

Inclusion complex formation of cyclodextrin with its guest and their applications

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Abstract

Cyclodextrin (CD) are cyclic oligosaccharides consisting of glucopyranosyl units linked by α -(1,4) bonds. The widely used natural cyclodextrins are α -, β - and γ -cyclodextrin consisting of 6, 7 and 8 glucopyranose units, respectively. The cyclodextrin molecules have a unique structure with a hydrophobic cavity and a hydrophilic surface which can form inclusion complex with a wide variety of guests. The use of cyclodextrins and their derivatives for the encapsulation of bioactive compounds can protect the compounds from environmental conditions and improve the aqueous solubility for increasing their capacity to functionalize the products. In some cases, there is a need to enhance water solubility of β -cyclodextrin by adding the hydroxyalkyl groups on the β -cyclodextrin surface. This review aimed to summarize the method for inclusion complex formation of cyclodextrin with its guests and its applications.

Cyclodextrin

Cyclodextrins (CD) (or cycloamyloses, cyclomaltooses and Scharinger dextrins) are cyclic oligosaccharides consisting of glucopyranosyl units linked by α -(1,4) bonds [1]. The widely used natural cyclodextrins are α -, β - and γ -cyclodextrin consisting of 6, 7 and 8 glucopyranose units, respectively. The main properties of those cyclodextrins are given in Table 1. The cyclodextrin molecules have a unique structure with a hydrophobic cavity and a hydrophilic surface in which a guest molecule can be entrapped. Cyclodextrin can form inclusion complex with a wide variety of solid, liquid and gaseous compounds. Complex formation is a dimensional, geometrically limited fit, between cyclodextrin cavity and the guest molecule [2].

Generally, hydrophobic molecules have greater affinity for the cyclodextrin cavity when they are in water solution. Moreover, the encapsulation changes the physical and chemical properties of the guests, such as solubility and stability. Therefore, cyclodextrins are suitable for application in food and flavors, pharmaceutical products, cosmetic, agriculture and chemical industries. Cyclodextrins can link specifically to other cyclodextrins (covalent or noncovalent). Because of this property, cyclodextrins can be used as building blocks for the construction of supramolecular complexes. Building blocks which cannot be prepared by common methods can be applied, such as separation of complex mixtures of molecules and enantiomers [3]. Cyclodextrins are produced by reacting gelatinized starch with the enzyme cyclodextrin glucosyltransferase (CGTase) as a result of intramolecular transglycosylation reaction from degradation of starch.

Inclusion complex formation

Cyclodextrins have an internal non-polar hole and hydroxyl groups placed on the surface, the inclusion of hydrophobic compounds takes place mainly by hydrophobic interactions between guest molecules and the walls of cyclodextrin cavity [5]. However, other forces, such as van der Waals and dipole-dipole interactions, may be involved in the binding of the guest. Despite the number of factors and different

forces involved in the complexation with cyclodextrins, the production of complexes is a rather simple process. There are several methods to obtain cyclodextrin-guest complexes depending on the properties of the guest and the nature of the chosen cyclodextrin.

Kneading method

Kneading technique is suitable for poorly water-soluble guests, because the guest is dissolved slowly during the formation of complex [6]. It affords a very good yield of inclusion formation but it is unsuitable for large scale preparation [7]. Firstly, the liquid or dissolved solid guest is added to slurry of cyclodextrin and kneaded (in a mortar), and then the paste is dried. The obtained solid is washed with a small amount of solvent to remove the free particles adsorbed on the cyclodextrin surface and then dried under vacuum. The inclusion complex formation of cyclodextrins by kneading method has been reported in the encapsulation of ibuprofen [8], omega-3 fatty acids in thymol essential oil [9], thyme essential oil [9] and European anchovy (*Engraulis encrasicolus* L.) oil [10].

Co-precipitation method

Co-precipitation technique is useful for non-water-soluble substances. Poor yields are obtained from this method because of the competitive inhibition from organic solvents used as the precipitant [11,12]. The guest is dissolved in organic solvents (such as chloroform, benzene and diethyl ether, etc), and appropriate amount of cyclodextrin dissolved in water is added with agitation. The solution is cooled and complex crystals occur. The crystals are washed with organic solvent

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and then dried at 50°C [11,13]. The co-precipitation technique has previously applied for encapsulation of drugs such as oxaprozin [14] and trans-anethole (major component of anise and fennel essential oils) [15].

