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Review

State of the art in cyclodextrin solubility enhancement. Are green solvents the solution?

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ABSTRACT

Interest in cyclodextrins (CDs) never gets old. Since their discovery, these natural macrocycles have played a dynamic role in almost every scientific and industrial field. Native CDs offer many advantages as complexing agents, scaffolds, excipients, etc., but suffer from a major drawback: limited aqueous solubility, especially for β -CD (18.5 g/L in water at 25 °C). It is therefore of particular interest to be able to achieve higher solubilities for these hosts. The critical point is to attain the desired solubility values while maintaining their complexing ability. Several strategies have been explored in the literature such as salting in, hydrotropy, deprotonation/ionization and solvation. This literature review summarizes the available data on the solubilization of CDs in aqueous solutions of inorganic salts, organic hydrotropes, acids, bases, organic solvents as well as in non-conventional solvents, e.g. ionic liquids (ILs) and deep eutectic solvents (DESs). The latter provide an interesting opportunity to address the problem of solubility of native CDs (i.e., the solubility of β -CD can reach 1000 g/L at 20 °C). The present review also clarifies the solubilization mechanism as well as the effect of these agents and solvents on the complexation ability of CDs. Finally, it helps to identify the gaps in the literature on this topic and provides some insights to fill them.

1. Introduction

Cyclodextrins (CDs) are a family of naturally occurring host molecules [1]. They are obtained from biomass (starch) and consist entirely of glucose units that are linked by α -1,4 glycosidic bonds. CDs are pioneers in supramolecular chemistry [2]. They have a hydrophilic outer surface and a hydrophobic central cavity. This cavity can accommodate guest molecules resulting in the formation of inclusion complexes [3]. Encapsulation can profoundly affect the properties of the encapsulated guest, such as improving its solubility, stability, release profile, bioavailability and shelf-life. CDs can also assist in the geometric pre-organization of the guest for enzymatic or chemical reactions [4]. In addition to their particular and unique structure, CDs are natural, sustainable, ecofriendly and safe [5]. To date, nearly 63,000 publications on CDs are counted (obtained by searching in Scopus (<https://Scopus.com>) on June 28, 2024 using the keyword “cyclodextrin”). The global market size of CDs exceeded 260 million USD in 2020 and is expected to grow at a Compound Annual Growth Rate of more than 5.5 % from 2021 to 2027. They have attracted great interest in almost every academic and industrial field [6]. CDs are used as food additives, pharmaceutical

excipients, cosmetic ingredients and as building blocks for several innovative materials [7]. Thus, CDs inclusion complexes are being incorporated into a wide range of formulations [8]. However, final industrial products may contain a specific combination of additives (i.e., excipients, adjuvants) and solvents that can affect the performance of CDs for several reasons. First, the solubility profiles of CDs can be challenging because they are strongly influenced by the type of the solvent and the physicochemical parameters such as pH and salinity in addition to the storage temperature of the formulation. For example, above a certain concentration, some CDs can aggregate, often in the form of an inclusion complex with the target compound, thereby limiting their use to a certain concentration range and limiting the maximum output that can be achieved [9]. In some cases, encapsulation can lead to the formation of inclusion complexes with limited aqueous solubility [10]. Moreover, the addition of excipients or solvents during the preparation of the final formulation may result in the formation of multicomponent complexes that may stabilize or destabilize the desired inclusion complex (i.e., the complex of the target active compound). Therefore, every precaution must be taken to ensure that the efficacy of CDs is maintained in the final formulation. Most importantly,

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fundamental studies are generally performed in near-ideal solutions (*i.e.*, very dilute solutions), whereas commercial formulations are non-ideal solutions (*i.e.*, concentrated solutions of target compounds and excipients/additives) and may therefore deviate from the classical physicochemical principles. The aim of this paper is to review the various data in the literature as well as the new possibilities that can be used to increase the solubility of native CDs. The effect of these media on the encapsulation capacity of CDs is also discussed.

2. Water

α -CD, β -CD and γ -CD have different aqueous solubilities [11–13]. This is due to their distinct ability to form intra- and intermolecular hydrogen bonds. In water, each glucose unit of a CD molecule can form approximately 4–5 intermolecular hydrogen bonds with bulk water molecules. This forms the first hydration shell. Adjacent C₂-OH and C₃-OH moieties of glucose units also form intramolecular hydrogen bonds. Remarkably, the intramolecular hydrogen bonds formed on the secondary hydroxyl side of β -CD are more stable leading to an inadequate hydration by water molecules due to the complete secondary belt [14], thereby making the scaffold of this macrocycle stiffer [15]. This can explain the anomalous solubility of β -CD, precisely the lowest solubility among the native CDs (Table 1). It has been shown that the three native CDs can all self-associate to form nanoscale, poorly soluble aggregates [16–21] with diameters ranging between 20 and 200 nm [22]. The amount of aggregates also increases with increasing CD concentration [23]. Even though these aggregates can dissociate upon filtration, they can be regenerated in the filtrate during storage [24]. In water, all native CDs become more soluble with increasing temperature (Table 1). However, the solubilities obtained are far from those obtained for CD derivatives at ambient temperature (>500 g/L) [25].

