Chapter 1

Introduction

1.1 Overview of Cyclodextrins

Cyclodextrins (CDs) are a class of oligosaccharides in which glucose units are connected by α-(1,4) glycosidic linkage which have strong capability of forming inclusion complexes with various guest molecules due to the presence of hydrophobic cavity. CDs are generally semi-natural products in which α-(6-glucose units), β-(7), γ-(8) CDs are common[1]. Larger cyclodextrins have also been identified and isolated but have little value in terms of applications. Most of the current interest in CDs arises from their ability to partially or fully complex a wide range of guest species within their cavity to form host-guest complexes[2, 3]. Their ability to form host-guest complexes has led to the use of CDs in a number of industries[4]. For example, CDs have been used in the pharmaceutical industry, as solubilizers, diluents and as tablet ingredients which improve the stability, bioavailability and pharmacokinetic properties of drugs[5-8], in food, cosmetic, toiletry and tobacco industries, either for the stabilization of flavors and fragrances or for the elimination of undesired tastes[9], in the chemical industry as catalysts or catalyst additives as separation media for some industrial-scale products and for stabilization of azo dyes[10-13] and in the analytical sciences and especially for enantioseparations in GC, HPLC, SFC and CE as a consequence of the ability of CDs to bind chiral organic molecules stereoselectively[14-16].

Cyclodextrins are generally produced through the degradation of starch by the enzyme CD glycosyl transferase (CGT), which is obtained from *Bacillus macerans* and related bacteria (Fig. 1.1) [17]. The first report in the literature of the isolation of a substance identifiable as a CD was that of Villiers[18] which appeared in 1891. In the period 1903-1911, during the course of work on food spoilage, Franz Schardinger had noted various strains of bacteria which survived the cooking process and which were thought to be responsible for some cases of food poisoning[19]. Schardinger found that one of these heat-resistant or “thermophilic” bacteria, which he called strain II, was able to dissolve starch and form crystalline polysaccharides (dextrins). The next major contributor to CD synthesis was Karl Freudenberg, who developed a method of obtaining pure α-CD and β-CD[20], and in the process also isolated another crystalline dextrin, which he named γ-CD.

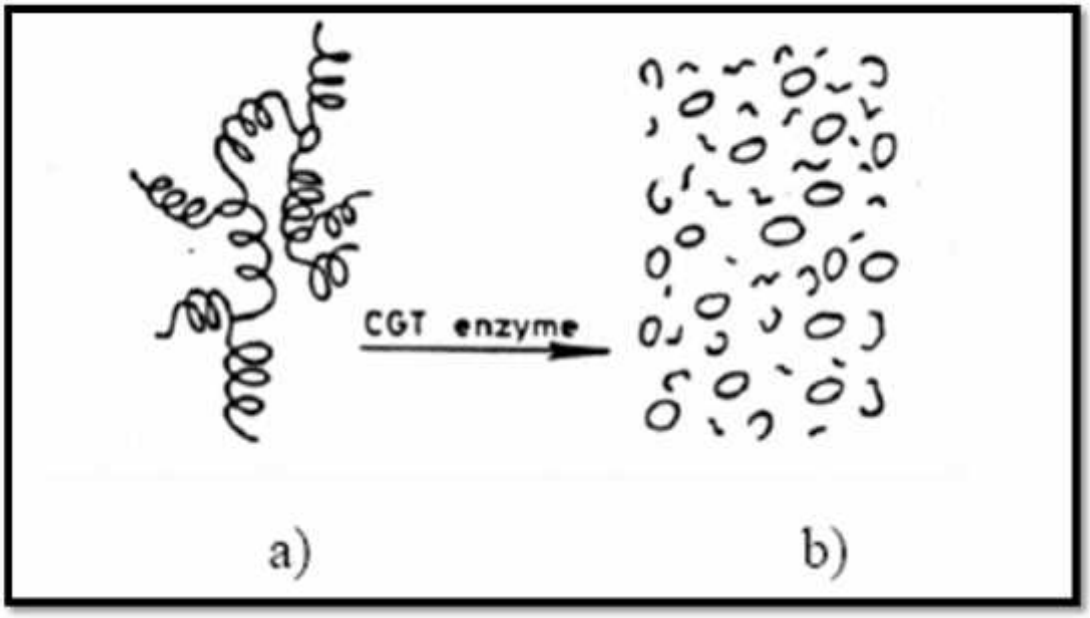

Figure 1.1 Formation of cyclic and acyclic dextrins from starch a) starch b) cyclic and acyclic dextrins

It was Freudenberg who first proposed a ring structure in 1936[21]. In subsequently he came to the conclusion that Schardinger's dextrins were cyclic oligosaccharides composed solely of glucose residues bonded by α-1,4-glycosidic linkages[22]. However, the molecular weights of the most common CDs were not determined until 1942[23].

1.2 Chemical structure of Cyclodextrins

The number of glucose units per CD ring varies from 6-13[9], as the enzyme produces a range of oligosaccharides[24]. A five glucose unit CD is unlikely due to ring strain and has not been observed[25]. The most common CDs contain 6, 7 and 8 units and are known as α-CD, β-CD and γ-CD, respectively. The glucose residues are labelled (A-H) in a clockwise direction when facing the primary hydroxyl group side[26]. As the numbers of glucose units increases the cavity dimensions of the cyclodextrins increases as shown in Figure 1.2. As a consequence of the $^4C_1$ chair conformation of the glucopyranose units, the hydroxyl functions are orientated to the cone exterior with the primary hydroxyl groups of the sugar residues at the narrow edge of the cone ("primary face") and the secondary hydroxyl groups at the wider edge ("secondary face"). Cyclodextrins have inner non-polar hydrophobic cavity and polar hydrophilic exterior. The diameter of the cavity is smaller on the primary face and wider on secondary face. This is because the free rotation of the primary hydroxyl groups reduces the effective diameter of the cavity. Because of their torus-like geometry, relatively hydrophobic surface of the internal cavity and the hydrophilic character of external hydroxyl groups CD molecules easily form inclusion complexes with a wide variety of molecules. This complex-forming capacity is the reason for their widespread application in various fields of chemistry. The native β-cyclodextrins (Figure 1.3) have 14 secondary hydroxyl groups on the wider rim and 7 primary hydroxyl groups on the narrow rim. The C-2-OH group of one glucopyranoside unit can form a hydrogen bond with the C-3-OH group of the adjacent glucopyranose unit. In the CD molecule, a complete secondary belt is formed by these H bonds therefore the β-CD is a rather rigid structure. This intermolecular hydrogen bond formation is probably the explanation for the lowest water solubility of β-CD. In aqueous solutions, the hydroxyl groups form hydrogen bonds with the surrounding water molecules resulting in a hydration shell around dissolved CD molecule[27-30]. Table 1.1 summarizes the important physical properties of the three major and most common cylodextrins[31].

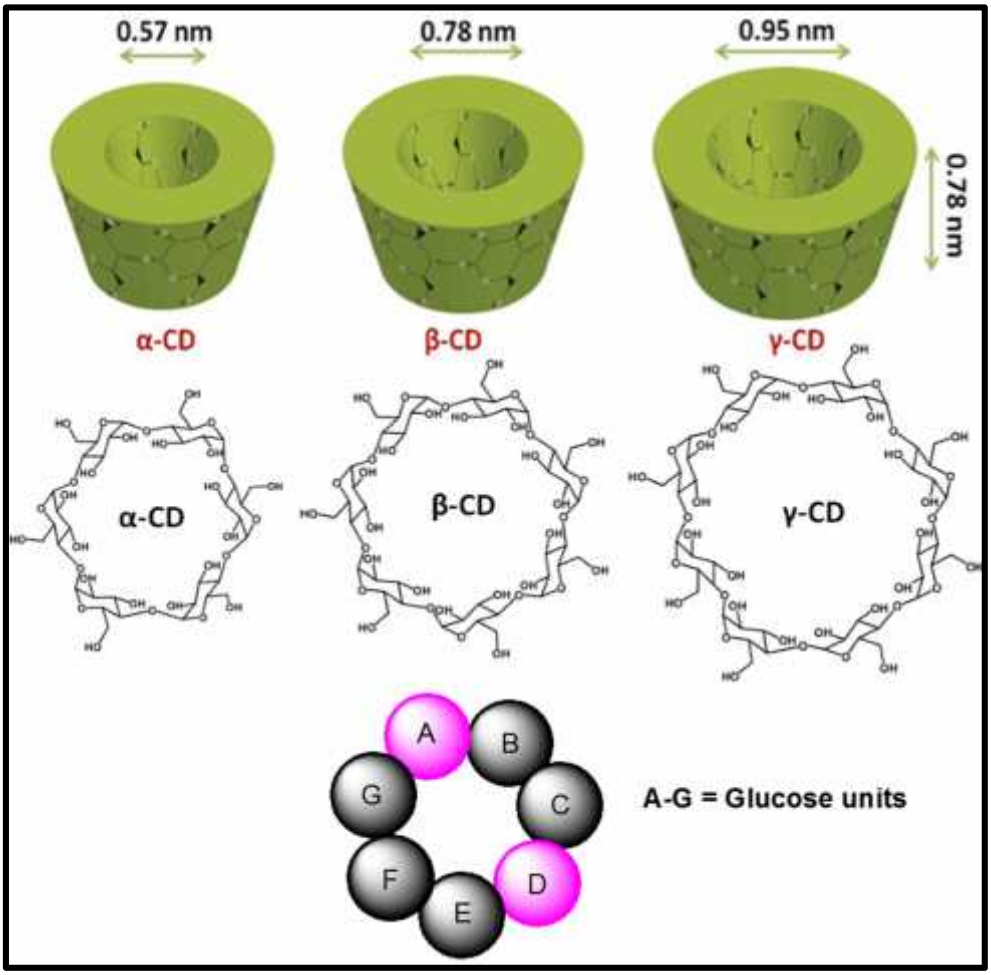

Figure 1.2 Schematic structures of native α-, β- and γ-cyclodextrins.

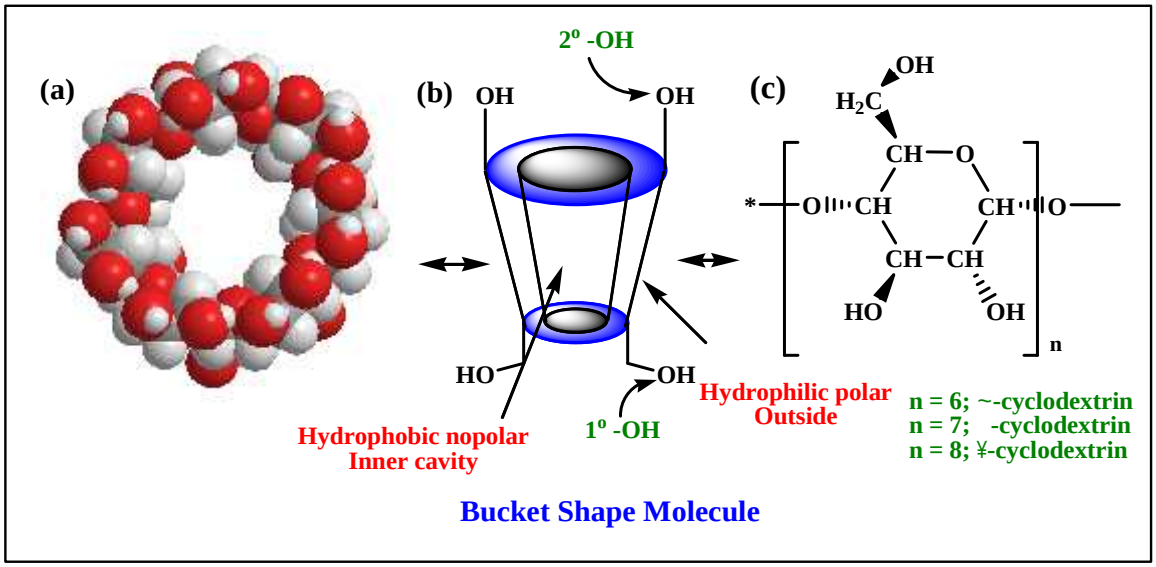

Figure 1.3 (a) 3D Molecular structure of β-CD, (b) Torus (Bucket) shape of CD and (c) Common structure of CDs.

