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Cyclodextrins-The Molecular Container

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ABSTRACT

Cyclodextrins (CDs) are cyclic oligosaccharides, which have recently been recognized as useful excipients in different fields. Cyclodextrin (CD) can form water-soluble complexes with lipophilic guests that hide in the cavity of CDs. This review paper will address the historical background of cyclodextrin discovery and highlights the chemistry and physico-chemical properties of three-well-known industrially produced cyclodextrins. Besides this, the article addresses the techniques for CD-complexation, determination of CD-complexes and the mechanism of guest release from cyclodextrin complexes and production of cyclodextrin. To list more, the present paper includes various utilities of cyclodextrins and cyclodextrin complexes in numerous fields, e.g. pharmaceutical, food, biotechnological, chemical and cosmetic industry.

Keywords: Cyclodextrins; Production of cyclodextrins; Mechanism of guest release; Utility of cyclodextrins; Cyclodextrin complexes; Physico-chemical properties.

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INTRODUCTION

Cyclodextrins are composed of D-(+) glucopyranose residues attached by α-(1, 4) glucosidic bonds [1]. In the year 1891, French scientist A. Villiers first discovered cyclodextrins (CD) as degradation products of starch and named this dextrin "cellulosine" [2-4]. In 1903, the Austrian microbiologist Franz Schardinger, who is supposed to be founder of cyclodextrin chemistry, identified two crystalline compounds (A , B) similar to cellulosine from bacterial digest of potato starch and replaced the name "cellulosine" by α-dextrin and β-dextrin [5, 6]. These were later known as α-cyclodextrin and β-cyclodextrin. After discovery of γ-cyclodextrin in 1935 Freudenberg and Cramer suggested the existence of larger cyclodextrin [7, 8]. Characterization and purification of δ-, ε-, ζ-, η-, θ-CDs, with 9, 10, 11, 12 and 13 glucopyranose residues have been accomplished recently. Cyclodextrins with fewer than 6 glucopyranose residues cannot be formed due to steric hindrances [9]. Cyclodextrin is unique compound with lipophilic inner cavity and hydrophilic outer surface that resembles a molecular container which holds non polar, non ionic guest molecules in its inner cavity. This results the formation of inclusion complex that confers unique property (enhanced solubilization capacity) on guest molecules due to hydrophilic outer surface of molecular container. This potential advantage has been nurtured in many investigations of drug administrations through different routes [10]. It is obvious that the fitting of guest molecule within the inner cavity of CD depends upon polarity, size of the guest molecule and the size of inner cavity [11].

Three well characterized and commercially available members of this family are α-, β-, and γ-CDs (with 6, 7 or 8 glucose units respectively). The α-cyclodextrin, also known as Schardinger's α-dextrin, cyclomaltohexaose, cyclohexaglucan, cyclohexaamylose, α-CD, ACD, and C6A; β-cyclodextrin, also known as Schardinger's β-dextrin, cyclomaltoheptaose, cycloheptaglucan, cycloheptaamylose, β-CD, BCD, and C7A; γ-cyclodextrin, also known as Schardinger's γ-dextrin, cyclomaltooctaose, cyclooctaglucan, cyclooctaamylose, γ-CD, GCD, and C8A [1]. After 100 years of its discovery, commercial production of these molecules started [2-4]. Commercialization of various inclusion complexes of drug products had been initiated since 1976. The world's first cyclodextrin-based pharmaceutical product, prostaglandin E2/ β-CD (Prostarmon E™ sublingual tablets), was marketed in Japan in the year 1976. Twelve years later, the first European cyclodextrin containing pharmaceutical product, piroxicam/ β-CD (Brexin® tablets), was marketed. In 1997, the first US-approved cyclodextrin product, itraconazole/2-hydroxypropyl-β-CD oral solution (Sporanox®) was introduced [12]. Cyclodextrins have been widely used to prepare inclusion complexes, which are utilized in pharmaceutical, food, biotechnological, chemical, and cosmetic industry to protect the physical and chemical properties of guest molecules [13-17]. Palanisamy and Khanam prepared solid dispersion of prednisolone using hydroxypropyl- β-cyclodextrin and polyethylene glycol as carrier to improve the dissolution properties. Their result suggested that solid dispersion with selected carriers is a powerful tool to accelerate the dissolution of poorly water soluble drugs [18]. Recently in another investigation, they encapsulate pure prednisolone and prednisolone-hydroxypropyl-β-cyclodextrin complex in cellulose-based matrix microspheres and their results suggests that the system simultaneously exploits the complexation technique to enhance the low solubility of

pure prednisolone and subsequent modulation of drug release from microspheres at a predetermined time [19].

The objective of this review article is to highlight (i) physico-chemical properties of cyclodextrins, (ii) techniques of complexation, (iii) mechanism of guest release from cyclodextrin complexes, (iv) production of cyclodextrins, and (v) the utility of cyclodextrins in pharmaceutical, food, biotechnological, chemical and cosmetic industry.

Physico-chemical properties of cyclodextrins:

Physical properties

Listed, in Table 1, are molecular dimensions and physical properties of three cyclodextrins. All three cyclodextrins are white crystalline powder. CDs have no definite melting point, but from about 200°C up they begin to decompose [1]. Cyclodextrins can be classified broadly into two types: one is naturally occurring and other is chemically modified cyclodextrins [20]. Biotechnologically produced cyclodextrins (α-, β-, and γ-CD) differ in the number of glucose residue. Schematic structure of α-, β-, and γ-CDs are shown in Fig. 1. Chemically modified CD derivatives have been prepared with an objective to enhance/modify desired physicochemical properties and inclusion capacity of parent CDs [21, 22]. The solubility of cyclodextrins depends strongly on the temperature as it is expressed by mathematical equations (1, 2, and 3) where c is the concentration of cyclodextrin in mg/ml and T is the temperature in K [1].

α-CD:

$$c = (112.71 \pm 0.45)\, e^{-(3530 \pm 31)[(1/T)-(1/298.1)]} \quad (1)$$

β-CD:

$$c = (18.3236 \pm 0.099)\, e^{-(14137 \pm 31)[(1/T)-(1/298.1)]} \quad (2)$$

γ-CD:

$$c = (219.4.71 \pm 9.8)\, e^{-(3187 \pm 320)[(1/T)-(1/298.1)]} \quad (3)$$

Table 1: Molecular dimensions and physical properties of α-, β-, and γ- cyclodextrins (CDs) [23]

Type of cyclodextrin	No. of Glucose units	Molecular weight	Molecular Dimensions (Å)			Solubility at 25°C (g/100ml H_2O)	$[\alpha]_{D,25}$
			Inside diameter	Outside diameter	Height		
α	6	973	5.7	13.7	7.0	14.50	150
β	7	1135	7.8	15.3	7.0	1.85	162
γ	8	1297	9.5	16.9	7.0	23.20	177

Cyclodextrins (CDs) are fairly water soluble; however, β-CD shows remarkably lower solubility than does α-CD, or γ-CD. At elevated temperatures the aqueous solubility of all cyclodextrins

increases [9]. During crystallization of cyclodextrins in aqueous medium some molecules of water are included into the cyclodextrin cavity, others molecules of water are present as integral parts of the crystal structure (crystal water). The cyclodextrin-inclusion complexes are formed by the substitution of included water from cyclodextrin cavity by the appropriate guest molecule. Cyclodextrins are insoluble in most organic solvents but they are soluble in some polar, aprotic solvents [1]. Temperature dependent solubility of cyclodextrin may change due to its complexation with the guest molecule. The inclusion complex is more soluble than cyclodextrin itself when the guest molecule is highly soluble in water. In contrast, inclusion complex with the guest molecule of poor water solubility generally results in a decrease in solubility of the cyclodextrin, although solubility of inclusion complex is generally less than that of the cyclodextrin, it is greater than that of the guest molecule [25].

