to its chemical structure, molecular weight and very low octanol/water partition coefficient. Only the free form of drug, which is in equilibrium with the drug-CD complexes are capable of penetrating lipophilic membranes.[25] The CDs will enhance drug delivery through aqueous diffusion-controlled barriers, but can hamper drug delivery through lipophilic membrane controlled barriers.[33] CDs can also enhance the drug bioavailability by stabilization of drug molecules at the bio-membrane surface. For example the CD-enhanced insulin bioavailability after nasal administration is partly due to this stabilizing effect.[34] (Table 4 and 5)

CYCLODEXTRIN DERIVATIVES

In the CDs, every glucopyranose unit has three free hydroxyl groups which differ both in their functions and reactivity. In β-CD, 21 hydroxyl group can be modified substituting the hydrogen atom or the hydroxyl group by a large variety of substituting groups like alkyl-, hydroxylalkyl-, carboxyalkyl-, amino-, thio-, tosyl-, glucosyl-, maltosyl etc. groups, thousands of ethers, esters, anhydro-, deoxy-, acidic, basic, etc. derivatives can be prepared by chemical or enzymatic reactions.[8]

The aim of derivatization may be:

- To improve the solubility
- To improve the fitting or association between the CD and its guest
- To attach specific groups to the binding site
- To form insoluble, immobilized CD-containing structures, polymers [24]

Hydrophobic CD derivatives are useful as sustained-release drug carriers for water soluble drugs and peptides. [35] More than 1500 different cyclodextrin derivatives have now been synthesized and described in the literature and more than 100 are available as fine chemicals.[36] However, since toxicological evaluations are very costly, only very few of these derivatives are available as pharmaceutical grade excipients.[9]

- **Aggregates of native CDs**

1. **Structure in crystal**

There are two types of crystal structures for native CDs (α-, β-, and γ-CDs) as well as their complexes: cages and channels. In cage type, the

cavity of one CD molecule is blocked off on both sides by adjacent CDs, thus making the guest molecules not contact with each other by isolated cavities. The cage type structures have two different categories: herringbone and brick type. In channel type, CD molecules are packed linearly on top of each other with "infinite" channels including guest molecules.[37]

2. Structure in aqueous solution

Native CDs can form aggregates in water with the size of about 200-300nm. Two kinds of size distribution of CDs are existed in aqueous solution: one with hydrodynamic radius less than 1nm and the other larger than 60nm.[37]

CYCLODEXTRINS AND COMPLEXATION PHENOMENA

Inclusion complexation with CDs is like a "Host-Guest interaction". In this CD act as host molecule and the drug molecule to be entrapped in host cavity act as guest molecule. Comparing to other encapsulation methods, which involve entrapment of more than one guest, CD complexation involve entrapment of one molecule of guest in CD cavity. For high molecular weight molecules, more than one molecules of CD can bind to the guest.[10] In complexation guest molecule may be partially or fully included inside the host.[15]

Physical and chemical properties of included molecules may be favorably modified, and in particular the physical stability and the aqueous solubility can be improved.[38] CD complexes have been shown to increase the stability, wet-ability and dissolution of the guest molecule. CD complexes have been variously reported to both increase and decrease skin penetrations.[25] CD complexes of water-soluble compounds are usually prepared by joint crystallization from hot aqueous solution on cooling.[39] Generally water is preferred as a solvent for complexation.[10] Complexation phenomenon is represented in figure 2.

COMPLEXATION APPROACHES

- **Kneading method**

Kneading is the most common and simple method used to prepare inclusion complex. In this method CD is impregnated with little amount of water or hydroalcohalic solutions to converted into a paste. The drug is then added to the paste and kneaded for a specified time (45 min). The kneaded mixture is then dried at 45^0 C and stored in vacuum desiccators. Then it is passed through 80 no. sieve to get desired product. In large scale, the kneading can be done by utilizing the extruders and other machines.[10,15,20,40] Various drugs are successfully encapsulated by using this method, for example paracetamol,[41] gemfibrozil,[42] glipizide,[43] carvedilol,[44] celecoxib,[45] etc.

