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Interactions between Bio-Based Compounds and Cyclodextrins

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Additional information is available at the end of the chapter

Abstract

Bio-based compounds, such as "green" surfactants and phytochemicals, are regarded as future sustainable resources for a vast range of applications in a modern society increasingly demanding economical, social, and environmental awareness. Natural compounds from plants (phytochemicals) are very sought by the pharmaceutical, cosmetic, and food industries. On the other hand, the growing interest in "green" surfactants (e.g., carbohydrate-based) is due to, inter alia, their preparation from renewable raw materials, ready biodegradability, and biocompatibility, among other reasons of fundamental, practical, economical, and environmental orders. Despite the wide range of potential applications of these bio-based compounds, their practical use is still limited due to many reasons such as poor aqueous solubility, volatility, reactivity, etc. Generally, when complexed with cyclodextrins, these bio-based compounds enhance considerably their performance and potential applications. Thus, this chapter aims at recalling some general fundamental aspects of phytochemicals and "green" surfactants, such as structure, function, and applications. In addition, their interactions with cyclodextrins are discussed from a physicochemical point of view with special focus on the techniques, mathematic modeling, and thermodynamic parameters (e.g., interactions, stoichiometries, association constants, etc.).

Keywords: sugar-based surfactants, phytochemicals, essential oils, polyphenols, cyclodextrins, host-guest complex

1. Cyclodextrins: general considerations

Due to its structure, cyclodextrins (CDs) readily form inclusion complexes through noncovalent interactions with molecular guests. The lipophilic cavity of CDs provides a microenvironment into which appropriately sized nonpolar moieties can enter. The hydrophobicity of the cavity enables the accommodation of a broad range of hydrophobic guests such as the alkyl chains of surfactants or different phytochemicals [1]. The hydrophilic exterior usually imparts CDs and their complexes, considerable solubility in water. The charge and polarity of the guest molecule play also an important role in the CD-substrate host-guest interaction [2]. However, this aspect is obviously less important than the geometric fitting. In the case of the charge, the complexation of neutral molecules is easier than the ionized counterpart. In general, molecules can be encapsulated by CDs when they are less hydrophilic or less polar than the solvent and when the formed complex is stable.

The main driving force for the formation of the complex is the release of enthalpy-rich water molecules from the cavity; water molecules are displaced by more hydrophobic guest molecules present in the solution to achieve the apolar-apolar interactions and decrease of CD ring strain resulting in a favorable lower energy state. The beneficial modification of guest molecular properties after the formation of the inclusion complex leads to a large number of applications in areas as diverse as encapsulation of active substances (i.e., flavoring agents, metallic cations, fragrances, and pesticides), enzymatic synthesis, catalysis, and energy transfer studies [3, 4]. Additionally, CDs also find important uses in cosmetics, environment protection, bioconversion, packing, textiles, and food domain [1, 5].

Less than 10% of all produced CDs and CD derivatives are used by the pharmaceutical industry. The largest CD users are the food and the cosmetic industry. CDs have a high level of biocompatibility, are absorbed in the gastrointestinal tract, and are completely metabolized by the colon microflora [6]. Some of them are approved by the Food and Drug Administration or have been accredited as being "generally recognized as safe" (GRAS) [7]. In the cosmetic area, CD performance stands out in the following: solubilize and stabilize specific sensitive components, stabilize emulsions, improve the absorption of active components onto the skin, reduce or eliminate bad aromas from certain components, and reduce the loss of the active components through volatilization, rapid oxidation, destruction by light, etc. [8].

2. Plant phytochemicals: brief introduction to polyphenols and essential oils

Plants are a remarkable source of biologically active compounds with potential applications in cosmetic, pharmaceutical, and food industries. Among the bioactive compounds synthesized as secondary metabolites by plants, phenolic compounds are probably the most relevant ones. Physiologically, they play a vital role in plant protection and contribute to plant odors, plant pigmentation, and/or their flavors. Structurally, phenolic compounds have, at least, one aromatic ring, with one or more hydroxyl groups attached [9]. The great diversity of phenolic

compounds present in nature (i.e., more than 8000 different structures have been identified up to now) results from variations in the basic chemical skeleton (e.g., degree of oxidation, hydroxylation, methylation, glycosylation, and conjugation with further molecules, particularly lipids, proteins, other phenolics, and biomolecular metabolites) [9]. Phenolic compounds are grouped by the number of phenol rings they contain and the structural elements that bind these rings to another; flavonoids, phenolic acids, tannins, stilbenes, and lignans are examples of important representatives of these groups [10].

On the other hand, plant essential oils (EOs) are mixtures of numerous highly complex volatile compounds (hydrogenated and oxygenated monoterpenes, sesquiterpenes, phenols, simple alcohols, ketones, coumarins, etc.) present in variable concentrations whose aroma depends on the individual constituents present [11]. Due to their natural properties, EOs have been used as therapeutic remedies and flavoring agents since ancient times. In the last decades, many investigations showed that EOs have a wide range of valuable biological activities, such as antimicrobial, herbicidal, insecticidal, antioxidant, etc.

Although many investigations demonstrated the broad range of biological activities of many phytochemicals, they still have restricted applicability as pharmaceuticals or in food products due to their poor water insolubility and bioavailability, high volatility, rapid oxidation, or degradation when exposed to environmental factors. New approaches have been developed to overcome these drawbacks, and among them, CDs have been suggested as excellent vehicles for the protection of phytochemicals for food and drug delivery proposes [12–14].