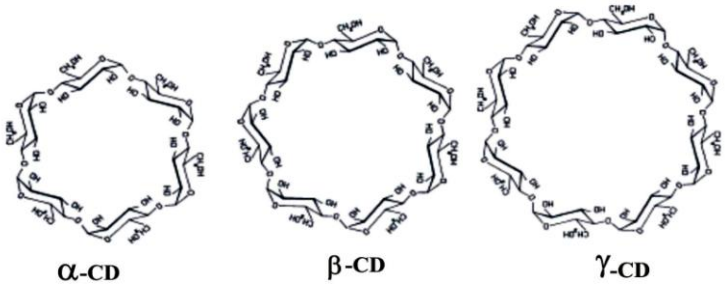

Fig: 1 Schematic structure of α-, β-, and γ- CDs [24]

Chemical properties

Cyclodextrins (CDs) have no reducing end groups. Periodate oxidation of α-, β-, and γ-CD will open the glucopyranose ring, but no formic acid or formaldehyde is formed, consistent with the fact that cyclodextrins do not contain free end groups. The glycosidic bonds of CDs are fairly stable towards the alkali and even at elevated temperature [26]. CDs are more resistant to acid hydrolysis than is starch. Strong acid such as hydrochloric acid will hydrolyze the cyclodextrins to yield a mixture of oligosaccharides ranging from opened ring down to glucose. The rate of acid hydrolysis increases as functions of both increased temperature and the concentration of acid. The hydrolysis of cyclodextrins is minimal in presence of weak acids such as organic acids [27]. CDs are more resistant to acid-catalyzed hydrolysis, compared with that of linear sugars, and the ring-opening rate of cyclodextrins increases with increasing cavity size (α- cyclodextrin < β- cyclodextrin < γ-cyclodextrin) [14].

Modified cyclodextrins:

The aqueous solubility of natural CDs is lower due to the relatively strong intramolecular hydrogen bonding in the crystal lattice [1]. Particularly β-cyclodextrin shows low aqueous solubility among all naturally occurring cyclodextrin. Hydroxylation or methylation of the hydroxyl groups of β-cyclodextrin enhances solubility and inclusion capacity of parent CDs [1, 14]. The functionality of cyclodextrins is greatly increased by chemical modification because of

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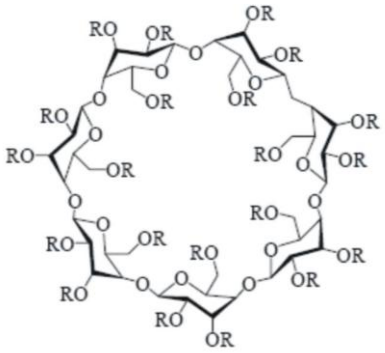
the availability of multiple reactive hydroxyl groups [28]. The structure of β-cyclodextrin and some of its derivatives are shown in Fig. 2 [29].



Cyclodextrin	R= H or
β-cyclodextrin	-H
2-hydroxypropyl-β-cyclodextrin	$-CH_2CHOHCH_3$
Sulfobutylether-β-cyclodextrin	$-(CH_2)_4SO_3^-Na^+$
Randomly methylated- β-cyclodextrin	$-CH_3$
Branched β-cyclodextrin	Glucosyl or maltosyl group

Fig: 2 The structure of β-cyclodextrin and some of its derivatives [29]

Techniques for CD-complexes:

The uniqueness of molecular geometry of a cyclodextrin enabled a variety of guest compounds to be accommodated in the inner hydrophobic cavity to form molecular inclusion complexes of guest-host [1]. A variety of non-covalent forces, Van der Waals forces, hydrophobic interactions and other forces are responsible for the formation of stable CD-complex that protects the guest molecule against the attack by various reactive molecules and thus, it reduces the rate of hydrolysis, oxidation, steric rearrangement, racemization and even enzymatic decomposition [10]. Depending on the molecular dimensions of cyclodextrins, α-cyclodextrin can typically complex low molecular weight molecules or compounds with aliphatic side chains, β-cyclodextrin will complex aromatics and heterocycles and γ-cyclodextrin can accommodate lager molecules for e.g. macrocycles and steroids. Complexes can be formed either in solution or in the crystalline state. Water is typically the solvent of choice for inclusion complexation but complexation can be accomplished in a co-solvent system and in the presence of any non-aqueous solvents [28]. Generally, guest /cyclodextrin complexes have a molar ratio, [guest]/[cyclodextrin] of 1:1. The molar ratio can be higher or lower and this depends on the size of the guest molecule and the identity of the cyclodextrin. Many techniques which are used to form CD-complexes are kneading, co-precipitation, dry mixing, sealing, slurry complexation, neutralization, spray drying, freeze-drying, and solvent evaporation.

Kneading

The kneading process is similar to the wet granulation process and requires conventional kneaders (e.g., low and high shear mixers) [30]. The inclusion complex of guest molecule with CD is prepared in the laboratory by wetting the physical mixture in a mortar with a minimum volume of water and subsequently kneading thoroughly with a pestle-mortar to

obtain a paste which is then dried under vacuum at room temperature and sieved through appropriate sieve and is stored in a desccicator until further evaluation [28, 31-33].

Co-precipitation

The co-precipitation method is the most widely used method in the laboratory. Sapkal *et al.* [34] have prepared inclusion complex of guest molecule of poor aqueous solubility with β-CD by co-precipitation method. At first guest molecule is dissolved in minimum quantity organic solvent like acetone and is added drop wise to the β-CD in minimum quantity of water previously maintained at 75^{o}C while stirring. Stirring is maintained for 1 h at 75^{o}C. Then gradually it is cooled to room temperature while stirring. The precipitates is then filtered, dried and stored at ~25° ± 2.0°C and relative humidity of 40-50%. Some time the precipitate may be washed with a small amount of water or other water-miscible solvent such as methanol, ethyl alcohol, or acetone [35, 36]. Unfortunately, the use of organic solvents as precipitants can interfere with complexation and therefore this approach is less attractive than the kneading method. Another disadvantage of this method lies in the scale-up [37, 38] but the co-precipitation method yields a highly pure and crystalline inclusion complex [30].

Dry mixing

In dry mixing, guests are added to the CD and simply mixing them together results complexation. Parlati et al. have prepared solid complexes with a modified dry mixing method by milling the reactants in the molar ratio 2:1 for 3 days [39]. This method works best with oils or liquid guests. The main advantage of this method is that no water needs to be added, unless a washing step is required. The disadvantages of this method are the risk of caking on scale-up, insufficient mixing that leads to incomplete complexation, and prolonged mixing time. The duration of mixing is variable and depends on the guest [28].

Sealing

The solid guest-cyclodextrin complexes can be formed by grinding definite amount of physical mixtures of guest and cyclodextrin, sealing the mixture in a glass container and keeping in a temperature range of 60 to 90°C. Wang *et al.*, [40] prepared the inclusion complex of paeonol with β-cyclodextrin by a simple, quick 'Sealed-control temperature method'. The complex formation was confirmed by infrared (IR) spectrum and powder X-ray diffraction. The study also revealed that the inclusion complex formation by this method was affected by heating temperature, heating time, and crystallinity of β -cyclodextrin.