- **Freeze drying / Lyophilization**

In order to obtain a porous, amorphous powder with high degree of interaction between drug and CD freeze drying/ lyophilization technique is suitable.[40] In this method stoichiometric amount of drug and CDs are dispersed in hydroalcohalic solution using a magnetic stirrer. After agitating a specified time, the resulting solution is frozen and lyophilized under reduced pressure in a freeze dryer. This technique is suitable for thermolabile substances.[20]

- **Spray drying/ Atomization**

Spray drying is a common technique used in pharmaceuticals to produce a dry powder from a liquid phase. It is also used as preservation method, increasing the storage stability due to water elimination.[40] In this method monophasic solution of drug and CD is prepared by using a suitable solvent generally in ethanol: water 50% v/v. the resulting mixture is stirred for 24 hrs.[20] Then spray dried by observing following conditions- air flow rate, atomizing air pressure, inlet temperature, outlet temperature, flow rate of solution etc.[10]

- **Melting**

This method involves melting excess amount of guest followed by mixing with powdered CD. The drug-CD mixture is cooled and the excess amount of guest is then removed by carefully washing with weak complex forming solvent or by sublimation under vacuum.[20, 46] The method is restricted to sublimable guest like menthol.[10]

- **Physical blending**

The method involves homogenous blending of the physical mixture of drug and CD followed by passing the mixture through an appropriate sieve to get the desired product.[20] In laboratory mixing is done by triturating in a mortar and in industry mixture ix prepared by extensive blending of the drug with CD in a rapid mass granulator usually for 30 min.[40] Various drugs are reported to be encapsulated by this method, such as aspirin.[1] celecoxib,[45] glipizide,[47] .

➢ **Grinding/ Milling**

A solid binary inclusion compound can be prepared by grinding and milling of the drug and CDs with the help of mechanical devices. Drug and CDs are mixed intimately and physical mixture is introduced in an oscillatory mill and grinded for suitable time. This method differs from the physical mixture method where simple blending is sufficient and in co-grinding it requires to achieve extensive combined attrition and impact effect on power blend.[15, 40]

➢ **Neutralization precipitation method**

This method is based on the precipitation of inclusion compound by neutralization technique and consists of dissolving the drug in alkaline solution and mixing with an aqueous solution of CDs. The resultant solution is neutralized under agitation using hydrochloric acid solution till reaching the equivalence point. A white precipitate is formed corresponding to the formation of the inclusion compound, which is filtered and dried. This method is unsuitable for acid and alkaline susceptible drugs.[15,40]

➢ **Microwave irradiation method**

This is a novel method for industrial scale preparation which requires a shorter reaction time and higher aim product. It involves the microwave irradiation reaction between drug and CD by using a microwave oven.[20] In this method drug and CD are dissolved in water or organic solvent and reacted for short time at 60^{0}C in the microwave oven. After the reaction completion residual and uncomplexed drug and CD are removed by adding solvent. Obtained precipitate is dried at 40^{0}C and stored.[40] This method is mainly developed for rapid organic synthesis.[10]

➢ **Solid dispersion / Co-evaporation/ Solvent evaporation method**

This method involves mixing of alcoholic solution of drug and aqueous solution of CDs with stirring to get a molecular dispersion, followed by evaporation of the solvent under vacuum until dried mass is obtained. The dried mass is then pulverized and sieved to get the complexed product.[10,15,20] This method is quite simple and economic both on laboratory and large scale production.[40] Complexation of aspirin,[1] gemfibrozil,[42] domperidone,[48] carvedilol,[44] and celecoxib[45] are reported to be formed by this method.

