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Importance of cyclodextrins into inclusion complexes

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Abstract

Cyclodextrins are natural cyclic oligosaccharides formed by glucose unites that were discovered in 1891, and the structures were confirmed in the mid-1930s. Their industrial significance became obvious in the 1970s. The most common natural cyclodextrin consist of six (α- cyclodextrin), seven (β-cyclodextrin), and eight (γ- cyclodextrin) glucopyranose units, the macrocyclic cyclodextrins consist of a hydrophilic outer surface and a lipophilic central cavity. The mainly uses of cyclodextrins are complexing agents to increase aqueous solubility of poorly soluble drugs, as well as, increase their bioavailability and stability. The other application of CDs is to crosslink for forming polymers which used in drug delivery. CDs can be used to prepare pseudorotaxanes and rotaxanes via inclusion complexes. The first rotaxane incorporating CDs was prepared 1981. This review will discusses the structures, preparation and properties of CDs. Industrial and pharmaceutical application of CDs will also be included in this review. Hydrophilic- hydrophobic interaction routes to pseudorotaxanes and rotaxanes will be explained.
Keywords: Cyclodextrines; Complexation; Drug delivery; Rotaxanes

1. Introduction

The most common organic compounds in nature are polysaccharides such as dextrin, cellulose, and starch. These substances were used for a long time ago in shelter, clothing and food. For ancient time people have processed carbohydrates through fermentation and observed their enzymatic degradation. Now a day this dissociation brings about formation of mixtures of monosaccharides, disaccharides and various oligosaccharides[1]. Cyclodextrins[2] are produced by different methods which will be discussed intensively in this review later. There are several common structures of CDs. α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin are examples of CDs famous structures .These structures include a lipophilic central cavity and a hydrophilic exterior surface. The distinctive properties[3,4] of CDs enhance their application in everyday life. Many cyclodextrin derivatives[5-8] have been synthesized. The importance of these derivatives will be discussed in this paper. Also CDs played a chief role as a host in inclusion complexes[9-12] with various insoluble drugs in order to enhance the efficiency of the drug molecule. Also, rotaxanes and pseudorotaxanes complexes[13-15] are considered as examples of inclusion complexes. There are many applications of CDs in natural world in drugs [16-20] and food industry[21].

2-Preparation of cyclodextrins

In the beginning of 1970s, only little amount of cyclodextrins could be produced with extremely high expense. For this reason the common usage of CDs in pharmaceutical were limited. At this time, CDs can be prepared by new biotechnological advancement manufacture. This method has reduced the CDs manufacture costs, leading to the ability of obtain highly purified CDs. This technique depend on treatment of starch with amylase from Bacillus macerans gives a crude mixture of α, β , and γ- cyclodextrins with different amount [22] . There is another method which is more efficient and better to produce α-, β- and/or γ-cyclodextrin by use genetic engineering. This enable the

production different types of CGTases . This method produced extremely purified α-,β- and γ-cyclodextrin available to be used as pharmaceutical excipients[23].

3-Structure of cyclodextrins

Cyclodextrins are example of supramolecular structure which associated natural products. There are several types of CDs, however the most popular CDs be composed of six (α-cyclodextrin), seven (β-cyclodextrin) and eight (γ-cyclodextrin) glucopyranose units. There is no existence of CDs which that consists less than six glucopyranose units. There are many CDs that have been reported such as δ, €, £, η and θ-CDs which contain nine, ten, eleven, twelve, and thirteen glucopyranose units[24,25,26] . All these structures of CDs consist of lipophilic inner cavity and a hydrophilic external surface. The chair conformation of the glucopyranose units is the reason of creating this structure. CDs are almost as formed as a truncated cone instead of perfect cylinders. The structure of CDs has got also two types of hydroxyl groups, the first primary which placed in narrow edge of the cone. The second type of hydroxyl groups are secondary that located at wider edge of the cone. The central cavity is created by the carbon chain and peptide linkage of the glucose residues that causes a lipophilic nature. The polarity of the cavity is roughly the same as that in ethanolic solution[26].

The torus of CDs have got the same structure of macrocyclic molecules but CDs are less soluble in water and have got lipophilic cavity comparing with super molecule ring. Stability and synthesis of CDs complexes can be affected by several factors such as, hydrophobic forces, size of molecule and cavity and guest features [28].

CDs have almost limitation in solubility, especially β-cyclodextrin owning to the relative strength of binding between CDs molecules in crystal configuration[30]. CDs complexes are more hydrophilic than CDs themselves. However, aqueous solution of CDs is less soluble than acyclic saccharides.