Slurry-complexation

In this method, cyclodextrin is suspended in water up to a 40-45% w/w concentration and stirred in a reactor. Cyclodextrin which is in solution forms complexes with the guest and the complex precipitates. Generally ambient temperatures are required for slurry complexation. With many guests, some heat may be applied to increase the rate of

complexation, but care must be applied as too much heat can destabilize the complex [28, 35]. The amount of time required to complete the complexation depends on the particular characteristics of guest and the r.p.m. of stirring [40]. The complex can be collected in the same manner as with the co-precipitation method. The main advantage of this method is the reduction of the amount of water required and the size of the reactor [28].

Neutralization

Solid complexes of ionizable guests can be prepared by neutralization method, wherein the guest is dissolved in an acidic (for basic guests) or basic (for acidic guests) aqueous CD solution. Then the solubility of the guest is lowered by appropriate pH adjustments to force the complex out of solution. Terfenadine has relatively low bioavailability after oral administration due to its limited solubility in water. Choi *et al.*, [41] prepared the terfenadine-β-cyclodextrin (1:2) inclusion complex by the neutralization method to enhance the antihistaminic activity of terfenadine. The formation constant of inclusion complex was higher at lower pH, while its formation ratio was 1:2 irrespective of pH. They concluded that this inclusion complex enhanced the antihistaminic activity of terfenadine following the enhanced solubility and dissolution of terfenadine.

Spray drying

In spray drying, cyclodextrin is dissolved in 200 ml of a solution previously alkalinized with 25% aqueous ammonia (final pH 9.5). The guest is dissolved in 100 ml of 96% ethyl alcohol. Both solutions are mixed and sonicated; the final solution is spray-dried to get the complexes [42].

Freeze-drying (lyophylization)

In freeze-drying, physical mixture of guest and cyclodextrin is wetted with a small amount of buffer solution and is kneaded forming a homogeneous suspension which is then freeze-dried. The final complexes are pulverized and sieved through appropriate sieve. Freeze-drying is an industrially applicable method for heat labile guests, but large amount of water, if it is used as solvent, and excessive CD would be required because of the low solubility of hydrophobic guest in aqueous solution and makes the process time consuming [43].

Solvent evaporation

In this method organic solvents are used and therefore residual solvents need to be removed. Osadebe *et al.* [44] have prepared solid dispersion (SD) of piroxicam and β-CD by solvent evaporation method. At first appropriate amounts of piroxicam and β-CD are dissolved in a common solvent, methanol and stirred for 24 h at 28°C to prepare inclusion complex with 1:1 and 1:2 molar ratios. After that the mixture is concentrated under vacuum, filtered, and dried under vacuum at 25°C for 24 h to get the complex.

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Mechanisms of guest release from CD-complexes:

Complexation of the guest to cyclodextrin occurs through a non-covalent interaction between the molecule and the cyclodextrin (cavity). Complex formation is a dynamic process whereby the guest molecule continuously associates and dissociates from the host CD. In case of a 1:1 complex, the interaction is as follows [45]:

$$CD + G \underset{\leftarrow}{\overset{\rightarrow}{}} CD - G;\ K = \frac{k_R}{k_D}$$

Where, CD is the cyclodextrin, G is the guest molecule, CD-G is the inclusion complex, k_R and k_D are the recombination constant and dissociation constant respectively. K, equilibrium constant is the important characteristic of this association. The larger is the guest molecule, the slower the formation and dissociation of the inclusion complex. Ionization decreases the rate of complex formation and dissociation [45]. Dissociation due to dilution appears to be major drug release mechanism [46], although other factors such as competitive displacements of the drug from the complex, drug uptake by tissues, binding to protein, and ionic strength and temperature should also be considered to assess the stability and dissociation of CD-drug complex [13].

Dilution

Dissociation due to dilution appears to be a major release mechanism for the guest molecules from cyclodextrin complexes [38]. Guo *et al.*, [47] developed a novel drug dosage form of amphotericin B, a potential fungicidal agent that forms a very tight complex with sodium cholesteryl sulfate, and it does not readily dissociate after i.v. injection, although most of the CD-complexes dissociate upon dilution in the blood. In case of oral drug delivery, complexes also dissociate rapidly upon dilution in the stomach and intestinal contents and it is believed that only the drug, and not the complex, is absorbed. Dilution is minimal when a drug-CD complex is administered by ophthalmic, transmucosal, and transdermal routes. After oral administration, some dilution is likely to occur but here also dilution is probably insufficient to account for the relative good absorption of drugs as administered as CD-complexes [48].

Competitive displacement

Competitive displacement of drugs from cyclodextrin complexes probably plays a significant role in physiological environment. The beta-cyclodextrin complex of a poorly water-soluble drug, cinnarizine, is more soluble *in vitro* than cinnarizine alone. Oral administration of the complex showed less bioavailability, and it was suggested that cinnarizine was too strongly bound to the cyclodextrin to dissociate and this was limiting the bioavailability of cinnarizine [38]. Co-administration of phenylalanine (displacing agent) improved the availability of cinnarizine from the complex in comparison to that from the conventional tablets of cinnarizine [13].

Drug uptake by tissue

A potential mechanism for drug release from cyclodextrin is drug uptake by tissues. If the nature of the drug is lipophilic and has access to tissue, the tissue then acts as a sink causing dissociation of the complex based on simple mass action principles. This mechanism may become most relevant for strongly bound drugs or when the complex is administered at a site (e.g., ocular, nasal, sublingual, pulmonary, dermal or rectal) where dilution is minimal [13]. In ophthalmic delivery, cyclodextrins have been used to increase the solubility and/ or stability of poorly water soluble drugs in the tear fluids and in some cases to reduce irritation [49, 50].

Protein binding

Drug binding to plasma proteins may be a vital mechanism by which the drug may be released from drug-CD complex. Frijnik *et al.*, [51] studied the effect of cyclodextrin (HPβCD) on the displacement of both naproxen and flurbiprofen from plasma binding sites in vitro. After parenteral administration they estimated, after 10 and 60 minutes, the tissue distribution of both naproxen and flurbiprofen either as HPβCD complex or as plasma solutions and concluded that more drugs was free from cyclodextrin solution to distribute to tissues than from the plasma solutions.

Change in ionic strength and temperature

For most molecules of the ionized or charged form has poorer binding to cyclodextrins compared to that of the non-ionized or neutral form. Most of the drug-CD complexes are usually prepared and stored at/or below room temperature. Since, normal body tissue temperatures can be as high as 37°C; this temperature condition may be the contributing factor to drug dissociation, in physiological environment [13].

Determination of CD-complexes:

There are several instrumental techniques available to characterize the complex formation. For example, Phase solubility [30, 52-54], High performance liquid chromatography (HPLC) [55], Circular dichroism [56], Nuclear Magnetic Resonance (NMR) [30], X-ray powder diffraction (XRPD) [44], Differential scanning calorimetry **(**DSC) [57], Thermogravimetric analysis (TGA) [58], UV-Vis spectroscopy [12], Differential solubility [59], Fourier Transform Infrared Spectroscopy (FTIR) [60], and FT-Raman Spectroscopy [57] have been cited in the literature and are discussed below.

Phase solubility

There are several methods to determine the affinity, or binding constant between cyclodextrin (or derivatives of) and a substrate. Among the numerous methods the phase solubility method is the most widely used approach as pioneered by Higuchi and Connors [54]. It examines the change of solubility of a substance (guest) on the formation of the complex with

a ligand or solubilizer. This method involves preparation of series of aqueous solutions (buffered or unbuffered) of CD and subsequent addition of excess amount of low solubility guest molecule to each solution. Insoluble part of the drug left in the liquid is separated by filtration/centrifugation and the filtrate is collected. Total concentration of solubilized drug as free molecule and CD bound molecule in aqueous layer is determined by analytical techniques. The phase solubility diagram is then constructed by plotting the total molar concentration of drug or guest molecule on y-axis against the total molar concentration of host molecule (cyclodextrin) on x-axis [30, 52].