2.1. Interaction between phytochemicals and cyclodextrins

According to a recent review by Suvarna et al., there are many phytochemicals whose solubility, bioavailability, or therapeutic activity is significantly improved by complexation with CDs (e.g., quercetin, curcumin, artemisinin, resveratrol, naringenin, etc.) [12]. The methods used for the formation of inclusion complexes between CDs and bioactive compounds are essentially neutralization, slurry, solution, coprecipitation, kneading, and grinding [15].

The encapsulation of phytochemicals with CDs usually involves the formation of 1:1 inclusion complexes with the most versatile CD, the β-CDs, and its derivatives. These derivatives can be classified according to their interaction with the water molecules in hydrophilic, hydrophobic, and ionizable derivatives [13]. Examples of used hydrophilic β-CDs are the methylated β-CDs—2,6-dimethyl-β-CD (DM-β-CD) and 2,3,6-trimethyl-β-CD (TM-β-CD)—the hydroxyalkylated β-CDs such as 2-hydroxypropyl-β-CD (HP-β-CD), and the branched β-CDs, glycosyl-β-CD (G-β-CD). These molecules are suitable for the formation of host-guest inclusion complexes with poor water-soluble compounds. On the other hand, the hydrophobic derivatives, such as the alkylated β-CD 2,6-diethyl-β-CD (DE-β-CD), are used to decrease and modulate the released rate of water-soluble molecules. Finally, the ionizable β-CD can enhance the dissolution rate and the inclusion capacity and even decrease the side effects of some molecules [16, 17]. Among the ionizable CDs, O-carboxymethyl-β-CD (CM-β-CD), O-carboxymethyl-O-ethyl-β-CD (CME-β-CD), and sulfate and sulfobutylether-β-CD (SBE-β-CD) should be highlighted.

Owing to their potential health promotion effects particularly the antioxidant, anti-inflammatory, and antimicrobial properties, one of the actual promising applications of phenolic compounds is their use in the food industry as additives, e.g., in the development of functional foods. Nevertheless, the efficacy of these natural compounds is dependent on the preservation or improvement of their stability, bioactivity, and bioavailability [18]. Inclusion complexation with CDs improves water solubility of phenolics and enhances their shelf life and biological activity [15]. Additionally, it has been shown that the inclusion of phenolic compounds (e.g., hydroxycinnamic and chlorogenic acids) with CD (β-CD) strongly limited their interactions with proteins, which is important regarding the use of phenolics as food additives [19, 20]. Note that the interactions of these compounds with proteins, frequently added to functional foods to improve nutritional value and proper texture characteristics, often decrease the bioavailability of both proteins and phenolics [21].

There are many examples showing that the complexation of β-CD, or some of its derivatives, increases the biological activity of phenolics. For instance, Shao et al. observed that the complexation of chlorogenic acid (CGA) with CDs (β-CD and HP-β-CD) improved its antioxidant activity [22]. Moreover, the addition of CGA-CD complexes to grape juice reduced the degradation of anthocyanins due to copigmentation effect with the CGA/HP-β-CD complex showing the superior activity and copigmentation effects. Gabaldon et al. also used HP-β-CD to increase the aqueous solubility of kaempferol, quercetin, and myricetin and to improve their antioxidant activity due to the protection toward free radical attack [23]. The complexation of curcumin with an ionizable β-CD (SBE-β-CD) enhanced its water solubility and, thus, improved the *in vitro* cytotoxic (on HepG-2 cells) and antioxidant activity of these compounds [24]. This β-CD derivative and the HP-β-CD are the most used derivatives on the pharmaceutical industry due to their low toxicity and high solubility [16, 25, 26].

EOs can be regarded as mixtures of phytochemicals, and there are several studies reporting the complexation of EOs or their components with CDs mainly to overcome problems related with EO water insolubility, high volatility, rapid oxidation, heat damage, and degradation on exposure to air [14]. Although many studies focus the complexation of EO components with β-CDs or its derivatives, e.g., eugenol/HP-β-CD [27] and linalool/HP-β-CD [28], it has been observed that sometimes γ-CD is a better complexing agent. Ciobanu et al. showed that menthol, menthone, and pulegone are capable to form stable 1:1 inclusion complexes with β-CD, but eucalyptol forms a more stable inclusion complex with γ-CD due to the size of its cavity [29]. Polymeric CDs, which can be synthesized using cross-linking agents such as epichlorohydrin, also revealed promising results in some specific cases but are not matter of discussion in this chapter [29].

The inclusion complexes of EOs (or their components) with CDs have been mainly tested for food and pharmaceutical applications, but they could be an efficient tool to improve the use of EOs in aromatherapy, cosmetic, and household cleaning products. An interesting application of EOs is related to their incorporation in food packaging systems or edible films due to their antimicrobial, antioxidant, and insect repellent capacity. However, this is often limited due to flavoring and organoleptic considerations. CD inclusion complexes could overcome these limitations allowing EOs to reach effective concentrations in the food matrices without exceeding

organoleptically acceptable levels and even providing controlled release-rate kinetics. Recent studies encourage the use of CD-EO (e.g., β-CD/*Satureja montana* EO; γ-CD inclusion complex encapsulated electrospun zein nanofibrous webs/thymol) complexes as part of active packaging systems [30, 31] as well as promising candidates to be used as safe and effective antimicrobial agents (β-CD/eugenol) to control postharvest diseases in fruits [27].