Syntheses of CDs derivatives have been reported. The production of these derivatives is usually formed by aminations, esterifications or etherifications of primary and secondary hydroxyl groups of the CDs. Solubility of CDs derivatives are diverse than them parent. There are many factors that affect the solubility and stability of CDs derivatives such as substitutions, cavity size. These factors can also be reduced the sensitivity of these derivatives against light and air. In addition, these factors can command the chemical activity of guest molecules[2]. There are more than 20 substituent of β-cyclodextrin depending on regioselectivty. Uniform CDs production needs harsh conditions such as reagents that have the ability of selectivity and separations of products. The synthesis of ethers, esters by alkyl Halides, epoxides, acyl derivatives most regularly depends on electrophilic attack at the OH-groups. However, inorganic acid derivatives as sulphonic acid chloride and isocyanates derivatives have also been studied. This mechanism occurs by cleavage of C–OH bonds as nucleophilic attack by compounds such as azide ions, halide ions, thiols, thiourea, and amines, this necessitate activation of oxygen atom by an electron-withdrawing group[3]. This mechanism involves using of an electron-withdrawing group to activate oxygen atom[3]. Superamolecular complexes of CDs can be built by the ability of CDs to link together either covalently or noncovalently. CDs also form inclusion complexes with organic host molecules to build macromolecular threads. So catenanes, rotaxanes, polyrotaxanes, and tubes, can be created. Consequently, the aim of derivatizations of cyclodextrins [32-34] is expansion the solubility of the CDs and their complexes, as well as development the suitable and connection between the CDs and its gust, by stabilizing of the gust and decreasing its reactivity and mobility and synthesis of insoluble CDs containing structures polymers.

3- Properties

Cyclodextrins can be used as complexation agents and its study in supramolecular chemistry have been used in various fields [35]. CDs are crystalline, homogeneous, non-hygroscopic substances. They are biocompatible, non-toxic even with high concentration. The cavity size increases with the number of glucose units, while the height is constant (6.7-7.0). The solubility of CDs do not follow this rule, β-CD is considerably less soluble in water than α-CD and γ-CD. The less solubility of β-CD is owing to the hydrogen bridges between OH groups of C2 and C3, leading to a rigid structure. Although, the solubility of β-CD is smaller, the size of its cavity is more appropriate to include large variety of molecules which have got biological and pharmacological properties. In γ-CD, its glucose units are not in the same plane and its structure is more elastic, that feature make γ-CD more soluble in aqueous solutions[29,36] . While α-CD one glucose unit distorted and only 4 of 6 possible hydrogen bridges are formed. Therefore, the solubility α-CD is more than that in β-CD. The most important properties of these CDs are given in Table 1.

4- Cyclodextrin Complexes

The most significant property of CDs is their facility to form solid inclusion complexes (host–guest complexes) by methods of a molecular complexation[2].Formation of these complexes depend on linking of hydrophobic molecules (guest molecule) within the cavity of the cyclodextrin (host molecule). In this complex there is a proper dimension between host cavity and guest molecule [37]. In which non-polar molecules can enter into the hydrophilic cavity of the cyclodextrin molecules which affords suitable micro situation to produce inclusion complexes [38]. The essentially driving forces of complex formation is the evolve of enthalpy -rich water molecules from the cavity and displace that molecules by more hydrophobic guest molecules which present in the solution. That process occurs to achieve an apolar–apolar association and reduce of cyclodextrin ring tension leading to more stable and lower energy state[3]. The linking of guest molecules inside the host cyclodextrin is not rigid or permanent. In reality, this binding is a dynamic equilibrium because there are no covalent bonds are broken or formed during production of the inclusion complex [39].

The linking strength between the cavity and the gust molecules rely on exact local connections between surface atoms. The binding strength also depends on the away which host-gust complex fits together. Formation complexes can be occurred in the crystalline state and /or in solution, best solvent in this process is water. Moreover, inclusion complexation can be processed in a co-solvent system and in the presence of any non-aqueous solvent. The chemical arrangement of CDs provides these molecules a extensive range of chemical properties more than non-cyclic carbohydrates which contain the same molecular weight [40]. There are many of physical and chemical properties of hydrophobic guest molecules which can be improved during the inclusion in cyclodextrins. These properties include solubility of insoluble guests, stabilization of changed guests against the oxidation agents, visible or UV light, heat control of volatility and sublimation. Physical isolation of incompatible compounds, chromatographic separations, taste modification by masking off flavors, unpleasant odors and controlled release of drugs and flavors are other properties of gust molecule. Consequently, CDs are used in many applications such as food [41], pharmaceuticals [42], cosmetics [43], environment protection [44], bioconversion [45], packing, the textile industry [44] and packing and the textile industry[46].
There are two factors affect on the ability of CDs to form an inclusion complex with a guest molecule, the size of the CDs to the size of the guest molecule or functional groups within the guest. The major factor that affects the ability f CDs for creation an inclusion complex is thermodynamic aspect between (cyclodextrin, hydrophobic molecule, solvent). Commonly there are several factors which effect on equilibrium to form the inclusion complexes which has preference low state of energy. These factor include , the replacement of water molecules from cyclodextrin pores , Enhancing number of hydrogen bonds created , decreasing non favored interactions between the guest and the solvent surroundings and raising the hydrophobic interaction between the gust and the CDs pores. Because of the various reactivity of hydroxyl group in CDs, the chemical modifications can be enhanced. The potential guest fits molecular insertion in CDs is relatively varied. That involves branched and non branched aliphatics, aldehydes, ketones, alcohols, organic acids, fatty acids, aromatics, gases, and polar compounds such as halogens, oxyacids and amines [40].