The thermodynamic parameters for CDs dissolution were calculated using the van't Hoff plot (Table 2) [12].

The low solubility of CDs is a consequence of the unfavorable dissolution enthalpies, which are only partially compensated by the more favorable entropies. When β -CD dissolution is concerned, both the enthalpy and the entropy are less favorable (more positive ΔH° and more negative ΔS°) than for α -CD and γ -CD. This can explain the much lower solubility of this macrocycle.

Authors suggested empirical equations that correlate the thermodynamic parameters of the three native CDs: $\Delta H^\circ/n = -0.155n + 2.232$ and $\Delta S^\circ/m = 1.95n - 8.10$, where n stands for the number of glucose residues per CD and m is the number of CD molecules per unit cell of crystalline hydrate. These empirical equations could be useful for predicting values for large-ring CDs [12].

β -CD is the least soluble but, at the same time it has the most suitable cavity size for complex formation with many guests and it is the most common and the cheapest CD [26]. Therefore, increasing its solubility could be interesting to broaden its applications. This can be achieved either by the disruption of the hydrogen bond system, through derivative formation, or by altering the structural properties of the bulk solvent without direct interactions between the CD and the co-solute or by using co-solvents. Nevertheless, care should be taken when assessing CDs solubility.

In the solid state, CDs are present in the form of stable hydrates

Table 1
Solubility of native CDs in water (g/L) at different temperatures [12,25].

Temperature (°C)	α -CD	β -CD	γ -CD
23.7	117.1	17.8	
25	130.0	18.5	249
35	210.2	28.3	396
40	246.3	34.9	452
45	290.1	45.3	
48	330.5	52.5	

Table 2

Thermodynamic parameters for dissolution of CDs in aqueous saturated solution [12].

Cyclodextrin	ΔG° Kcal.mol ⁻¹	ΔH° Kcal.mol ⁻¹	ΔS° cal.mol ⁻¹ .K ⁻¹
α -CD	3.58	7.67	13.8
β -CD	4.81	8.31	11.7
γ -CD	3.34	7.73	14.7

containing several water molecules. The average water content is 2, 6 and 8.8 molecules in CD cavities, and 4.4, 3.6 and 5.4 molecules bound to the outer wall, for α -CD, β -CD and γ -CD, respectively [9]. The outer shell has been proposed to be involved in the solubility properties of CDs [15]. This dramatically alters the aqueous solubility values determined and often causes discrepancies in literature data. Therefore, CDs must be dried immediately prior to experiments, as dried CDs are highly hygroscopic and readily absorb water.

3. Inorganic salts

It has been reported that the solubility of CDs can be increased in aqueous solutions of certain inorganic salts. Table 3 gathers the solubility values of β -CD in the presence of some inorganic metal salts [27].

The influence of salt type and concentration on the solubility of native CDs was observed. Both cations and anions showed remarkable discrete effect on the solubilization of β -CD. In general, the solubility enhancement can be classified into 3 groups according to the cation charge: $M^+ < M^{2+} < M^{3+}$. For nitrates, the solubility increase remained constant within the group regardless of the cation. For chloride as an anion, the solubility increase was cation dependent. For divalent metals, the solubility increased down group II for a given salt concentration: $Ba^{2+} > Sr^{2+} > Ca^{2+} > Mg^{2+}$ [27].

Chaotropic anions (anions that disrupt the hydrogen bond network between water molecules), such as Br^- , I^- , SCN^- , N_3^- , ClO_4^- and NO_3^- , have been shown to induce pronounced shifts in the signals of H-5 of the α -CD, indicating that these ions were included into CD cavity. Anti-chaotropic anions such as F^- , HCO_3^- , $H_2PO_4^-$, HPO_4^{2-} caused no or very small shifts [28]. Similar but smaller effects were observed with β -CD and γ -CD.

