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Cyclodextrins : Structure and Applications

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KEYWORDS

Cyclodextrins

Cyclodextrins are homogeneous cyclic, non-reducing malto-oligosaccharides in which 6-12 glucose units are joined to one another by α-(1,4) glycosidic linkages. Generally, there are three types of cyclodextrins, α, β, and γ-cyclodextrin that consist of 6, 7 and 8 glucose units, respectively (Szejtli, 1988) (Table 1).

Properties	α-CD	β-CD	γ-CD
No. of glucopyranose units	6	7	8
Molecular weight (MW)	972	1135	1297
Internal cavity diameter (A°)	5	6	8
Outer cavity diameter (A°)	14.6	15.4	17.5
Height of torus (A°)	7.9	7.9	7.9
Surface tension (mN/m)	71	71	71
Melting range (°C)	255 - 260	255 - 265	240 - 245
Solubility in water @ 25°C	14.2	1.85	23.2
Water of crystallization	10.2	13 to 15	8 to 18
Water molecules in cavity	6	11	17
Approx. cavity volume (A°)	174	262	427

Table 1: The properties of cyclodextrins (Szejtli, 1988

Cyclodextrins possess both hydrophilic and hydrophobic properties and are able to form inclusion complex with various kind of organic compounds inside its central cavity. From the X-ray structures it appears that in cyclodextrins the secondary hydroxyl (–OH) groups (C_2 andC_3) are located on the wider edge of the ring and the primary hydroxyl groups (C_6) on the other edge, and that the hydrophobic C_3 and C_5 hydrogens and glycosidic oxygen are located inside the cavity of the torus like molecule. This results in a molecule with a hydrophilic outside, which can dissolve in water and an apolar cavity, which provides a hydrophobic matrix, described as a 'micro heterogeneous environment' (Szejtli, 1998)(Fig. 1).

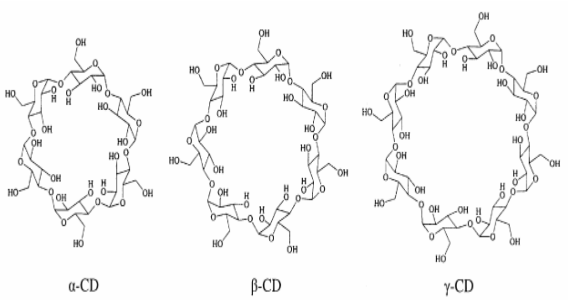

Fig.1 structure of α, β, and γ-cyclodextrin

Because of this unique property, CDs can form molecular inclusion complexes (host-guest complexes) with a wide range of solid, liquid and gaseous compounds and hence have found various applications (Hedges, 1998). Inclusion in cyclodextrins exerts a profound effect on the physicochemical properties of guest molecules as they are temporarily locked or caged within the host cavity giving rise to beneficial modifications of guest molecules, which are not achievable otherwise (Schmid, 1989). These properties are:

Enhanced solubility, stability and bioavailability

Reduced evaporation and flavour stabilization

Stabilization of light- or oxygen-sensitive substances.

Fixation of very volatile substances.

Modification of liquid compounds to powders

Modification in taste by masking off flavors, unpleasant odors

Chromatographic separations

Controlled release of drugs and flavors.

Applications of cyclodextrins

Cyclodextrins are proved as versatile tool, used in many industries in high to low order of food and flavours, pharmaceutical, chemical, analytical, environmental etc. for different purposes (Fig.2)(Szejtli, 2004).

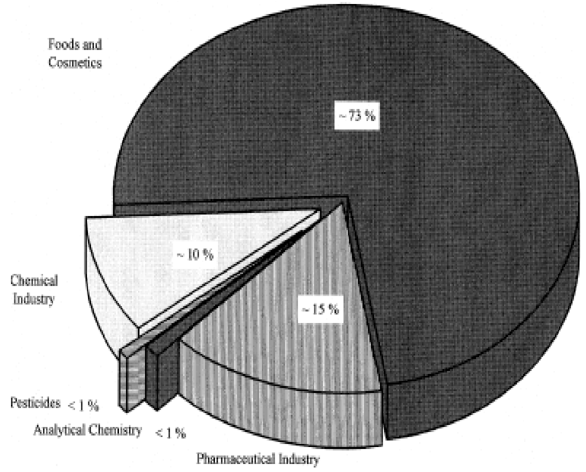

Figure 2 : Applications of cyclodextrins in industries.