5- Cyclodextrins in rotaxane compounds

Rotaxanes are compounds that consists of a linear species and cyclic species , linked together in a threaded architecture by non-covalent interaction. There are two types of these compounds which are rotaxanes and pseudorotaxanes [47]. pseudorotaxanes means half rotaxanes are illustrated in Figure 5

There are three different patterns for the rotaxanes formation. The first process is threading for supermolecular preparation. This approach start with encircle macrocycle then bulky group work as stopper. Second rout is clipping in that technique macrocycle segments cut in to two parts then the macrocyclic molecule insert in to (thread/axle) which has already been covered in the first way. The third method is slippage. In this method the selectivity of macrocyclc size is highly important, as the identical size or at least fit size of macrocycle permit to slip over bulky group through the thread at high temperatures.

The forces that affect the threading, pseudorotaxanes and rotaxanes can be classified to seven types: statistical threading, chemical conversion, hydrogen bonding, hydrophilic-hydrophobic interaction, metal-ligand complexation, π-π stacking and charge transfer. This literature review will be focuce on hydrophilic-hydrophobic forces of pseudorotaxanes and rotaxane. CDs have the ability to form pseudorotaxanes and rotaxanes with a number

of linear specie. Inclusion complexes are other expression of pseudorotaxanes and rotaxanes. Because of the functionality and configuration of CDs, the inclusion complexes are formed [49] . The CDs have cylindrical pores that posses hydroxyl functionalities on the two edges and hydrocarbon and ether linkage in the internal of the cavity [49] . Consequently a hydrophobic located in the inner side of CDs and hydrophilic is in outside the faces.

Rotaxane containing CD was produced for first time was prepared in 1981 by Ogino[48]. In recent times rotaxanes and pseudorotaxanes [51] that include α-CD which have long hydrophobic fragments was prepared [52,53] . Pseudo-rotaxanes and rotaxanes of this type do not form unless in polar solvents. Pseudorotaxanes and rotaxanes driven by hydrophilic-hydrophobic forces are also published[54]. A cyclodextrin macrocycle is employed by Nakashima et al [55] to prepare 2- rotaxane by photo chemistry.

While rotaxanes include no covalent bond between axes and rings, rotaxanes are considered stable unit, due to a highely free activation energy, which allow to be prevail over withdraw a ring from the axis of a rotaxane. Similar to other molecular entity. Rotaxanes can be covalently connected together by many methods to produce polymeric species, called polyrotaxanes. Synthesis of rotaxanes are needed an axis to enter through a CD ring, this called axial inclusion compound. The CDs arrangement in an inclusion compounds mostly depend on the polarity model of the guest. Thus, guest molecules can be classified into three main groups, channel inclusion compounds of no polar guests, inclusion compounds of amphiphilic guests, and axial inclusion compounds of bola-amphiphiles. CDs played important role in formation of rotaxane compounds due to two reasons, first is the ability of CDs in shielding of the guest, since guest molecule within a CD cavity shows distinct unreactive nonpolar environment. This result is found in rotaxanes than other inclusion compounds, as the CD environment stays always around the guest. Therefore the CD environment can be decreased thermal deactivation of the excited state of a gust molecule. Which leads to improve both quantum yields and stabilities of rotaxanes compounds[56,57]. The second significance is progress of changing processes during formation of rotaxanes. Gust molecules that their properties changed by external effects such as light, magnetic field, or pH changes are called molecular switches[58].These changing processes in rotaxanes will assist in reducing undesirable side reactions.

6. Applications of cyclodextrins

In recent years CDs were played significant role in many applications, such as using in food[21,41] , cosmetic[43], and toiletry production[59] , agricultural industries[46], polymers, pharmaceutical applications[16-20,60] and analytical chemistry[61,62,63] and as catalysts in chemical reactions[28,64] (hydrolysis and oxidation).

6.1- Foods and flavours

Cyclodextrins form inclusion complexes with many of molecules contain fats, flavors and colors. Therefore, CDs are used in large range in food industrial. CDs give the natural and artificial flavors stability and protection. Because of most of flavors are volatile oils or liquids and complexation with CDs improves their properties. Also, CDs are use as process aids, Such as removing cholesterol from animal products such as milk, butter and eggs. Many types of CDs using for these proposes. Such as branched CDs are using in flour-based items like noodles, pie dough's, pizza sheets and rice cakes to provide flexibility and elasticity to bread [21] . Branched CDs are very important substances in synthesis of antimicrobial food preservatives containing trans-2-hexanalin in apple juice formation[65] CDs are used in chewing gum to keep taste for extended time[66] .CDs used to improve a quality of pastry, decreasing unpleasantness smell and tast. Also, CDs are treated with Fruits and vegetable juices to remove phenolic and polyphenoloxidase compounds by complexation [67.] These compounds cause changing in colour of juices. Thus CDs react as activator as well as inhibitor.CDs improve the properties of flavanoids and terpenoids[68] compounds which extracted from plants like ginger root[69] .this technique proceed by complexation with these Components.

6.2 **Cosmetics, personal care and toiletry**

Cyclodextrins are used in cosmetic manufacture, essentially in volatile inhibition of perfumes, room fresheners and detergent s by controlled release of delicate scent from inclusion compounds. The most significant of CDs in this field is stability and control in odour . The applications of CDs comprise skin creams, liquid and solid fabric softeners, toothpaste, paper towels, tissues and underarm shields.These uses of CDs depend on reacting of gust with CDs to create a higher energy divider to decreasing volatil, therefore producing long-lasting scent[70]. Thus a scent is inserted inside cavity of CDs and the resulting inclusion compound is complexes with calcium phosphate to stabilize the scent in industrialized bathing formation [71].