A recent study showed that salts, except Na_2SO_4 , are able to efficiently increase the solubility of β -CD according to their ranking along the Hofmeister series and the effect of cations is significantly lower than that of anions. Thus, anions are the main species that preferentially interact with β -CD [29]. $NaClO_4$ was shown to have the highest solvation capacity and $LiCl$ the lowest. A previous work has also showed a high

Table 3
Solubility of β -CD in the presence of inorganic metal salts [27].

Salt	Salt concentration (M)	Solubility of β -CD (g/L)	Solubility of β -CD (mM)
NaCl	2.00	21	18.2
KCl	2.00	19	17.1
NaNO ₃	2.00	44	38.5
KNO ₃	2.00	40	35.6
AlCl ₃	2.00	252	221.6
Al(NO ₃) ₃	1.60	212	187.1
MgCl ₂	2.19	78	68.7
CaCl ₂	2.00	129	113.2
SrCl ₂	2.00	152	133.8
BaCl ₂	1.39	101	89.4
Mg(NO ₃) ₂	2.00	200	176.4
Ca(NO ₃) ₂	2.00	194	171.3
Sr(NO ₃) ₂	2.00	192	169.6
Ba(NO ₃) ₂	0.30	36	31.9
La(NO ₃) ₃	2.50	334	294.4
Pr(NO ₃) ₃	2.25	311	274.4

solubilization ability of NaClO₄ and found no effect for Na₂SO₄ [30]. The same authors also showed that a mixture of NaClO₄ and NaCl has lower solubilization ability than NaClO₄ alone [30].

The dissolving enthalpy and entropy of β-CD in organic salt solution (*i.e.*, NaCl 8 %) were determined. The results showed that both the enthalpy and entropy of dissolution are positive and they increase with temperature [31]. However, there is no strong evidence that either anions or cations are included into the CD cavity. The complexes formed by CDs and inorganic salts are considerably unstable (K_f values < 100 M⁻¹) [28]. Thus, the fact behind the solubility enhancement effect of inorganic salts is that, in the presence of high concentrations, massive ion pairing and clustering strongly disturbs the normal hexagonal dynamic water symmetric structure [32]. The perturbation of the water structure results in less unfavorable interactions with CD aggregates, namely β-CD, leading to its solubilization without any inclusion interaction.

Interestingly, salts may increase the complexation affinity for some guests. This could be due to the salting out effect and thus the decrease in solubility of the guest molecule. However, this may not lead to a general rule and the presence of salts may have different effects on the apparent formation constants of inclusion complexes [30]. This cannot be due to the formation of real inclusion complex with salts, but most likely to the binding of the ions to the inclusion complex by electrostatic interactions or by hydrogen bonding.

These results show that salts have a significant influence on the intermolecular interaction between CD and guests. Therefore, complexation studies performed in buffer solution should be carefully investigated [33].

4. Urea

Urea is commonly used as a chemical denaturant agent. The first attempt to quantify the effect of urea on CDs solubility dates back to 1989 [34]. The authors studied the evolution of native CDs solubility as a function of urea concentration. The results showed that, the solubility of β-CD and γ-CD increased steadily with increasing urea concentration. The maximum urea concentration tested was 10 M. At this point, the achieved solubilities of β-CD and γ-CD were higher than 0.35 and 0.45 M, respectively [34]. On the contrary, the authors observed that urea decreased the solubility of α-CD. A recent study also demonstrated that the solubility of β-CD increased with urea concentration to almost 0.25 M at the solubility limit of urea [35], and more recently an increase in the solubility of β-CD to 107 mM in the presence of 7 mol/kg urea was reported [29]. The overestimated solubility values reported in the first study [34] may be due to the experimental method used for CDs quantification (*i.e.*, drying CD solutions at 108 °C for 4 h prior to weighing).

In another study, the effect of urea on the self-assembly process of α-CD and γ-CD was investigated [23]. Permeation studies showed that urea can break large CDs aggregates into smaller aggregates or even monomers. The apparent critical aggregation concentration (*cac*) values of both CDs increased with increasing urea concentration values, compared to pure CDs aqueous solutions (Table 4). However, these data were not sufficient to estimate the exact solubility limit of these CDs in

Table 4

Apparent critical aggregation concentration values for α-CD and γ-CD in absence or presence of different concentrations of urea. The values were specifically calculated based on CD permeation through 3.5–5 kDa MWCO semi-permeable membrane [23].

Urea (% w/v)	α-CD Apparent <i>cac</i> (% w/v)	γ-CD Apparent <i>cac</i> (% w/v)
0	2.5	4.2
0.5	Not studied	5.1
1.0	Not studied	6.0
2.5	3.5	7.1
5.0	5.7	8.5
10	Not studied	10.9

urea solutions because not only monomers but also smaller aggregates can penetrate the semi-permeable membrane.