Table 1.1 Physical properties of the three major cyclodextrins

Cyclodextrin Type	**α-CD**	**β-CD**	**γ-CD**
Number of glucose units	6	7	8
Mw (Da)	972	1135	1297
Solubility in water (g/100 mL, 25°C)	14.5	1.85	23.2
$[\alpha]_D$ at 25°C (°C)	150 ± 0.5	162.5 ± 0.5	177.4 ± 0.5
Cavity diameter (pm)	470 - 530	600 - 650	750 - 830
Height of torus (pm)	790 ± 10	790 ± 10	790 ± 10
Diameter of outer periphery (pm)	1460 ± 40	1540 ± 40	1750 ± 40
Approximate volume of cavity (10^6 pm^3)	174	262	427
Approximate cavity volume in 1 mol of CD (mL)	104	1257	256
Crystal form (from water)	hexagonal plates	monoclinic parallelogram	quadratic prisms
Surface tension (mN/m)	71	71	71
Melting range (°C)	255-260	255-265	240-245
Crystal water (wt. %)	10.2	13.2-14.5	8.13-17.7
Water molecules in cavity	6	11	17
Diffusion constant at 40°C	3.443	3.224	3.000
pK (by potentiometry) at 25°C	12.332	12.202	12.081

1.3 Solubility of Cyclodextrins

Solubility is the major parameter for the many applications of cyclodextrins. The water-solubility of the cyclodextrins and their derivatives varies and does not depend on the number of glucose units. The solubility of β-CD is only 1.85 g per 100 mL at ambient temperature[32], while the solubility of α-CD and γ-CD are higher at 14.5 and 23.2 g per 100 mL, respectively. The solubility of methylated CD decreases with an increase of temperature, whereas the native cyclodextrins are more soluble in water at higher temperature. The solubility of β-CD increases when up to two thirds of the all hydroxyl groups are methylated and then decrease when all hydroxyl groups are methylated. The solubility of CDs depends strongly on the temperature[33]. At 50ºC the solubility of the all three CDs are about three times that at 20ºC. J. Szejtli[34] explain the surprisingly low water-solubility displayed by β-CD by the fact that it has a rather rigid molecular structure consisting of a sevenfold axis of symmetry, making it more prone to crystallization than α-CD or γ-CD. The intermolecular interaction of β-CD molecules in the solid state requires a high energy to break the molecular association, due to the greatest overall molecular dipole, thereby imparting a lower solubility than the α- or γ-CD. Also, the interruption of β-CD crystallinity can reduce the intermolecular interaction and in turn increase its aqueous solubility.

The temperature dependence of the solubility of the three CDs in water is described by equation (1-3), the parameters of the functions being determined by a least-squares method from the data of M. J. Jozwiakowski and K. A. Connors[35].

$$c = (112.71 \pm 0.45)\, e^{-(3530\pm31)[(1/T) - (1/298.1)]} \quad \text{(for α-CD)} \quad (1)$$

$$c = (18.3236 \pm 0.099)\, e^{-(14137\pm31)[(1/T) - (1/298.1)]} \quad \text{(for β-CD)} \quad (2)$$

$$c = (219.4 \pm 9.8)\, e^{-(3187\pm320)[(1/T) - (1/298.1)]} \quad \text{(for γ-CD)} \quad (3)$$

Where, c is the concentration of the CD in milligram per milliliter. T is the temperature in kelvin. The temperature dependence of solubility is shown in Table 1.2.

Table 1.2 Solubility of cyclodextrins in water as a function of temperature

Temperature (ºC)	Solubility (mg/g water)		
	α-CD	β-CD	γ-CD
20	90	16.4	185
25	127	18.5	256
30	165	22.8	320
35	204	28.3	390
40	242	34.9	460
45	285	44.0	585
50	347	52.7	651

Relative to the solubilities of acyclic saccharides, the low solubilities of CDs are a consequence of the relatively unfavorable enthalpies of solutions, partially offset by the more favorable enthalpies of solution. The thermodynamic properties of α-CD and γ-CD are very similar, whereas the much lower solubility of β-CD is a consequence of a less favorable (more positive) ΔH^o and a less favorable (more negative) ΔS^o. The thermodynamic parameters for α-CD, β-CD and γ-CD, are ΔH^o = 32.1 $kJmol^{-1}$, 34.8 $kJmol^{-1}$ and 32.4 $kJmol^{-1}$; and ΔS^o = 57.8 $JK^{-1}mol^{-1}$, 49.0 $JK^{-1}mol^{-1}$ and 61.5 $JK^{-1}mol^{-1}$ causing a compensation of the favorable enthalpy by the unfavorable entropy of solution[36].

In presence of organic solvents the solubility of CDs changes owing to the formation of inclusion complex. The solubility of β-CD as a mobile-phase additive was studied in methanol, ethanol, propanol, acetonitrile, THF and DMSO[37]. The solubility decreased monotonically with increasing methanol concentration, but increased to double its value in water with increasing acetonitrile concentration up to 30%[38]. Figure 1.4 shows the solubility of β-cyclodextrin in presence of cosolvents with water. In presence of relatively non-polar solvents the solubility of β-CD increases rapidly with increasing the concentration of cosolvent in water up 50% after that the solubility decreases quickly, whereas in case of polar solvent the solubility remains constant up to 40% after that increases rapidly.

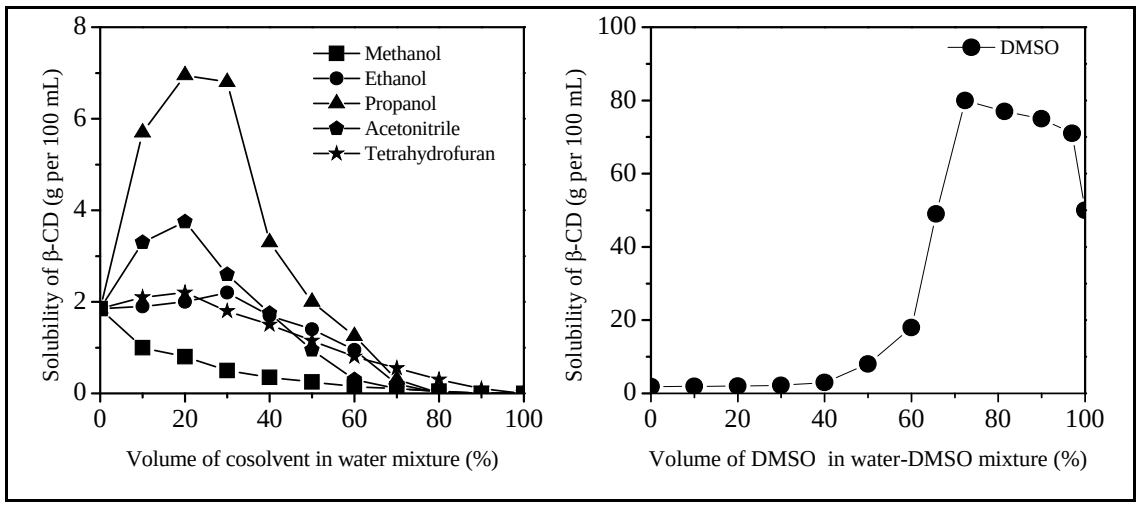

Figure 1.4 (a) Solubility of β-CD as a function of different cosolvent in water mixture and (b) Solubility of β-CD as a function of DMSO in water-DMSO mixture.

1.4 Aqueous Viscosity and Stability of Cyclodextrins

The viscosity of an aqueous cyclodextrin solution does not differ significantly from that of water. Measured at 25.1ºC, the viscosity of pure water is 8.93 x 10^{-4} Pa s, whereas the viscosity of a 9.5 x 10^{-4} M α-CD solution is 8.99 x 10^{-4} Pa s, and that of 9.98 x 10^{-3} M β-CD solution is 9.4 x 10^{-4} Pa s[39]. Both the concentration and temperature dependences of the viscosities of α-CD and γ-CD solutions, and their apparent molar volumes, are similar to those of linear saccharides, such as maltose and maltotriose. This indicates that α-CD and γ-CD are structural-forming solutes. The concentration dependences of the activity coefficients of CDs differ significantly from those of maltose and maltotriose owing to dimerization[40].

The cyclodextrins are thermally stable (up to at least 200ºC). They are very stable in alkaline solutions (pH < 14) and moderately stable in acidic solutions (pH > 3). Cyclodextrins can be hydrolyzed in strong acidic condition. The rate of hydrolysis depends on the concentration of acid and the temperature[41]. Cyclodextrins are stable in presence of (enzymes) glucoamylases or γ-amylase and β-amylase and can be hydrolyzed by some α-amylase[42].

1.5 Cyclodextrin Inclusion complex formation

The word inclusion complex (Einschlussverbindung) was introduced by Schlenk in 1950[43]. The most notable feature of CDs is their ability to form solid inclusion complexes (host-guest complexes) with a very wide range of solids, liquids and gases by a molecular complexation[44]. In these complexes (Figure 1.5), a guest molecule is held within the cavity of the CD host molecule[45]. The hydrophobic cavity of CD molecules provides a microenvironment into which appropriately sized non-polar moieties can enter to form inclusion complexes[46]. No covalent bonds are broken or formed during the formation of the inclusion complex[47].The main driving force of complex formation is the release of enthalpy-rich water molecules from the cavity. Water molecules are displaced by more hydrophobic guest molecules present in the solution to establish an apolar-apolar association and to decrease the CD ring strain resulting in a more stable lower energy state[48].