6.3- Agricultural and chemical industries

Cyclodextrins are played principally role in agricultural industries, thus CDs form complexes with large number of agricultural chemicals which consist of herbicides, insecticides, fungicides and pheromones.Also, CDs can be used as growth controller because their ability to inhabitation seeds. This occurred when seeds treated with β-cyclodextrins. In the beginning the growth of plant is very slowly then gradually improved, even 20–45% larger yield [3] . Now there are new progress of CDs glucanotransferases (CGTases) in plants[3,46] .

6.4 Cyclodextrins in chemical industry and environmental science.

CDs can be used to tseparate isomers and enantiomers.Via high efficiency liquid chromatography (HPLC) or gas chromatography (GC). Thus fixed phases in column chromatography consist of cyclodextrins or other derivatives of supra molecular molecules. CDs also, used to remove detoxify waste materials. CDs have important role in environmental field. CDs can be used to enhance solubility of organic contaminants, improvement and elimination of organic pollutants and heavy metals from soil and atmosphere[72] . CDs are employed in water treatment to enhance the adsorption of contaminant[73].Thus CDs played lage role in purification of water from highly toxic substances which involve insecticide trichlorfon and aromatic compounds by inclusion complex formation .Thus 90% of the toxic material is disappear [3,46] . Also CDs are used to clean gaseous release from organic chemical industries[3,46] . Other applications of CDs and its derivatives in environmental field, using for testing of soil toward pollutants[74] , increasing ability of soil to fungicides such as thiabendazole, carbendazim and fuberidazole,and increasing microbial and plant growth.

6.5-Polymers, adhesives and coatings

CDs enhance viscosity and adhesives in polymer manufacture. Thus CDs increase the interaction between hot melts molecules in associative thickening emulsion-type coatings such as paints tend to enhance viscosity also CD can be used to counteract this undesirable effect[46].

6.6- Pharmaceuticals

Cyclodextrins have largely importance in pharmaceuticals applications, most of drug substances have not enough solubility in water to absorb through the cellular membrane. In addition these drug molecules have unpleasant odor, taste also have irritation effects on stomach, skin or eye. These drugs must be developing by encapsulation into CDs molecules to form inclusion complex. CDs have special ability to increase drug delivery during biological membranes. Therefore CDs perform as true carrier by keeping the hydrophobic drug molecules in solution and delivering them to the surface of the biological membrane, e.g. skin, mucosa, and the eye cornea, where they partition into the membrane. CDs also act as dispersion enhancers by increasing drug availability at the surface of the biological barrier. There are several applications for CDs in the pharmaceuticals industry [16-20,60] . CDs have essentially role to enhance aqueous solubility of insoluble drugs, to increase their bioavailability that reducing the dose of the drug administered. CDs also can be used to increase stability of drug molecules, as well as CDs can be used to reduce the main concentration of free active ingredients which causes irritation by formation of inclusion complexes .CDs can be used to transport liquid drugs into amorphous powder and avoid drug–drug and drug–incipient interactions. There is another application of CDs is decreasing or forbidden the unpleasant taste and odor of drugs through insertion of drug molecules within the CD cavity molecules consequently, functional groups that causes distasteful taste and odor become masking[75,76,77] .

7. Conclusions

Cyclodextrins are a group of cyclic oligosaccharides with a hydrophilic outer surface and hydrophobic central cavity. CDs were first described by Villiers in 1891. CDs can be produced by many methods, such as biotech-nological advancements and genetic engineering. In recent years CDs have been played important role in formation inclusion complexes with different gust molecules by insertion the gust molecules into the cavity of CDs. This encapsulation technique will affect on many of the physicochemical properties of the guest molecules. Therefore CDs use in several applications in many fields, such as the pharmaceutical, food, cosmetic and agricultural industries. CDs have been used as complexing agents to increase aqueous solubility of little soluble drugs, and to increase their bioavailability and stability. In this review we interest also, using of CDs in preparation of rotaxane complexes which used in different applications. At present time CDs revealed to share in many types of non-inclusion complexes with organic salts and water-soluble polymers. Although, CDs were discovered since more than one hundred years, the chemistry of cyclodextrins is a novel field.

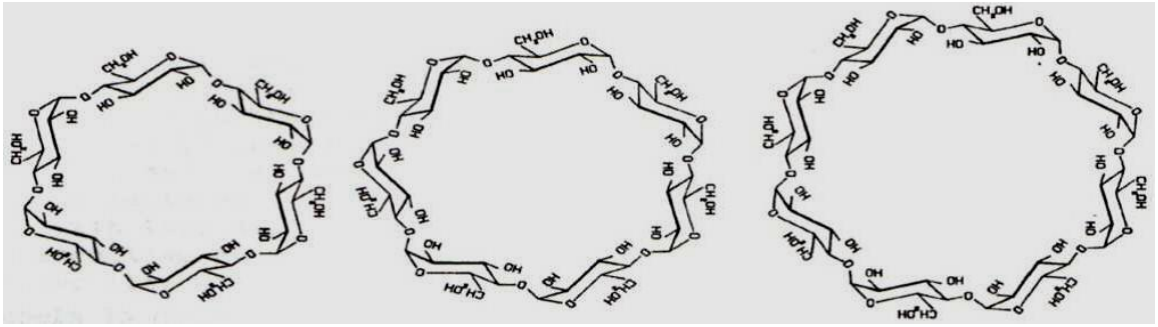


Fig.1 Chemical structures of α-CD, β-CD, γ-CD[27]