Experimental and theoretical data have been used to elucidate the mechanism by which urea increases the solubility of CDs. Several hypotheses can explain this phenomenon. Urea may act as a salting-in type of molecule [34]. Others have explained the increase in CD solubility by the fact that urea is a structure-breaking solute that reduces the structure of water leading to the solubilization of CD's aggregates. Structure disruptors such as urea destabilize the water structure by destroying clusters of associated water molecules and releasing water of solvation. This is known as the hydrotropic effect [36]. However, more recent investigations have shown that urea only slightly disrupts the molecular structure despite the strong hydrogen bonding interactions between urea and water molecules [37].

The formation of favorable hydrotrope-solute (*i.e.*, urea-CD) interactions leads to fewer unfavorable water-solute (*i.e.*, water-CD) contacts, thereby reducing the free energy penalty for the solvation of the target compounds. It has been observed that in urea solutions, a large density of urea molecules is assembled in the vicinity of the β-CD and within its cavity suggesting that the exclusion of thermodynamically frustrated water molecules from the immediate vicinity of the β-CD (cavity and surface) is a driving force for CD solubilization [35]. The replacement of water by the larger urea molecule in the solvation shell of CD results in a lower free energy of cavity formation. The free energy cost of cavity formation in water is greater than in the organic solvents, for example, for solutes that are less soluble in water than in these solvents [38]. However, no evidence for the formation of inclusion complexes between CDs and urea has been reported in the literature. ¹H NMR studies revealed that urea does not interact with CDs (α-CD or γ-CD). It acts only by hindering the formation of hydrogen bonds, thus preventing α-CD and γ-CD self-aggregation [23]. Calorimetric studies also proved that no inclusion complex could be formed between α-CD and urea [39]. A more recent study demonstrated that even at a high concentration (25 wt%), the stability of the β-CD/guest inclusion complex was not affected by its presence proving that it has no competitive effect for the CD cavity [40].

5. Mixtures of organic and inorganic compounds

The combined effect of salts and organic compounds has also been investigated. Recently, the simultaneous ability of a number of salts and urea to increase the solubility of β-CD was studied [29]. At 1 mol/kg, all salts (LiCl, NaCl, KCl, CsCl, NaBr, KSCN, NaSCN and NaClO₄) provided a weaker solubility enhancement than urea at 7 mol/kg. In the presence of urea, higher solubility values of β-CD were achieved without affecting the ranking of the solubilizing potency of the salts when tested alone, highlighting the potential of mixed hydrotropes to achieve unique enhanced solvation capacity. The difference in β-CD solubility as a function of the type of salt addition was also enhanced and more discriminating between ions that are close in the Hofmeister scale, such as NaSCN and NaClO₄. Nevertheless, it was shown that urea and salts can form either antagonistic, additive or synergistic solubilization of β-CD, showing that the salt variation affects solvation in a significant way. It was observed that the changes in the standard free energy of β-CD solvation are linearly correlated with the air–water surface tension of the salt and urea solutions.

The highest solubility was obtained with urea and NaClO₄. The authors showed that both cosolutes accumulate together in the vicinity of β-CD and that urea strongly assist in salt accumulation. However, a competition may result in a net decrease in the accumulation of one or both of them (*e.g.*, at elevated salt concentrations). Similar investigations have not been performed for other salts, and these specific results for urea and NaClO₄ could not be generalized because solvation is expected to depend on the charge, size, polarizability, hydrogen bonding, and other molecular descriptors of the solution. All of these can be affected by varying cosolutes (*i.e.*, salts and urea) and solvent types.

Another study investigating the solubilizing ability of sucrose 6 % and NaCl 8 % as well as their mixture showed that at high temperature the solubility of β -CD was lower in the sucrose/NaCl mixed solution, concluding that the medium composition and temperature influence the solvent–solute interactions and affect the solubility [31].

6. Acids

There are very few available data on the effect of acids on the solubility of CDs [13]. The results showed that only organic hydroxy acids (*i. e.*, tartaric acid and citric acid) are able to significantly increase the solubility of β -CD. In the presence of 140 g/L of citric acid or 110 g/L of DL-tartaric acid, around 180 g/L and 80 g/L of β -CD were solubilized, respectively [13]. Also, 130 g/L of ascorbic acid were able to solubilize more than 60 g/L of β -CD. Lactic acid showed lower solubilizing efficacy. However, a recent study showed that β -CD can successfully form low melting mixtures with lactic acid and that these eutectics are liquid at room temperature and can be mixed with water without precipitation [41]. Malic acid, hydrochloric acid and acetic acid did not improve the solubility of β -CD compared to water while malonic acid, succinic acid and maleic acid decreased the solubility of β -CD. This was attributed to their possible inclusion in the CD and concomitant precipitation of the formed inclusion complexes.