Co-precipitation method based on phase solubility

In the co-precipitation technique, the solid inclusion complex could be recovered from the saturated aqueous solution. This technique is not for a system which has an A-type phase solubility diagram. And it is not suitable for large-scale preparations because of large quantities of water and time consuming. The amounts of host and guest used are estimated from the B_s-type phase-solubility diagrams (no more undissolved guest and cyclodextrin are still within its solubility limit). Cyclodextrin and guest are dissolved in hot water and cooled slowly. The precipitate inclusion powder is separated by filtration and it is then dried [12,13].

Heating in a sealed container

After adsorbing a definite amount of water vapor, a physical mixture of active compound and the host molecule is sealed in a container and heated to a temperature ranging from 43°C to 142°C to obtain a crystalline inclusion compound. This technique is also performed under nitrogen gas pressure and can be used for thermostable volatiles [16].

Freeze-drying or lyophilization

The freeze-drying technique is suitable for thermolabile or water soluble guests [11]. The required proportion of cyclodextrin and the guest molecule are dissolved in water with stirring. The solution is freeze-dried and the obtained powder is washed with organic solvent and then dried under vacuum [12,17]. This method can produce a very good yield of inclusion complex and it is possible to scale up [18]. Comparing with other available techniques, freeze-drying technique has been widely applied for cyclodextrin inclusion complex formation, especially water soluble hydroxypropyl-β-cyclodextrin. Several essential oils and their pure major active compounds have been encapsulated in hydroxypropyl-β-cyclodextrin. These include cinnamon and clove [19], estragole (major component of basil and tarragon essential oils) [20], black pepper essential oil [21], thymol and thyme essential oil [9], kamebakaurin (kaurane diterpene) [22], ITH12674 (multitarget drug) [23] and chloramphenicol [24].

Spray drying

Cyclodextrin and guest molecule are dissolved in deionized water and then the solution is dried by the spray-dryer. The spray-dryer is operated under the most appropriate conditions such as inlet temperature and sample feeding speed [17,25,26]; As temperatures of 50–70°C are used, this technique is only used for thermostable molecules. Recently, the spray-drying technique has been used for encapsulation of folic acid in cyclodextrin [27].

Inclusion complex confirmation

Inclusion complex formation can be confirmed by studying the interaction between a guest molecule and cyclodextrin using various techniques.

Visible and ultraviolet (UV) spectroscopy

Sometimes complex formation with cyclodextrin changes the original visible or ultraviolet absorption spectrum of the guest (a shift or band broadening). [28] used UV-vis spectrophotometer to

characterize the inclusion complex formation of β-caryophyllene with β-cyclodextrin. The samples were diluted in ethanol and the spectra of the physical mixture of β-cyclodextrin with β-caryophyllene and spectra of β-caryophyllene were identified with maximum absorption wavelength (λ_{max}) at 205 nm. β-cyclodextrin in ethanol had no UV absorption, and the absorption peak of the inclusion complex was not observed also.

Phase solubility

The persistence of an inclusion complex in aqueous solution does not guarantee the existence of the same complex in the crystalline state. Therefore, the powder derived from inclusion complexation must be determined whether it is an inclusion complex or just a physical mixture of the guest and cyclodextrin molecules [3]. The limited water soluble organic compounds frequently increase their water solubility in the presence of cyclodextrins because of the formation of water soluble complexes between the dissolved cyclodextrin and the guest molecule. The stability of the complex form is characterized by the stability (or equilibrium) constant, K_s , of the complex.

$$K_s = \frac{k_r}{k_d} = \frac{[\text{complex}]}{[\beta\text{-CD}][\text{guest}]} \quad (1)$$

where k_r ($M^{-1} s^{-1}$) is the recombination rate constant and k_d (s^{-1}) is the dissociation rate constant.

The greater K_s value the greater stability of the complex. In solution, the fundamental parameters for inclusion compound formation (such as stability constant, stoichiometry and thermodynamic parameters) can be accurately obtained and the equilibrium of complexes and free compounds can be managed by altering the environmental conditions (such as concentration, temperature, pH and polarity of the solvent), by addition of a competitive molecule, or by choosing the most suitable cyclodextrin or its derivative.