According to the solubility of the complex formed, phase solubility diagrams are generally classified into type A and type B (Fig. 3). Consider the inclusion complex formed is S_mL_n where S is the substrate or guest and L is the ligand or host and m, n are the complex orders. Type-A curves indicate the formation of soluble inclusion complexes while type-B indicates the formation of inclusion complexes with poor solubility. In type-A curves, three subtypes have been identified, these are: A_L, A_P, and A_N. Solubility profile is linear as represented by A_L, when all complexes are of first order (n=1). A nonlinear plot with concave upward curvature (A_P) indicates that at least one complex is present having n > 1. A nonlinear plot with concave downward curvature (A_N) may be evidence of non ideality effects (non constancy of activity coefficient) or of self association by the ligand. Type-B curves are traditionally observed with naturally occurring CDs, especially β-CD. In type-B curves, two subclasses have been described, these are B_S and B_I [48, 52].

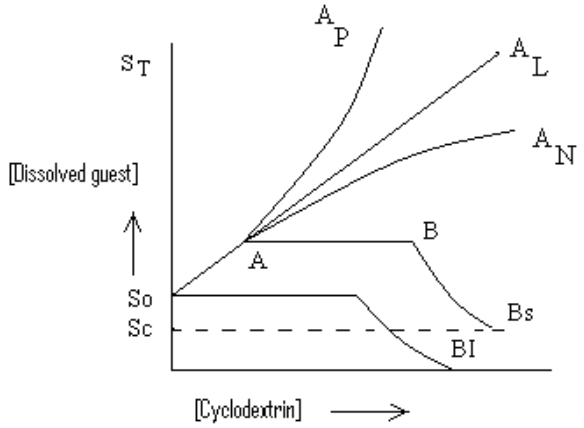

Fig: 3 Phase solubility diagram [52]

In type-B_S curve, the initial ascending portion of the solubility change is followed by a plateau region then a decrease in solubility at higher CD concentrations, indicating a microcrystalline precipitation of the complex. The plateau region representing a constant value of S_T that indicates additional quantity of ligand/host does not alter solubility of guest molecule. Concentration of guest molecule (S_T) remains constant owing to precipitation of the complex with simultaneous dissolution of solid guest. At point B, further addition of ligand causes depletion of guest molecule in solution by complex formation and simultaneous precipitation of

the complex [48]. The type B_l curve is indicative of the formation of insoluble complexes in water [14]. The extent of solubility alteration depends directly on the binding affinity of the two compounds. Therefore, it is possible to evaluate equilibrium constant from solubility data. If a single 1:1 complex is formed by combining the mass balance on guest molecule (S) and host molecule (L), stability constant (K) can be obtained. Mass balance expression for guest molecule gives the following equation:

$$[S]_T = S_0 + KS_0[L] \qquad (4)$$

Where, $[S]_T$ is the total concentration of guest in complex and S_0 is the guest molecules (free) concentration. Similarly, mass balance on host molecule leads to the following equation:

$$[L]_T = [L] + KS_0[L] \qquad (5)$$

Therefore,

$$[L] = \frac{[L]_T}{1 + KS_0} \qquad (6)$$

Where, $[L]_T$ is the total concentration of host molecule.
Putting value of [L] in equation (4), we get

$$[S]_T = S_0 + KS_0 \{[L_T]|(1 + KS_0)\} \qquad (7)$$

Thus a plot of $[S]_T$ against $[L]_T$ is linear from this expression, the stability constant is given by

$$K = \frac{\text{Slope}}{S_0\ (1 - \text{Slope})} \qquad (8)$$

Thermodynamic functions for the interaction of guest and host molecules are related to overall stability constant K by the following relationship:

$$\Delta G^0 = -2.303\ RT \log K \qquad (9)$$

ΔG^0 is the change of free energy at constant pressure (P) and temperature (T) and R is the universal gas constant. The standard enthalpy change, ΔH^0, can be obtained from the slope of a plot of log K versus 1/T, following the expression:

$$\log K = -\frac{\Delta H^0}{2.303\ RT} + \text{constant} \qquad (10)$$

When the values of K at two temperatures are known, the following equation can be used:

$$\log(K_2|K_1) = \frac{\Delta H^0 (T_2 - T_1)}{2.303\ R\ (T_1 T_2)} \qquad (11)$$

The standard entropy change, ΔS^0, is obtained from the expression

$$\Delta G^0 = \Delta H - T\Delta S^0 \qquad (12)$$

ΔH^0 generally become more negative as the stability constant for molecular complexation increases. Although large negative value of ΔS^0 is not favorable for complexation, still large negative value of ΔH^0 overcomes the unfavorable entropy contribution, leading to a negative ΔG^0 [61].

High performance liquid chromatography (HPLC)

Carolina *et al.*, [55] prepared an inclusion complex between lidocaine (LDC) and hydroxypropyl-β-CD (HP-β-CD) and characterized the inclusion complex by thermal analysis (DSC), UV absorption and HPLC. They found that the rate of LDC release decreased after complexation and thermodynamic parameters from the HPLC studies revealed that a stable complex was formed.

Circular dichroism

Marconi *et al.*, [56] worked on the conformational and circular dichroism studies on cyclodextrin inclusion complexes. They presented the structure of inclusion complexes between cyclodextrins and several chromophores of photochemical interest. The method proposed by them proves to be a suitable enough to elucidate different geometrical configurations and to gain insight into the relationship between structural and dynamic properties of the complexes.

Nuclear magnetic resonance (NMR)

Only NMR studies prove that a complex is formed. A shift in the peaks can be observed for both the guest and CD [57]. Proton and ^{13}C-NMR have been used to determine the formation of inclusion complexes and to give an idea of how the guest substrate is positioned in the cyclodextrin cavity. ^{13}C-NMR spectroscopy is utilized in determining the stoichiometry of inclusion complexes and the technique have wide applicability because it can be used on solid samples or samples dissolved in aqueous medium [30]. NMR spectroscopy is applicable to calculate the stability constant. In addition to quantitative and qualitative information about complex formation, NMR can be used to probe the solution geometry of CD-based complexes as well as give kinetic information about their association and dissociation [12].

X-ray powder diffraction analysis (XRPD)

Osadebe *et al.*, [44] prepared the inclusion complexes of piroxicam and beta-cyclodextrin by different methods such as physical mixture, kneading, coprecipitation,

evaporation and heating under reflux. XRPD analysis of different 1:1 complexes showed that there was increase in the halo of the diffractograms seen between the arbitrary units of 0 and 0.25 (y-axis) formed on mixing of two compounds and the reduction of intensity of the prominent piroxicam peak at $2\theta=8.7^{o}$ and resulted in increase in the volume of the beta-cyclodextrin due to inclusion of piroxicam.