7. Bases

The pKa of the secondary hydroxyl groups is 12.3 ± 0.2 , while that of the primary hydroxyl groups is 15–16. Thus, strong bases can be used to deprotonate and thus solubilize CDs. It has been shown that NaOH can be used to readily dissolve significant amount of CD in aqueous solution. The increase in aqueous solubility of α -CD, β -CD and γ -CD in 0.75 M NaOH was 3.7, 21 and 2.6-fold, respectively [34]. A study investigating the variation of CD solubility and aggregate size as a function of pH showed that both size and solubility remain constant up to pH 12.5, at which point the solubility of β -CD increases sharply to 750 g/L and the apparent aggregate diameter decreases rapidly to 20 Å [16]. This phenomenon was explained by ionization of the hydroxyl groups ($\text{pH} > \text{pK}_a$) leading to dissociation of the aggregates as a result of electrostatic repulsion. Less dramatic changes in the solubility of α -CD and γ -CD were also observed at high pH values. The same authors, previously showed that in KOH solution OH^- was found within the CD cavity giving rise to an inclusion complex structure isostructural with β -CD. 12 H_2O . Thus, they suggested that the first step in the ionization process involves complexation of OH^- by the CD. Interestingly, ^1H NMR studies showed that no epimerization occurs after treatment at pH 13 and subsequent neutralization [16].

8. Organic solvents

The conventional solubilization approach generally used to improve the aqueous solubility of solutes is the use of organic solvents. However, CDs exhibit a peculiar behavior. CDs are insoluble in most common organic solvents such as methanol, ethanol, acetonitrile, acetone and THF. The literature also reported the solubility of β -CD in a number of water/cosolvent mixtures [42]. The curves of solubility variation obtained are different depending on the organic cosolvent used. For methanol, the solubility of β -CD decreased with increasing concentration. The curves of ethanol, THF, acetonitrile and isopropanol showed maxima at 10, 5, 8 and 8 % mole fractions of cosolvent (30, 20, 20 and 25 % cosolvent), respectively. The maximum β -CD solubilities obtained at these maxima were 22, 22, 37 and 87 g/L at 25 °C, respectively. Compared to water, the increase was not huge. The order of magnitude was similar to that obtained with inorganic salts. This indicates that all these organic solvents have a limited capacity to dissolve CD. For all these solvents above 15–20 % mole fraction of cosolvent the solubility of β -CD was lower than in water and equal to zero in the pure solvents. In

water/cosolvent, the solubility of β -CD increased with increasing temperature without affecting the shape of the curve as observed for propanol/water mixtures [42].

DMSO showed a distinct behavior, two plateau regions were observed. For mixtures containing less than 20 % mole fraction of DMSO (40 % cosolvent), the solubility of β -CD was unchanged. Then, it started to increase in parallel with the DMSO content to reach again a plateau between 40 and 90 % mole fraction of DMSO (70–96 % cosolvent), where β -CD reached a solubility around 760 g/L. Surprisingly, above 90 % mole fraction of DMSO, the solubility of β -CD starts to decrease disproportionately, but it remains very well soluble in DMSO (around 500 g/L). The solubility variations were explained by changes in the intrinsic solvent properties, in particular the excess partial molar volume and the viscosity. However, the decrease in β -CD solubility observed above 90 % mole fraction of DMSO (96 % cosolvent) was attributed to the fact that at low water content the solvent molecules can be encapsulated in β -CD. Authors attributed that to the formation of β -CD/DMSO inclusion complex that is less soluble than free β -CD which leads to a decrease in the apparent solubility of β -CD. Nevertheless, the size of DMSO molecules is too small to form a stable inclusion complex with CD.

Other literature data are ambiguous. Authors reported the solubility of CDs in organic solvents without specifying the type of CD [43]. Nevertheless, the three native CDs may not exhibit the same behavior in different media. For all of solvents studied, caution should be taken when relying on literature results for the unit of solvent concentration to adequately determine the composition of the solvent/water mixture.