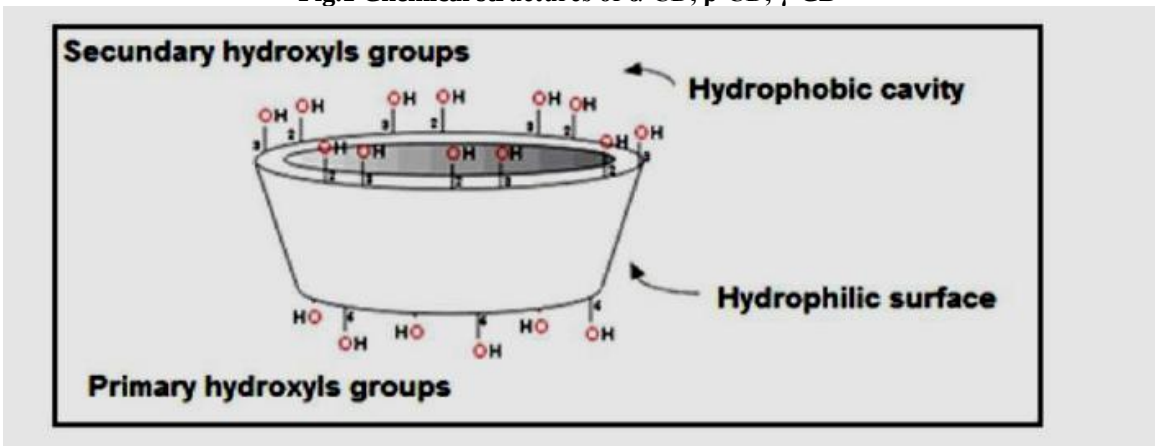


Fig. 2 Cyclodextrins structure in torus similar to macro ring shape with the hydroxyl groups[29]

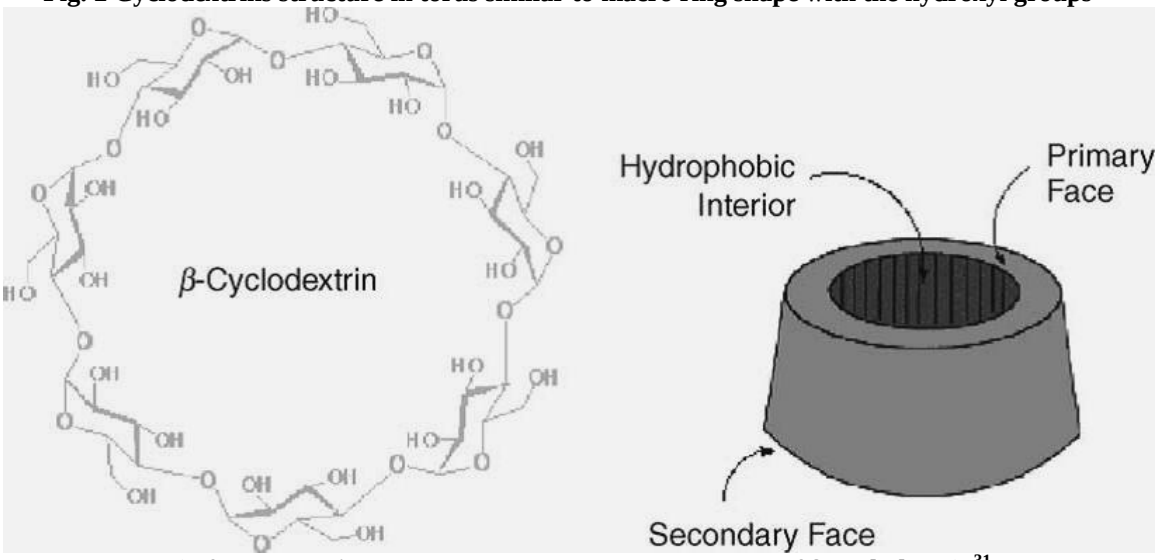


Fig.3 The chemical structure and the molecular shape of β-cyclodextrin[31]