Food and Flavours
In Japan, cyclodextrins have been approved as 'modified starch' for food applications for more than two decades, serving to mask odours in fresh food and to stabilize fish oils. One or two European countries, for example Hungary, have approved γ-cyclodextrin for the use in certain applications because of its low toxicity (Szejti, 1988). CDs eliminates the bitter aftertaste of other sweeteners such as stevioside, glycyrrhizin and rubusoside (Tanaka, 1997). Enhancement of flavour by CDs has been also claimed for alcoholic beverages such as whisky and beer (Parrish, 1988). CGTase can also be used in the preparation of doughs for baked products, which incorporated the CGTase into the dough to increase the volume of the baked product (Szejtli *et al.*, 1998).

Quaglia *et al.* (2007) have developed the process which makes use of β-CD for the treatment of tomato products, turns to be of great interest to obtain a bulk material for neutraceuticals displaying superior bioavailability of lycopene. Mourtzinos *et al*. (2008) have shown the protection of neutraceutical monoterpenes against oxidation using β-Cyclodextrin and modified starch. β-Sitosterol is a plant sterol that has received much attention because of its effectiveness in reducing the absorption of dietary cholesterol, as well as in offering protection from cardiovascular diseases and cancer development. β-cyclodextrins have shown improved uptake of β-sitosterol by phospholipid membranes (Castelli *et al*., 2006). Cross-linked β-CD with adipic acid was used to remove cholesterol (90.7%) in cream (Han *et al.,* 2007).

Cosmetics and Toiletries
The major benefits of cyclodextrins for the cosmetics sector are stabilization, odour control, process improvement upon conversion of a liquid ingredient to a solid form, protection and delivery of fragrance in lipsticks and water solubility and enhanced thermal stability of oils. Some of the other applications include use in toothpaste, skin creams, liquid and solid fabric softeners (Szetjli 1998; Buschmann and Schollmeyer, 2002). Cyclodextrins are used to increase the solubility of triclosan and triclocarban (an antimicrobial agents) by cyclodextrin complexation (Duan *et al.,* 2005).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. The antimicrobial efficacy of the product is also improved (Hedges, 1998). Dishwashing and laundry detergent compositions with CDs can mask odors in washed items (Foley *et al.,* 2000).

Controlled release of fragrance materials like linalool and benzyl acetate using cyclodextrins as a cosmetic delivery system was demonstrated by Numanoglu *et al*. (2007). A sunscreen agent octyl methoxycinnamate was incorporated into monochlorotriazinyl-β-cyclodextrin (β-CDMCT) cavities which are covalently bound to cloth fibres markedly enhanced by impregnation with octyl methoxycinnamate of the β-CDMCT grafted textile (Scalia *et al.*, 2006).

Pharmaceuticals
Cyclodextrins act as potential drug delivery candidates in many applications because of their ability to alter the physical, chemical, and biological properties of guest molecules through the formation of inclusion complexes (Uekama *et al.*, 2006). Their bioadaptability and multi-functional characteristics make them capable of alleviating the undesirable properties of drug molecules in various routes of administration including oral, rectal (Szetjli, 1998), nasal, ocular (Loftsson and Jarvinen, 1999), transdermal and dermal (Matsuda and Arima, 1999).

Grgurevich *et al*. (2002) investigated the direct role of cholesterol lowering on human platelet aggregation by *in vitro* cholesterol depletion using methyl-β-cyclodextrin. The tumor targeting properties of a new drug carrier synthesized by bioconjugation of folic acid (FA) to β-cyclodextrins through a poly(ethylene glycol) (PEG) spacer (CD-PEG-FA) were investigated (Salmaso *et al*. 2004).