Although some solvents may be useful in increasing the solubility of CDs, they may unfortunately affect the inclusion complex formation. Organic cosolvents have been shown to inhibit the formation of inclusion complexes with CDs. Several studies have reported a decrease in inclusion complex strength in the presence of organic cosolvents [44–47]. It has also been observed that K_f decreases as the relative permittivity of the medium decreases [47,48]. Results from the literature suggest that neither the relative permittivity of the medium nor its hydrophobic character and dielectric properties allow predicting the effect of the cosolvent on the complexation process. The magnitude of the effect depends on the nature and amount of cosolvent added, the type of the CD and the guest [49]. In addition, findings from the literature suggest that the influence induced by the presence of the solvent is more important when the guest volume better fits the cavity of the CD [44,48,49]. Therefore, each system (CD, guest and cosolvent) should be investigated alone.

Thermodynamic studies supported these observations. Calorimetric investigations showed that the presence of cosolvent affects both the enthalpy and entropy of the complexation. In the presence of ≤ 50 wt% ethanol, an increase in the exothermicity of the complexation is observed, accompanied by a decrease in the entropic contribution to the change in the Gibbs energy, leading to a decrease in the stability of the inclusion [40]. For DMSO, a general tendency is not observed for the studied guests and CDs [46].

9. Non-conventional solvents

The use of alternative solvents, which have been proposed to replace conventional hazardous organic solvents, has become a key current research challenge. Two neoteric classes of solvents have gained increasing popularity in this field: ionic liquids (ILs) and deep eutectic solvents (DESSs) [50]. They differ in two fundamental ways, namely the nature of the starting materials and the methods of their formation [51]. ILs consist of a cation and an anion linked mainly *via* ionic bonds, hydrogen bonds and van der Waals forces, showing liquid state at room temperature. They combine the advantages of molecular liquids (liquid state) and ionic compounds (ionic character). DESSs are eutectics formed by a combination of two or more solid or liquid components linked by hydrogen bonds [52–54].

ILs and DESs are highly attractive due to their unique properties (*i.e.*, tunability, low volatility, high stability, wide liquid range, large electrochemical window, high conductivity, and high dissolubility) [55]. Recently, they have been widely applied in many fields including dissolution of active compounds [56,57]. Several studies have attempted to evaluate whether these solvents are able to dissolve macrocycles namely CDs and their solubilization capacity as well as dissolution mechanism.

9.1. Ionic liquids (ILs)

These solvents have been shown to significantly increase the solubility of CDs. Several ILs have been investigated. Table 5 provides a synopsis of the data collected from the literature on the solubility of CDs in different ILs.

The results showed that ILs can indeed act as solvents for CDs with different maximum potencies. At room temperature, among the investigated ionic liquids, 1-ethyl-3-methylimidazolium acetate [C₂mim][OAc] was the best solubilizer for CDs.

From the thermodynamic point of view, the results proved that the dissolution of β -CD in ionic liquids is thermodynamically unfavorable. The solvation process is endothermic and accompanied by positive entropy changes [60,64]. This means that an increase in temperature is necessary to increase the solubility of CD.

The amphiphilic nature of these solvents plays a key role in the solvation performance [60]. The dissolution process is dominated by hydrogen bonding interactions between CDs and both the anion and cation of the IL [60,66]. It has also been observed that ILs can approach the interior part of CDs while forming solvation shells around the macrocycle [60]. Thus, the mechanism of CD dissolution in ILs seems to consist of two main steps: *a*) the partial disruption of the attractive interactions between the IL components (cation and anion) which can be affected by the strength of the interaction between the IL components, as indicated for example by the melting temperature of the solvent. ILs with weak anion/cation interactions could be therefore more appropriate for CD dissolution; and *b*) the formation of the inclusion

Table 5
Solubility of CDs in ionic liquids.

Ionic liquid	CD	Solubility	Reference
[C ₂ O ₁ mim][Br]	α -CD	350 g/L	[58]
[C ₃ O ₁ mim][Br]			
[bmim][BF ₄]		<1 wt%	[59]
[bmim][Cl]		30 wt%	[59]
[bmim][PF ₆]		<1 wt%	[59]
[MeOetmim][Br]		350 g/L	[58]
[C ₂ mim][OAc]		270 g/l (15 °C)	[60]
[bmim][BF ₄]	β -CD	<1 wt%	[59]
[bmim][Br]		25 wt% (25 °C)	[61]
[bmim][Cl]		21 wt%	[59]
[bmim][PF ₆]		<1 wt%	[59]
[bmim][dca]		750 g/l (75 °C)	[62]
[emim][Ac]		25 wt%	[63]
[bmim][Cl]		69.7–106.7 g/100 g (70–90 °C)	[64]
[hemim][Cl]		78.4–110.4 g/100 g (65–85 °C)	[64]
[amim][Cl]		79.4–112.3 g/100 g (60–80 °C)	[64]
[bmim][N(CN) ₂]		73.0–105.1 g/100 g (60–80 °C)	[64]
[hemim][N(CN) ₂]		90.5–121.1 g/100 g (60–80 °C)	[64]
[amim][N(CN) ₂]		102.3–132.2 g/100 g (60–80 °C)	[64]
[emim][Cl]		15 mol % (150 °C)	[65]
[emim][Br]		15 mol % (150 °C)	[65]
[bmim][Cl]		15 mol % (150 °C)	[65]
[C ₂ mim][OAc]		1000 g/L (15 °C)	[60]
[bmim][BF ₄]	γ -CD	<1 wt%	[59]
[bmim][Cl]		30 wt%	[59]
[bmim][PF ₆]		<1 wt%	[59]
[C ₂ mim][OAc]		1500 g/L (15 °C)	[60]