Higuchi and Connors [29] have established a classification of the complexes from the phase solubility profiles derived from the interaction between the guest and the host in the solution. A-type curves suggest the formation of soluble inclusion complexes. B-type indicates the formation of inclusion complexes with poor solubility. B_s-type reveals complexes of limited solubility and a B_i-type curve shows the formation of insoluble complexes. A-type curves are subdivided into A_i-type (linear enhances of guest solubility as a function of cyclodextrin concentration), A_p-type (positively deviating isotherms) and A_N-type (negatively deviating isotherms) subtypes.

K_s can be obtained from the linear portion of the phase solubility diagrams [29] by the Eq.2:

$$K_s = \frac{[\text{slope}]}{[\text{intercept}][1-\text{slope}]} \quad (2)$$

where *intercept* is the dissolved guest in the aqueous complexation medium when no ligand (cyclodextrin) is present.

Complexes with stability constants (K_s) about 100 - 5000 L/mol, seem to be suitable for practical applications. Weak interaction of the very labile complexes ($K_s < 100$) results in premature release of the guest and insignificant improvement in solubility. In cases of very high K_s ($K_s > 5000$), the complexes are very stable and the release of the guest from the cyclodextrin cavity is incomplete or obstructed. This property can be applied for modification of drug [6] or fragrances [30] release especially slow release control.

In some cases of small K_s values, complexation promotes finer

physicochemical, biopharmaceutical and pharmaco-technical properties of drugs or other guest molecules. For inclusion, complex formation in solution, the molar ratio of host to guest molecules is usually 1:1, except for complex formation with long-chain or bifunctional guest molecules (e.g. have two aromatic rings on opposite sides of a small central molecule segment).

As most flavor components are monoterpenoids and sesquiterpenoids and phenylpropane derivatives of an average molecular weight of 120–160, a 1:1 complex formation is observed [31]. But there are reports of complexes exhibiting other host: guest molar ratios, such as β -cyclodextrin: allyl isothiocyanate (1:2) [32] and β -cyclodextrin:(-)- α -bisabolol (2:1) [33].

Differential scanning calorimetry (DSC)

The inclusion complex can be confirmed using DSC indirectly by comparing the thermal stability of the free compound with the encapsulated form [8,34]. At the temperature of its melting point or boiling point, an endothermic peak can be observed for the compounds and the physical mixture but will be absent for the complex [19,35] used DSC technique to characterize the formation of inclusion complexes of β -cyclodextrin with essential oils from cinnamon and clove. The exothermic peaks at approximately 265°C and 260°C could be interpreted as resulting from the hydrolysis or oxidation of trans cinnamaldehyde and eugenol of cinnamon and clove oil, respectively [34]. The peaks of inclusion complex of the tested essential oils with β -cyclodextrin were not detected in the thermogram, indicating active compounds were protected within the cavity of the β -cyclodextrin. The exothermic peaks around 300°C for the β -cyclodextrin sample due to melting and thermal decomposition of the β -cyclodextrin itself [5]. Besides UV-vis spectra, Phase solubility study and Differential Scanning Calorimetry (DSC), there are other several techniques to characterize inclusion complex formation of cyclodextrin which are Infrared Spectroscopy [3], Vacuum Methods [33], X-ray Diffraction [36], Chromatography [37], Mass Spectrometry [3], Nuclear Magnetic Resonance Spectroscopy [38], Fluorescence Spectroscopy [39] and Optical Methods [40].

Cyclodextrin derivatives

Although β -cyclodextrin can be used in several fields and is fitted to many types of guest, its solubility in water is quite low. About 14 g α -cyclodextrin or 23 g γ -cyclodextrin can be dissolved in 100 mL water at 25°C, while only 1.8 g of β -cyclodextrin can be dissolved [3]. β -cyclodextrin has a low solubility in water because of intra-molecular and inter-molecular interaction via their hydroxyl group. To improve water solubility, the structure of β -cyclodextrin has been modified [41,42]. The OH groups on C₂, C₃ and C₆ are points for structural modification. The hydroxyl groups on C₆ are the most reactive while the OH groups at C₃ are much less reactive than those at C₂. By various molecular manipulations, cyclodextrins can be modified to derivatives with different physicochemical properties [43].