There are scientific evidences that inclusion complexation with CDs improves the pharmacological effects of EOs or their components [28, 32, 33]. For instance, the complexation of *Hyptis pectinata* L. EO with β-CD improved its analgesic effect in a mice model [34]. Also Bomfim et al. observed that β-CD complexation increased *in vivo* tumor growth inhibition capacity of *Annona vepretorum* EO [32]. Recently, Lima et al. reviewed the preclinical and clinical studies published on complexes between CDs and terpenes [33]. These are the major components of EOs that exhibit a wide range of biological activities on the human body. Their survey shows that there is robust experimental evidence that CDs improve the oral absorption and pharmacological properties of terpenes. Nevertheless, more pharmacokinetic and clinical studies are required before they can be effectively used in clinical targets.

3. Natural surfactants: brief introduction to sugar-based amphiphiles

Despite the production of surfactants based on fats, oils, and carbohydrates, being a known area for several decades, on an industrial scale, this is a relatively new issue [35]. These amphiphilic molecules that have one of the main building blocks from a natural source are often called "natural surfactants" [36, 37]. For example, alkyl glycosides which are synthesized from a "natural" sugar unit and a "nonnatural" fatty alcohol are often regarded as natural surfactants. Considering their amphiphilic nature, it has been always a challenge to attach a carbohydrate molecule, such as the hydrophilic group (due to the numerous hydroxyl groups) to a fat and oil derivative, such as a fatty acid or a fatty alcohol. However, nowadays, several successful synthesis routes are well established, and numerous types of natural surfactants are known and available, even on a commercial scale [38]. Nowadays, carbohydrate-based surfactants (CBS) are among the most important classes of amphiphilic compounds [39–41]. Their structure results from the combination of sugar and lipids, naturally biosynthesized within living cells or, alternatively, synthetically prepared by sequential reactions using carbohydrate and fatty materials. The growing interest in such compounds is due to, inter alia, their preparation from renewable raw materials, biodegradability, mildness to the skin, and biocompatibility, among other reasons [42, 43]. In particular, CBS can be relatively easily prepared from the most abundant renewable vegetable raw materials (e.g., cellulose, pectin, hemicellulose, starch, etc.) in a wide range of structures and geometries by modular synthesis thanks to the presence of numerous reactive hydroxyl groups. Such structural diversity makes CBS excellent models to get insight on the surfactant mechanisms in modifying interfacial properties. This knowledge is crucial for the control of the formation and stability of diverse colloidal systems such as micelles, vesicles, foams, and emulsions [44]. An important structural feature of these surfactants is the typical sugar headgroup, a voluminous and relatively rigid moiety that can be functionalized by a myriad of reagents and synthetic schemes. Numerous properties and

functionalities can be expected from such almost unlimited number of different compounds that can find specific applications in different industrial areas [45, 46]. CBS also present great advantages on the environmental side; their higher biodegradability and lower toxicity profile are important reasons to consider CBS as valid alternatives to the more common petrochemical-based surfactants.

3.1. Case study: alkyl polyglycosides

In recent years there has been a growing focus on three classes of surfactants with sugar or a polyol derivative as polar headgroup: alkyl polyglycosides (APGs), alkyl glucamides, and sugar esters. In this chapter, we will focus on APGs, which are regarded as "perfect amphiphilic structures" with excellent surface activity as well as solubility. APGs have been synthesized, for the first time, more than 100 years ago [47]. APGs are completely based on renewable resources and combine very good performance, multifunctionality, and competitive price with mildness. This explains why APGs are the most successful sugar-based surfactants nowadays. It is important to mention that not pure alkyl monoglucosides but rather a complex mixture of alkyl mono-, di-, tri-, and oligoglycosides is produced in the industrial processes. Because of this, the industrial products are called alkyl polyglycosides. The surfactants are thus characterized by the length of the alkyl chain and the average number of glucose units linked to it, the degree of polymerization (DP). Alkyl glycosides are stable at high pH and sensitive to low pH where they hydrolyze to sugar and fatty alcohol. The sugar unit is more water-soluble and less soluble in hydrocarbons than the corresponding polyoxyethylene unit; hence, APGs and other polyol-based surfactants are more lipophobic than their polyoxyethylene-based surfactant counterparts [48]. This makes the physicochemical behavior of APG surfactants in oil/water systems distinct from that of conventional nonionic surfactants. Moreover, APGs do not show the pronounced inverse solubility vs. temperature relationship that normal nonionics do [49]. This makes an important difference in solution behavior between APGs and polyoxyethylene-based surfactants. The critical micelle concentration (cmc) values of the pure alkyl monoglycosides and the technical APG are comparable with those of typical nonionic surfactants and decrease distinctly with increasing alkyl chain length. The alkyl chain length has a far stronger influence on the cmc than the number of glycoside groups of the APG. The influence of the DP of APGs on their phase behavior has been described by Fukuda et al. [50]. The region in which the liquid crystalline phases occur is only slightly dependent on the concentration with a greater expansion in the case of APGs with a higher DP.

