CHAPTER - IV

CYCLODEXTRIN COMPLEXATION: AN OVERVIEW

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Cyclodextrins (CDs), homologous cyclic oligosaccharides have long been known to increase the apparent solubility of many lipophilic drugs through non-covalent inclusion complexation[1,2]. Cyclodextrins and their derivatives play an important role in the formulation development due to their effect on solubility, dissolution rate, chemical stability and absorption of a drug[3,4]

The α–, β- and γ-cyclodextrins are cyclic oligosaccharides consisting of six, seven and eight glucose units respectively. While it is thought that, due to steric factors, cyclodextrins having fewer than six glucopyranose units cannot exist, cyclodextrins containing nine, ten, eleven, twelve and thirteen glucopyranose units, which are designated δ-, ε-, ζ-, η, and φ–cyclodextrin, respectively, have been reported[5,6]. Of these large-ring cyclodextrins only δ-cyclodextrin has been well characterized[7, 8]. Chemical and physical properties of the four most common cyclodextrins are given in Table 4.1. The melting points of α-, β- and γ-cyclodextrins are between 240° and 265°C, consistent with their stable crystal lattice structure[9].

Table 4.1

Some Characteristics of α-, β-, γ- and δ-Cyclodextrins

	α	β	γ	δ
No. of glucopyranose units	6	7	8	9
Molecular weight	972	1135	1297	1459
Central cavity diameter (A°)	4.7-5.3	6.0-6.5	7.5-8.3	10.3-11.2
Water solubility at 25°C (g/100 ml)	14.5	1.85	23.2	8.19

They are enzymatic conversion products of starch. The enzyme cyclodextrin-glucosyl transferase produced by B. *macerans* acts on partially hydrolysed starch (a mixture of linear dextrins) and produces a mixture of cyclic and acyclic dextrins, from which pure cyclodextrins (CDs) are isolated[10]. The structure of the most important CD β-cyclodextrinis shown in Fig. 4.1.

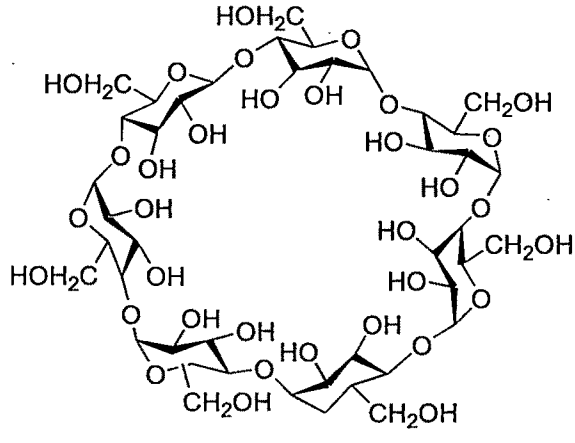

Fig. 4.1 : The Structure of β-cyclodextrin

The 'torus' shaped macro-ring is built of α-1,4-D-glucose units. As a consequence of conformation of glucopyranose units, all secondary OH- groups are located on one edge (wider edge) of the 'torus' like CD molecule while all primary OH-groups are on the other side (narrow side of torus). The lining of the internal cavity is formed by OH-atoms and glucosidic oxygen-bridge atoms, therefore, the inner surface is hydrophobic, but outer surface is hydrophilic.

Absorption and Toxicity

Cyclodextrins are not absorbed orally and not hydrolyzed during their transit through the small intestine. They are totally resistant to β-amylases, but can be attacked by α-amylases. Hydrolysis occurs only in colon (partial hydrolysis occurs with α-CD). The oral administration of CDs does not result in acute toxicity. Long term administration leads to no significant change in organs or biological values. Natural CDs are highly toxic when given parenterally. α- and β-cyclodextrins induce haemolysis and nephrotoxicity upon i.v. injection γCD is relatively less toxic parenterally[11].

Formation of Complexes

One of the most important characteristics of CDs are their ability to form inclusion complexes. Inclusion complexation involves entrapment of a guest molecule totally or partially in the cavity of host molecule without formation of any covalent bonds. CDs are typical host molecules and can entrap a wide

variety of drug molecules resulting in the formation of monomolecular inclusion complexes[12].