➢ **Co-precipitation method**

In this method CD is dissolved in water and the guest is added while stirring the CD solution. By heating more CD about 20% can be dissolved if the guest can tolerate the higher temperature. Solution must be cooled while stirring before a precipitate is formed. The precipitate can be collected by decanting, centrifugation or filtration.[16] The main disadvantage of this method lies in the scale up. In addition, non-ionic surfactants have been shown to reduce CD complexation of diazepam and preservatives to reduce the CD complexation of various steroids. On the other hand, additives such as ethanol can promote complex formation in the solid or semisolid state.[11] Complexation of CD with glipizide, [43] nimesulide, [49] promethazine, [50] and many other drugs by this method have been reported.

➢ **Solution-enhanced dispersion by the supercritical fluids(SEDS)**

SEDS is novel, single step method, which can produce solid drug-cyclodextrin complexes. The optimization of processing condition is essential in order to achieve the optimum complexation efficiency as compared to kneading, freeze drying, spray drying etc. [51]

This method has various advantages over others, such as:

- Preparation of complex in single step process
- Achievement of high complexation efficiency
- Minimize the contact of drug with cyclodextrin
- Achievement of enhanced dissolution rate[10]

➢ **High pressure homogenization method**

In this method drug and CD are mixed in an appropriate solvent and passed through a high-pressure homogenizer causing the disintegration of particles and dispersion throughout the product. The eventual solution was filtered and evaporated to dryness until the solid complex is acquired.[20]

➢ **Supercritical anti-solvent technique**

This method was introduced in the late 1980s. [40] In this method carbon dioxide is used as anti-solvent for the solute but act as a solvent with respect to the organic solvent. Drug and CD are dissolved in a suitable solvent followed by feeding the solution through a nozzle into a pressure

vessel containing supercritical fluid anti-solvent. When the solution is sprayed, the anti-solvent rapidly diffuses into that liquid solvent as the carrier liquid solvent counter diffuses into the anti-solvent. Because of the supercritical fluid expandation, the mixture becomes supersaturated resulting in the precipitation of the solute and the solvent is carried away with the supercritical fluid flow. This is a non-toxic and fast process. [20, 38, 53]

- **Slurry complexation**

It is not necessary to dissolve the CD completely to form a complex. CD can be added to water, as much as 50-60% solids and stirred. The aqueous phase will be saturated with CD in solution. Guest molecule will complex with the CD in solution and, as the CD complex saturates the water phase, the complex will crystalline or precipitate.[16] The amount of time required to complete the complexation is variable, and depends on the guest. Slurry complexation is performed at ambient temperatures.[11]

- **Paste complexation**

In this method a small amount of water is added to form a paste, which is mixed with the CD using a mortar and pestle, or on a large scale using a kneader. The resulting complex is dried directly or washed with a small amount of water and collected by filtration or centrifugation.[11, 16]

- **Damp mixing and heating**

This method uses little or no added water. The guest and CD are thoroughly mixed and placed in a sealed container. The sealed containers and its content are heated to about 100^{0}C and then contents are removed and dried. The amount of water added, the degree of mixing and the heating time have to be optimized for each guest.[11, 16]

- **Extrusion**

In this method CD, guest and water can be premixed or mixed as added to the extruder. The extruded complex may dry as it cools or the complex may be placed in an oven to dry. Heat labile guest can get decomposed. [11, 16]

- **Dry mixing**

Some guest can be complexed by simply adding guest to the CD and mixing them together. This method is for oils and liquid guests. The main advantage of his method is that no water needs to be added. But sometimes caking may occurred.[11, 16]

DRYING OF COMPLEXES [11]

The complexes can be dried in an oven, fluid bed dryer or other dryers. Care has to be taken that the complex is not destroyed during the drying process.

1. **Highly volatile guests**

For guests with boiling temperature below 100^{0}C, a lower temperature must be used during drying. Otherwise guest may be lost during drying.

2. **Spray drying**

Complexes can also be spray dried. Precipitation must be controlled in order to avoid the particles becoming too large. It is not a viable means for drying highly volatile and heat labile guest.

3. **Low temperature drying**

A desiccators or freeze dryer is used to dry complexes. The low temperature minimizes the loss of extremely volatile guests. Freeze drying is useful for heat labile guests.