Regarding their applications, APGs are mainly used in personal care products such as cosmetics, manual dishwashing, and detergents [51]. APGs have also been used in more advanced applications such as the extraction and purification of membrane proteins, which plays a major role in the determination of protein structures and functions [52]. This is because APGs have reduced protein-denaturing properties in comparison to conventional surfactants. Generally, the environmental fate of surfactants is inextricably linked with their biodegradation behavior. Thus, fast and complete biodegradability is the most important requirement for an environmentally compatible surfactant. The general environmental impact of chemicals lies mainly in their ecotoxicity, which is relatively high in the case of surfactants because of their

surface activity and the resulting effects on biological membranes [47]. In the case of CBS (APGs in particular), they present a quite favorable environmental profile: the rate of biodegradation is usually high, and the aquatic toxicity is low. In addition, APGs exhibit favorable dermatological properties, being very mild when exposed to the skin and eye [53]. The interested reader can find excellent overviews on APGs elsewhere [45–47, 51, 54].

3.2. Interaction between alkyl polyglycosides and cyclodextrins

Saenger and Mullerfahrnow [55] and Casu et al. [56] were pioneers in the study of the interactions between APGs and CDs. By surface tension measurements, it was shown that the addition of CDs leads to an increase of surfactant critical micelle concentration. Furthermore, the interaction is most pronounced when the CD cavity and hydrophobic part of the surfactant exhibit the tightest fit. Such a view was also supported by ^{1}H and ^{13}C NMR spectroscopy. By the analysis of NMR chemical shifts of octyl- (C_8G_1) and dodecyl ($C_{12}G_1$) α- and β-D-glucopyranoside and octadecyl β-D-glucopyranoside ($C_{18}G_1$), in the absence and presence of α-CD, two main conclusions were taken: the presence of α-CD only affects the chemical shifts of the surfactant alkyl chain, and the chemical shift of the protons H-3 and H-5, located inside the CD cavity, increases by increasing the length of the alkyl chain [57]. Furthermore, it was observed that no chemical shift is observed for γ-CD/$C_{12}G_1$ mixed systems. These conclusions corroborate previous and subsequent studies, showing that the CD cavity is protruded just by the surfactant tail and the magnitude of the interaction is dependent on the relationship between the volumes of the CD cavity and the surfactant hydrocarbon chain [56, 58]. A better characterization of these complexes was accomplished by the quantification of the binding process. The effect of the length of the alkyl chain and surfactant head group on the association constant of APGs with different CDs was studied by ^{1}H NMR spectroscopy, NMR self-diffusion, and surface tension (**Table 1**) [58–60]. Although the comparison between association constants computed on the basis of different physical parameters is a difficult task [5], the analysis of the data allowed concluding that by increasing the alkyl chain length and decreasing the CD cavity volume (from β- to α-CD), the association constant increases. Furthermore, some authors stated that no interactions were observed when γ-CD was used [59, 58]. It is also worth noticing that for all mentioned systems, by subtracting the critical aggregation concentration (cac) of the surfactants from the CD concentration, the critical micelle concentration

	α-CD	β-CD	Obs.
β-C_8G_1	3.68 ($\pm$1.6) $\times 10^3$	0.99 ($\pm$0.17) $\times 10^3$	Self-diffusion NMR [58]
	1.85 ($\pm$0.35) $\times 10^3$		Surface tension [60]
β-C_9G_1	76 ($\pm$750) $\times 10^3$	275 ($\pm$5300) $\times 10^3$	Self-diffusion NMR [58]
β-$C_{10}G_1$		340 $\pm$ 30	[CD] = 1 mM, ^{1}H NMR [59]
β-$C_{12}G_1$		440 $\pm$ 40	[CD] = 2 mM, ^{1}H NMR [59]
		410 $\pm$ 40	[CD] = 1 mM, ^{1}H NMR [59]
β-$C_{12}G_2$		125 $\pm$ 10	[CD] = 1 mM, ^{1}H NMR [59]

Table 1. Binding constants, $K_{1,1}$ in dm^3 mol^{-1}, for the inclusion complexes CD/APG.

value is obtained. This clearly suggests a 1:1 APG/CD complexation [4], and actually it finds support by the Job's plot [61] reported by Bernat et al. [60]. Another important issue is to understand the reliability of the binding constants reported in **Table 1**. Rymdén et al. found that an increase of a methylene group for a series of alcohols decreases the standard free energy of the alcohol: β-CD binding for ca. 3.0 kJ/mol [62]. This variation is similar to that observed for $K_{1,1}$ values obtained by self-diffusion coefficients (**Table 1**). On the other hand, comparing $K_{1,1}$ values for C_8G_1 with those from other monoalkyl surfactants, one can conclude that the APG/CD complex is more stable [63, 64]. This has been justified by the occurrence of hydrogen bonds between the sugar structure and the hydroxyl groups located at the rim of the CD. However, studying the effect of the number of sugar moieties in the surfactant head on the free energy of binding, an algebraic increase in the Gibbs free energy is observed. Indeed, comparing the binding constants for the interactions between β-$C_{12}G_1$ and β-$C_{12}G_2$ with β-CD, it is possible to conclude that the addition of an extra sugar moiety in the surfactant head decreases the K values for the supramolecular association. Thus, it can be hypothesized that no significant sugar-sugar interactions are involved in the interaction with CD, as it was previously discussed. Another hypothesis arises from the effect of carbohydrates on the water structure, for example, Ribeiro et al. have found that the presence of carbohydrates leads to an increase of the entropy in water [65], also called a structure "breaking effect" [66]. Consequently, an increase of the concentration of the sugar molecules in solution may contributes for a decrease in the binding entropy change and, consequently, to an increase in the binding Gibbs free energy.