Cyclodextrin derivatives have been developed to extend the physicochemical properties and the inclusion capacity of original cyclodextrins. There are several kinds of cyclodextrin derivatives such as hydrophilic, hydrophobic and ionic derivatives. The hydrophilic cyclodextrins, such as methyl- β -cyclodextrin, 2,6-di-O-methyl- β -cyclodextrin and 2,3,6-per-O-methyl- β -cyclodextrin, alter the release rate of poorly water-soluble drugs, which can be used to enhance drug absorption across biological barriers [44]. On the other hand, the hydrophobic cyclodextrins are used as sustained-release carriers

for water-soluble drugs such as protein and peptide drugs. The amorphous hydrophilic cyclodextrins, such as hydroxyalkylated- β -cyclodextrin or hydroxypropyl- β -cyclodextrin, are useful for inhibiting polymorphic transitions and crystallization rates of poorly water-soluble drugs during storage, which can consequently maintain higher dissolution characteristics and oral bioavailability of the drugs [44]. A hydroxyalkylated β -CD derivative is relatively high aqueous solubility with low toxicity and satisfactory inclusion ability [45]. This modified β -cyclodextrin has higher water solubility (above 60g β -cyclodextrin in 100 mL water) and a proven safe profile.

Applications of cyclodextrins and cyclodextrin derivatives

Due to each guest molecule is individually surrounded by a cyclodextrin, the molecule is micro-encapsulated from a microscopical point of view leading to advantageous alter in the chemical and physical properties of the guest molecules. Encapsulation in cyclodextrins provides an intimate effect on the physicochemical properties of guest molecules as they are temporarily locked within the host cavity giving rise to beneficial modifications of guest molecules, which are not achievable otherwise [46]. The advantages of these characteristics are solubility improvement of highly insoluble guests, stabilization of labile guests against the degradative effects of environment (oxidation, light and heat), control of volatility and sublimation, physical isolation of incompatible compounds (via chromatography), taste modification by masking off flavours, odour elimination and controlling of drug and flavour release. Therefore, cyclodextrins can be used several fields as follows:

Application in foods and flavors

Cyclodextrins are used in food formulations for flavor protection throughout many rigorous food-processing methods of freezing, thawing and microwaving, and used for flavor preservation to a greater extent and longer period [47]. They also have been used for removal of cholesterol from animal products such as eggs and dairy products [48], removal of bitter components from citrus fruit juices [4], removal of phenolic compounds which cause enzymatic browning [49] and enhancement of flavor in alcoholic beverages such as whisky and beer [50]. Aqueous solubility and bitter taste of flavonoids and terpenoids, the plant components which are rich of antioxidant and antimicrobial properties, can be improved by cyclodextrin complexation [51].

Application in cosmetics personal care and toiletry

Cyclodextrins can be used for control release of fragrances from the inclusion compounds in perfumes, room fresheners or detergents [4] and used for odor control in diapers, menstrual products, paper towels [52] and washed items [53,54]. They also used in silica-based toothpastes to increase the availability of triclosan, an antimicrobial agent [55]. Cyclodextrins and their derivatives (such as hydroxypropyl β -CD) are used in sunscreen lotions to reduce the side effects of the formulation by limiting the interaction between the UV filter and the skin, and improve performance and shelf-life of self-tanning emulsions or creams.

Application in environment protection

Highly toxic substances can be removed from industrial effluent by inclusion complex formation. In the mother liquor of the insecticide trichlorfon, the uncrystallisable trichlorfon can be converted into a β -cyclodextrin complex and in a single treatment 90% of the toxic material is removed [3,48]. [56] have pointed out that inclusion of a guest

compound by cyclodextrin can prevent from hydrolytic degradation. The effect of inclusion complex formation on antimicrobial activity and antioxidant property of chlorogenic acid and its complex was also tested by [22]. No significant difference of antimicrobial activity against three bacteria; *Staphylococcus aureus*, *Bacillus subtilis* and *Escherichia coli*, was observed between chlorogenic acid and its complex. The 1, 1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activities of chlorogenic acid and its complex were not significant ($P > 0.05$). Both exhibited stronger DPPH radical scavenging activity than butylated hydroxytoluene (BHT) (positive control) when a concentration higher than 10 µg/ml was taken.