complexes with CD (which may be affected by the strength of binding between the IL and the cavity of the CD) [64]. It has been shown that a small amount of β -CD added to the IL is able to lower the equilibrium temperature, producing the eutectic point [65] and that CD dissolution in ILs can also affect the other IL properties, such as electrochemical properties [67], as well as rheological properties and can lead to gel formation [63].

Numerous studies have demonstrated the formation of inclusion complexes between CDs and ionic liquids in aqueous solution. A literature review collected data on the binding strength of inclusion complexes between β -CD and various ILs, expressed as formation constant (K_f) values [68]. The analysis of the collected data revealed that the complexation between CD and IL is a function of the hydrophobicity and the size matching of the cation and the anion with a predominance of the inclusion of the hydrophobic tail of the IL in the CD cavity. ILs with longer carbon chains tend to form more stable inclusion complexes [68]. Therefore, to reduce the possibility of inclusion complex formation between CD and IL, researchers tend to explore the replacement of long chains (*i.e.*, butyl) with relatively shorter groups, such as ethyl or propyl [69].

Finally, the polarity of the IL and the medium should also be considered [65]. Care should be taken when handling ILs in different buffer solutions, as metathesis reaction (*i.e.*, exchange between the ionic liquid and buffer ions) may occur, leading to misinterpretation of the binding strength or discrepancies between different techniques.

9.2. Deep eutectic solvents (DESs)

The first paper on deep eutectic solvents (DESs) appeared in 2001 [70], and the first solubilization of CDs in these green solvents was performed in 2016 [71]. The solubility enhancement of native CDs in the ChCl:urea (1:2) DES was then quantified. The obtained solubilities were greater than 500 g/L for α -CD, and greater than 1000 g/L for β -CD and γ -CD corresponding to solubility enhancements of 3.5, 55 and 4, respectively [72]. The dissolution of β -CD in ChCl:urea 1:2 was found to be an exothermic process with a dissolution enthalpy of -23.3 J/g (-26.4 kJ/mol) [73]. In this work, the enthalpy was measured using calorimetry and it corresponds to the dissolution of solid β -CD in DES at 60 °C while the thermodynamic parameters for CD dissolution in other media (water, salt solutions and IL) described in the different sections above were obtained using the van't Hoff plot. Although β -CD was found to be perfectly soluble in ChCl:urea (1:2), it was insoluble in other DESs such as ChCl:ethylene glycol (1:2), ChCl:glycerol (1:2) [74] and tetrabutylammonium chloride:lactic acid (1:2) [75]. Interestingly, this very high solubilization of β -CD in dry ChCl:urea (1:2) DES is achieved without the occurrence of aggregation phenomena as demonstrated by SAXS [74]. The solubility of β -CD doesn't only depend on the type of DES but also on the hydration level of the solvent. It decreases with increasing hydration level of ChCl:urea (1:2) DES [35,76]. However, it has recently been shown that the eutectic point would not be the optimal point for β -CD solvation. On the contrary, it is very close to the point of worst β -CD solvation for a given hydration [76]. This means that varying the ChCl:urea ratio would lead to higher solvation levels of β -CD. Therefore, the optimal ChCl:urea ratio for each hydration level should be determined experimentally.

All these observations result from the unique solvation mechanism of β -CD in ChCl:urea (1:2) DES; *a*) this huge solvation capacity of DES has been attributed to its unique highly ordered liquid structure, which consists of an enormous network of hydrogen bonds. CDs with multiple hydroxyl groups can be incorporated into this network through further hydrogen bonding interactions [72]. This observation can be supported by the fact that methylated CDs are not soluble to this extent in ChCl:urea [74], *b*) all DES moieties (choline, chloride and urea) mutually and favorably interact with β -CD. This can explain the observation that at the eutectic point the DES components interact strongly with each other, leading to a weaker interaction with β -CD and thus to a lower solvation

of the macrocycle and c) the importance of urea which can explain why ChCl:urea (1:2) containing urea succeeds in dissolving large amounts of β -CD while ChCl:ethylene glycol (1:2), ChCl:glycerol (1:2) containing ethylene glycol and glycerol, respectively, do not.