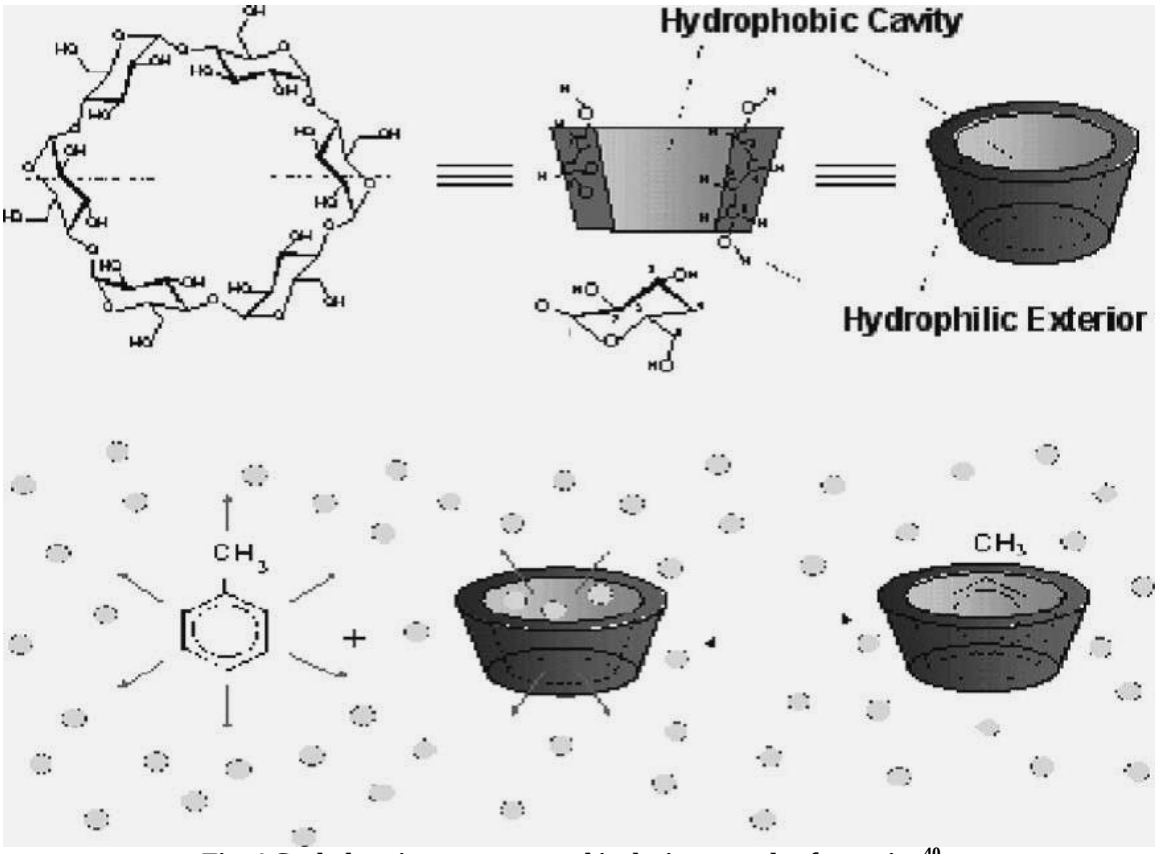
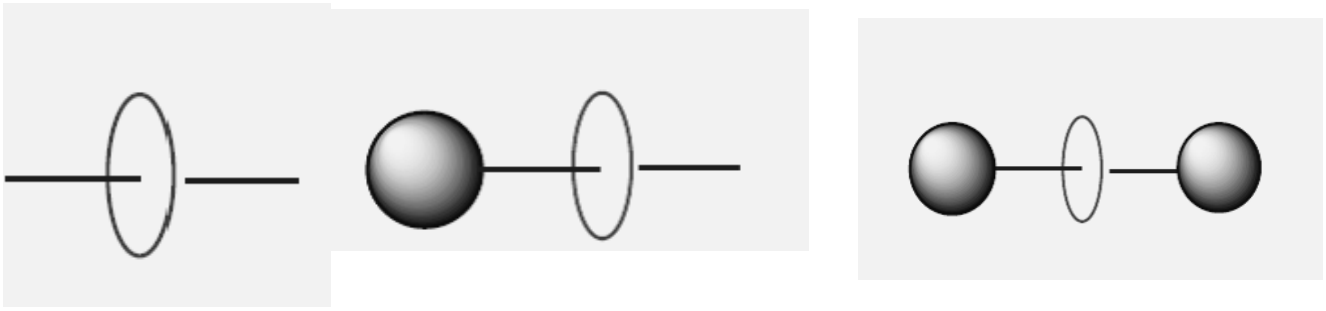


Fig. 4 Cyclodextrins structure and inclusion complex formation[40].



a-Pseudorotaxanes **b-Rotaxanes**

In fig. 5 The black balls indicate stoppers. These stoppers are bulky groups that do not allow the dethreading of the cyclic. Pseudorotaxane that contains only one stopper is called semirotaxane. Three various approach can be distinguished for rotaxane synthesis [48].