Differential scanning calorimetry (DSC) and Thermogravimetric analysis (TGA)

Thermal analyses (DSC and TGA) are useful for determining whether the product of the complexation protocol is true complex or not [58]. In DSC, The samples (10 mg) are placed in aluminum pans and the experiments run in a calorimeter at a 10^{o}C/min heating rate over a wide range (0-450^{o}C). An empty pan served as reference and indium is used to calibrate the temperature. Thermograms are determined for the samples: CD, guest or drug, physical mixture of guest/CD and solid complex guest-CD. DSC analysis gives supporting evidences for the complexation of guest or drug with CD. Araujo *et al*., [62] worked on the development and pharmacological evaluation of ropivacaine-2-hydroxypropyl-β-cyclodxtrin inclusion complex and they studied DSC thermograms of HP-β-CD, Ropivacaine (RVC), RVC/HP-β-CD 1:1 physical mixture and RVC/HP-β-CD 1:1 complex, shown in Fig. 4. They reported that HP-β-CD and RVC gives a characteristic endothermic peak at 336.0^{o}C and 117.6^{o}C respectively corresponding to their melting point and HP-β-CD also gives a peak at 50^{o}C due to loss of water molecule. Thermogram of the RVC/HP-β-CD physical mixture (1:1) shows two endothermic peaks at 246.5 ^{o}C and 116.0^{o}C whereas the solid complex of RVC/HP-β-CD presents only a broaden peak at 248.2^{o}C. The absence of fusion peak of pure RVC at 117.6^{o}C in the thermogram and the shift of endo or exothermic peaks of drugs is a clear indication of the complexation phenomenon.
In DSC or TGA, the guest must have a melting or boiling temperature below about 300^{o}C, the temperature at which cyclodextrins decomposes. In DSC, no energy absorption is observed at the melting temperature of the guest when the guest is complexed. With both DSC and TGA, an increase in the boiling temperature (about 10^{o}C) is observed because of interaction of the guest with cyclodextrin provides a higher energy barrier to overcome for volatilization [57].

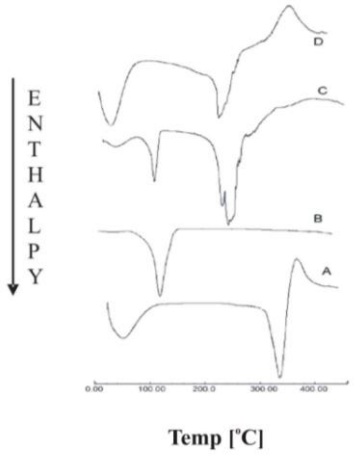

Fig: 4 DSC thermograms of (A) HP-β-CD, (B) Ropivacaine (RVC), (C) RVC/HP-β-CD 1:1 physical mixture, (D) RVC/HP-β-CD 1:1 complex [62]

Ultraviolet-visible (UV-Vis) spectroscopy

Spectrophotometric methods are useful to determine the value of stability constant, if the complexation events induce changes in the compound spectra as a function of the guest-host interaction. These changes in the compound spectra generally reflect an alteration in the microenvironment of the drug. The changes observed in UV and related processes are similar to those associated with dissolution of the drug in a solvent of decreased polarity [12].

Differential solubility

Van Hees *et al.*, [59] determined the concentration of free and bound piroxicam from piroxicam-β-cyclodextrin complex using differential solubility method and compared these results with the results of conventional DSC. In this method, a mixed solvent system of water-acetonitrile (1:1, v/v) is used to measure the total drug concentration in complex form and free drug in solution.

FTIR and FT-Raman spectroscopy

The infrared spectra of the complexes were analyzed and compared with the spectra of the pure compounds and their physical mixtures respectively. Due to complexation of the guest, shifts or changes in the spectrum occur [57]. Bratu *et al.*, [60] prepared the inclusion complexes of β-cyclodextrin with fenbufen and ibuprofen by the two different methods such as co-precipitation and the freeze-drying methods and they used FTIR spectroscopy to characterize the inclusion complexes. They found the fundamental changes which appear in the FTIR spectra of inclusion complexes of fenbufen and ibuprofen are mainly in the C=O stretching region. These changes suggest drug-CD complex formation. FT-Raman spectroscopy has also been used to characterize the inclusion complexes. Shifts or changes in the spectrum occur due to the complexation [57].

Production of cyclodextrins:

CDs are produced from starch by the action of an enzyme, cyclodextrin glycosyltransferase (CGTase; ED 2.4.1.19). Starch containing both amylopectin and amylose can be used as raw materials for cyclodextrin production but higher percentage of amylopectin (70-75%) found in potato starch is preferred as it gives higher yield [63-65]. CGTases have attracted major interest from industry due to their unique capacity of forming large quantities of cyclic α-(1,4)-linked oligosaccharides (cyclodextrins) from starch. CGTase(s) are predominantly extracellular enzymes which are produced by various bacteria that are listed in Table 2.

Table 2: Bacteria which produce CGTase

Name of the bacteria	References
Bacillus macerans	[66]
Bacillus circulance	[67]
Bacillus megaterium	[68]
Klebsiella pneumoniae	[69]
Bacillus stearothermophillus	[70]
Bacillus amyloliquefaceins	[71]
Alkolophilic *Bacillus sp.*	[72]
Bacillus lentus	[73]
Thermoanaerobacter sp.	[74]
Micrococcus	[75]

Commercially available CGTases have been produced from *Bacillus macerans* [63, 76-79]. Most CGTases studied so far are characterized as α- or β- and only few as γ-CGTase [80, 81]. Treatment of starch with amylase from *Bacillus marcerans* produces a crude mixture of cyclodextrins comprised of 6, 7, and 8 glucose units (α, β, γ-CDs respectively) together with small amounts of cyclodextrins with more than eight glucopyranose residues [66, 82, 83]. With the advent of biotechnology specific enzymes are produced and used selectively in the commercial production of pure α, β or γ cyclodextrin (Sicard and Saniez 1987). Recently attempts were made to isolate thermotolerant CGTase-producing bacteria, i.e. *B. stearothermophilus* [84] since industrial production of cyclodextrins is usually carried out at high temperature. The starch or starch hydrolyzate forms a complex with the enzyme, cleavage and joining of the ends results in cyclization to form the CD [76].

Generally two different types of cyclodextrin production processes are used; these are solvent process, and non-solvent process. Fig. 5 represents the production of cyclodextrin from starch using solvent process. Solvent process requires an organic solvent mainly toluene, ethyl alcohol or acetone that acts as a complexing agent which extracts one type of cyclodextrin selectively and thus directs the enzyme reaction to produce particular type of cyclodextrin of interest. Non-solvent process does not require complexing agents and produces a mixture of cyclodextrins [63]. The preparation process of cyclodextrins consists of four principal steps: (i) culturing of the microorganism that produces the cyclodextrin glucosyl tranferase (CGTase); (ii) separation, concentration and purification of the enzyme from the fermentation medium; (iii) enzymatical conversation of prehydrolyzed starch in mixture of cyclic and acyclic dextrins; and (iv) separation of cyclodextrins from the mixture, their purification and crystallization. Cyclodextrin glucosyl tranferase (CGTase) enzymes degrade the starch and produce intramolecular reactions without the participation of water producing cyclic and acyclic dextrins. Two ends of acyclic dextrins make a link through the glycosidic oxygen bridges by α (1, 4) bonds (Fig. 6) [45].

In solvent process, the first step is to liquefy starch (starch concentration 20-30%). Using α-amylase, acids and mechanical disintegration, starch is liquefied to make it suitable for its incubation with CGTase at low temperature. In industry liquefaction of starch is generally

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carried out by α-amylase treatment and jet cooking. Next, the liquefied starch is treated with CGTase and complexing agent (CA) under controlled temperature and pH. Thus cyclodextrins are produced by enzymatic conversion. A particular type of CD forms a complex with complexing agent (CA) and then it is precipitated. Then CD-CA complex is separated from the reaction solution either by centrifugation or filtration. The separated complex is then washed. Next, the separated complex is decomplexed and filtered. The filtrate is either steam distilled or extracted to recover CA. Recovered CA is reused. Then product solution is concentrated under vacuum distillation and treated with activated carbon and then CD is crystallized and filtered. The CD crystals are washed and dried [64, 85].