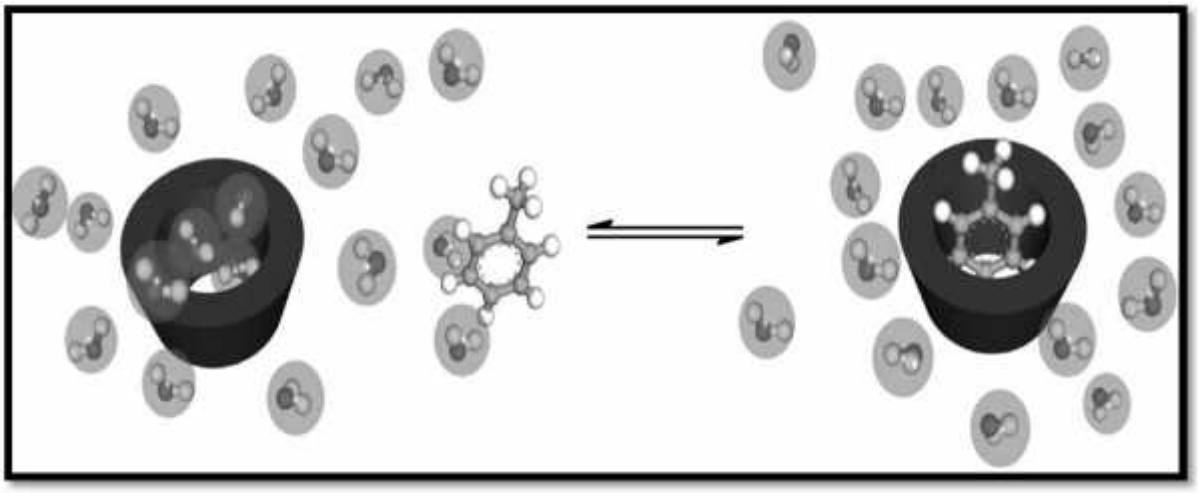

Figure 1.5 Host-Guest Inclusion Complexation.

The binding of the guest molecule within the host CD is not fixed or permanent but is rather a dynamic equilibrium. Binding strength depends on how well the "host-guest" complex fits together and on specific local interactions between surface atoms. Complexes can be formed either in solution or in the crystalline state. Inclusion complexation can be accomplished in a co-solvent system and in the presence of any non-aqueous solvent. Inclusion of a guest molecule in CD has a deep effect on its physicochemical properties as it is temporarily locked or caged within the host cavity[49-51].These properties are solubility enhancement of highly insoluble guests, stabilization of labile guests against oxidation, visible or UV light and/or heat, control of volatility, chromatographic separations[52-55] taste modification by masking flavors, unpleasant odors and controlled release of drugs and flavors. Therefore, CDs are used in food[56, 57], cosmetics[58], packaging[59, 60] and textile[61] industries, environment protection[62, 63], bioconversion[64], or pharmaceuticals[65]. The potential guest list for molecular encapsulation in CD is large and includes compounds from aliphatic chains to gases going through fatty acids and aromatics. The ability of CD to form an inclusion complex with a guest molecule is function of two key factors. The first is steric and depends on the relative size of the CD to the size of the guest molecule or some key functional groups within the guest. If the guest size is inappropriate, it will not fit properly into the CD cavity. The second critical factor is the thermodynamic interactions between the different components of the system (CD, guest, solvent). If the energetic driving forces that pull the guest into the CD are not favorable, the complex will not be formed[66]. While the height of the CD cavity is the same for all three types, the number of glucose units determines the internal diameter of the cavity and its volume (Table 1.1). Based on these dimensions, α-CD can complex low molecular weight molecules or compounds with aliphatic side chains, β-CD will complex aromatics and heterocycles and γ-CD accommodates larger molecules such as macrocycles and steroids. In general there are four energetically favorable interactions that help to shift the equilibrium to form the inclusion complex:

- The displacement of polar water molecules from the apolar CD cavity.
- The increased number of hydrogen bonds formed as the displaced water returns to the larger pool.
- A reduction of the repulsive interaction between the hydrophobic guest and the aqueous environment.

- An increase in the hydrophobic interactions as the guest inserts itself into the apolar CD cavity.

Complexes can be formed by various techniques depending on the properties of the active material, the equilibrium kinetics, the other formulation ingredients and processes, and the final dosage form required[67, 68]. However, each of these processes depends on a small amount of water to help to drive the thermodynamics. Among the methods used are simple dry mixing, mixing in solutions and suspensions followed by suitable separation, the preparation of pastes and several thermo-mechanical techniques[69].

Dissociation of the inclusion complex is a relatively rapid process usually driven by a large increase in the number of water molecules in the surrounding environment. The resulting concentration gradient shifts the equilibrium in Figure 1.5 to the left. In highly dilute and dynamic systems like the body, the guest has difficulty for finding another CD to form a complex again and is left free in solution. The formation of a 1:1 inclusion complex of host and guest is an equilibrium process between the dissociated and associated species in solution (Eq. 1), which is characterized by the stability constant, *K* (Eq. 2). This is the simplest and is more frequent. However, 2:1, 1:2 or 2:2 stoichiometries also exist for CD host-guest complexes[70].

$$Host + Guest \overset{K}{\Leftrightarrow} Host.Guest \quad (1)$$

$$K = Host.Guest \ \frac{Host.Guest}{Host \ \ Guest} \quad (2)$$

Considerable interest has been centered on the nature of interaction during the host-guest complexation as well as the structure of the CD complexes[71]. Molecular modeling, simulation, X-ray crystallography, NMR spectroscopy, optical spectroscopy (UV-Vis, fluorescence, circular dichroism) and thermal characterization methods have been frequently used to determine the molecular structure of inclusion complex.

1.6 Selective Modification of Cyclodextrins

It has been constant effort to modify or enhance the solubility of cyclodextrins by suitable modifications. However, the presence of the hydrophobic cavity and the large number of hydroxyl groups make the challenge of selective conversion a very difficult task[72]. The three types of hydroxyl groups present at the 2-, 3-, and 6-positions compete for the reagent and make selective modification extremely difficult. The strategy for modification depends on the purpose of the final product. For application in drug formulation, a highly water soluble CD is wanted. A random conversion of hydroxyl groups into hydroxypropyl group was easily achieved[73, 74]. But the final compound is not homogeneous and cannot be subjected to rigorous characterization. On the other hand, if an enzymatic mechanism has to be investigated using a CD derivative, then this compound needs to be homogeneous with a well-characterized structure including the exact number of substituent attached to, the stereochemical changes that have taken place during its synthesis.

Strategies for selective modification of CDs can be divided into three categories[75]

1. the “clever” method, where the chemistry of CD is exploited to get the desired product by the shortest route;

2. the “long” method, where a series of protection and deprotection steps have taken place in order to selectively reach the positions which would otherwise not be selectively accessible;

3. the “sledgehammer” method, where CD is indiscriminately reacted to give a mixture of products, and then the desired product is painstakingly separated out from other isomers and homologues by chromatographic methods.

As the first strategy is most productive and least painful, it is always chosen first. However, a method in the first category is not always available when a modified CD of a specific structure is needed. The two main factors to be considered in the chemistry of CDs for their modification are the nucleophilicity of the hydroxyl groups and the ability of CDs to form complexes with the reagents used. All modifications of CDs take place at the hydroxyl groups. Since hydroxyl groups are nucleophilic by themselves, the initial reaction is an electrophilic attack.

The hydroxyl groups at the 6-position are the most basic of the three types of hydroxyl groups present in CDs, those at the 2-position are the most acidic, and those at the 3-position are the most inaccessible[76, 77]. Thus, under normal conditions, an electrophilic reagent attacks the 6-position (I in Figure 1.6). If more reactive reagents are used, the hydroxyl groups will be attacked less selectively. Thus, more reactive reagents will not only react with hydroxyl groups at the 6-position but also with those on the secondary side; whereas, less reactive reagents will react more selectively with the 6-position hydroxyl groups. Since the hydroxyl groups at the 2-position are the most acidic, they will be the first to get deprotonated[78]. The oxyanion formed is then more nucleophillic than the undeprotonated hydroxyl groups at the 6-position (II in Figure 1.6). However, this situation is complicated by proton transfers between these two positions which can lead to a product mixture consisting of modifications at the 2- as well as at the 6-position.

The ability of CDs to form complexes provides an interesting factor affecting the chemistry of the hydroxyl groups (III in Figure 1.6). If the electrophilic reagent forms a complex with CD, the orientation of the reagent within the complex introduces an additional factor in determining the nature of the product[79]. If the complex is weak, relative nucleophilicities of the hydroxyl groups will direct the product formation. But if the formed complex is strong, the predominant formed product will be dictated by the orientation of the reagent within the complex. Solvents also influence in determining the strength and the orientation of the complex between the reagent and CD[80]. The most inaccessible hydroxyl groups at the 3-position can be modified using the complexing ability of CD[81]. However, designing reagents which can bind CDs with a specific orientation to give a substitution at a specific hydroxyl group has not yet been developed.

A strategy used to avoid difficulties due to the binding of the reagent into the CD cavity, and so obtain unexpected product, is to protect the hydroxyl groups and direct the incoming reagent exclusively to the other open hydroxyl groups. For example, if the 2-position of CD is protected, one can direct the incoming electrophile to the 6-position[82] (IV in Figure 1.6). Similarly, protection of the primary side enables one to direct the incoming electrophile exclusively to hydroxyl group at the 2-positions[83-85] (V in Figure 1.6).

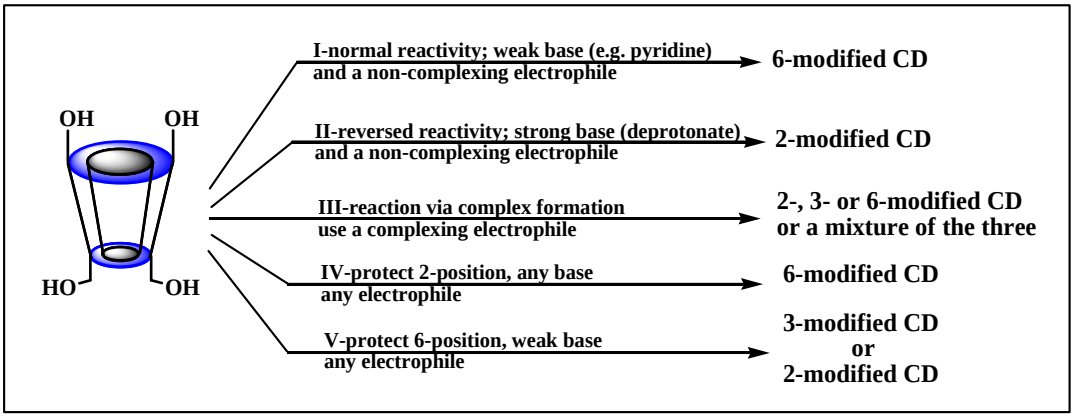

Figure. 1.6 Overview of the strategies for modification of CDs[74]

1.6.1 Selective monosubstitution at the 6-position

Since primary hydroxyl groups are more nucleophilic than secondary ones, they are easily modified into other functional groups by reaction with an electrophile to produce the substituted counterpart. All kinds of electrophiles can be used but very reactive reagents lead to uncontrolled substitutions. If the reaction time and the amount of reagent is not controlled, a mixture of mono-, di-, tri- and per-substituted compounds is obtained with a slightly advantage to the permodified one. Mono-, di-, tri-, and per-substitution refers to modification at one, three, and all hydroxyl groups at one site (either the 2-, 3-, or 6- positions) of CD.