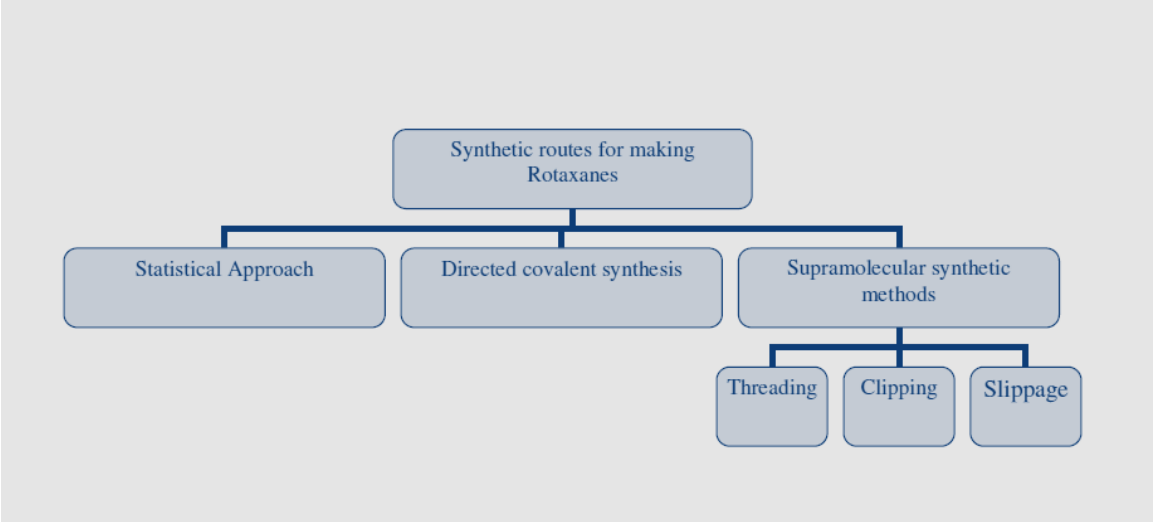


Fig. 6 Synthetic methods of rotaxanes

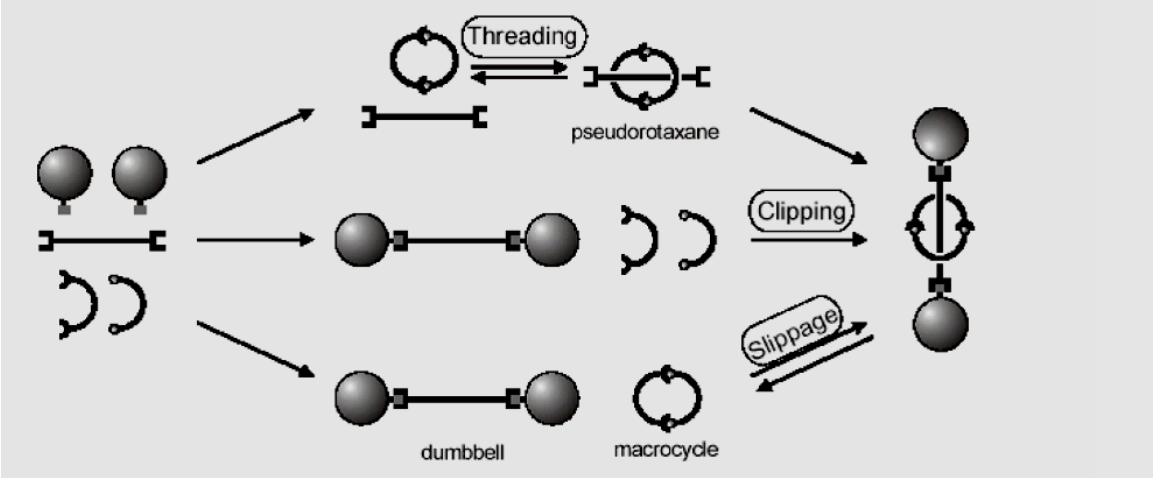


Fig.7 Different supramolecular strategies for making rotaxanes

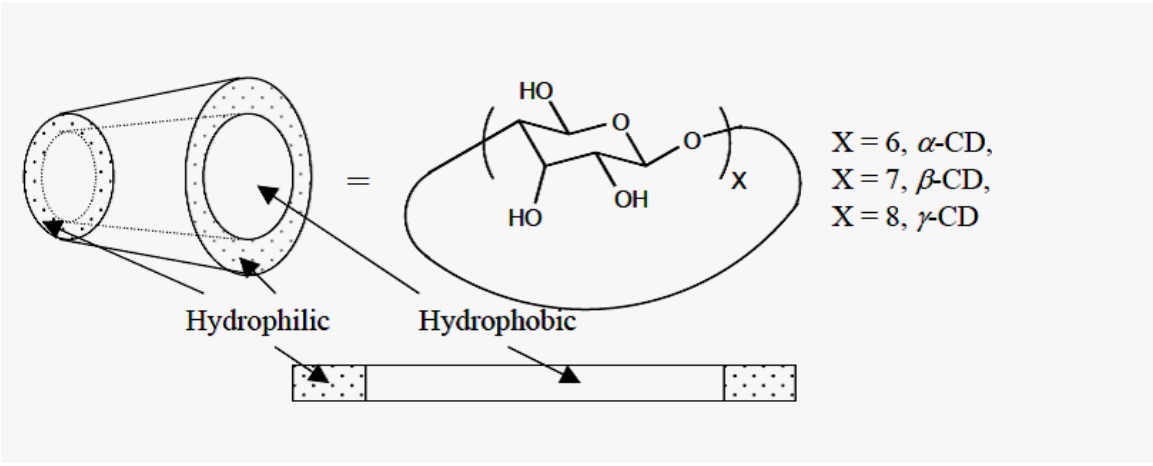


Fig. 8: Cyclodextrins and their gust[47]

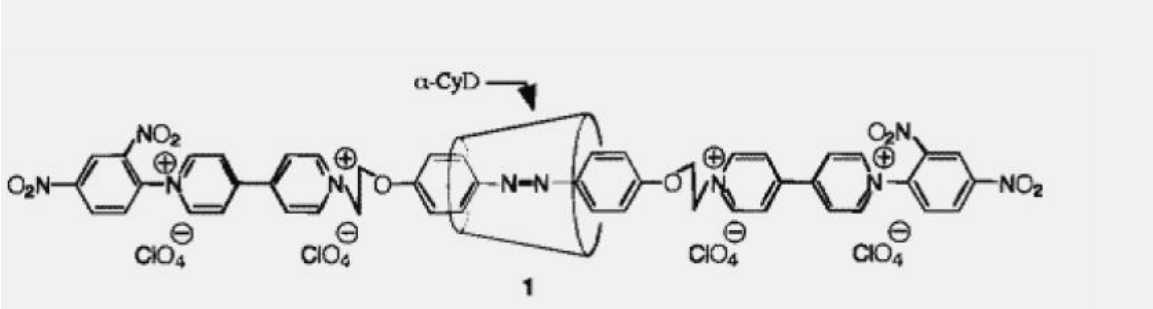


Fig. 9: 2- rotaxane in which the position of the macrocycle can be controlled by light