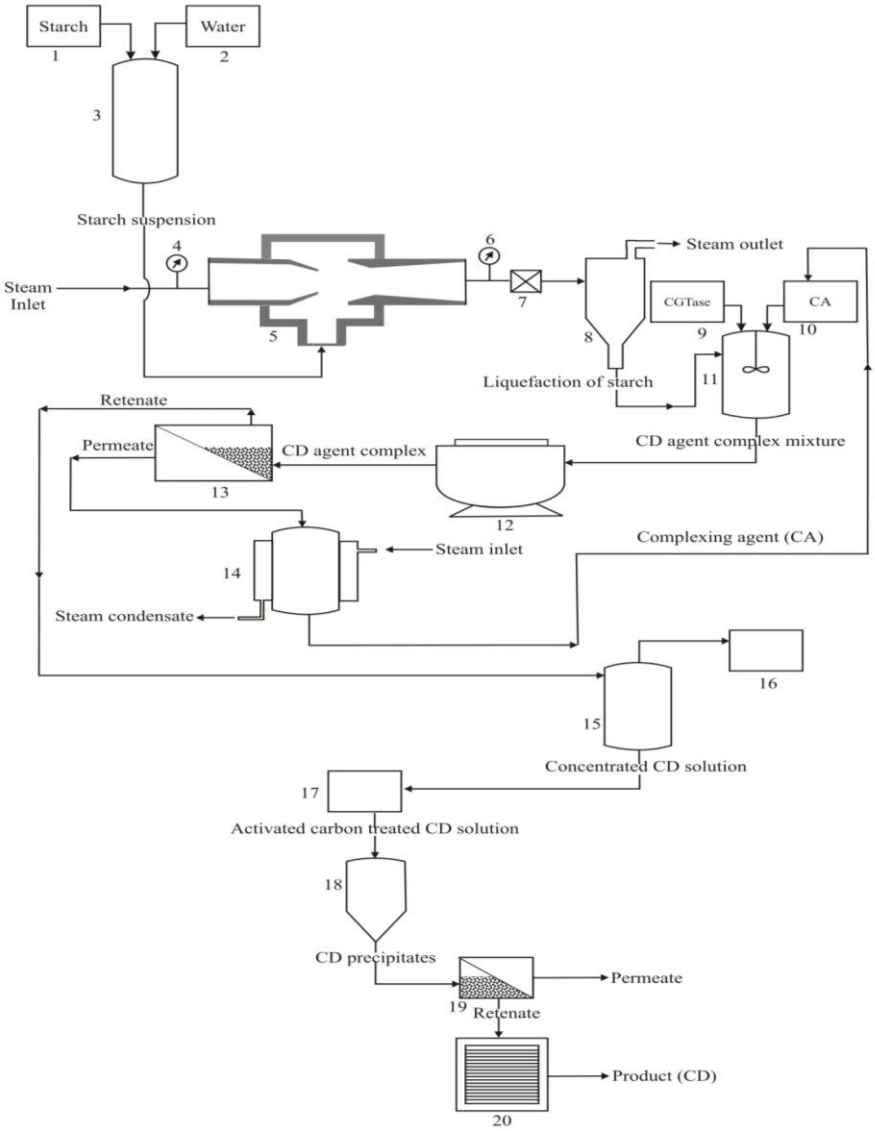

Fig: 5 Schematic representation of cyclodextrin production from starch using solvent process

Abbreviations: 1, 2, 9 and 10: Storage tanks; 3: Vessel; 4 and 6: Pressure indicators; 5: Hydroheater; 7: Back pressure valve; 8: Cooked starch collection vessel; 11: Bio-reactor; 12: Centrifuge; 13 and 19: Filtration unit; 14: Steam distillation apparatus; 15: Vacuum distillation unit; 16: Barometric condenser; 17: Activated carbon treatment unit; 18: Crystallizer; 20: Dryer.

In non-solvent process, β-CD production starts with starch liquefaction followed by enzymatic conversion identical to that used in solvent process but no complexing agent is added to this process. Cyclodextrins produced by non-solvent process can be applied in food without restriction, in contrast to cyclodextrins produced in solvent processes [64].

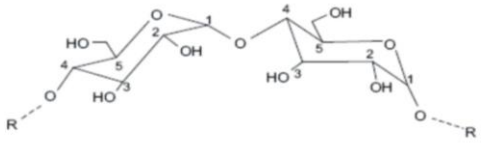

Fig: 6 Glycosidic oxygen bridge α (1, 4) between two molecules of glucopyranose [45]

Applications:

Cyclodextrins in pharmaceutical industry:

The uses and benefits of cyclodextrin complexation are well recognized in pharmaceutical industries that were evidenced by several reviews in the past years [38, 52, 86-88]. These benefits are bioavailability enhancement [14], active stabilization [1], odors or taste masking [89], irritation reduction [90] and material handling benefits [30, 91]. Practical use of natural cyclodextrins as drug carriers is restricted owing to their low aqueous solubility. The β-cyclodextrin is essentially nontoxic when given orally but it can not be given in parenteral preparation owing to its low aqueous solubility and nephrotoxicity [92]. Rate of metabolism of α-cyclodextrin is slower and that of γ-cyclodextrin is much faster than that of β-cyclodextrin. Cyclodextrins are metabolized in the colon. CD derivatives (hydroxypropyl-β-cyclodextrin and sulfobutylether-β-cyclodextrin) have been widely investigated for parenteral drug delivery. These have several advantages: enhancement of drug's aqueous solubility, minimization of toxic effect, reduction of tissue irritation and lesser or no precipitation of drug in the physiological pH [52, 93]. Table 3 lists cyclodextrin based commercially available pharmaceutical products.

Effect of CD on drug bioavailability

Pharmaceutical scientists have been renewing their interests on the complexation technique to enhance the bioavailability of insoluble drugs by increasing the drug solubility, dissolution rate and drug's permeability through biomembrane. HP-β-CD improves corneal permeation by solubilizing the hydrophobic prodrug of Ganciclovir and delivering it across the mucin layer at the corneal surface [94]. Shewale *et al.*, worked on the effect of pH and hydroxypropyl-β-cyclodextrin on solubility and stability of glicazide and they found that the solubility of glicazide can be increased either by the addition of HP-β-CD or by lowering of pH [95]. The bioavailability of Δ^9-tetrahydrocannabinol after sublingual administration of solid Δ^9-tetrahydrocannabinol/β-CD complex powder is higher than the bioavailability of Δ^9-tetrahydrocannabinol after oral administration of ethanolic Δ^9-tetrahydrocannabinol solution [96].

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Table 3: Commercially available pharmaceutical products based on cyclodextrin [12, 29, 87]

Drug /Cyclodextrin	Trade name	Formulation and indications	Company(Country)
Voriconazole/SBE-β-CD	Vfend	IV solution, Fungal infections	Pfizer(USA, Europe)
Ziprasidone mesylate/SBE-β-CD	Geodon, Zeldox	IM solution, Antiscizophrenic	Pfizer(USA, Europe)
PGE_1/α-CD	Prostavastin	Parenteral solutions, Chronic arterial occlusive disease	Ono(Japan)
Alprostadil/α-CD	Caverject Dual	IV solution, symptomatic treatment of erectile dysfunction in adult males due to neurogenic, vasculogenic, psychogenic, or mixed etiology	Pfizer(Europe)
Nicotine/ β-CD	Nicorette	Sublingual tablets, stop smoking	Pfizer(Europe)
Nitroglycerine/ β-CD	Nitropen	Sublingual tablets, Coronary dilator	Nihon Kayaku(Japan)
OP-1206/γ-CD	Opalmon	Tablets, Buerger's disease	Ono(Japan)
Diclofenac Na/HP-γ-CD	Voltaren	Eye drop solution, Nonsteroid Anti-inflammatory	Novartis(Europe)
Mitomycin/HP-β-CD	MitoExtra	IV infusion, Anti-inflammatory	Novartis(Europe)
Hydrocortisone/HP-β-CD	Dexocort	Solution, Mouth wash against aphta, gingivitis, etc.	Actavis(Europe)
Cloramphenicol/RM-β-CD	Clorocil	Eye drop solution, Antibiotic agent	Oftalder(Europe)
17β-Estradiol/RM-β-CD	Aerodiol	Liquid, Nasal spray	Servier(Europe)