Up to now, we have been discussing the binding process assuming a 1:1 APG/CD (α- and β-) binding stoichiometry. However, it should be stressed that from the study of the interactions between $C_{12}G_1$, and $C_{18}G_1$, and CDs, there are strong evidences for the occurrence of other species consistent with 1:2 complexes [56]. More recently, Haller and Kaatze, studying the interaction between C_8G_1 and α-CD by ultrasonic attenuation spectroscopy, concluded that besides 1:1 (APG/CD) complexes, the formation of 1:2 and 2:1 complexes (although in very low concentration) should not be ruled out [67].

4. On the methods to follow the interactions between cyclodextrins and phytochemicals and sugar-based surfactants

As it must have already been understood from the previous subsections, an accurate choice of the technique to follow the host-guest association is a key issue for a reliable thermodynamic and kinetic characterization of the association process. In general, the experimental techniques can be subdivided into two different categories, labeled as I and II [68]. Methods from group I (e.g., surface tension) are measuring changes in physical properties that are proportional, in some ways, to the extent of binding, while those from group II (e.g., ^{1}H NMR spectroscopy) rely on direct measurements of the free and bound ligand in a solution containing a known amount of the CD and guest molecule. Comments on such a division can be found in a couple of reviews (see, e.g., [69]), and it is outside of the scope of this chapter. The same is valid for computational techniques as relevant tools to infer on the structure of the supramolecular compounds [70–72].

In this section, the most relevant techniques used to study the interactions between CDs and sugar-based surfactants (e.g., APGs) and phytochemicals (e.g., polyphenols, EOs, and their components) will be highlighted (**Table 2**).

NMR spectrometry falls in the group II techniques, and it is used to determine association constants through the chemical shift changes noticed either by the guest or by the CD [73–75]. Focusing on EOs, and as previously discussed, they may present undesired features, such as volatility, poor aqueous solubility, and stability. Therefore, host-guest supramolecular complexes are often obtained by using solid-state-based methods [14] such as freeze-drying [76, 77], coprecipitation [78], and the saturated approach [27], improving the solubility of the EO and thus allowing the use of NMR techniques for the quantitative and qualitative assessment of the complexation process [74]. For example, the complexation of eugenol with β-CD was obtained by using the saturation method, and the obtained complex, in the solid state, was characterized by either ^{1}H, ^{13}C, or 2D NMR techniques, confirming the thread of CD's cavity by the aromatic ring of the eugenol [27]. Other techniques will be mentioned later since they fall on the so-called group II.

DOSY ^{1}H NMR has been used to study inclusion complexes between CD and different sugar-based substrates [79]. Kfoury et al. report a comprehensive study on the complexation between two phenol isomers (thymol and carvacrol) and CDs by using different NMR techniques, including DOSY [80]. The data allowed concluding that those isomers have a binding constant of 1344 M^{-1} and 1336 M^{-1}, respectively.

The self-diffusion measurements are, in principle, applicable to any systems as long as the free and complexed guests are soluble to an extent that allows for a good signal-to-noise ratio. It is important to note that on account of the rapid exchange on the NMR time scale, average diffusion coefficients for both the guest and for the CD are typically obtained. This method, as well as that involving chemical shift changes analysis, is also limited to systems where no overlapping of well-defined resonances is observed. The method relies on the fact that the self-diffusion coefficients of the uncomplexed guest are higher than the self-diffusion of the host-guest complex, as defined by the Stokes-Einstein equation. The change in the self-diffusion coefficient of the CD upon complexation is often small since the complex is often of the same size as the CD molecule, and thus the information from the CD self-diffusion is rather limited [58].

Ultrasonic relaxation technique falls into group II techniques and is based on the application of ultrasound to a given solution, with a frequency ranging from 20 kHz to several GHz, and subsequently measuring the molecular structural relaxation. The relaxation is sensitive to molecular volume changes [81], and thus, it may convey information on the stability constants of the host-guest complexes [82]. Furthermore, the use of a large frequency range allows to follow processes with relaxation times in the range from 20 ps to 20 μs [83], and thus the kinetics of the CD-surfactant association can be investigated. Haller and Kaatze, by using ultrasonic attenuation spectroscopy, were able to quantify the dynamics of unimer-micelle exchange of a sugar-based surfactant (i.e., octyl-β-D-glucopyranoside (C_8G_1)) in the presence of α-CD [67].

Also from group II, surface tension has also been used to follow the effect of CDs on the aggregation and interfacial properties of surfactants in CD-surfactant-containing solutions