STUDY OF COMPLEX

Various methods are used for studying the drug-CD complexes.

- **Computational studies of complexes[53- 56]**

In the few last years there has been an increase in research involving CDs, given that their ability to form complexes with a variety of compounds makes them particularly useful for catalysis and chiral separation. The decisive factor for the inclusion complexes is that the guest molecule should fit into the cavity, the driving force being more or less independent of the nature of the guest molecule. Computational study of complex involve following studies:

- Conformational search
- Complex formation
- Interaction energy
- Molecular dynamics simulations
-

- **Phase Solubility method**

The most widely used approach to study inclusion complexation is the phase solubility method described by Higuchi and Connors.[21] They classified the complexes on the basis of their effect on substrate solubility and it is indicated by the phase solubility profile.[12] Phase solubility diagram are classified into A and B types. A type curve indicates the formation of soluble inclusion complexes while B type suggest the formation of inclusion complexes with poor solubility.[21] In general, the water soluble CD derivatives form A-

type phase solubility profiles, whereas the less soluble natural CD forms B-type profiles.[14]

- **A-type profiles**

In A-type profiles, the apparent solubility of the substrate increase as a function of CD concentration. It is further classified in three subtypes: AL-type, AP-type and AN-type.[17] When the complex is of first order with respect to ligand and first or higher order with respect to substrate then AL-type profile is obtained. If the complex is first order with respect to the substrate, but second or higher with respect to the ligand then AP-type profile is obtained. It is difficult to interpret the AN-type profile.[24, 25]

- **B-type profiles**

Type B phase solubility profiles indicate the formation of complexes with limited water solubility and are traditionally observed with naturally occurring CDs, especially β-CD. Two subclasses have been described including B_S and B_I systems.[17]

Phase solubility study of CD complexes with aspirin,[1] gemfibrozil,[42] carvediol,[44] etoricoxib,[57] and citric acid [58] have been successfully performed and reported in literature.

DRUG RELEASE FROM COMPLEX

Two parameters are very important for the drug release mechanism:

- Complexation constant
- Lifetime of the complex[16]

After administration, the drug is released from the complex upon dilution and in some cases by competitive displacement with endogenous lipophiles.[10] In general, two steps are involved in the release of the complexed guest. First, the complex is dissolved. The second step is the release of the complexed guest when displaced by water molecules. Equilibrium will be established between free and complexed cyclodextrin, the guest and the dissolved and undissolved complex[11].

Dilution: Dissociation due to dilution appears to be a major release mechanism. Dilution is minimal when a drug-CD complex is administered opthalmically.[16]

Competitive displacement: Competitive displacement of drugs from their CD complexes probably plays a significant role *in vivo*.[16] Stain et al showed that alcohol displaces 2-napthol from β-CD complex.[59] Tokumara et al reported that the β-CD complex of a poorly water-soluble drug, cinnarazine, was more soluble *in vitro* than cinnarazine alone.[60]

Protein binding: Drug binding to plasma proteins may be an important mechanism by which the drug may be released from a drug-CD complex. It is evident that proteins may effectively compete with CDs for drug binding and thus facilitate the *in vivo* release of drugs from drug-CD complexes.[16] Frijlink et al studied the effect of HP-β-CD on the displacement of both naproxen and flurbiprofen from plasma binding sites *in vivo*.[61]

Drug uptake by tissue: A potential contributing mechanism for drug release from CD is preferential drug uptake by tissues. When the drug is lipophilic and has access to tissue, and is not available to the CD or the complex. The tissue than acts as a sink causing dissociation of the complex based on simple mass action principles.[16]

Change in ionic strength and temperature: In the case of weak electrolyte, the strength of binding to CD is dependent on the charged state of the drug, which is dependent on dissociation constant of the drug and the pH of environment. For most molecules, the ionized or charged form of the molecule has poorer binding to CD compared to the non-ionized or neutral form of the drug, especially when bound to a neutral CD.[16] Loftsson et al[13] and Inoue et al[62] have shown that binding of substrate to CD is an exothermic process.

