Natural and Modified Cyclodextrins as Packaging Additives

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Cyclodextrins (CDs) have been used by the pharmaceutical and food industries since the 1970s. Their cavities allow the accommodation of several hydrophobic molecules, leading to the formation of inclusion complexes (ICs) increasing the guest molecules' stability, allowing their controlled release, enhancing their water solubility and biodisponibility.

polymers | food packaging | active packaging | cyclodextrins

1. Introduction

Discovered in 1891 from starch degradation by the action of the microorganism Bacillus amylobacter, cyclodextrins (CDs) were patented for the first time almost sixty years later as an important agent for obtaining drug inclusion complexes (ICs) [1]. However, it was only in the 1970s, when toxicological studies ensured their innocuousness, that their use by the pharmaceutical industry in fact began, being used to this day in the elaboration of drugs, cosmetics, and hygiene products [2]. CDs have become an essential ingredient for these areas as they act as carriers of substances of interest, promote the controlled release of drugs, and increase the water solubility of poorly soluble compounds, enhancing their biodisponibility [3][4][5].

Biotechnological advances that occurred between the 1970s and 1980s allowed the large-scale production of more purified CDs, increasing the interest in their use by sectors other than Pharmaceutical and Biomedical. In food-related areas, for example, their use was firstly authorized in the late 1970s, in Japan, in the production of spices, chocolates, teas, among other products. However, it was only in the early 2000s that the CDs entered the list of substances generally recognized as safe (GRAS) from the Food and Drug Administration (FDA), being recognized as a food additive [1][6]. Nowadays, enzymes involved in the formation of cyclodextrins from starch can be found in the market, as well as several types of cyclodextrins and their inclusion complexes for both pharmaceutics and food usage [7][8][9][10].

In addition to the aforementioned properties, CDs are also able to form complexes with a wide range of substances, from small molecules of low molecular weight to bigger compounds, depending on the type of CD used [11][12][13]. Besides, they can increase the stability of the guest molecules against external factors such as temperature, light, and oxygen [14][15]. Due to these, the CDs have come to be considered potential additives for packaging with active properties, especially when the active compound can be easily degraded or oxidized [16]. Since the production of packaging generally involves the use of high temperatures for polymers to melt, the use of

several active compounds becomes unfeasible due to their thermal instability, an obstacle that can be overcome when performing the complexation of these substances with CDs.

2. Natural and Modified Cyclodextrins

2.1. Structure, General Characteristic and Properties of Interest

CDs are cyclic molecules composed of glucose subunits linked through α-1,4-glycosidic bonds. Their classification is made according to the number of glucopyranoses units, being α-CD (6 units), β-CD (7 units), and γ-CD (8 units) the three native or "parent" CDs [17]. CDs containing 9 or more glucose units in their structure are also described in the literature and have been conventionally named large ring CDs [18]. The cyclic conformation and molecular arrangement of the hydroxyl groups give the CDs a toroidal shape, similar to a hollow cone, with an external face of polar nature due to the presence of hydroxyl groups, and a non-polar cavity, in which hydrophobic compounds can be accommodated [2].

One of the main characteristics of CDs of importance for application in food-related areas is their water solubility. Native CDs have a certain solubility in water, γ-CD being the most soluble of the three (249 $mg \cdot mL^{-1}$) and β-CD the least soluble (18.5 $mg \cdot mL^{-1}$) [19]. Such functionality allows, by forming ICs with nonpolar compounds, that the solubility of the guest molecule when compared to the pristine substance to be increased, consequently enhancing its bioavailability in the medium. In general, the formation of inclusion complexes with CDs also allows the controlled release of the compound of interest and protects unstable substances from external factors as well as from undesirable interactions that may occur in the environment, being an interesting alternative for the food packaging industry [14][19][20]. The main properties of the native CDs, as well as their commercial names, are briefly described in **Table 1**.

Table 1. Main properties of α-, β-, and γ-cyclodextrins.

Property	α-Cyclodextrin	β-Cyclodextrin	γ-Cyclodextrin
Commercial name on the Market	Cavamax® W6 [8], Trappsol® Native Alpha [10]	Cavamax® W7 [8], Kleptose® [9], Trappsol® Native Beta [10]	Cavamax® W8 [8], Trappsol® Native Gamma [10]
Functions on Markets products	Solubilizer, stabilizer, delivery of drugs [8][10]	Solubilizer, stabilizer, delivery of drugs and taste-masking agent [9][10]	Solubilizer, stabilizer, stabilization enhancer, delivery of drugs [8][10]
Number of glucose subunits	6	7	8

Property	α-Cyclodextrin	β-Cyclodextrin	γ-Cyclodextrin
Molar mass ($g \cdot mol^{-1}$)	972	1135	1297
External size (nm)	1.4–1.5 [19]	1.5–1.6 [19]	1.7–1.8 [19]
Internal diameter (nm)	0.47–0.52 [21]	0.60–0.80 [21]	0.75–1.00 [21]
Water solubility at 25 °C($mg \cdot mL^{-1}$)	145 [21]	18.5 [21]	232 [21]
Solubility in organic solvents	Insoluble in chloroform, isopropanol, acetone, ethanol, glycerin, methanol, and ethyl ether. Soluble in propylene glycol (10 $mg \cdot mL^{-1}$), dimethyl sulfoxide (20 $mg \cdot mL^{-1}$), and dimethylformamide (540 $mg \cdot mL^{-1}$) [21]	Insoluble in chloroform, isopropanol, acetone, ethanol, methanol, and ethyl ether. Soluble in dimethyl sulfoxide (350 $mg \cdot mL^{-1}$), ethylene glycol (210 $mg \cdot mL^{-1}$), dimethylformamide (320 $mg \cdot mL^{-1}$), and glycerin (43 $mg \cdot mL^{-1}$) [21]	Insoluble in chloroform and ethyl ether. Soluble (>1 $mg \cdot mL^{-1}$) in isopropanol, acetone, ethanol, and methanol [21]