Gene delivery
A new class of linear, CD-based polymers was introduced by Davis and co-workers in 1999 for gene delivery applications (Pack *et al*., 2005). These polycations contain CDs in the polymer backbone and self-assemble with anionic nucleic acids to form condensed 'polyplex' structures with diameters ≈100 nm that can mediate cellular delivery. Pun *et al*., (2004) reported that transferrin modified, PEGylated CD-based polyplexes containing DNAzyme administered by tail vein injection to tumour-bearing mice were well tolerated, even up to doses of 40 mg DNA per kg mouse, and were specifically internalized by tumour cells.

Enviornment
Cyclodextrins can play a major role in environmental science in terms of solubilisation of organic contaminants, enrichment and removal of organic pollutants and heavy metals from soil, water and atmosphere (Gao and Wang, 1998). From mother liquor of the insecticide trichlorfon, the uncrystallizable trichlorfon can be converted into a β-CD complex and 90% of the toxic material was removed (Szetjli, 1988). CD complexation also resulted in the increase of water solubility of three benzimidazole-type fungicides (thiabendazole, carbendazim, and fuberidazole) making them more available to soil (Lezcano *et al*., 2002). Geosmin and 2-methyl isoborneol are the two main compounds responsible for the unpleasant smell found in the vicinity of water-processing plants, CD derivatives have been demonstrated as better hosts for these highly hydrophobic compounds (Baudin *et al*., 2000). CDs are used in the preparation of an insecticide from neem seed extract by forming water soluble inclusion complex of neem seed kernel extract containing azadirachtin-A in a CD carrier molecule (Subba *et al*., 2000).

Elemental and organic iodine emitted into the air by chemical and nuclear power plants can be removed in aqueous solutions of cyclodextrins or its polymer gel beds, specially α-cyclodextrin and its methyl derivatives can be employed in the air filtration of nuclear waste gases (Szente *et al.*, 1999).The effect of β-cyclodextrin on the removal of the herbicide norflurazon (NFL) from soils has been investigated by Villaverde *et al*. (2005). Mamba *et al.* (2006) reported the use of cyclodextrin nanoporous polymers which are capable of absorbing organic pollutants like *p*-nitrophenol and pentachlorophenol from water to parts per billion levels.

Role in catalytic reactions
One novel use of CDs in catalytic reactions is their ability to serve as enzyme mimics. These are formed by modifying naturally occurring CDs through substituting various functional compounds on the primary or secondary face of the molecule or by attaching reactive groups. These modified CDs are useful as enzyme mimics because of the molecular recognition phenomenon (Szetjli, 1998) attributed to the substituted groups on the CD. The oxidation of xenobiotics by the hydroperoxidase activity of lipoxygenase in the presence of cyclodextrins was studied by Nunez-Delicado *et al*. (1999).

Analytical applications
Cyclodextrins have been used extensively in separation science because they have been shown to discriminate between positional isomers, functional groups, homologues and enantiomers. This property makes them one of the most useful agents for a wide variety of separations using various techniques including gel electrophoresis, isotachophoresis, isoelectric focusing, preparative scale electrophoretic techniques, thin-layer chromatography, electrochemically modulated liquid chromatography, use of monolithic media in liquid chromatography, microdialysis, separation on hollow fibers, foam flotation enrichment, solid- and liquid-phase extractions, countercurrent chromatography, separation through liquid andcomposite membranes and molecularly imprinted polymers (Schneiderman and Stalcup, 2000). In forensic analysis dimethyl-β-cyclodextrin and sulphobutylether-β-cyclodextrin have been used for the analysis of the enantiomers of the components contained within illicit drugs such as cocaine, khat leaves, and

amphetamines (Lurie *et al.*, 1994). A sensitive electrode was made to detect cations in aqueous solution using partially benzylated β-cyclodextrins deposited with no coupling agent on the silica surface of a wafer which was used as an electrolyte–insulator–semiconductor (EIS) heterostructure (Bouzitoun *et al.*, 2006). A competitive fluorescence inclusion method was developed using β-cyclodextrin and hydroxypropyl-β-cyclodextrin for the determination of Vitamin B_6 in synthetic samples, tablets and injections with satisfactory results (Zhu *et al.*, 2007).