APPLICATIONS OF CYCLODEXTRINS [12, 15, 20]

➢ **Cyclodextrin in oral drug delivery [12,15,20]**

Most common application of cyclodextrin in oral drug delivery includes enhanced drug solubility in aqueous solutions thus resulting in an enhanced drug solubility in aqueous solutions thus resulting in an enhanced dissolution and bioavailability and stability of the drug at the absorption site or in formulation.

Examples: Ketoprofen, Griseofulvin, Phenytoin, Digoxin, Rutin, Tolbutamide, Albendazole, Danazole, Tacrolimus, Gliclazide, Diacerein and Etoricoxib etc.

➢ **In sublingual drug delivery[12]**

Sublingual drug delivery is one of the most efficient ways to bypass hepatic first-pass metabolism .In this method the drug enters the systemic circulation by dissolving in the mucosa. In the sublingual formulations the complexation of poorly water soluble drugs with cyclodextrin has

been shown to increase the bioavailability of various lipophilic drugs.

➢ **In Ophthalmic drug delivery** [12,15,20]

CDs are shown to be well tolerated in aqueous formulations and are non-toxic to the eye, thus providing to be beneficial excipients for ocular formulation. Benefits of CDs in ophthalmic formulation include:

i. Provides sustained release of drug
ii. Enhancing solubilization and chemical stabilization of drug
iii. Enhancement of ocular drug permeability
iv. Reduced ophthalmic drug irritation and discomfort

Examples: Lidocaine, Pilocarpine, Indomethacine, Tropicamide, Econazole nitrate, Fluconazole and Ganiclovir prodrug etc.

➢ **In transdermal drug delivery** [12,15,20]

The main limitation of this route is to overcome the stratum corneum. For this permeation enhancers are used. CDs play an important role in optimizing drug delivery.

Examples: Ibuprofen, Nicotine, Ascorbic acid, Human growth harmone and Avobenzone etc.

➢ **In nasal drug delivery** [12,15,20]

CDs are used as solubilizers and absorption enhancers in nasal drug delivery. CDs decrease the nasal toxicity and act as a carrier for sustained release of drug across nasal mucosa. CDs also increased the bioavailability of drug by nasal route. Various drug with CDs are successfully used for nasal route.

Examples: Risperidone, Pirodavir, Granisetron and Artemether etc.

➢ **In parentral drug delivery** [15]

HP-β-CD and SBE-β-CDs have been widely investigated for parenteral use because of their high aqueous solubility and minimal toxicity. Applications of CDs in parenteral delivery are solubilization of drugs, reduction of drug irritation at the site of administration and stabilization of drugs unstable in aqueous environment etc.

Examples: Oridonin, Diclofenac Sodium and Valdecoxib etc.

➢ **In rectal drug delivery** [12,15]

The 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. 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.

Examples: Midazolam, Flurbiprofen, Ketoprofen and Human chronic gonadotropin etc.

➢ **In novel drug delivery** [12,15,20]

i. In liposomes

The concept of entrapping CD-drug complexes into liposomes in drug delivery combines the advantages of both CDs by increasing the solubility of drug and liposomes for drug targeting into a single system and thus circumvents the problems associated with each system.

Examples: Prilocaine, Betamethasone, Curcumin, Irinotican, Colchicine, Asialofetuin and Benzocaine etc.

ii. In nanoparticles

CDs increasing the loading capacity of nanoparticles and the spontaneous formation of either nanocapsules or nanospheres are achieved by nanoprecipitation of amphiphilic CDs diesters. CDs increased the loading capacity of poly (isobutyl cyanoacrylate) nanoparticles. Amphiphilic β-CDs (β-CDsa) have been characterized and evaluated as potential novel excipients in the preparation of nanocapsules.