One of the best strategy is to substitute 6-hydroxyl group(s) by sulfonyl group(s). The sulphonyl group acts as a good leaving group and can be displaced by nucleophiles to synthesize useful derivatives. Thus 6-sulfonates serve as precursors for the preparation of the 6-deoxy CD compounds. A large number of nucleophiles attack the carbon atom at the 6-position in these sulfonates to give the corresponding modified CDs. However, alkaline bases cannot be used as nucleophlies due to the elimination reaction resulting in a 3, 6-anhydro product[86] as shown in Figure 1.7.

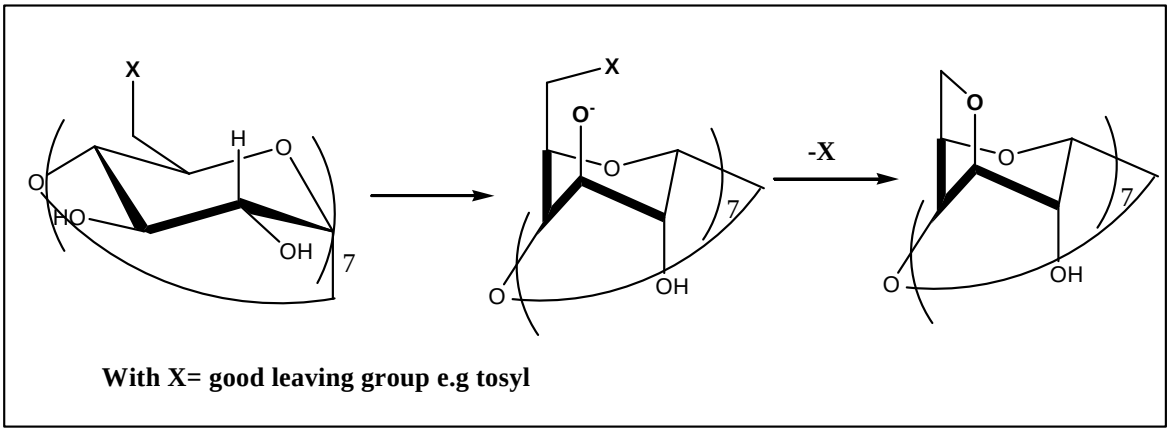

Figure 1.7 Conversion of a 6-substituted CD to a 3, 6-anhydro CD

1.6.2 Selective Di-, Tri-substitution at the 6-position

Many of the cyclodextrin derivatives reported in literature are the complex mixture of compounds that contains number of positional isomers. The number of possible positions for a substituent is given by the number of possible positions at a glucose unit (2, 3 and 6) multiplied by the number of different glucose units A, B, C….in the cyclodextrins. These are shown in Figure 1.8. Thus mono-, di-, tri- and permodifications refers to modification at one, two, three or all hydroxyl groups at one site that is either the 2-, 3- or 6-positions of cyclodextrins[74].The possible positional isomers of di and tri substituted α-cyclodextrin and β-cyclodextrin are shown in Figure 1.8. Disubstitution of α-CD at one site (either 2- or 3- or -6) can give 3 positional isomers. The same is true for β-CD. However trisubstitution at one site (either 2- or 3- or -6) can give 4 positional isomers for α-CD and 5 positional isomers in the case of β-CD. Disubstituted cyclodextrins are obtained most easily by bridging the two primary hydroxyl groups of cyclodextrin molecule with difunctional reagent. In this method, disubstitued sulfonates of cyclodextrins are synthesized by reaction of arenedisulfonyl chlorides with cyclodextrin to give AB, AC and AD isomers[87-89]. Though disulfonyl chlorides give a mixture of regioisomers, they show distinct regiospecificity based on their structures. An elegant method to control the regiospecificity to produce AB, AC or AD isomers by the use of the geometry of reagent has been described[90]. For example, trans-stilbene and biphenyl based capping reagents have been used to give AD isomers, benzophenone-based reagents to give AC isomers and 1,3-benzenedisulfonyl chlorides gives the AB isomers[91-92]. Antraquinone-2,6-disulfonyl chloride gives AC and AD isomers in low yield after purification by HPLC[93], where as Bis(9,10-dicyanoanthracenesulfonyl chloride) gave two isomers (AD and AC) in a ratio of 3:1, showing some degree of selectivity[94]. The synthesis and isolation of the trisustituted cyclodextrin is very difficult because of the large number of possible positional isomers. Tosylation pf cyclodextrin leads to $6^{A},6^{C},6^{E}$-tri-O-tosyl-β-cyclodextrin with very low yield (2.6%)[95,96]. In contrast the tritylation of cyclodextrin gives $6^{A},6^{C},6^{E}$-trityl derivative in a reasonable yield of 23%. In a different method S. Cottaz *et al*. synthesized the $6^{A},6^{C},6^{E}$-tri-O-methy-α-cyclodextrin with 43% yield[97] from and also synthesized the same from enzymatic cyclotrimerization of 6-O-methyl maltose[98]. Figure 1.9 gives a schematic representation of the mono-, di-, and trisubstituted cyclodextrin using different strategies.

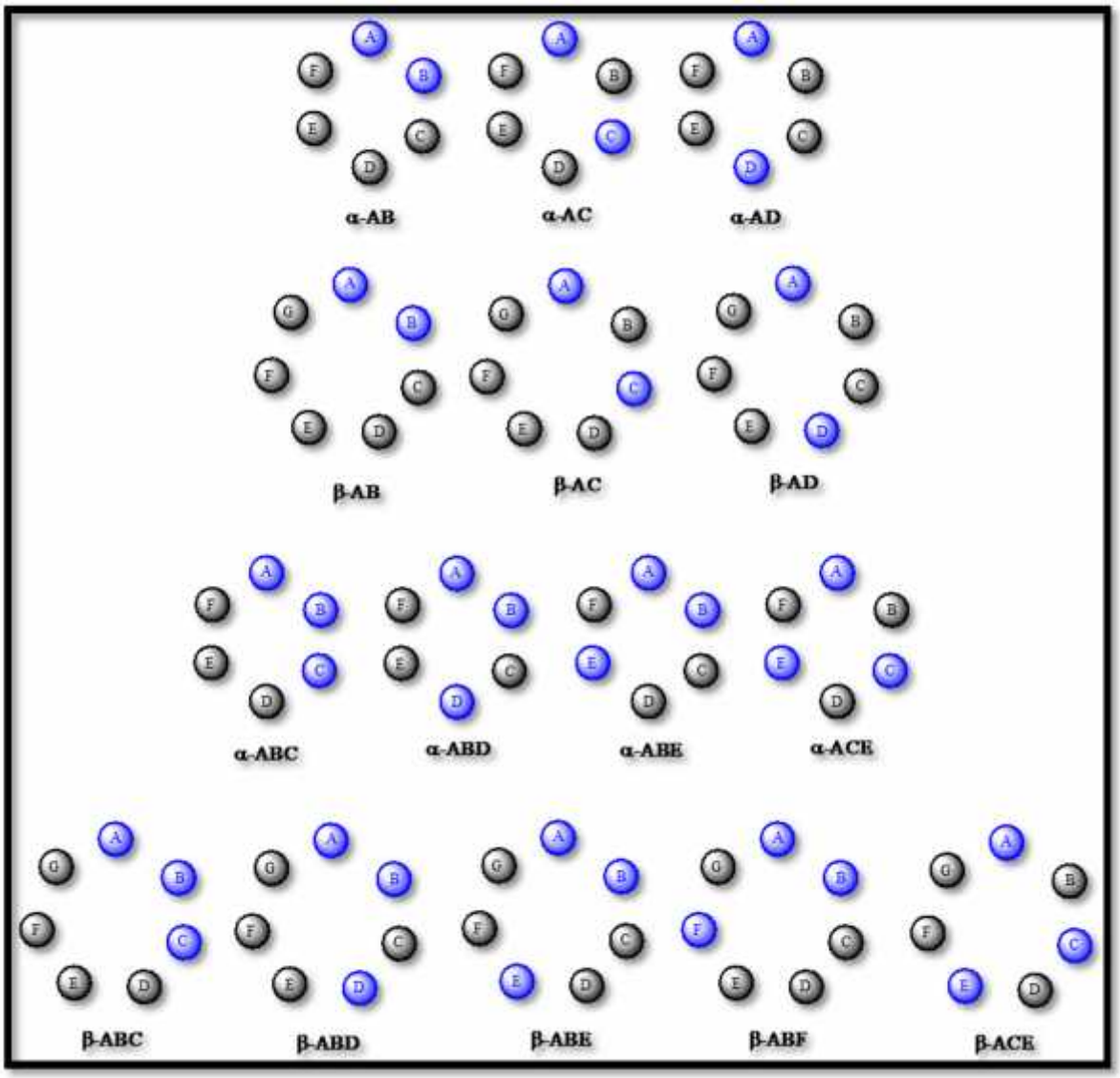

Figure 1.8 Possible positional isomers of mono, di and tri-modified α-CD and β-CD.

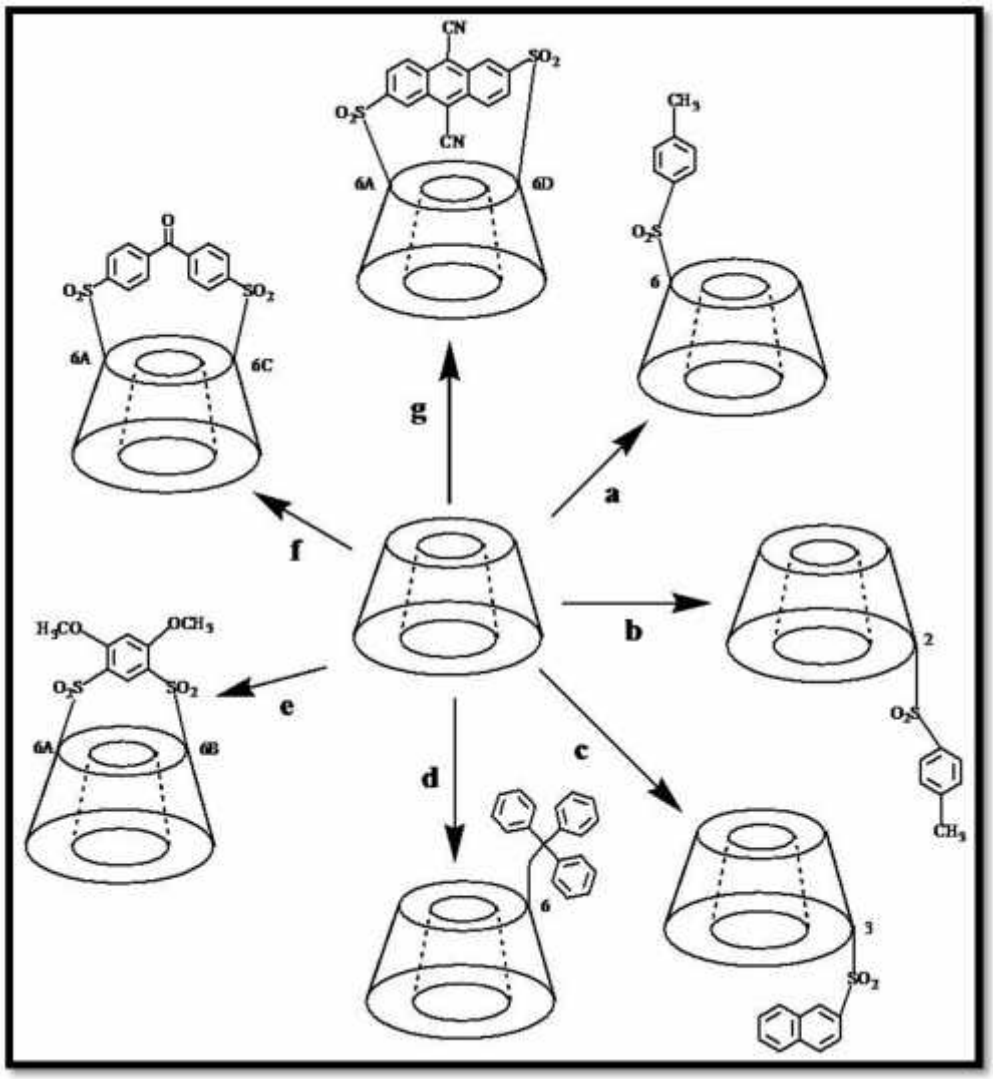

Figure 1.9 Specific introductions of mono-, di- and tri- substitutents to cylclodextrins. a) Ts/Pyridine, b) 3-nitrophenyltosylate/DMF/H_2O (pH 10), c) NsCl/MeCN/H_2O (pH 12), d) TritCl/Pyridine, e) 4,6-dimethoxy-benzene-1,3-sulfonyl chloride/Pyridine, f) Benzophenone-disulfonyl chloride and g) Bis(9,10-dicyano-anthracene-2,6-sufonyl chloride)/Pyridine.