Experimental methods	System	Obs.
NMR	Nerolidol + β-CD	[74]
UV-vis	Nerolidol + CDs[1]	[74]
Phase solubility studies	Cabreuva essential oil + HP-β-CD	[74]
Phase solubility studies	β-caryophyllene + HP-β-CD	[76]
UV-vis	Black pepper essential oil + HP-β-CD	[76]
Phase solubility studies	CDs[1] + PPs[2]	[77]
Phase solubility studies, NMR, TGA, DSC	β-CD + estragole	[78]
NMR	β-CD + eugenol	[27]
NMR	β-CD + rosmarinic acid	[75]
NMR	Cyclohexylacetic acid + β-CD	[79]
NMR	Cholic acid + β-CD	[79]
UV-vis, NMR	Thymol and carvacrol + CDs[1]	[80]
NMR	n-Octyl-β-D-glucoside and n-nonyl-β-D-glucoside + α-CD and β-CD	[58]
UAS[3]	Octyl-β-D-glucopyranoside + α-CD	[67]
Surface tension, NMR	APGs[4] + β-CD	[59]
Surface tension	Octyl-β-D-glucopyranoside + α-CD	[60]
Phase solubility studies, ITC, NMR	Nootkatone + β-CD and HP-β-CD	[71]
TGA	Cinnamon essential oil + β-CD	[90]
NMR, FTIR, release kinetics	Monochlorotriazinyl β-CD + EOs[5]	[91]
XRD, NMR, TGA	Thymol + γ-CD	[30]
DSC, TGA, FTIR, XRD, GC/MS, NMR	Isopulegol + α-CD and β-CD	[72]
Phase solubility studies, NMR, HPLC	Polymethoxyflavones + HP-β-CD	[93]
GC, total organic carbon, phase-solubility studies	SBE-β-CD, SBE-γ-CD and HP-β-CD + EOS[6]	[94, 95]

[1]CDs: alpha-cyclodextrin (α-CD), beta-cyclodextrin (β-CD), gamma-cyclodextrin (γ-CD), 2-hydroxypropyl-β-cyclodextrin (HP-β-CD), randomly methylated-beta-cyclodextrins (RAMEB), low methylated beta-cyclodextrin (CRYSMEB), and sulfobutylether β-cyclodextrin (SBE-β-CD)
[2]PPs: *trans*-anethole, estragole, eugenol, isoeugenol (phenylpropenes), caffeic acid, *p*-coumaric acid, and ferulic acid (hydroxycinnamic acids)
[3]UAS: ultrasonic attenuation spectroscopy
[4]APGs: glucopyranosides (octyl G8, decyl G10, dodecyl G12, tetradecyl G14) and two maltosides (decyl M10, dodecyl M12)
[5]EOs: essential oils of cedarwood, clove, eucalyptus, and peppermint
[6]EOS: essential oils of *Artemisia dracunculus*, *Citrus reticulata Blanco*, *Citrus aurantifolia*, *Melaleuca alternifolia*, *Melaleuca quinquenervia*, and *Rosmarinus officinalis cineoliferum*

Table 2. Compilation of the most relevant techniques used to study the interactions between CDs and bio-based compounds.

[59, 60]. Surface tension is a measure of cohesive forces between liquid molecules present at the surface, and it represents the quantification of force per unit length of free energy per unit area [84]. In general, the presence of CDs will increase the surface tension of an APG solution. Knowing that natural CDs are not surface-active, they cannot replace APG at the air interface [85]. Therefore, CD molecules contribute for the depletion of APG unimers from the interface due to the great interaction between these unimers and CDs. There are several examples where surface tension measurements have been used to assess the stoichiometry and stability constants of host-guest complexes [60, 86].

Isothermal titration calorimetry (ITC) is a sensitive and powerful technique to study host-guest interactions by measuring the enthalpy and the free energy of binding [86, 87]. There are also some cases where the kinetic constants of the binding process can be obtained by ITC (see, e.g., [88]). For example, the heat produced by a stepwise addition of HP-β- and β-CD solution to a nootkatone allowed to characterize the complexation process with a binding enthalpy and binding constant of -6.99 kJmol^{-1} and 4838 M^{-1}, and -14.38 kJmol^{-1}, and 5801 M^{-1}, respectively [71]. Unfortunately, the strict conditions required by this technique do not allow its routine implementation on a large scale [89].

As has been pointed out before, some phytochemicals (EOs, in particular) are, in general, poorly soluble in aqueous solutions; therefore, the formation of complexes with CD in solid state is a strategy for further applications. Consequently, there are several available techniques used to evaluate the complexation. Thermal techniques, such as thermal degradation analysis and differential scanning calorimetry, are classical examples of methods used to assess complexation. Moreover, thermal degradation also allows evaluating the thermal stability of the EO upon complexation [90, 78].

Other spectroscopic techniques, such as FTIR and XRD, which can be included in group II, have also been used, but the information is, in our opinion, rather qualitative [30, 72, 78, 91]. Another interesting approach to learn about the formation of host-guest complexes, in solid state, is to study the release kinetics of the EO. These studies, although do not allow to quantify the total amount of EO incorporated into the CDs, are of utmost importance to evaluate the presence of the EO in the complex as well as to provide hints on the release mechanism; the latter is quite relevant for EOs used as fragrances [91, 92].

For such poor soluble compounds, the complexation can also be evaluated by carrying out phase-solubility studies. These can be performed by using complexes in solid state or by checking the ability of increasing concentrations of CD to solubilize saturated solutions of EO. This allows assessing how much the solubility of the EO is improved upon complexation as well as the corresponding complex binding constant. The details on the quantitative determination of those parameters will be given in the next section. Different techniques can be applied to obtain the phase-solubility profiles. For instance, the solubility of black pepper EO in the presence of hydroxypropyl-beta-CD (HP-β-CD) was evaluated by UV-visible spectroscopy [76]. On the other hand, phase-solubility profiles for the encapsulation of polymethoxy-flavones, obtained from mandarin EO, into HP-β-CD were obtained by using HPLC [93]. Kfoury et al. have used gas chromatography to study the ability of sulfobutylether-β- and sulfobutylether-γ-CD to encapsulate EOs components, such as limonene, estragole, and α- and

β-pinene; their solubility in water was improved more than one order of magnitude [94]. It is worth noticing that, recently, a technique based on the total organic carbon determination has been reported and validated to follow the solubility improvement of EOs when increasing the concentration of CD [95].