Abbreviations: PGE_1: prostaglandin E_1; SBE-β-CD: sulfobutylether-β-cyclodextrin sodium salt; α-CD: α-cyclodextrin; β-CD: β-cyclodextrin; γ-CD: γ-cyclodextrin; HP-γ-CD: 2-hydroxypropyl-γ–cyclodextrin; HP-β-CD: 2-hydroxypropyl-β-cyclodextrin; RM-β-CD: randomly methylated-β-cyclodextrin; IV: intravenous; IM: intramuscular

Effect of CD on stability of drug

Cyclodextrins are known to accelerate or decelerate various kind of reactions i.e., catalyst-substrate complex formation, competitive inhibition, and stereospecific reaction. When an ester group of any guest molecule is fixed in close proximity to the catalytic site of cyclodextrins, i.e., secondary hydroxyl groups, the ester group experiences acceleration in hydrolysis due to catalysis and to the contrary, the hydrolysis is decelerated when the ester group is included deeply inside the cyclodextrin cavity. The addition of cyclodextrins decelerated the acid-catalyzed hydrolysis of the glycoside bonds in digoxin [14]. It has been reported that cyclodextrin-induced 'enhancement of drug stability' may be a result of inhibition of drug interaction with vehicles and due to the inhibition of drug bioconversion at the absorption site [52]. Large drug molecules like proteins and peptides can also form complexes with cyclodextrin and thus complexation results in both enhanced physical and chemical stability of this type of peptide drug. The mechanism of stabilization is qualitatively different in case of small molecular weight pharmaceuticals. The maximum benefit is usually obtained at low concentrations of cyclodextrins, and the benefits are often partly concentration dependent [10].

Effect of CD on odors or taste masking of drug

Taste is one of the most important parameters governing patient compliance and the oral administration of bitter drugs with an acceptable degree of palatability is a key issue: products need to be masked suitably especially for pediatric patients [97]. Cyclodextrin complexation is a useful technique to suppress the bitter taste of drugs like oxyphenonium bromide. With assumption that only the free drug molecule is responsible for bitter taste, the extent of the bitterness was reported to be dependent on the availability of free drug molecule, regardless the nature and the concentration of cyclodextrin [52].

Effect of CD on adverse effect of drug

The complexes of a drug with cyclodextrin eventually dissociate into its components in a controlled manner, and these dissociations depend on the magnitude of the corresponding stability constant, and there is no significant loss of the therapeutic benefits of the drug. Thus delivery rate of drug in contact with biological surfaces (e.g. gastric membrane) and its entry into the cells of non targeted tissues is controlled. This helps to reduce local irritation. Various drugs such as neuroleptics, anti-inflammatory drugs, antibiotics, etc. cause hemolysis of erythrocytes as adverse effect that can be protected if drug is complexed with CD. This protection is probably due to the reduction of effective concentration of drugs in contact with the membrane [14].

Cyclodextrin in food industry:

Cyclodextrins have been used in food processes with a variety of objectives: (i) to protect lipophilic food components that are sensitive to oxygen and light or heat; (ii) to stabilize fragrances, flavors, vitamins, and essential oils against degradation; (iii) to suppress unpleasant tastes and odors (iv) to convert liquid food ingredient to solid powder; (v) to solubilize vitamins and food color; (vi) to control the release of certain food ingredients and to remove undesirable component; and (vii) to maintain food quality during storage by improved packaging technology.

There are various regulatory authorities that control the use of various cyclodextrins in terms of safety (GRAS, Generally Recognized as Safe), limit of addition, acceptable daily intake etc. These are: The Joint FAO/WHO Expert Committee on Food Additives (JECFA), USFDA (US Food and Drug Administration) and U.S. Environmental Protection agency (EPA). The maximum level of β-CDs recommended in foods is 5 mg/kg per day. For α-CD and γ-CDs no Acceptable Daily Intake (ADI) was mentioned owing to their toxicological profiles [45, 98].

Molecular encapsulation of flavor components within the cavity of cyclodextrin has been proven to be most effective method of stabilizing flavor in food item and thus it provides protection against heat and evaporation [45, 99, 100]. The taste and flavor of spray-dried powdered products are the most important quality factors. To prevent the loss of a hydrophobic flavor compound (*l*-menthol) during the drying of a droplet, Liu *et al.*, [101]

adopted complexation technique. They found β-cyclodextrin appeared to be a better host for menthol than α- and γ-CD. Flavors are generally volatile in nature which deteriorates readily and cyclodextrin form stable dry complexes with flavor and remain stable for longer periods without any further protection at room temperature. Fresh citrus juice is not bitter initially but turns bitter in the course of storage at a rate that depends on the pH and storage temperature. Therefore, CDs can be used for the removal or masking of undesirable components [45]. Bhandari *et al.*, [102] microencapsulated the lemon oil by kneading with β-CD, at a β-CD to lemon oil ratio of 88:12 (w/w) and the resulting paste samples of the complex were vacuum or spray-dried. They found the optimum mixing time was 15 min, at which time the maximum entrapment of lemon oil (97.7 mg/g of β-cyclodextrin) was obtained in the complex powder. When β-CD is mixed with molten butter, β-CD forms complexes with cholesterol but not with triglycerides, and β-CD complex is easily removed from the butter. More than 90% of the cholesterol can be removed in single step [103]. Cyclodextrins have been approved as 'modified starch' for food applications for more than two decades in Japan and γ-CD have been approved in one or two European countries, for example Hungary for use in certain applications because of its low toxicity [28]. Over the past decade, new packaging technologies have replaced the conventional forms of food and beverage packaging [104]. Another interesting application of cyclodextrins in food is the CD-containing food packaging materials. Use of cyclodextrin in packaging materials reduces residual organic volatile contaminants and improves its barrier properties. CDs or CD-complexed antimicrobial agents incorporated into food packaging materials effectively reduce the loss of the aroma substances and improve the microbial preservation during storage. Therefore CD complexes can be utilized as antiseptic or conserving agents, 0.1% iodine- β-CD inhibits putrefying for 2 months at 20°C in frozen sea-food or in fish paste products [105]. Thus packaging materials complexed with CD improve the sensory properties of food and maintains the food quality and safety [106]. Table 4 lists some marketed food products based on cyclodextrin.