1.7 Cyclodextrin based polymers

Two or more covalently linked cyclodextrin rings would form cyclodextrin polymers. Initial work on cyclodextrin polymers was started by Friedman *et al* [99]. ln the last 25 years lots of work has been done for the preparation, properties and possibilities for the applications of cyclodextrins polymers. The cyclodextrin fixed into polymeric structures behave differently from their monomeric derivatives.

Cyclodextrin polymers can be classified into the following types. These are shown schematically in Figure 1.10.

(a) Linear polymers
(b) Cross-linked polymers
(c) Necklace Type CD polymers (Polyrotaxanes)

1.7.1 Linear Cyclodextrin polymers

Linear homopolymers containing CD on the side chain have been synthesized by two methods such as addition polymerization and condensation polymerization. In the addition polymerization, the first step was the preparation of allyl group containing monomer, for example, acryloyl and methacryloyl cyclodextrins can be obtained by reacting acryloyl nitrophenol with cyclodextrin or from monotosyl cyclodextrin[100,101]. The monomers were also copolymerized with other water-soluble monomers, such as acrylamide, acrylic acid and vinyl pyrrolidone. Linear or cross-linked structure can be obtained depending on the functionality of comonomer. A typical synthesis of such polymers is shown in Figure 1.11.

Similarly, M. Yoshinaga *et al.*[102] and G. Crini *et al.*[103] synthesized the addition polymerizable monomers by modifying monotosyl β-cyclodextrin into monomethylol cyclodextrin and vinylamine β-cyclodextrin which can be polymerized to give linear cyclodextrin based polymers.

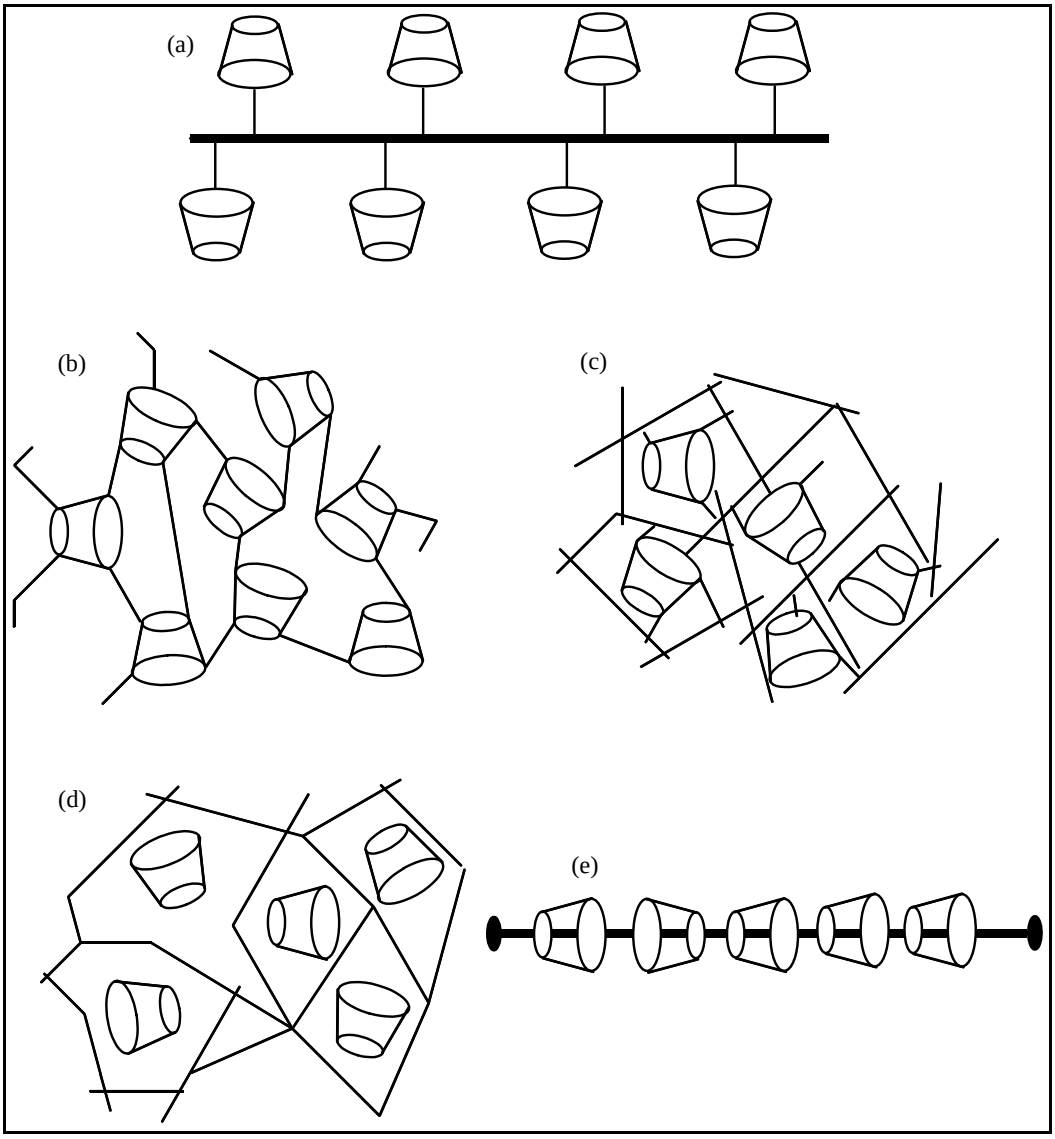

Figure 1.10 Structural classifications of cyclodextrin polymers.

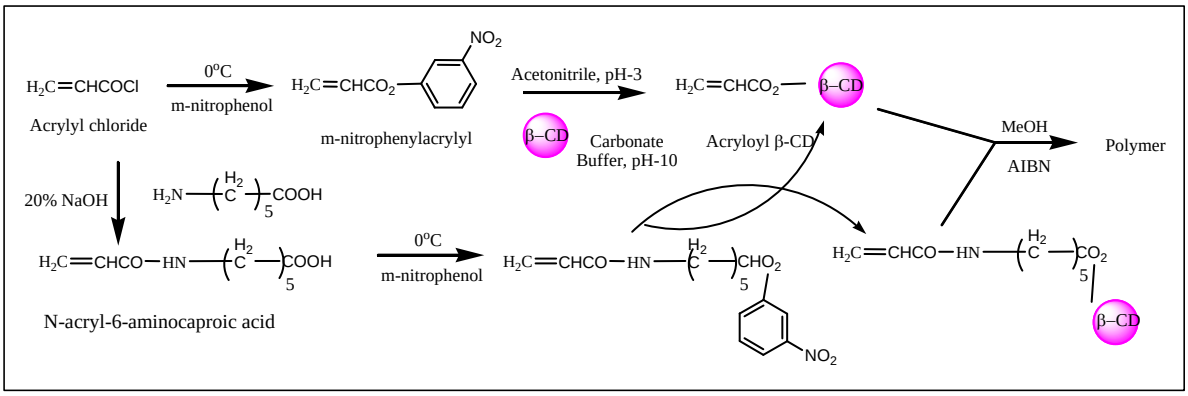

Figure 1.11 Synthetic scheme of linear pendent-cyclodextrin polymer.

In the condensation polymerization cyclodextrin can be coupled with the presynthesized polymers by using the two different functionalities and coupling agent, for example cyclodextrin can be attached with polyallyamine[104] and carboxy methylated chitosan[105] using DMA and EDC as coupling agents, respectively. A typical synthesis of such polymers is shown in Figure 1.12. Similarly, T. Seo *et al.*[106], A. Ruebner *et al.*[107] and P. Caliceti *et al.*[108] synthesized the covalent bonded cyclodextrin as pendent-chain polymers by condensation polymerization using tosylated β-CD and polyallylamine as monomers. In another variation of synthesizing polymers containing cyclodextrin as pendent group, β-cyclodextrin was grafted on to poly(methyl vinyl ether)-co-maleic anhydride where the monoalkoxide of β-cyclodextrin was prepared and then attached to the maleic anhydride site of the copolymer thus giving a polymer with pendent β-CD[109]. This is schematically shown in Figure 1.14. M. E. Davis *et al.*[110,111] synthesized a class of linear polymers that contains CD as part of the backbone. The key step in preparing this type of CD-containing polymer is the synthesis of difunctionalized CD-containing monomers. Figure 1.14 illustrates the strategy of preparing either cationic or anionic polymers starting from difunctional CD-monomers.

Linear cyclodextrin containing polymer have also been obtained by non-covalent integrations that is the cyclodextrin units are not linked by any covalent bond, thus 6-deoxy-(6-t-butyl)-β-cyclodextrin forms a polymer where the *t*-butyl group of one is included into the cavity of the other monosubstituted cyclodextins when the other substituent form the complex through proper guest[112]. Similarly, 2-hydroxypropyl β-cyclodextrin has been prepared where the 2-hydroxypropyl β-cyclodextrin is included into the cyclodextrin nanocavity of the next molecule and helically extended polymeric structure is formed by repetition of the intermolecular inclusion[113].

M. Masahiko *et al.*[114] synthesized the supramolecular polymeric structure by preparing cinnamide functionality among α-CD at 6-position or 3-position. The cinnamide group gets included into the nanocavity of cyclodextrin. This is shown in Figure 1.15.

K. Iwata *et al.*[115] attached the β-cyclodextrin on copolymers of glycidyl methacrylate and ethylene glycol methacrylate or via linking with the *N*, *N*'-carbonyldiimidazole.