5. Methods for computation of binding constants: the case of EO-CD association

In this section a rather simple and straight overview of the most used model equations to compute binding constants for host-guest association is provided. To do so, EO will be used as the guest compound.

As discussed before, the phase-solubility plots are a widely applied method to get knowhow on the improvement of the EO solubility driven by complexation and also for computation of the EO-CD association constant. Assuming that the most common type of EO/CD complex has a 1:1 stoichiometry, the corresponding reaction and equilibrium (binding) constant, K_1, can be written as

$$CD + G \underset{}{\overset{K_1}{\rightleftharpoons}} CD - G \tag{1}$$

$$K_1 = [CD - G] / \left([CD]_f [G]_f \right) \tag{2}$$

where G represents the guest (here the EO) and $[CD]_f$ and $[G]_f$ are the concentrations of uncomplexed (free) species in the system. Assuming that the change in the aqueous solubility of the EO (ΔS) is only due to the formation of the complex, we can write

$$\Delta S = S_T - S_0 = [CD - G] \tag{3}$$

where S_T is the measurable total solubility and S_0 is the solubility of the EO in water in the absence of CD (i.e., the intrinsic solubility). Thus, it follows that

$$[G]_f = S_0 \tag{4}$$

$$[CD]_f = [CD]_T - (S_T - S_0) \tag{5}$$

where $[CD]_T$ is the total concentration of CD in the solution.

Substituting Eqs. (3)–(5) in Eq. (2) and after algebraic manipulation, we obtain

$$S_T = S_0 + \frac{K_1 S_0}{1 + K_1 S_0} [CD]_T \tag{6}$$

Fitting Eq. (6) to experimental data of $S_T = f([CD]_T)$ allows the calculation of the intercept (S_0) and the association constant, K_1. As discussed by Loftsson et al., the determination of K is

highly dependent on the intercept accuracy [96]. In order to overcome this drawback, the authors have established the concept of "complexation efficiency" (CE) which can be obtained independently of S_0, according to the following relation:

$$CE = \frac{[CD - G]}{[CD]_f} = \frac{(S_T - S_0)/[CD]_T}{1 - (S_T - S_0)/[CD]_T} \tag{7}$$

where the term $((S_T - S_0)/[CD]_T)$ represents the slope of the phase-solubility profile.

The application of Eq. (7) is useful but limited by the dependence on S_0 and to 1:1 complexes.

Let us now assume the following reaction:

$$nCD + G \overset{K_n}{\rightleftharpoons} CD_n - G \tag{8}$$

where n is a stoichiometry coefficient and K_n is the corresponding binding constant. Thus, from the conservation of mass equations:

$$[G]_f = [G]_T - [CD_n - G] \tag{9}$$

and

$$[CD]_f = [CD]_T - n[CD - G] \tag{10}$$

the binding constant equation can be written as

$$K_a = \frac{[CD_n - G]}{([CD]_T - n[CD - G])^n ([S]_T - [CD - G])} \tag{11}$$

By measuring a physical parameter, known as ΔA, directly related with the formation of the complex $(CD_n - G)$, and performing the experiment in such a way that $[CD]_T >> [CD - G]$, Eq. (11) takes the form of the so-called "Benesi-Hildebrand" equation [97]:

$$K_a = \frac{\Delta A}{([CD]_T)^n ([S]_T - \Delta A)} \tag{12}$$

or its linear form

$$\frac{1}{\Delta A} = \frac{1}{[S]_T} + \frac{1}{K_n [S]_T ([CD]_T)^n} \tag{13}$$

However, it should be pointed out that nowadays, with the available software, such as Origin® and MatLab®, there is no need to linearize Eq. (12) once such methodology brings some restrictions to the computation of K and n.

It should be stressed that a key point in all these procedures is the accurate previous knowledge of the stoichiometry of complexation, but this is not always a simple task. The most

common method for the determination of stoichiometry is the method of continuous variation or the Job plot; the virtues and limitations of this method were recently reviewed [98], and thus it is not our intention to further discuss it in the present chapter.

Going back to the determination of the binding constants, the most accurate way to compute K is by using the first principles. Here, for the sake of simplicity, the 1:1 and 1:2 (G/CD) stoichiometric ratios will be focused. Additionally, these examples also correspond to the large majority of complexes formed between CDs and EOs. For more complex stoichiometries, the computational treatment of the resulting equations (not shown) is not straightforward as a consequence of multicollinearity [99]. Multicollinearity causes larger standard errors in the quantities calculated and lowers statistical significance of the results. In limiting cases, several local minima may be obtained by iteration; these correspond to noticeably different combinations of the quantities calculated and may be the reason why different K values are reported for the same host-guest systems.

Assuming that a 1:1 complex (CD-S) is formed, the binding constant (Eq. (2)) can be rewritten as

$$K_1 = \frac{f}{(1-f)\left([CD]_T - f[G]_T\right)} \tag{14}$$

where f is defined as $[CD - G]/[G]_T$.