2.2. α-CD

α-CDs are constituted of 6 subunits of d-glucopyranoses, being obtained enzymatically from starch and its derivatives, and, among the native CDs, they are the ones with the smallest internal diameter, ranging from 0.47 to 0.52 nm [22]. As functional properties, these molecules have moderate solubility in water (almost eight times greater than that presented by β-CDs, but less than γ-CDs), relative thermal stability, stability under extreme conditions of pH (alkaline and acidic solutions), and slightly pronounced sensory characteristics (imperceptible taste and odor) [23]. The molecule was granted GRAS status by the FDA in 2004 (GRN 000155), and in 2016, the agency waived the requirement for pre-marketing approval, provided it meets the maximum level of 3% (*w*/*w*) in processed foods and 1.05% in beverages [24].

Among the applications of α-CDs in the Food Industry, it is worth mentioning their role as an emulsifier agent, as a functional ingredient, and as a carrier and stabilizing agent for different molecules, such as hormones and flavorings [25][26][27]. Furthermore, its ability to act as a host for smaller bioactive components opens doors for its use in the development of active packaging. Besides, when we talk about sustainable packaging, the water solubility of α-CDs can be an advantage since several biopolymers investigated are dispersible in water [28][29][30][31]. In addition, the chemical structure of α-CDs makes their hydrolysis impossible by human saliva, as well as pancreatic amylases. Therefore, this characteristic gives a probiotic character to these substances and a possible application as dietary fibers [32].

2.3. β-CD

Among the three native types of CDs, β-CD is the most used and studied due its low cost when compared to the other two CDs, its good complexation efficiency, and the size of its cavity, which, in practice, allows a good accommodation of a large amount of molecules [14][19][33][34][35][36][37][38][39][40]. About 90% of the CDs produced and consumed are β-CDs [41]. In addition, the internal diameter of the β-CD's cavity makes it popular in the pharmaceutical industry since it is suitable for the inclusion of several substances with a molar mass between 200–800 $g \cdot mol^{-1}$ [22]. However, the β-CD low water solubility is a disadvantage and the reason why CD derivatives were developed with various substituents (methyl, carboxymethyl, hydroxypropyl, sulfobutyl, among others) [42]. Hydroxypropyl-β-CD and randomly methylated β-CD, for example, have water solubility greater than 600 $mg \cdot mL^{-1}$, a much more considerable value than the solubility of the native β-CD [2].

2.4. γ-CD

The last native CD to be discovered (1935), γ-CD consists of 8 subunits of glucopyranose, with a larger internal diameter among the three native molecules [22][43]. Due to its high solubility in water, γ-CD can be used as a solubilizing agent by carrying highly hydrophobic molecules [44][45]. Considering the pharmaceutical industry, several inclusion complexes γ-CD-based containing bioactive molecules tend to form aggregated structures in aqueous solutions, indicating potential activity as a drug-containing vehicle [44][46]. Other applications include the production of cosmetics (e.g., increased stability and solubility of components) [47]; chemical industry (e.g., separation of isomers, functional groups, homologous and enantiomers) [48]; textile industry (e.g., restoration of colors, good completion of cotton-based materials) [49]; and agriculture (e.g., immobilization of fragrances and repellents, reduction of the risk of contact with chemicals, increased effect of pesticides) [50].

2.5. Large Ring CDs

CDs composed of more than 8 units of glucopyranoses are known as large rings CDs and were first described in 1948. Compared to the other CDs, fewer studies have been conducted on this broad group of molecules [1]. In fact, some CDs can have more than 100 glucose units, which can be obtained through the use of specific enzymes or very specific conditions of temperature and incubation time [51]. The difficulties associated with their purification and very low yield are barriers to their use on a larger scale [52]. More recently, however, some works have been described in the literature seeking alternatives for the production and purification of large ring CDs, also aiming for their application by the chemical, pharmaceutical, and food industries [52].

2.6. Modified CDs

Although it has been discussed in the literature that the complexation with CDs can increase the guest compound solubility in water, the native CDs present limited solubilization in the solvent. β-CD, for example, the most affordable and the most suitable for the inclusion of substances due to its cavity volume, is also the least soluble of the three natives CDs, which is a disadvantage. In this regard, synthetic derivatives were developed from the substitution of hydroxyl groups in the structure of the original CD, conferring different properties and improving the molecule solubility in water, consequently, opening a wider range of applications [2][4][42][53].

The CDs' derivatives can be classified into three groups: anionic, cationic, and non-ionic, depending on the inserted group [54]. As an example of anionic derivatives, we can cite the sulfobutylether-β-CD and the per(6-carboxylate)-CD, which have potential in pharmaceutical research for controlled released and advanced targeted delivery of drugs [55]. 2-Hydroxypropyl-β-CD (HP-β-CD) is an example of a non-ionic structure largely studied both in pharmaceutical and food-related areas, and permethylated propylenediamine-β-CD is one of the synthesized cationic derivatives [54][56][57].

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