Table 4: Examples of some marketed food products based on cyclodextrin [107]

Trade name	Type of food product	Role of CDs used	Country
Cyroma-line	Flavored sugar for baking	To preserve flavor on heating	Hungary
Natual	Low cholesterol cheese	To reduce cholesterol	France
Balade	Low cholesterol butter	To reduce cholesterol	Belgium
Simply eggs	Low cholesterol eggs	To reduce cholesterol	USA
Flavono	Chewing gum	To stabilize flavor	Japan
Stick lemon	Instant tea drink	To preserve flavor	Japan
Poder Tea	Instant green tea	For stabilization of color	Japan
FlavorAktiv Standard Kit	Beer flavor standards	To preserve flavor standards	Great Britain

Cyclodextrins in biotechnological field:

The applications of cyclodextrin in biotechnological field began only in the 1980s and the majority of biotechnology processes mean an enzyme-catalyzed transformation of a substrate in an aqueous medium. CDs and its derivatives enhance the solubility of complexed substrates in aqueous media, and reduce their toxicity without damaging the microbial cells or

the enzymes. Hence, the enzymatic conversion of lipophilic substrates can be intensified, the yield of the product-inhibited fermentation can be improved, organic toxic compounds are tolerated and metabolized by microbial cells at higher concentrations, and the compounds in small amounts can be isolated simply and more economically from complicated mixtures [103]. Kumar *et al.*, [108] investigated a novel one step microbial transformation process for the production of testosterone from cholesterol by *Lactobacillus bulgaricus* and found that biotransformation of cholesterol was significantly increased in presence of cyclodextrin in the fermentation medium. Prabhu and Ramadoss reported enhancement of rate of production of benzyl penicillin when both phenylacetic acid and 6-aminopenicillanic acid were complexed with beta-methyl-cyclodextrin (β-m-CD) and γ-CD respectively and condensed in presence of catalyst penicillin acylase (EC 3.5.1.11) [109]. Fernández *et al.*, [110] prepared chemically modified Bovine pancreatic trypsin by the mono-6-amino-6-deoxy derivatives of α-, β-, and γ-CD and they used 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide as a coupling agent. They found that the specific esterolytic activity and the affinity of trypsin for substrate were improved by the attachment of the cyclodextrin residues. Jarho *et al.*, [111] prepared the complexes of spironolactone with CDs and studied the effect of pH on the CD catalyzed deacetylation of spironolactone in the presence of modified-β-cyclodextrins and reported the increase in the rate of deacetylation of spironolactone by modified-β-cyclodextrins. In 1995, Schwartz and Bar reported that cyclodextrin enhanced the degradation of toluene and *p*-Toluic acid by *Pseudomonas putida*. Liquid toluene is highly toxic to *Pseudomonas putida* and this phase toxicity was removed when crystalline β-CD complexed-toluene was provided as the substrate. In presence of β-CD degradation of toluene vapors was enhanced hence reduced molecular toxicity and facilitated absorption of gaseous substrate [112].

Cyclodextrins in chemical industry:

Cyclodextrins and their derivatives in the chemical industry are used as catalysts to improve the selectivity of reactions, as reaction inhibitors, as well as for the purification and separation of industrial-scale products [57, 113]. Cyclodextrins are extensively used in separations due to their unique property to form inclusion complexes with other smaller hydrophobic molecules. Most of the derivatized and all non-derivatized cyclodextrins are soluble in water; they are often used in aqueous environments as solubilizers of lipophilic compounds via inclusion complex formation and this property makes them potentially useful agents for various types of separations [114]. CD has been extensively used as chiral selector for enantiomer separation and as an additive for improving the separation of some cyclic compounds. CDs tend to form inclusion complexes with certain compounds whose molecular size and structure match with the CD's cavities by hydrophobic interaction. Wang and Ren predict that there is a certain interaction with CD as the cyclic size of thymine is smaller than that of adenine and they explore the possibility of improving the separations of purines and pyrimidines by using β-CD as an additive [115]. Cyclodextrins are widely used in the separation of enantiomer by HPLC or GC (gas chromatography) and other applications can be found in spectroscopic analysis. In NMR studies, cyclodextrins can act as chiral shift agents and in circular dichroism as selective agents altering spectra [28].

Cyclodextrins in cosmetics, personal care and toiletries:

A large number of cosmetic components are nearly insoluble in water and all these chemical substances are able to form inclusion complexes with cyclodextrins and results more soluble compared to the pure compounds. In many personal care products triclosan acts as a topical antiseptic and disinfectant and it is nearly insoluble in water, moderately soluble in alkaline solutions, and quite soluble in organic solvents. The cyclodextrin complex of triclosan is soluble in water and gives a clear solution. Cyclodextrins can be used in deodorant sticks and the cyclodextrins are able to complex perspiration malodors [116]. Perfuming cosmetic products is an important part of meeting consumer requirements and the essential functions of fragrance materials are to provide a pleasant odor, to mask the bad smell of the product, and to give the product an identity. The amount of fragrance materials in the product rapidly decreases during storage because of their volatility and poor stability. In cosmetic preparations, CDs are mainly used (i) to increase the water solubility of lipophilic guests; (ii) to convert the liquid or oily guests to powder form; (iii) to increase the physical and chemical stability of guest molecules by protecting against decomposition, oxidation, hydrolysis, or loss by evaporation; (iv) to provide the controlled release of guest; (v) to minimize or prevent skin irritation; (vi) to prevent interactions between various formulation ingredients; (vii) to increase or decrease the absorption of various compounds into skin; (viii) to stabilize emulsions and suspensions; and (ix) to reduce or eliminate undesired odors [117]. In some cosmetic preparations, more than one benefit is obtained by complexation with cyclodextrin. Cyclodextrins used in silica-based toothpastes increase the availability of triclosan, an antimicrobial agent, by cyclodextrin complexation results almost threefold enhancement of triclosan availability [28]. Table 5 lists the applications of cyclodextrin in cosmetics and personal care items. Various methyl ether derivatives are proposed on the market: dimethyl and trimethyl CDs and particularly methylated and randomly methylated β-CDs. Glucosyl and maltosyl CDs are marketed and are highly water-soluble. Hydroxyethyl cyclodextrins are not easily available in the market. Finally, CD polymers with low molecular weights are water-soluble, whereas high-molecular-weight products are water-insoluble but capable of swelling [118].

Table 5: Application of cyclodextrin in cosmetics and personal care items [57]

Cosmetics and personal care items	Role of CDs used	Country
Powdered hair bleach	Stability	UK, Belgium, USA
Cold cream	Solubility	USA
Skin cleanser	Tocopherol carrier	Italy

Cyclodextrins are suitable for skin treatment products and for makeup cosmetics, which are more durable on the surface of the skin. The use of cyclodextrin can prevent the growth of microorganism and improve the antimicrobial efficacy of the talc powders [118]. A solution of iodine-β-cyclodextrin can be used as deodorant for the body, for bath etc. Most perfume concentrates (rose oil, citral, and citronellal), aromatic essential oils can be stabilized by complex formation with CD and can be used in solid preparations, such as powdered detergents, perfumed tablet that dissolve easily in bath water. In toothpaste preparation, the

inclusion of a fragrance in a cyclodextrin is worthwhile simply for better stability, but it can also be a good indicator of duration of tooth brushing. Fragrance compounds can be stabilized by cyclodextrin and coated with oils and incorporated into soap [118, 119].

Applications of CDs can be summarized as follows:

1. Enhancement of solubility of materials with low solubility in water;
2. Controlled release of drugs and flavors;
3. Catalytic action in chemical reaction;
4. Protection of materials against oxidation and UV-degradation during storage or processing;
5. Conversion of liquid materials to dry form;
6. Stabilization of flavors and spices;
7. Masking of bitterness and unpleasant odor of foods and drugs.

CONCLUSION

Cyclodextrins are a group of structurally related saccharides, truncated cone-shaped molecules with a hydrophilic outer surface and hydrophobic central cavity. Nontoxic nature of cyclodextrins makes them suitable for oral administrations. Developments of easy and cost-effective production of cyclodextrin are a great challenge to the biotechnologists. Encapsulation of a guest molecule by cyclodextrin may affect many of physicochemical properties of the guest molecule without affecting its intrinsic pharmacological activities. We have focused on several aspects of cyclodextrins: namely the techniques for CD complex formation, mechanism of guest release from CD-complex, analysis of CD-complexes, and the application of cyclodextrin in pharmaceutical, food, biotechnological, chemical, cosmetics, personal care, and toiletries.

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