Examples: Camptothesin, Nimodipine, Diazepam, Silver acetate, Diclofenac sodium and Paclitaxel etc.

iii. In microspheres

CDs can be used as a polymer in microspheres that can be expected to improve the therapeutic efficacy of drug and patient compliance. Microspheres with CDs showed prolonged release pattern.

Examples: Theophylline and Bovine serum albumin etc.

Table 1: Natural cyclodextrins and their derivatives

Cyclodextrin	Substitution	Molecular weight	Solubility in water
α-cyclodextrin	-	972	14.5
β-cyclodextrin	-	1135	1.85
2-Hydroxypropyl-β-cyclodextrin	0.65	1400	>600
Randomly methylated β-cyclodextrin	1.8	1312	>500
β-cyclodextrin sulphobutyl ether sodium salt	0.9	2163	>500
γ-cyclodextrin	-	1297	23.5
2-Hydroxypropyl-γ-cyclodextrin	0.6	1567	>500

Table 2: Solubility enhancement of drugs by cyclodextrin and their derivatives

Cyclodextrin	Examples of CD-enhanced solubility
α-cyclodextrin	Praziquantel
β-cyclodextrin	Piroxicam, Nimesulide, Lorazepam, Ketoprofen, Praziquantel, Chlorthaidone, Itraconazole, Ibuprofen, Griseofulvin
Dimethyl- β -cyclodextrin (DM- β-CD)	Naproxen, Camptothesin
Randomly methylated β-cyclodextrin	Tacrolimus
Hydroxypropyl-β-cyclodextrin	Griseofulvin, Albendazole, Ketoprofen, Levemopamil, Sulfomethiazole, Itraconazole, Carbamazepine, Zolpidem

Table 3: Stability enhancement of drugs by cyclodextrin and their derivatives

Cyclodextrin	Examples of CD-enhanced stability
β-cyclodextrin	Glibenclamide, Diclofenac sodium, Flutamide, Atorvastatin Calcium
2-Hydroxypropyl-β-cyclodextrin	Promethazine, Quinaril, Doxorubicin, Rurin, Paclitaxel, Spiranolactone
SBE-β-cyclodextrin	Spirolactone, Melphalan, Carmustine
γ-cyclodextrin	Digoxin

Table 4: Modification of the Drug Release Site and/or Time Profile by Cyclodextrins

Used cyclodextrin	Release pattern	Aim
HP-β-CD, Dimethyl-β-CD, SBE-β-CD	Immediate release	Enhanced dissolution and absorption of poorly water soluble drug
Simultaneous use of different CDs	Modified release	More balanced oral bioavailability with prolonged therapeutic effects
Ethylated- β-CD, Acylated- β-CD	Prolonged release	Sustained release of water soluble drug
Drug-CD conjugate	Site specific release	Colon targetting
Carboxymethylethyl-β-CD	Delayed, pH-dependent release	Enteric (acid) protection of drug

Table 5: Cyclodextrins as penetration or absorption enhancers

Condition	Effect
No complexation	If the drug does not form a cyclodextrin complex then cyclodextrins will have no effect.
Water-soluble drugs that form cyclodextrin complexes	Formation of a cyclodextrin complex will drug permeability through biological membranes leading to reduced bioavailability.
Lipophilic water-insoluble drugs that form water-soluble cyclodextrin complexes	Cyclodextrins will enhance drug permeation through the membrane if, and only if, PM is greater than PAq, or in other words, when permeation through the aqueous layer is the rate determining step in the overall membrane permeation. Cyclodextrins are more effective enhancers for small MW drugs (have larger PM) than for high MW dugs.