Inclusion complexation occurs when aqueous solution of CD is shaken with drug molecules or its solution. In aqueous solution the hydrophobic cavities of CD are occupied by water molecules, which can be replaced by appropriate drug molecules that are less polar than water. The solubility of the complex is usually lesser than the solubility of CD and hence the complex maybe precipitated from its saturated solution, as microcrystalline powder and this powder is subsequently separated by filteration[13]. Usually 1 : 1 complexes are formed, but when a guest molecule is too long to find complete accommodation in one cavity, its other end is also amenable to complex formation leading to 2 : 1 (CD : drug) or sometimes 3 : 1 or 4 : 1 complexes. It may also be possible to form 1 : 2 and 1 : 3 (CD : drug) complexes.

The central cavity of the cyclodextrin molecule is linked with skeletal carbons and ethereal oxygens of the glucose residues. It is therefore lipophilic the polarity of the cavity has been estimated to be similar to that of aqueous ethanolic solution[14]. It provides a lipophilic microenvironment into which suitably sized drug molecules may enter and be included. No covalent bonds are formed or broken during drug-cyclodextrin complex formation, and in aqueous solutions, the complexes are readily dissociated. Free drug molecules are in equilibrium with the molecules bound within the cyclodextrin cavity

Measurements of stability or equilibrium constants (K_c) or the dissociation constants (K_d) of the drug-cyclodextrin complexes are important properties of a compound upon inclusion.

Methods for Detection of Inclusion Complex Formation and Determination of Complex Stability Constant

One of the most interesting properties of CDs is their ability to form inclusion complexes with a wide variety of guest molecules. Molecular encapsulation may occur both in solution and solid state. In solution there is equilibrium between complexed and non complexed guest molecules, in solid state guest molecules can be enclosed with in. the cavity or may be aggregated to the outside of CD molecule[15] . Upon inclusion with in the CD cavity a guest molecule experiences changes in its physicochemical properties. These changes provide methods to detect whether guest molecules are really included in the CD cavity.

Detection of inclusion complexation in the solution state

Detection of inclusion complexation in solution state can be done by spectroscopic methods like Ultraviolet/Visible (UV/VIS), Fluorescence, Circular Dichroism, Electron Spin Resonance (ESR), and Nuclear Magnetic Resonance (NMR) methods. The ^{1}H-NMR and ^{13}C-NMR spectroscopic studies can also be used to determine the direction of penetration of guest molecules in to the CD cavity. Other methods include Polarography, Conductivity measurement, Microcalorimetry and Solubility methods[2].

Phase solubility technique[16] is the one of the widely used methods to detect the inclusion complexation in solution state.

The general experimental operation in studying molecular interactions by means of phase solubility method entails the addition of an equal weight (inconsiderable excess of its normal solubility) of a slightly soluble compound, S (substrate or guest) into each of several vials containing increasing concentrations of a relatively soluble compound, L (ligand or host or complex agent), which are closed and brought to solubility equilibrium at constant temperature. The solution phases are then analyzed, by any suitable means, for their total concentration of compound S (guest), no matter what its molecular state may be.

A phase diagram is constructed by plotting, on the vertical axis, total molar concentration of S found in the solution phase against the molar concentration of L.

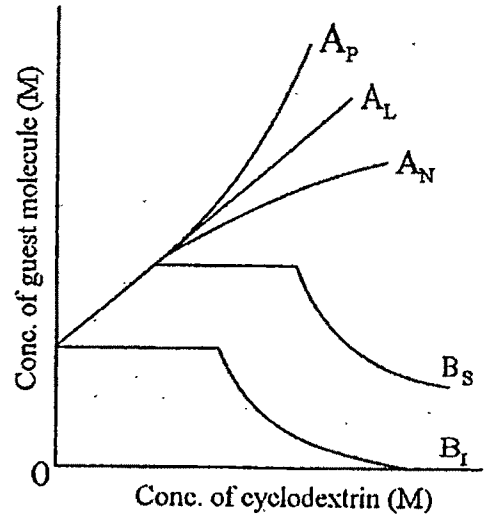

Fig. 4. 2. Phase solubility diagram

The phase diagrams are observed to fall into two main classes, type A and type B with some variation with in the classes (Fig. 4.2).