Antimicrobial activity of allyl isothiocyanate entrapped in α - and β -cyclodextrin was also evaluated by [57]. Allyl isothiocyanate entrapped in β -cyclodextrin exhibited the most antimicrobial effect, with minimum initial concentrations with fungistatic effect of 0.5-1 µL/L air and bacteriostatic concentrations of 25 and 50 mL/L for *E. coli* and *L. monocytogenes*, respectively. Allyl isothiocyanate entrapped in α -cyclodextrin also effectively inhibited *P. expansum* with a minimum initial concentration with fungistatic effect of 1 µL/L, while allyl isothiocyanate alone inhibited growth at 5 µL/L.

Application in pharmaceuticals

The addition of α - or β -cyclodextrin increases the water solubility of several poorly water-soluble substances to improve bioavailability and increase the pharmacological effect allowing a reduction in the dose of the drug administered [4]. Cyclodextrins also have been used successfully in aqueous dermal formulations, nasal drug delivery systems [58] and several eyedrop solutions [59,60]. Furthermore, they can be applied to reduce the effects of bitter or irritant tasting and bad smelling drugs [3,48,61,62]. Cyclodextrins have been used for controlled release of drugs such as ciprofloxacin [63], triclosan [64], vancomycin and chlorhexidine digluconate [65]. The low water soluble anticancer drug candidates, Pt(IV)-bis(benzoato), was also encapsulated in β -cyclodextrin to enhance water solubility [66]. Cyclodextrin have been applied for encapsulation of antimicrobial drugs such as chloramphenicol [24]. The inclusion complex formation with multicomponent of β -cyclodextrin and amino acid, glycine or cysteine, improved aqueous solubility and maintained microbiological activity of chloramphenicol and reduced the generation of reactive oxygen species (ROS) in leucocytes induced by this drug [24]. Physicochemical and biological properties of chloramphenicol were improved by multicomponent complexation with β -cyclodextrin and N-acetylcysteine preparing by freeze-drying or physical mixture methods. The system was effective to reduce toxicity of chloramphenicol against leukocytes while enhancing its solubility and antibiofilm activity [24].

The encapsulations of cyclodextrin-drug inclusion complexes in liposome, phospholipid vesicles composed of lipid bilayers enclosing one or more aqueous compartments, have recently been reviewed by [67]. Because of its ability to enhance aqueous solubility of hydrophobic drugs, cyclodextrin can be used to increase drug entrapment in the aqueous compartment of liposomes and liposomes can protect CD/drug inclusion complexes until drug release. Anethole (ANE) (trans-anethole), a major component of anise and fennel essential oils, was used as a model of a volatile and highly hydrophobic drug [67,68].

Application in entrapment of essential oils

Essential oils are natural plant products composing of mixtures of several compounds. Because of their active compounds, they have been

used for several fields since ancient time. The components of essential oils can be classified into two groups: (1) hydrocarbons including mono-, di-, and sesquiterpenes and (2) oxygenated compounds including alcohols, aldehydes, esters, ketones, phenols, etc. Besides, they also contain some phytochemicals which play efficient role in biological activities such as flavonoids, terpenoids, carotenoids, coumarins, curcumines, etc. [69,70]. Entrapment of essential oils with β -cyclodextrin has been applied to protect essential oils against the damaging effects of the environment such as oxidation, degradation from heat and light, evaporation, and moisture [5,19,48]. Several types of essential oils have been entrapped in β -cyclodextrin (Table 2).

Other applications

Cyclodextrins were found to form inclusion complex with several agricultural chemicals including herbicides, insecticides, fungicides, repellents, pheromones and growth regulators [4]. They can also be applied to delay germination of seed [3]. Cyclodextrins have also been applied encapsulation of phenolic compounds. The encapsulation of rosmarinic acid, an efficient phenolic antioxidant from rosemary with a marketing authorization, with β -cyclodextrin was also characterized by [76] using 1H NMR (1D- and 2D-ROESY). They also found that rosmarinic acid spontaneously formed a relatively stable inclusion complex with CD in water.

Recently, cyclodextrins were applied in the encapsulation of lipase for biodiesel production. For enzymatic biodiesel production, the methanol tolerant of lipase, a biocatalyst, is a critical parameter. The methanol resistance of *Yarrowia lipolytica* Lipase 2 (YLLIP2) was significantly improved after encapsulated in β -cyclodextrin which exhibited approximately 7000 U/mg specific activity in 30 wt% methanol for 60 min compared with no activity of the free enzyme under the same conditions. β -cyclodextrin molecules weakened the conformational change of the enzyme and maintained a semi-open state of the lid by overcoming the interference caused by methanol molecules [15].

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