Textile industry

CDs are also incorporated to the fabrics to entrap and mask malodors from sweat and could release the perfumes (Buschmann *et al.*, 2001). CDs are also used for dying fabrics to increase dye uptake (3-fold) by the polyester fiber using derivatives of β-cyclodextrins which have increased the binding of dye to fabrics and reduce the amount lost in the wastewater (Hedges, 1998). The β-cyclodextrin with 3-glycidyloxypropyl-trimethoxysilane (GPTMS), tetraethoxysilane (TEOS), catalyzer and solvent is able to anchor β-CD on cotton fabrics in gelation process in order to impart new surface property of cotton (Wang *et al.*, 2006).

References:

1. Baudin C, Pean C, Perly B and Goselin P. (2000) Inclusion of organic pollutants in cyclodextrin and derivatives. International journal of Enviornmental Analytical Chemistry, 77:233–242
2. Bouzitoun M, Mlika R, Gam H, Ben Ouada H, Majdoub M and Sfihi H. (2006) A non-water-soluble modified β-cyclodextrin for sensitive electrode. Materials Science and Engineering, 26: 481-485
3. Buschmann HJ and Schollmeyer E. (2002) Applications of cyclodextrins in cosmetic products: a review. Journal of Cosmetics Science, 53:185– 91
4. Buschmann HJ, Knittel D and Schollmeyer E. (2001) New textile applications of cyclodextrins. Journal of Inclusion Phenomena and Macrocyclic Chemistry, 40:169–172
5. Castelli F, Sarpietro MG, Micieli D, Trombetta D and Saija A. (2006) Differential scanning calorimetry evidence of the enhancement of β-sitosterol absorption across biological membranes mediated by β-cyclodextrins. Journal of Agriculture and Food Chemistry, 54:10228-10233
6. Duan MS, Zhao N, Ossurardottir IB, Thorsteinsson T and Loftsson T. (2005) Cyclodextrin solubilization of the antibacterial agents triclosan and triclocarban: Formation of aggregates and higher-order complexes. International Journal of Pharmaceutics, 297:213–222
7. Foley PR, Kaiser CE, Sadler JD, Burckhardt EE and Liu Z. (2000) Detergent composition with cyclodextrin perfume complexes to mask mal odours. PCT International Application WO 01 23,516
8. Gao S and Wang L. (1998) Application of cyclodextrin in environmental science. Huanjing Kexue Jinzhan, 6:80–6
9. Grgurevich S, Krishnan R, White MM and Jennings IK. (2007) Role of in vitro cholesterol depletion in mediating human platelet aggregation. Journal of Thrombosis and Haemostasis, 1:576–586
10. Han EM, Kim SH, Ahn J and Kwak SH. (2007) Optimizing cholesterol removal from cream using β-cyclodextrin cross-linked with adipic acid. International Journal of Dairy Technology, 60:31-36
11. Hedges AR. (1998) Industrial applications of cyclodextrins. Chemical Reviews, 98: 2035-2044
12. Lezcano M, Ai-Soufi W, Novo M, Rodriguez-Nunez E and Tato JV. (2002) Complexation of several benzimidazole-type fungicides with alpha and beta-cyclodextrins. Journal of Agricultural and Food Chemistry, 50:108–12
13. Loftsson T and Jarvinen T. (1999) Cyclodextrins in ophthalmic drug delivery. Advanced Drug Delivery Reviews, 36:59–79
14. Lurie IS, Klein RFX, Dal Cason TA, Le Belle MJ, Brenneisen R and Weinberger RE. (1994) Chiral resolution of cationic drugs of forensic interest by capillary electrophoresis with mixtures of neutral and anionic cyclodextrins. Analalytical Chemistry, 66:4019–402
15. Mamba BB, Krause RW, Malefetse TJ and Nxumalo EN. (2007) Monofunctionalized cyclodextrin polymers for the removal of organic pollutants from water. Environmental Chemistry Letters, 2:79-84