The type A can be further classified in subtypes A_L, A_P and A_N, where the guest solubility of first type increases linearly with cyclodextrin concentration while those of the second and third types deviate positively and negatively, respectively from the straight line. The complex formation with a 1:1 stoechiometry gives the A_L type diagram, where as the higher order complex formation in which more than one cyclodextrin molecules are involved in the

complexation gives the A_P-type. The interaction mechanism for the A_N-type is complicated, because of a significant contribution of solute-solvent interaction to the complexation. In the case of the Bs type, the initial ascending portion of the solubility change is followed by a plateau region and then a decrease in the solubility at higher cyclodextrin concentrations accompanying a microcrystalline precipitation of the complex. The H_P-type diagram is indicative of the formation of insoluble complexes in water.

The stability constant (Ks) and stoechiometry of complexes are determined by analyzing quantitatively the phase solubility diagram.

Detection of inclusion complexation in the solid state

Detection of the inclusion complexation in solid state can be done by Powder X-ray diffractometry, Single crystal X-ray structure analysis, Thermo analytical technique, Thin layer chromatography, Paper chromatography, Infrared spectroscopy, Scanning electron microscopy and Dissolution study methods[2].

Applications of Cyclodextrins

All the applications of CDs in drug formulations involve complexation[11,17-19]. When a drug becomes part of a CD complex, its physical and chemical properties are modified[20]. . In terms of physical and chemical

stability, complexed volatile compounds are less prone to loss by evaporation and oxidizable compounds are protected against oxidation by air. In the complexes the rate of decomposition, disproportionation, polymerization and autocatalytic reactions are all considerably decreased and the sensitivity to light and gastric acid are reduced. The solubility and dissolution rate of drugs are improved in CD complexes, poorly soluble drugs reach the blood more quickly and in higher concentration, suggesting the possibility of reducing the dose[21].

The most important requirement for the complex formation is the tight fitting of the guest molecule within the CD cavity. αCD cavity is too small and γCD cavity is too large (Table 4.1) for most of the drugs. βCD is most widely used for complexation because of its unique cavity size and ease with which it can be obtained on industrial scale, leading to reasonably cheaper price of this compound[22].

The parent cyclodextrin, βCD, however, displays surprisingly low solubility in water than α- and γ-cyclodextrins (1.8 g /100 ml as compared to 14 g/100 ml - αCD and 23 g/100 ml -γCD).

β-Cyclodextrin complex formation with lipophilic drugs and other compounds with limited aqueous solubility, frequently gives rise to B-type phase-solubility diagrams as defined by Higuchi[16]. That is, addition of these

unmodified cyclodextrins to aqueous drug solutions or drug suspensions often results in precipitation of solid drug-cyclodextrin complexes. The aqueous solubility of the parent cyclodextrin is much lower than that of comparable acyclic saccharides, and this could partly be due to relatively strong binding of the cyclodextrin molecules in the crystal state (i.e. relatively high crystal lattice energy). In addition, β- and δ-cyclodextrin (Table 4.1) form intramolecular hydrogen bonds between secondary OH groups, which detracts from hydrogen bond formation with surrounding water molecules, resulting in less negative heats of hydration[8,14]. Thus, intramolecular hydrogen bonding can result in relatively unfavourable enthalpies of solution and low aqueous solubilities. Substitution of any of the hydrogen[8,14] bond forming hydroxyl groups, even by hydrophobic moieties such as methoxy and ethoxy functions, will result in a dramatic increase in water solubility[14]. For example, the aqueous solubility of β-cyclodextrin is only 1.85% w/v at room temperature but increases with increasing degree of methylation. The highest solubility is obtained when two-thirds of the hydroxyl groups (i.e., 14 of 21) are methylated, but then falls upon more complete alkylation. That is, the permethylated derivative has a solubility that is lower than that of, e.g., heptakis (2,6-o-dimethyl)-β-cyclodextrin but that is still considerably higher than that of unsubstituted β-cyclodextrin[23].