Despite the binding process being followed by ΔA (e.g., for ^{1}H NMR, ΔA will be equal to the chemical shift of a given ^{1}H resonance), the observed ΔA for a host molecule is expressed as

$$A_{obs} = (1-f)A_{CD,f} + f A_{CD-G} \tag{15}$$

where $A_{CD,f}$ and A_{CD-G} represent the measurable physical parameter related to CD in free and complexed states, respectively.

The variation of the physical parameter in the presence and absence of a guest molecule, $\Delta A_{obs} = \Delta A_{obs} - \Delta A_{CD}$, can be expressed as

$$\Delta A_{obs} = \frac{\Delta A_{CD-G}}{[CD]_T} [CD - G] \tag{16}$$

which, after some algebraic manipulation and simplification, results in [100, 101]:

$$\Delta A_{obs} = \frac{\Delta A_{CD-G}}{2\,[CD]_T} \left\{ \left([G]_T + [CD]_T + \frac{1}{K_1}\right) - \left(\left([G]_T + [CD]_T + \frac{1}{K_1}\right)^2 - 4\left([G]_T[CD]_T\right)\right)^{1/2} \right\} \tag{17}$$

It should be stressed that the application of Eq. (17) shows some drawbacks when the total concentrations of CD and guest are low and/or the binding constant is very weak, i.e., for the simplest 1:1 case, when y is sufficiently small, $x - \sqrt{x^2 - y} \approx y/2x$, and, consequently, Eq. (17) reduces to

$$\Delta A_{obs} = \frac{\Delta A_{CD-G}}{T + \left(1/\kappa_1\right)} [G]_T \tag{18}$$

where $T = [CD]_T + [S]_T$. If T is kept constant in the experiments, as is common practice when Job plots are used to obtain stoichiometries, the observed displacement varies linearly with $[S]_T$ or $[CD]_T$, but the fitting parameters are present in the form of a ratio that generates an infinite number of acceptable solutions. Consequently, it is suggested that T should be chosen in such a way that its value should be of the same order of magnitude than K_1^{-1} [102].

Another approach lays on the assumption of a 2:1 (CD/G) complexation, in a two-step mechanism. In these circumstances, the complexation process is defined by two binding constants K_1 and K_2, and the corresponding mass balances are defined as

$$[G]_f = [G]_T - [CD - G] - [CD_2 - G] \tag{19}$$

and

$$[CD]_f = [CD]_T - [CD - G] - 2[CD_2 - G] \tag{20}$$

From the equilibrium constants and Eqs. (19) and (20), we can write

$$A_{obs} = \frac{[CD]_f A_{CD} + [CD - G]A_{CD-G} + 2[CD_2 - G]A_{CD_2-G}}{[CD]_f + [CD - G] + 2[CD_2 - G]} \tag{21}$$

where A_{CD}, A_{CD-G}, and A_{CD2-G} are the contributions of the CD and 1:1 and 2:1 CD/G complexes, with concentrations $[CD]$, $[CD - G]$, and $[CD_2 - G]$, respectively, for the observed (experimental) physical parameter A. Using a similar procedure to that used for a 1:1 complexation, it is possible to write Eq. (21) as a function of $[CD]$, that is

$$A_{obs} = \frac{A_{CD} + [CD]K_1 A_{CD-G} + K_1 K_2 [CD]A_{CD_2-G}}{1 + K_1 [CD]_f + K_1 K_2 [CD]^2} \tag{22}$$

On the other hand, the free CD concentration is given by

$$[CD]^3 + \left(\frac{1}{K_{2,1}} - [CD]_T + 2[S]_T\right)[CD]^2 + \left(\frac{1}{K_{1,1}K_{2,1}} - \frac{[CD]_T}{K_{2,1}} + \frac{[S]_T}{K_{2,1}}\right)[CD] - \frac{[CD]_T}{K_{1,1}K_{2,1}} = 0 \tag{23}$$

One method for estimation of the free CD concentration is through an analytical solution of the real solution of a third-degree equation [103]:

$$f(x) = x^3 + ax^2 + bx + c \tag{24}$$

using a Cardin-Tartaglia formulae

$$x = r - \frac{1}{3}a - \frac{q}{r} \tag{25}$$

where

$$q = \frac{1}{3}b - \frac{1}{9}a^2 \tag{26}$$

and

$$r = \sqrt[3]{\frac{1}{6}ab - \frac{1}{2}c - \frac{1}{27}a^3 + \sqrt{\frac{1}{27}b^3 - \frac{1}{6}abc + \frac{1}{4}c^2 + \frac{1}{27}a^3c - \frac{1}{108}a^2b^2}} \tag{27}$$

6. Conclusions

Despite the huge potential of many bio-based compounds in several diverse areas, their use is still limited due to different reasons such as poor aqueous solubility, volatility, reactivity, etc. Therefore, advanced strategies have to be developed in order to minimize some of these weaknesses to make bio-based molecules usable on a larger scale. It became patent in this chapter that CD interaction with bio-based compounds, such as different phytochemicals or sugar-based surfactants, has generally a remarkable positive impact on their performance, improving their aqueous solubility and availability and decreasing their degradation rate, etc. Moreover, it is clear that this is not only interesting and beneficial from an application point of view but also very stimulating from a fundamental perspective where thermodynamics, modeling, and different experimental methodologies get together for a deep and challenging characterization of the systems. Eventually, such knowledge will be crucial for the future development of improved formulations and make use at full extent of the exciting properties of bio-based compounds.

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