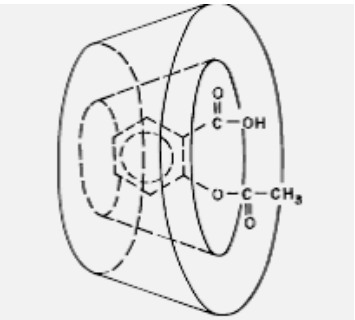


Fig. 10 Structure of Aspirin-β-CD complex and stabilization of aspirin by CD complexation[78]

Table 4: properties of Aspirin-β-CD complex[78]

Drug	pH	Temp (°C)	k_u (min^{-1})	Cyclodextrin[a]	k_c (min^{-1})	k_u/k_c	K_c (M^{-1})
Aspirin	Ca. 1	65	4.76×10^{-3}	H_7β-CD	1.11×10^{-3}	4.3	76.0
				M/DM-β-CD	8.25×10^{-4}	5.8	53.3
				HP-γ-CD	1.18×10^{-3}	4.0	23.2

[a] HP-β-CD: (2-hydroxypropyl)-β-cyclodextrin. M/DM-β-CD: mixture of maltosyl- and dimaltosyl-β-cyclodextrin (3:7). HP-γ-CD: (2-hydroxypropyl)-γ-cyclodextrin.

Table 5: Some examples of marketed products containing cyclodextrin[46,79]

Drug	Formulation	Trade name	Company
α-Cyclodextrin			
Alprostadil (PGE_1)	IV solution	Prostavasin	Ono (Japan)
Cefotiam hexetil HCl	Oral tablet	Pansporin T	Takeda (Japan)
β-Cyclodextrin			
Benexate HCl	Oral capsule	Ulgut	Teikoku Kagaku Sangyou (Japan)
Dexamethasone	Dermal ointment	Glymesason	Fujinaga (Japan)
Nicotine	Sublingual tablet	Nicorette	Pharmacia (Sweden)
Nitroglycerin	Sublingual tablet	Nitropen	Nihon Kayaku (Japan)
Piroxicam	Oral tablet	Brexin	Chiesi (Italy)
Tiaprofenic acid	Oral tablet	Surgamyl	Roussel-Maestrelli (Italy)
2-Hydroxypropyl-β-cyclodextrin			
Cisapride	Suppository	Propulsid	Janssen (Belgium)
Indomethacin	Eye drop solution	Indocid	Chauvin (France)
Itraconazole	Oral and IV solutions	Sporanox	Janssen (Belgium)
Mitomycin	IV solution	Mitozytrex MitoExtra	SuperGen (USA) Novartis (Switzerland)
Randomly methylated β-cyclodextrin			
17β-Oestradiol	Nasal spray	Aerodiol	Servier (France)
Chloramphenicol	Eye drop solution	Clorocil	Oftalder (Portugal)
Sulfobutylether β-cyclodextrin			
Voriconazole	IV solution	Vfend	Pfizer (USA)
Ziprasidone maleate	IM solution	Geodon, Zeldox	Pfizer (USA)
2-Hydroxypropyl-γ-cyclodextrin			
Diclofenac sodium	Eye drop solution	Voltaren ophtha	Novartis (Switzerland)

Table 1: Cyclodextrins properties [34]

Properties	αCD	βCD	γCD
Number of glucopyranose units	6	7	8
Molar mass / (g/mol)	972	1135	1297
Solubility / (g/100 mL)	14.5	1.85	23.2
Inner cavity diameter / (Å)	4.7-5.2	6.0-6.4	7.5-8.3
Outer cavity diameter / (Å)	14.6	15.4	17.5
Cavity height / (Å)	6.7	7.0	7.0
Specific rotation $(\alpha)_D^{25*}$	150.5 ± 0.5	162.5 ± 0.5	177.4 ± 0.5
Volume of the cavity / ($Å^3$)	174	262	427
ΔH^0 (aq) / (kcal/mol)	7.67	8.31	7.73
ΔS^0 (aq) / (cal/(mol K))	13.8	11.7	14.7

Table 2: Some methods that can be use to improve the complexation efficiency [9,30,38,] **.**

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

Table 3: uses of Cyclodextrins in recent years

uses of CDs in 2009	uses of CDs in 2010

74% Cosmetic+Toiletry Industry 2% Others applications 6% Pharmaceutical Industry 4% Chemical Industry 14% Food Industry	2% Agrochemical Industry 6% Food & Cosmetic Industry 2% Cell Biology 15% Chemical & Biochemical Industry 25% Pharmaceutical Industry Food 23% Chemistry of CD Complexes Food & Cosmetic Industry 18% Chemistry of CDs 12% Analytical Chemistry

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