Recently, the derivatives of βCD have received considerable attention because of their high water solubility (> 50 g/100 ml)[24]. They belong to classes of

- Methylated derivatives of βCD
- 2-hydroxy propylated β and γCDs
- Sulfobutylated-βCDs
- Branched CDs (glucosyl- and maltosyl-β-cyclodextrins)
- Acetylated β and γCDs
- Sulfated CDs

The main reason for the solubility enhancement in these derivatives is that chemical manipulation frequently transforms the crystalline cyclodextrins into amorphous mixtures isomeric derivatives. For example, (2-hydroxy propyl)-β-cyclodextrin is obtained by treating a base-solubilized solution of β-cyclodextrin with propylene oxide, resulting in an isomeric system that has an aqueous solubility well in excess of 60% (w/v)[25].

Research Work on CD Complexation:

Several studies reported the cyclodextrin complexation of a variety of drugs for various purposes. A summary of recent research work on

cyclodextrin complexation for enhancing the dissolution rate and bioavailability is given in Table 4.2.

Table 4.2

Summary of Recent Research Work on Cyclodextrin Complexation

S.No.	Drug	Cyclodextrin (CD)	Purpose/Result	Ref. No.
1.	Acetaminophen	α- and β-cyclodextrins	Effect of humidity on inclusion complex formation and their characterization by XRD, DSC and IR are reported	28
2.	Albendazole	α–, β– and HPβCD	Improved solubility and dissolution rate	29
3.	Amlodipine	β– and HPβCD	Improved solubility and characterization of inclusion complexes by DSC and thermogravimetric methods	30
4.	Benzthiazide	β–, γ– and Dimethyl βCD	Increased dissolution rate and inclusion complexes in solution and solid state were prepared and characterized by IR and DSC	31
5.	Bromozepam	Dimethyl βCD	Characterization of inclusion complexes by IR, XRD and DSC techniques	32
6.	Broperimine	βCD	Improved dissolution rate and stability studies	33
7.	Butyl methoxy dibenzoyl methiane (Sunscreen agent)	α–, β–, γ– and HPβCD	Characterization by phase solubility analysis, circular dichroism, DSC and XRD studies and improved solubility and photostability of complexes are reported	34
8.	Chenodeoxycholic acid	β– and Dimethyl-βCD	Improved aqueous solubility and dissolution rate	35

9.	Clotrimazole	Dimethyl-βCD	Improved aqueous solubility, dissolution rate and antimycotic activity	36
10	Danazol	HPβCD and sulfobutyl ether of β-cyclodextrin	Improved aqueous solubility and dissolution rate	37
11.	Diclobutrazol	α–, β–, Dimethyl β- and HPβCD	Improved aqueous solubility and dissolution rate	38
12.	Felodipine	β- and HPβCD	Improved solubility and characterization of inclusion complexes by DSC and thermogravimetric methods	30
13.	Fenabufen	α-, β- and γ-cyclodextrins	Improved dissolution rate and oral bioavailability of inclusion complexes	39
14.	Fucosterol	β–, Maltosyl-β- and Dimethyl-βCD	Improved solubility, dissolution rate and stoichiometry and stability constants were reported	40
15.	Furosemide	Cyclodextrins	Improved solubility and dissolution rate	41
16.	Glibenclamide	β-. HPβ- and Dimethyl-βCD	Improved dissolution rate	42
17.	Glisentide	α,– β– and γCD	Complexation in aqueous solution and solid state is investigated	43
18	Griseofulvin	β– and HPβCD	Improved dissolution rate	44
19.	Ibuprofen	β–Methyl β-, HPβ- and Hydroxyethyl βCD	Improved dissolution rate	45
20	Indomethacin	β– and HPβCD	The methods of preparation of inclusion complexes and their characterization in liquid and solid phases were reported	46
21.	Indomethacin	β– and HPβCD	Decreased G.I irritation	47
22.	Indomethacin	α,– β– and γCD	Enhanced solubility	48