Table 6: Cyclodextrin containing pharmaceutical products

Drug/Cyclodextrin	Trade Name	Formulation	Company/Country
PGE2/□CD	Prostarmon E	Sublingual tablet	Ono, Japan
PGE1/αCD	Prostavastin	i.v. solutions and infusions	Ono, Japan Schwarz, Germany, USA
OP-1206/αCD	Opalmon	Tablet	Ono, Japan
Piroxicam/□CD	Brexin, Flogene Cicladon	Tablet, Suppository Liquid	Chiesi, Italy several European countries Aché, Brasil
Benexate HCl/□CD	Ulgut Lonmiel	Capsule	Teikoku, Japan Shionogi, Japan
Iodine/□CD	Mena-Gargle	Solution	Kyushin, Japan
Dexamethasone/□CD	Glymesason	Ointment	Fujinaga, Japan
Nitroglycerin/□CD	Nitropen	Sublingual tablet	Nihon Kayaku, Japan
Cefotiam-hexetil/□CD	Pansporin T	Tablet	Takeda, Japan
Tiaprofenic acid/□CD	Surgamyl	Tablet	Roussel-Maestrelli, Italy
Diphenhydramin, Chlortheophyllin/□CD	Stada-Travel	Chewing tablet	Stada, Germany
Chlordiazepoxide/□CD	Transillium	Tablet	Gador, Argentina
Hydrocortisone/HP□CD	Dexocort	Solution	Actavis, Iceland
Itraconazole/HP□CD	Sporanox	Oral and i.v. Olutions	Janssen, Belgium and USA
Cisapride /HP□CD	Propulsid	Suppository	Janssen, Belgium
Nimesulide/□CD	Nimedex	Tablets	Novartis and others, Europe
Alprostadil/□CD	Rigidur	i.v. solution	Ferring, Denmark
Nicotine/□CD	Nicorette	Sublingual tablets	Pharmacia, Sweden
Chloramphenicol/M□CD	Clorocil	Eye drop solution	Oftalder, Portugal
Diclofenac-Na/HP□CD	Voltaren	Eye drop solution	Novartis, France
17□-Estradiol/RM□CD	Aerodiol	Nasal Spray	Servier, France
Indomethacin/HP□CD	Indocid	Eye drop solution	Chauvin, France
Omeprazol/□CD	Omebeta	Tablet	Betafarm, Germany
Voriconazole/SBE□CD	Vfend	i.v. solution	Pfizer, USA
Ziprasidone mesylate/ SBE□CD	Geodon, Zeldox	im solution	Pfizer, USA & Europe
Dextromethorphan/□CD	Rynathisol		Synthelabo, Italy
Cetirzine/□CD	Cetrizin		Losan Pharma, Germany
Mitomycin/HP□CD	MitoExtra ,Mitozytrex	i.v. infusion	Novartis, Switzerland

Table 7: Summarizes various drugs: CD complexes as sited in literature

Drug	Aim	Indication	Conclusion	Reference
Pioglitazone	Preparation and Characterization of Pioglitazone cyclodextrin Inclusion Complexes	Antibiotic	Inclusion complexes exhibited higher rates of dissolution than the corresponding physical mixtures and pure drug	Pandit V. *et al* 2011
Aspirin	Preparation and Characterization of β-Cyclodextrin Aspirin inclusion complex	NSAIDs	Improve the solubility and dissolution rate of a drug Aspirin by complexation of β-Cyclodextrin.	Shekh I. *et al* 2011
Rizatriptan benzoate	Preparation and Evaluation of Cyclodextrin Based Binary Systems for Taste Masking	Antimigraine	The effective taste masking by β-Cyclodextrin in both binary systems, which can be utilized as a novel alternative approach for effective taste masking.	Birhade, S.T. *et al* 2010
Domperidone	Preparation and Characterization of Domperidone-CD complexes	Proton-pump inhibitor	The dissolution rate of Domperidone may be enhanced to a great extent by solid dispersion technique.	Swami, G. *et al* 2010
Acyclovir	Enhancemnt of solubility of acyclovir by solid dispersion and inclusion complexation methods	Antiviral	HP-β-CD inclusion complex could improve the dissolution characteristics of acyclovir.	Tomar, V. *et al* 2010
Ketoprofen	Influence of β-Cyclodextrin Complexation on Ketoprofen Release from Matrix Formulation	NSAIDs	The effect of polymer on Ketoprofen release can affect the drug solubility (complexation) and polymer water uptake (swelling).	Shukla, V. *et al* 2009
Carvediol	Design of buccal drug delivery system for poorly soluble drug.	β-Antiadrenergic	Buccal tablet containing Complexed CAR would have improvement in bioavailability.	Hirlekar and Kadam 2009