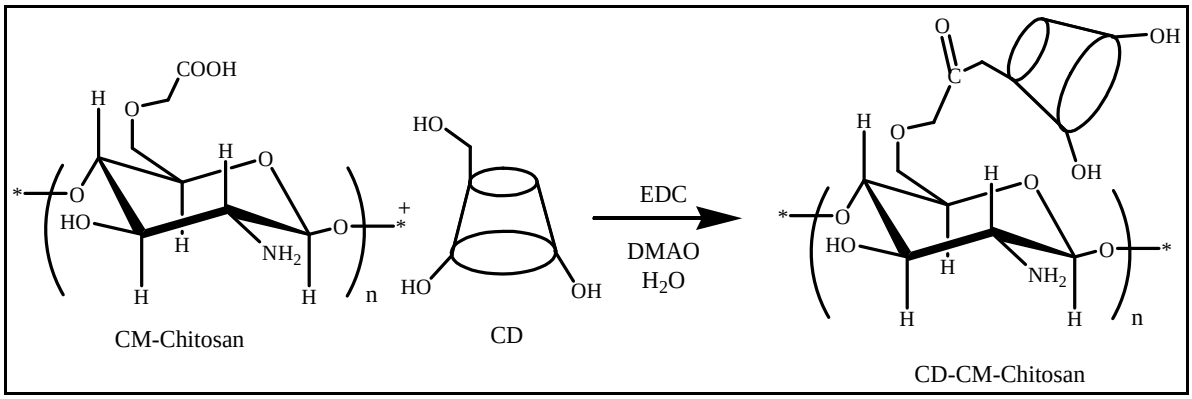

Figure 1.12 Synthetic scheme of CD-CM-Chitosan polymer.

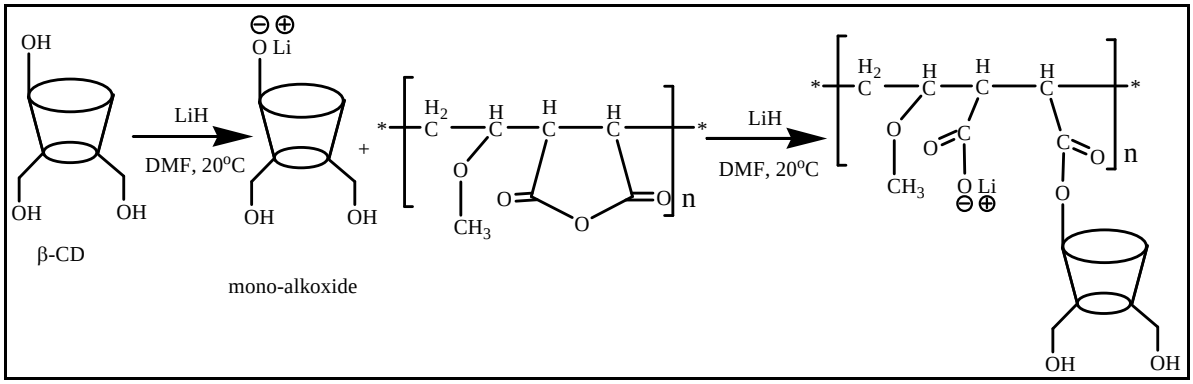

Figure 1.13 Synthesis of novel linear water-soluble polymer.

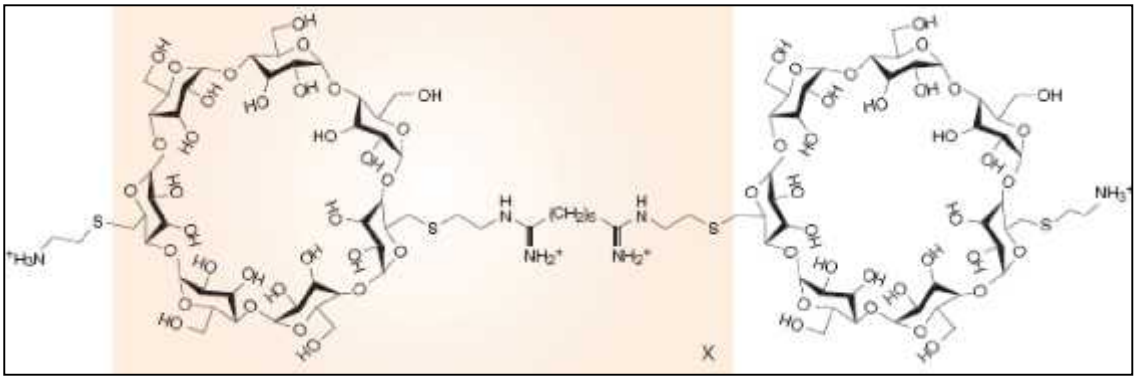

Figure 1.14 Synthesis of linear cationic cyclodextrin main-chain polymer.

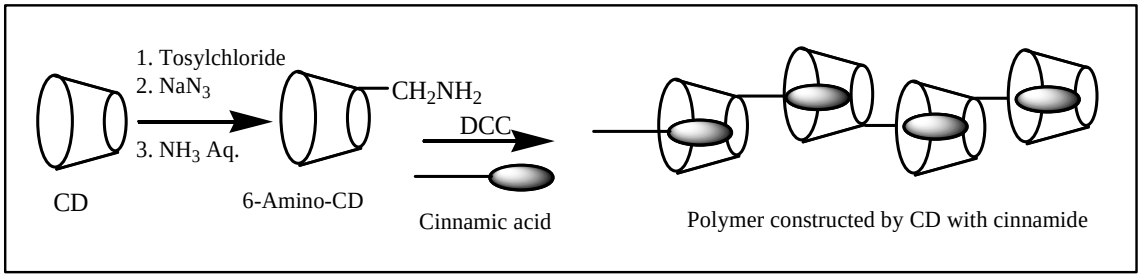

Figure 1.15 Synthesis of supramolecular polymers constructed by cyclodextrins with cinnamide.

1.7.2 Cross-linked polymers

Cross-linked polymers have been synthesized by reaction of cyclodextrins and cross-linking agents containing bi- or polyfunctional groups. Effective crosslinking agents that have been reported include: epichlorohydrin[116-118], diisocyanates[119], polycarboxylic acids[120], anhydrides[121], diepoxides[122] etc. These crosslinking nucleophilic substitution reactions with crosslinking agent usually occur in the alkaline medium. The water-solubility and molecular weight of the obtained polymers generally depends on the concentration of the crosslinking agent, pH of the reaction mixture and temperature of the reaction. E. Renard *et al.*[123] have investigated the relation between preparation conditions and water-solubility of the cyclodextrin polymers. Usually, lower molar ratio of crosslinking agent gives water-soluble polymers whereas higher molar ratio of crosslinking agent gives water-insoluble polymers. Figure 1.16 shows the typical synthesis of cyclodextrin and epichlohydrine cross-linked polymers.

T. R. Thatiparti *et al.*[124] synthesized cyclodextrin and diisocyanate crosslinked hydrogels by simple reaction of β-cyclodextrin with hexamethylene diisocyanate in dry DMF. This hydrogel was used for antibiotic delivery. Similarly, M. Bhaskar *et al.*[125] synthesized water-insoluble polyurethane using β-cyclodextrin and hexamethylene diisocyante which was used as a column material for the extraction of aromatic amines from water. Figure 1.17 depicted the synthesis of cross-linked cyclodextrin and hexamethylene diisocyanate polymers.

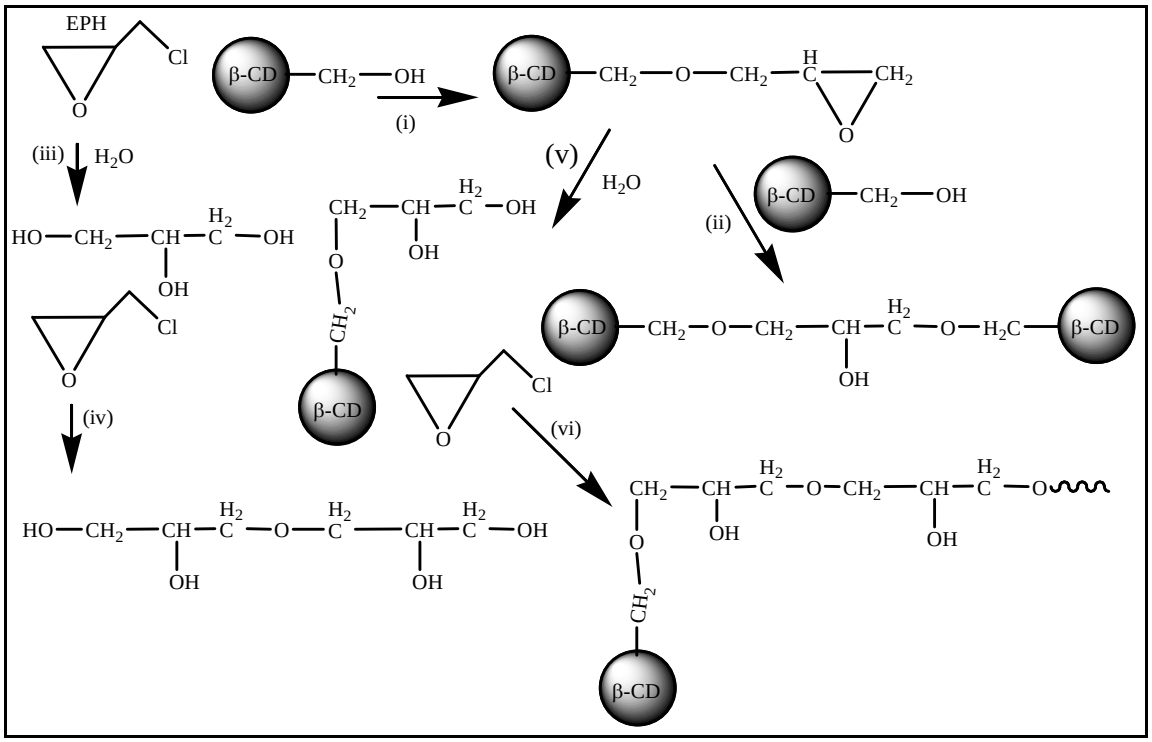

Figure 1.16 Synthesis of β-cyclodextrin-epichlorohydrin polymer.