23.	Insulin	α–, β–, γ–, HPβ and Dimethyl βCD	Enhanced pulmonary absorption	49
24.	Ketoconazole	β– and HPβCD	Phase solubility studies and improved dissolution of complexes prepared by spray drying and kneading methods were reported	50
25.	Ketoprofen	α–, β–, HPβ and Dimethyl βCD	Improved dissolution rate and bioavailability	51
26.	Ketoprofen	β–Methyl β-, HPβ- and Hydroxyethyl βCD	Improved dissolution rate	45
27.	Meclizine HCl	α,– β– and γCD	Improved dissolution rate	52
28	Menadione	βCD	Increased stability, solubility and decreased skin irritation were reported	53
29.	Mesalamine	α– and βCD	Physical characterization by XRD, SEM, thermo-microscopy, DSC and mass spectrometry	54
30.	Miconazole	HPβCD	Crystallinity was investigated in solid complexes	55
31	Miconazole	α–, β–, γ– Methyl β-, HPβ- and Hydroxyethyl βCD	Improved solubility, skin retention and oral bioavailability	56
32.	Naproxen	βCD	Improved dissolution rate of complexes and their characterization by XRD and DSC were reported	57
33.	Norfloxacin	β– and HPβCD	Improved dissolution rate	58
34.	Oxazepam	Dimethyl βCD	Improved dissolution rate and complex formation in solution by solubility. UV spectroscopy methods , DSC, XRD and SEM techniques were reported	59

35.	Psoralen	βCD	Improved dissolution rates	60
36.	Spironolactone	α,– β– and γCD	Improved aqueous solubility of inclusion complexes and phase solubility studies were reported	61
37.	Spironolactone	Cyclodextrins	Improved dissolution rate by direct compression was reported	62
38.	Spironolactone	β–, γ–, HPβ- and HPγCD	Improved dissolution and bioavailability	63
39.	Temazepam	β– and HPβCD	Improved dissolution rate	64
40	Terfenadine	α and βCD	Improved dissolution rate	65
41.	Tolbutamide	βCD	Improved dissolution and phase solubility studies were reported	66
42.	Tolbutamide	βCD	Improved absorption and bioavailability were reported	67
43.	Tolnaftate	β– and HPβCD	Increased solubility and dissolution rate	68
44.	Tretinoin	Dimethyl βCD	Increased solubility	69
45.	Urodeoxycholic acid	β- and Dimethyl βCD	Increased solubility and dissolution rate	35
46	Anandamine	HPβCD	Increased solubility and stability	70
47.	Ampicillin	βCD	Increased solubility, dissolution rate and bioavailability	71
48.	Allopurinol	βCD	Increased solubility, dissolution rate	71
49.	Paracetamol	βCD	Increased solubility	72
50.	Ibuproxam	α,– β– and γCD	Increased solubility, dissolution rate was increased	73
51.	Mebandazole	α–, β–, γ–,and HPβCD	Improved solubility and characterization of inclusion complex formation by phase solubility	74
52.	Nimesulide	βCD and L-lysine	Increased solubility	75