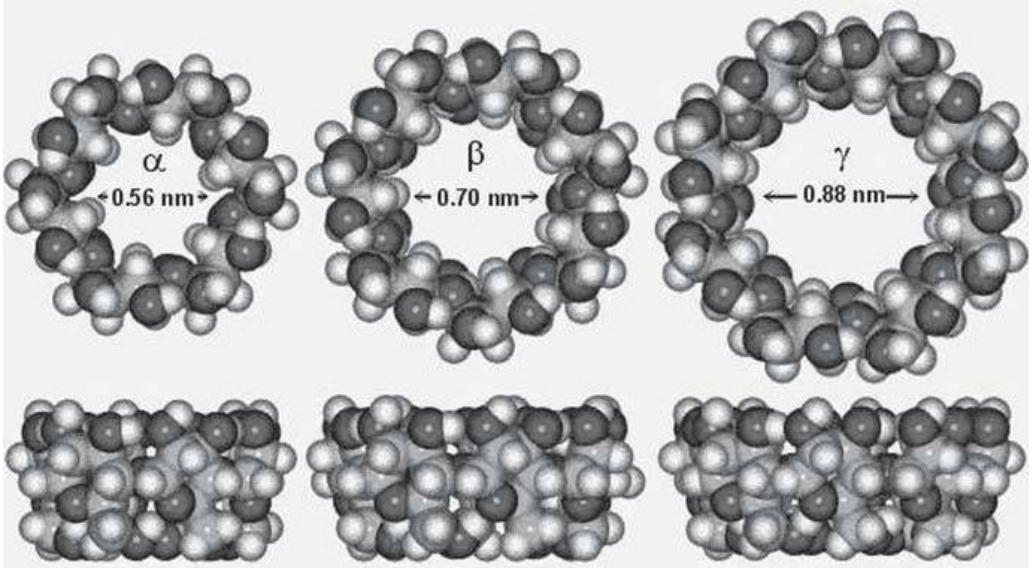

Fig. 1: Chemical structure of cyclodextrins

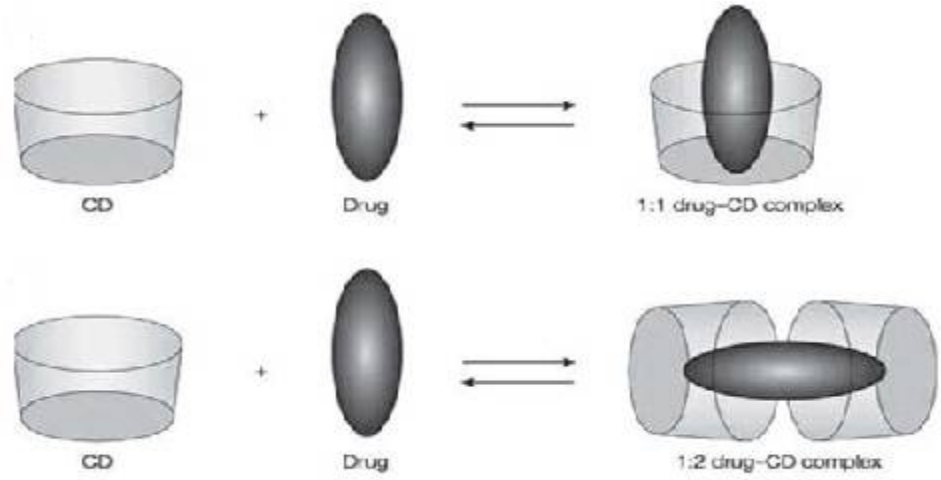

Fig. 2: Complexation phenomenon

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