16. Matsuda H and Arima H. (1999) Cyclodextrins in transdermal and rectal delivery. Advanced Drug Delivery Reviews,36:81–99
17. Mourtzinos I, Kalogeropoulos N, Papadakis SE, Konstantinou K and Karathanos VT. (2008) Encapsulation of nutraceutical monoterpenes in β-cyclodextrin and modified starch. Journal of Food Science, 73:89-94
18. Numanoglu U, Tangul S, Nilüfer T, Kartal M, MY Koo and Onyuksel H. (2007) Use of cyclodextrins as a cosmetic delivery system for fragrance materials: linalool and benzyl acetate. AAPS Pharm SciTech, 8:E1-E9
19. Nunez-Delicado E, Sojo MM, Sanchez-Ferrer A and Garcia-Carmona F. (1999) Hydroperoxidase activity of lipoxygenase in the presence of cyclodextrins. Archives of Biochemistry and Biophysics, 367:274–280
20. Pack DW, Hoffman AS, Pun S, Stayton PS. (2005) Design and development of polymers for gene delivery. Nature Reviews Drug Discovery 4, 581-593
21. Pun SH. (2004) Cyclodextrin-modified polyethylenimine polymers for gene delivery. Bioconjugugate Chemistry, 15:831–840
22. Quaglia F, Fusco G, De Rosa G, Ungaro F, Miro A and La Rotonda MI. (2007) Compositions for health products obtained by treatment of tomato with beta-cyclodextrin. Journal of Inclsion Phenomena and Macrocyclic Chemistry, 57:669–674
23. Salmaso S, Semenzato A and Caliceti P (2004) Specific Antitumor Targetable α-cyclodextrin-Poly(ethylene Glycol)-folic acid drug delivery bioconjugate. Bioconjugate Chemistry, 15: 997-1004
24. Scalia S, Tursilli R, Bianchi A, Lo Nostro P, Bocci E, Ridi F and Baglioni P. (2006) Incorporation of the sunscreen agent, octyl methoxycinnamate in a cellulosic fabric grafted with β-cyclodextrin. International Journal of Pharmaceutics, 308:155–159
25. Schmid G. (1996) Preparation and industrial production of cyclodextrins. In: Comprehensive supramolecular chemistry, Cyclodextrins. Pergamon, Oxford, 3: 41–56
26. Schneiderman E and Stalcup AM. (2000) Cyclodextrins: a versatile tool in separation science. Journal of Chromatography, 745:83-102
27. Subba R, Pillarisetti V, Kumble SP, Annadurai RS, Srinivasan M, Rao AS and Ramadoss CS. (2000) Insecticidal CD inclusion complexes of neem extract. PCT Int Appl WO 00 54,596
28. Szejtli J. (1988) Cyclodextrin Technology. Netherlands: Kluwer Academic Publishers, pp: 1-39
29. Szejtli J. (1998) Introduction and general overview of cyclodextrin chemistry. Chemical Reviews, 98:1743-1753
30. Szejtli J. (2004) Past, present, and future of cyclodextrin research. Pure and Applied Chemistry, 76:1825-1845
31. Szente L, Fenyvesi EV, Szejtli J. (1999) Entrapment of Iodine with Cyclodextrins: Potential Application of Cyclodextrins in Nuclear Waste Management. Environ. Sci. Technol. 33, 4495-4498
32. Tanaka O. (1997) Improvement of taste of natural sweeteners. Pure & Appl. Chem., 69(4) pp. 675-683
33. Uekama K, Hirayama F and Arma H. (2006) Recent aspects of cyclodextrin-based drug delivery system. Journal of Inclusion Phenomena and Macrocyclic Chemistry, 56: 3-8
34. Villaverde J, Maqueda C and Morillo E. (2005) Improvement of the desorption of the herbicide norflurazon from soils via complexation with α-cyclodextrin. Journal of Agriculture and Food Chemistry, 53:5366-5372
35. Wang CX and Chen SL. (2006) Surface treatment of cotton using β-cyclodextrins sol–gel method. Applied Surface Science, 252:6348–6352
36. Zhu XX, Brizard F, Wen CC and Brown GR. (1997) Journal of Macromolecular Science and Pure Applied Chemistry, A34: 335-347