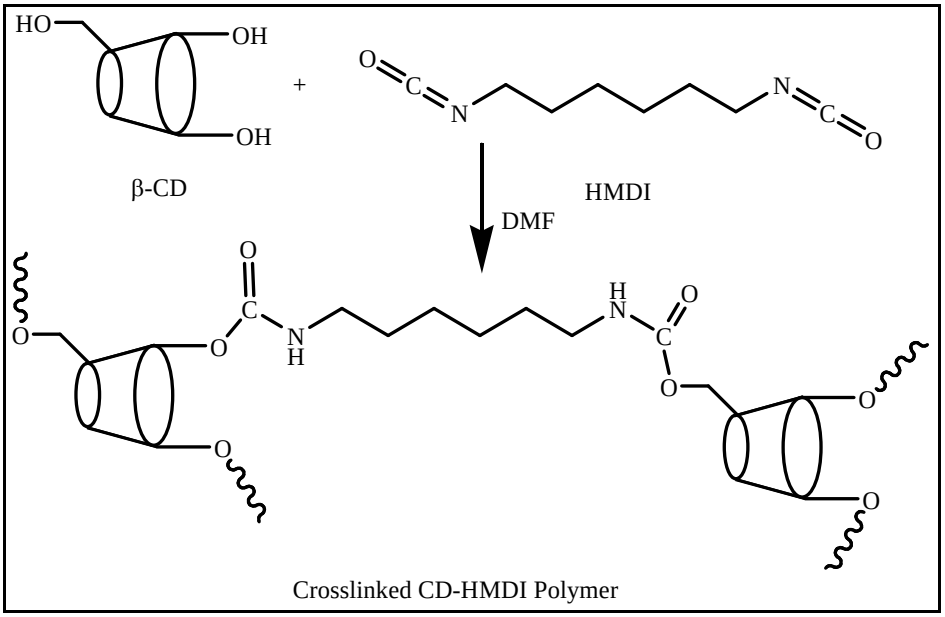

Figure 1.17 Synthesis of β-cyclodextrin-hexamethylene diisocyanate polymer.

1.7.3 Necklace Type CD polymers (Polyrotaxanes)

The necklace type cyclodextrin polymers are mainly polyrotaxanes where cyclodxtrins rings are strung on a polymers chain. Polyrotaxanes containing cyclodextrin can be synthesized by first threading many cyclodextrins on a polymer chain and then blocking the ends of the polymer chain with bulky groups[126]. Polyrotaxanes consist of three key components: the wheel (i.e., a macrocycle, such as cyclodextrins), the axle (i.e., molecule threading through the macrocyle, usually a linear polymer) and the bulky blocking groups appended to the axle, which prevent the treading of the wheel(s). The threading efficiency and polyrotaxane dynamics are governed by non-covalent interactions between the wheel(s) and axle and between the adjacent wheels. If the bulky blocking groups (also called end caps or stoppers) on the ends of the axle are smaller than the cavity of the macrocycle, then the complex is termed as psedorotaxane (i.e., false wheel and axle). Different types of polyrotaxanes are obtained, when a polymer with reactive groups in the main-chain is threaded by cyclodextrins [127-129]. These polyrotaxanes cyclodextrins polymers have not only remarkable structures, but they also provide fundamental insight for the development of new materials. They are expected to show different physical, mechanical and rheological properties, as compared to classical polymers, due to topological differences[130-132]. Figure 1.18 shows the synthesis of a typical polyrotaxane.

1.8 Applications of cyclodextrins and cyclodextrin polymers

Cyclodextrins are able to encapsulate wide range of molecules to form host-guest inclusion complexes which given the unique nature imparted by their structure. As a result, these macrocyclic molecules have found tremendous applications in a wide range of fields.

1.8.1 Food industry

CDs could form inclusion complexes with a wide variety of molecules including fats, flavors and coloring agent. So CDs could be used in food industry. By encapsulating these agents (colorants, fatty acids, etc.), CDs will improve their chemical stability towards oxidation. CDs could also be used to modify the physical property of foods. Water-in-oil emulsions such as mayonnaise or salad dressing can be stabilized by CD[133].

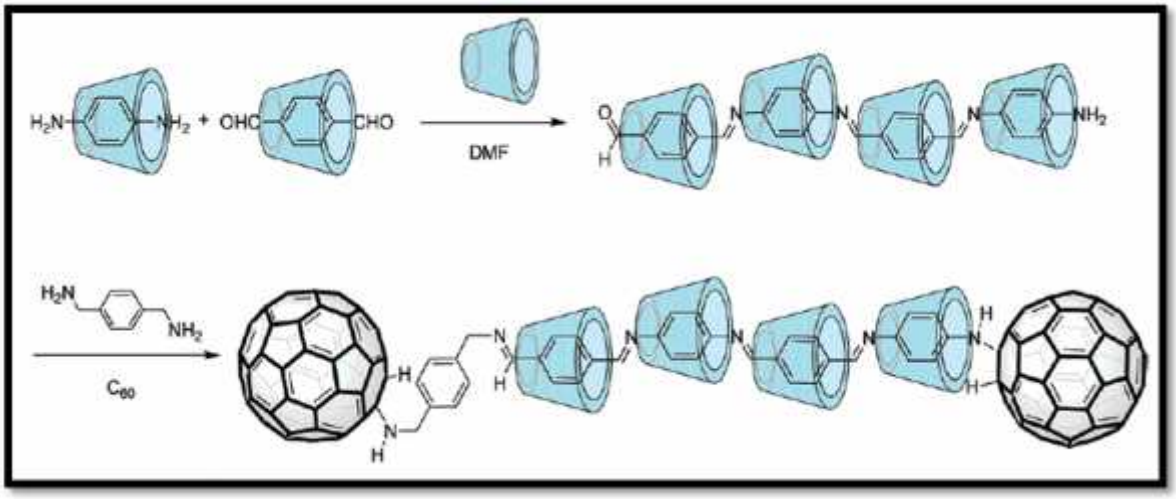

Figure 1.18 Synthesis of necklace type CD polymer Polyrotaxane.

Natural food coloring components in tomato ketchup can be stabilized by adding 0.2% β-CD[134]. Addition of CDs to emulsified foods or cheese can increase the water retention and the shelf life. In processed meat products, CDs improve water retention and texture[135]. CDs are also used to mask or reduce undesired taste such as bitterness in grapefruit juice[136] or in coffee[137].Empty CDs are employed as selective complexation agents in process, for example, to remove cholesterol from dairy products such as mayonnaise[138], butter[139], and eggs[140]. More than 90% of the cholesterol could be removed by adding βCD. CDs were reported to have ability to reduce bitterness[141], ill smell and taste, and to stabilize flavors when subjected to long-term storage[142]. In Table 1.3, some marketed food products are listed, which contain CD-encapsulated ingredients or are manufactured by a CD-assisted technology.

1.8.2 Cosmetics, toiletries and personal care

Cosmetic preparation is another area which uses benefits of CDs. The major benefits of CDs are stabilization, odor control (retention of perfume and controlled release of fragrances) and process improvement upon conversion of a liquid ingredient to a solid form, flavor protection and flavor delivery in lipsticks, enhanced water solubility and thermal stability of oils[144, 145]. Applications include toothpaste, skin creams, liquid and solid fabric softeners, paper towels, tissues and underarm shields. Long-lasting fragrances[146] are produced when fragrance is enclosed in CD. Indeed the fragrance is not volatilizing because the energy needed to volatilize is high. Malton *et al.* prepared cosmetic compositions containing CDs to create long-lasting fragrances[147]. CD-based compositions are also used in various cosmetic products to reduce body odors[148]. The use of CD-complexed fragrances in skin preparations such as talcum powder stabilizes the fragrance against the loss by evaporation and oxidation over a long period. Dry CD powders of size less than 12 mm are used for odor control in diapers, menstrual products, paper towels, etc. They are also used in hair care preparations to reduce the volatility of odorous mercaptans. The HP-β-CD surfactant, either alone or in combination with other ingredients, provides improved antimicrobial activity[149]. Dishwashing and laundry detergent compositions with CDs can mask odors in washed items[150]. CDs used in silica-based toothpastes increase the availability of triclosan (an antimicrobial) by CD complexation and resulting in an almost threefold enhancement of triclosan availability[151]. CDs are used in the preparation of sunscreen lotions in 1:1

Table 1.3. Some marketed food products containing CDs or made by CD-aided technology[143]

Trade name	**Type of food product**	**Role of CDs**
Natual (France)	Low cholesterol cheese	To reduce cholesterol
Cyroma-line (Hungary)	Flavored sugar for baking	To preserve flavor on heating
Balade (Belgium)	Low cholesterol butter	To reduce cholesterol
Simply Eggs (USA)	Low cholesterol egg	To reduce cholesterol
Flavono (Japan)	Chewing gum	To stabilize flavor
Choco Bar (Japan)	Chocolate	For emulsification
Poder Tea (Japan)	Instant green tea	For stabilization of color
Gymet (Japan)	Dietary fiber drink	For taste masking
Stick Lemon (Japan)	Instant tea drink	To preserve flavor

proportion (sunscreen/HP-β-CD) as the CDs cavity limits the interaction between the UV filter and the skin, reducing the side effects of the formulation[152]. Similarly, by incorporating CD in self-tanning emulsions or creams, the performance and shelf life are improved.

1.8.3 Chemical industries

In the chemical industries, CDs are widely used to separate isomers and enantiomers, to catalyze reactions, to help in various processes and to remove or detoxify waste materials.

1.8.3.1 Analytical chemistry

Chiral separations are one of the most significant areas of application of CDs and their derivatives. CDs are used because of their ability to discriminate between positional isomers, functional groups, homologues and enantiomers by inclusion complexes formation[153]. Molecular recognition is the base of CD selectivity. This property of CDs makes them one of the most useful agents for broad range of separations. CDs are used in gel electrophoresis[154], capillary zone electrophoresis[155,156], isotachophoresis[157], capillary gas chromatography[158, 159], electrokinetic chromatography[160], microdialysis[161], ion exchange[162], affinity chromatography[163], thin layer chromatography[164], and separation through membranes[165]. CDs are also used in bulk scale preparations such as extractions, dialysis, foam flotation, membrane separation and electrophoresis[166]. The shape, size, and selectivity of CDs influence separations[167]. CDs are used as chemically bonded or sorbed ligands in stationary phase or in mobile phase[168]. Several chiral stationary phases (CSPs) for liquid chromatography based on modified CD have been developed and their enantioseparation characteristics have been studied. 10-Undecenoate/phenylcarbamate derivatives of β-CD have been prepared and linked to allylsilica gel by means of a radical reaction[169]. Their resolution abilities for a variety of racemic compounds (mainly pharmaceuticals and herbicides) were investigated and compared to analogous cellulose derivative based CSPs (Chiralcel OD-H). The prepared columns showed high separation selectivity and a good resolution for most injected solutes. The modified CD phases seem to have better chiral

recognition abilities towards the tested NSAIDs in comparison to the commercial Chiralcel OD-H.

Guo *et al*[170] have synthesized a native β-CD stationary phase by click chemistry (Huisgen [3+2] dipolar cycloaddition between the organic azide and a terminal alkyne). Separation of very polar components, such as nucleosides and oligosaccharides, and chiral separation under hydrophilic interaction liquid chromatography mode were successfully achieved. In addition, click β-CD was chromatographically evaluated with a set of flavone glycosides. Yu *et al* have grafted HP-β-CD to silica gel which can be used for preparation of thin-layer chromatography plates[171]. The resolution of clenbuterol and propranolol enantiomers were investigated on these thin-layer chromatography plates using different combinations of solvent systems at ambient temperature. The best simultaneous resolution was achieved in a solvent system of acetonitrilebutanol (50:50, v/v). The R values of resolution of clenbuterol hydrochloride and propranolol hydrochloride are 3.6 and 4.3, respectively. The spots of different enantiomers are clearly separated. Another field of applications of CDs as stationary phase is gas chromatography. Seventeen chiral sulfoxides and eight chiral sulfinate esters have been separated by gas chromatography (GC) on four derivatized CD CSPs (ChiraldexTM G-TA, G-BP, GPN, B-DM)[172]. It has been shown that the G-TA CSP exhibited a superior enantioselectivity for most compounds and that the B-DM CSP exhibited the best enantioselectivity for the sulfinate esters. In a lesser extent, CD (i.e. sulphated CD) could be dynamically adsorbed onto the surface of packing materials i.e. bare silica, strong cation-exchange and strong anion-exchange. The adsorbed molecules dramatically changed the properties of the original packing and thereby functioned as a new stationary phase.