53.	Nimesulide	HPβCD and βCD	Increased solubility and dissolution rate	76
54.	Leteprednol etabonate	γ–, HPβCD, Maltosyl-β- and Dimethyl-βCD	Higher solubility and stability was observed in Dimethyl-βCD than HPβCD	77
55.	Tolbutamide	βCD	Improved dissolution by presence of CD and surfactant	78
56	Omeprazole	γCD	Improved dissolution rate prepared by coprecipitation method	79
57.	Gliclazide	βCD	Improved dissolution rate	80
58	Nimesulide	βCD	Higher rates of dissolution and dissolution efficiency	81
59.	Ofloxacin	βCD	Enhanced solubility, but not photostabilization	82
60.	Piroxicam	HPβCD	Increased permeation and release of drug from the gel	83
61.	Sulfamethiazole	βCD, HPβCD	Improved dissolution rate	84
62.	Ciprofloxacin	βCD	Conformation of existence of inclusion complexation	85
63.	Bromazepam	βCD, HPβCD	Enhanced solubility	86
64.	Furosemide	HPβCD	Characterization of inclusion complexes by DSC and XRD	87
65.	Nifedipine	βCD, HPβCD and DMβCD	Enhanced solubility and photo stability and Characterization of inclusion complexes by DSC, XRD and IR	88
66.	Nicardipine HCl	Triacetyl βCD	*In vitro* release was markedly retarded	89
67.	Nicardipine	βCD, HPβCD	Enhanced dissolution rate	90
68.	Natamycin	βCD, γCD, HPβCD	Enhanced dissolution rate	91
69	Nimodipine	βCD, HPβCD and HEβCD, MβCD.	MβCD was found as efficient solubilizer.	92

70.	β–lapachone	α-, β–, γ– and HPβCD	Improved solubility and bioavailability, complex formation proved by ^{1}H-NMR and fluorescence spectroscopy	93
71.	Ciprofloxacin	HPβCD	Better stability, biological activity and ocular tolerance was observed	94
72.	Nifedipine	βCD	Enhanced solubility and dissolution rate	95
73.	Isoproturon	βCD	Improved dissolution rate	96
74	Artemisinin	α-, β– and γ– CD	Enhanced solubility and dissolution rate	97
75.	Acitretin	HPβCD and RMβCD	Enhanced solubility and photostability. Characterization of inclusion complexes by IR, DSC, XRD	97
76.	Nimesulide	α-, β– and γ– CD	Enhanced solubility and photostability. Characterization of inclusion complexes by IR, DSC, XRD	99
77.	Carbamazepine	βCD	Improvement in release rate	100
78.	Furosemide	HPβCD	Preparation and characterization of inclusion complexes by phase solubility studies, DSC, NMR improvement in solubility and dissolution rate	101
79.	Dehydroepiandro-sterone	αCD	Improved dissolution rate, solubility and bioavailability	102
80	Nicardipine	β-cyclodextrin	Critical combination of cyclodextrin offered prolonged therapeutic activity.	103
81	Triflumizole	βCD	Increased dissolution rate	104
82	Nitrendipine	HPβCD	Complexes showed better dissolution rates	105

83	Nimesulide	β cyclodextrin	Enhancement of drug dissolution rate.	106
84.	Carbamazepine	SBE-βCD	Solubility of drug increased	107
85	Azadirachtin	βCD/DMβCD/ permethyl βCD/ HPβCD	Dissolution properties for superior compared to pure drug	108
86.	Celecoxib	DMβCD	Exhibited higher rate of dissolution	109
87.	Quinlukast	αCD/βCD/HPβCD /MEβCD	Complexes showed better dissolution rates	110
88.	Lorazepam	HPβCD/ HPγCD/ SBE-βCD/ MEβCD	Improved dissolution rates and bioavailability	111
89.	Fenoxaprop-p-ethyl	βCD/ HPβCD/ RMβCD	Improved dissolution rates and bioavailability	112
90	Diazepam	HPβCD/ HPγCD/ SBE-βCD/ MEβCD	Dissolution rate was markedly increased	113
91.	Diclofenac sodium	β cyclodextrin	Drug dissolution rate was improved in presence of cyclodextrins.	114
92.	Azelaic aicd	HP-β cyclodextrin	Release rate enhanced.	115
93.	Melasoprol	β-CD and its derivatives.	Complexes had a pronounced effect on drug hydrolysis and dissolution rate.	116
94	Etyleneoxide	β cyclodextrin	Enhancement of dissolution rate	114
95	Piribedil	β cyclodextrin	Dissolution profile was improved too great extent.	118
96	Glimpiride	β cyclodextrin, HP-β cyclodextrin	Enhanced dissolution rate & therapeutic efficacy of drug	119

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