The dynamically adsorbed stationary phases of sulfated CD were used for separation of enantiomers in capillary electrochromatography[173] (CEC). Lu *et al*. presented a dynamically adsorbed dual-coating for chiral open tubular CEC separation[174]. Cationic surfactant such as hexadimethrine bromide was first coated to the capillary wall due to electrostatic interaction, and then anionic SBE-β-CD was dynamically adsorbed as a second coating onto the cationic surfactant coating. The second coating acted as a CSP for separation of chiral compounds. Two test compounds, disopyramide and warfarin, were both baseline separated. It was observed that the chiral separation capability of the OT-CEC with the dynamically adsorbed dual-coating was stronger than that of capillary zone electrophoresis with SBE-β-CD alone.

Hydrophilic CDs have been used as buffer modifiers to perform chiral separation of drugs and chemicals[175, 176]. The enantiomeric separation of basic chiral pharmaceuticals such as pheniramine, brompheniramine, metoxyphenamine, cyclopentolate, doxylamine and ketamine has been investigated in capillary electrophoresis (CE) and liquid chromatography (LC) using negatively charged sulfated-β-CD (S-β-CD) and neutral CDs (HP-β-CD, DM-β-CD, TM-β-CD)[177]. In chromatography there is no difference in the separation mechanism process between charged and uncharged CDs. The only difference arises from molecular interaction between CD and analyte. For the investigated compounds in CE, a better enantioselectivity was obtained for S-β-CD than for neutral CD. Rocco *et al* used nano-LC to separate some racemic nonsteroidal anti-inflammatory drugs, namely naproxen, indoprofen, ketoprofen, flurbiprofen, carprofen, cicloprofen, flunoxaprofen and suprofen into their enantiomers[178]. Chiral recognition was achieved by adding to the mobile phase TM-β-CD. The most favorable mobile phase for enantiodiscrimination was obtained with relatively low concentrations of acetonitrile (30%, v/v), 30 mM of TM- β-CD and pH value of 3.0. It was found that the retention time of all studied enantiomers decreased by increasing the CD derivative concentration. A chromatographic-densitometric method for the identification and determination of S (+) and R(-) ibuprofen has been carried out on RP-TLC plates using β-CD in mobile phase[179]. This method showed high sensitivity, high repeatability and high recovery for both isomers.

1.8.3.2 Catalytic chemistry

By modifying naturally occurring CDs through substituting various functional compounds on the primary or secondary face of the molecule or by attaching reactive groups, CDs can serve as “enzyme mimics” in catalytic reactions. These modified CDs are useful as “enzyme mimics” because of the molecular recognition phenomenon attributed to the substituted groups on the CD and because of the enantiomeric specificity of CDs. This ability results from binding of substrates into the hydrophobic cavity with the subsequent reaction initiated by catalytic groups linked to the CD. Rates of reaction are enhanced by almost 1000-fold by such modified CDs versus free solution due to the chelating effect of the CD catalysts.

A β-CD derivative with a nicotinamide group attached to the secondary face of β-CD was synthesized[180]. This simple dehydrogenase enzyme mimic can be used as a

substituted for a dehydrogenase enzyme and NAD $^{+}$ co-enzyme. This biomimetic material could be used as highly sensitive and specific electrochemical and optical sensor for biomolecules. McNaughton[181] demonstrated that novel CD-derived diorganyl tellurides catalyzed the reaction of hydrogen peroxide, *tert*-butyl hydroperoxide, and cumene hydroperoxide in the presence of glutathione. These mimics of the gluthatione peroxidase antioxidant enzymes could find use in pathologies characterized by an oxidative stress such as chronic inflammatory disorders,atherosclerosis etc.

1.8.3.3 Environmental

CDs can play a major role in environmental sciences in terms of solubilisation of organic contaminants, enrichment and removal of organic pollutants and heavy metals from soil, water and atmosphere[182]. CDs are also applied in water treatment to increase the stabilizing action, encapsulation and adsorption of contaminants[183]. Highly toxic substances can be removed from industrial effluent by inclusion complex formation. Twenty mercury compounds were treated with α-CD to product stable non-toxic mercury in soil and water[184]. It was found that organic and inorganic mercury pollutants could be mineralized in the environment with CD as the toxicity of the Hg-contaminated soil decreased to 80% after treatment. Moreover the bound mercury compounds resist to biodegradation and were found to be non-toxic to environmental microorganisms under laboratory conditions. A β-CD polymer was synthesized and its ability to remove bisphenol A (BPA), a possible endocrine disrupter, was evaluated[185]. It was found that 98% of BPA was adsorbed on the polymer. Moreover, the polymer was BPA selective as it did not absorb hydrophobic amino acids. This polymer was found to be an effective adsorbent to decontaminate liquid foods from BPA, used as the raw material of polycarbonate and epoxy resins and as a plasticizer of polyesters. Solubility enhancement phenomenon of CDs is used for testing of soil remediation[186]. Bardi demonstrated that β-CD at 1% concentration increased significantly the bioavailability of aliphatic and polycyclic aromatic hydrocarbons towards microorganisms[187]. This increase led to an enhancement of the degradative activity of a natural microbial soil population influencing the growth kinetics, producing higher biomass yield and better utilization of hydrocarbon as a carbon and energy source. The low cost, biocompatible and effective degradation makes β-CD a useful tool for

bioremediation process. β-CD may also be used as a remediation agent to enhance the mobility of butachlor and thus the bioavailability of butachlor in contaminated soil[188]. Due to soil adsorption, higher amounts of the herbicide butachlor are necessary to achieve herbicidal activity, hence increasing its environmental risks. The interaction of butachlor with β-CD produced the formation of an inclusion complex. The complexation significantly reduced the sorption of butachlor by soil and improved butachlor solubility and its aqueous dissolution rate. Therefore, β-CD as formation additive may obtain controlled release of butachlor, increase the availability of butachlor for weeds, avoid the use of higher amounts of herbicide, and diminish the use of organic solvents.

1.8.3.4 Pharmaceuticals

Within the pharmaceutical industry, the nature of drug screening has evolved over the years such high throughput screening techniques have become routine. These hit identification strategies put a type of evolutionary pressure on emerging drug candidates, which has led to a systematic increase in molecular weight, lipophilicity and a decrease in water solubility of lead compounds over time [189, 190,191]. Retrospective studies in the late 1980's showed that over 40% of drug failures in development could be traced to poor biopharmaceutical properties namely, poor dissolution or poor permeability[192]. Based on an analysis completed in the 2000's, this situation has improved. However poor solubility continues to impact the development of a large number of potential drug candidates[193]. CDs represent a true added value. These starch derivatives are useful solubilizers, enabling both liquid oral and parenteral dosage forms. In addition they can improve the oral bioavailability of solids through an increase in dissolution rate secondary to enhancing the apparent solubility of a compound. Many CDs including α-CD, β-CD, γ-CD, RM-β-CD, HP-β-CD and SBE-β-CD have become standard tools in formulation and are applied not only to formulation design but also to the early testing of drug candidates. In Table 1.4, a number of commercially available CD-containing formulations are listed. In addition of their solubility effect, CDs are also not irritant and offer distinct advantages such as the stabilization of active compounds against hydrolysis, oxidation, heat and light, reduction in volatility of drug molecules, and masking of malodors and bitter tastes.

Table 1.4. Some marketed pharmaceutical products containing CDs[194]

Drug/CD	Trade name	Formulation	Company (country)
α-*CD*			
Alprostadil	Caverject Dual	i.v. solution	Pfizer (Europe)
Cefotiam-hexetil HCl	Pansporin T	Tablet	Takeda (Japan)
PGE1	Prostandin, Protavasin	Parenteral solution, sublingual and oral tablets	Ono (Japan); Schwarz (Europe)
β-*CD*			
Benexate HCl	Ulgut, Lonmiel	Capsule	Teikoku (Japan); Shionogi (Japan)
Betahistidine	Betahist	Tablet	Geno Pharmaceuticals (India)
Cephalosporin	Meiact	Tablet	Meiji Seika (Japan)
Cetirizine	Cetrizin	Chewing tablets	Losan Pharma (Germany)
Chlordiazepoxide	Trinxillium	Tablets	Gador (Argentina)
Dexamethasone	Glymesason	Ointment	Fujinaga (Japan)
Diphenhydramin and chlortheophyllin	Stada-Travel	Chewing tablet	Stada (Europe)
Flunarizine	Fluner	Tablet	Geno Pharmaceuticals (India)
Iodine	Mena-Gargle	Solution	Kyushin (Japan)
Meloxicam	Mobitil	Tablet and suppository	Medical Union Pharmaceuticals (Egypt)
Nicotine	Nicorette	Sublingual tablets	Pfizer (Europe)
Nimesulide	Nimedex	Tablets	Novartis (Europe)
Omeprazole	Omebeta	Tablet	Betafarm (Europe)
PGE2	Prostarmon E	Sublingual tablet	Ono (Japan)
Piroxicam	Brexin, Flogene, Cicladon	Tablet, suppository	Chiesi (Europe); Ache (Brazil), Ranbay (India)
Refocoxib	Rofizgel	Tablet	Wockhardt (India)
Tiaprofenic acid	Surgamyl	Tablet	Roussel-Maestrelli (Europe)
HP- β-*CD*			
Alfaxalone	Alfaxan	i.v.injection	Vetoquinol (UK)
Cisapride	Propulsid	Suppository	Janssen (Europe)

Hydrocortisone	Dexocort	Solution	Actavis (Europe)
Indomethacin	Indocid	Eye drop solution	Chauvin (Europe)
Itraconazole	Sporanox	Oral and i.v. solutions	Janssen (Europe, USA)
Mitomycin	MitoExtra, Mitozytrex	i.v. infusion	Novartis (Europe)
SBE- β-CD			
Aripiprazole	Abilify	i.m. solution	Bristol-Myers Squibb (USA); Otsuka Pharm. (USA)
Maropitant	Cerenia	Parenteral solution	Pfizer Animal Health (USA)
Voriconazole	Vfend	i.v solution	Pfizer (USA, Europe, Japan)
Ziprasidone mesylate	Geodon, Zeldox	i.m. solution	Pfizer (USA, Europe)
RM- β-CD			
17β-Estradiol	Aerodiol	Nasal Spray	Servier (Europe)
Cloramphenicol	Clorocil	Eye drop solution	Oftalder (Europe)
Insulin		Nasal spray	Spain
γ-CD			
Minoxidil	Alopexy	Solution	Pierre Fabre (EI)
HP- γ-CD			
Diclofenac sodium salt	Voltaren	Eye drop solution	Novartis (Europe)
Tc-99 Teboroxime	CardioTec	i.v. solution	Bracco (USA)

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