Nevertheless, the importance of using DESs goes beyond the consideration of its individual components. The components of DES (*i.e.*, choline chloride and urea) synergistically enhance each other's stabilizing effect (*i.e.*, β -CD has higher solubility in hydrated ChCl:urea (1:2) solutions than in binary urea-in-water solutions). All reline components are found within the reference β -CD (*i.e.*, for $r \leq 4 \text{ \AA}$), with an average number of 0.1, 0.5, and 2 cations, anions, and urea species, respectively [74]. However, there is no evidence that these species can form stable inclusion complexes with CDs.

Regarding the hydrophobic exterior of CDs, literature results showed that the walls of CDs are surrounded by well-defined solvation shells. A first chloride anion solvation shell developed at $\sim 9 \text{ \AA}$ (containing ≤ 11 chloride anions). Choline cations formed a more relaxed solvation shell at larger distances, containing ~ 15 members at $\sim 11 \text{ \AA}$, presumably due to their larger size. Urea formed two hydration shells at $\sim 10 \text{ \AA}$ (containing ~ 34 molecules) and at a larger distance (14 \AA) [35,74]. In addition, the solubility of urea, the key species for CD solvation, is limited in water, so the very high concentration of this neutral species found in ChCl:urea cannot be achieved in aqueous urea solutions [35].

Regarding the complexation ability of CD in these media, literature data showed that CDs have a reduced tendency to encapsulate guests in dry DESs [73,77]. The binding strength increased when the hydration level in DES solutions was increased [78,79]. The destabilizing effect depended on the type and wt % of DES in the complexation medium [40]. Several DESs (*i.e.*, ChCl:urea (1:2), ChCl:glycerol (1:2), ChCl:xylitol (1:2), ChCl:sorbitol (1:1), ChCl:glucose (2:1), ChCl:fructose (2:1)) didn't show any competitive effect on the complexation up to 25 wt% [40]. However, at higher DES contents ($>25 \text{ wt\%}$), a significant destabilization of the complexation was observed, not only due to the competitive effect of DES components, but also to the disruption of the solvophobic forces [40]. Nevertheless, DESs were much less destabilizing than organic solvents (*i.e.*, ethanol). It has also been shown that the inclusion mechanism in DES solutions is similar to that in water, with analogous thermodynamic signatures and maintained stoichiometry [40,80].

10. Conclusion and remarks

Native CDs, especially β -CD, have limited aqueous solubility. Finding the right way to boost their solubility while preserving their encapsulation ability is the key step to expand their application and fully exploit their unique potential. Increasing the solubility of native CDs will favor their use instead of derivatives or polymers that are specially synthesized, heterogeneous, more expensive and have lower naturalness index. Various strategies have been explored to increase the solubility of CDs (*i.e.*, inorganic salts, organic hydrotropes, acids, bases, ionic liquids (ILs) and deep eutectic solvents (DESs)). Mixtures of different strategies were also examined. Almost all of them were effective in increasing the solubility of native CDs in comparison to water. However, they showed different enhancement factors.

However, with the exception of a few studies, most of the data presented, mainly for salts, acids, bases and organic solvents, are old (performed before the year 2000) and need to be reviewed using new sophisticated techniques and perhaps better purified CDs. Also, for all strategies, the temperature dependent solubilities and thermodynamic parameters (ΔG° , ΔH° and ΔS° of the dissolution) are not thoroughly investigated. However, this is a key requirement for predicting the behavior of the mixtures at application conditions. In addition, the aging of the mixtures has never been studied. This can allow the modulation and optimization of the composition to avoid the occurrence of some collateral phenomena such as precipitation with time or due to moisture entrapment. Also, no study has attempted to investigate the capacity of

CDs to encapsulate guests at these high solubility levels.

Salts alone were not very efficient, but their combination with organic hydrotropes such as urea, which itself was able to remarkably solubilize native CDs, increased the solvation capacity. Among acids, only citric acid and tartaric acid were effective in increasing the solubility of the tested CDs. CDs are highly soluble and stable in highly basic solutions. However, the basicity of the medium may limit the application range. Regarding solvents, literature showed that neoteric solvents (ILs and DESs) are much more convenient than organic solvents and are the best CD solubilizers. Moreover, DESs could be the most relevant because they not only replace organic solvents but also overcome all the drawbacks of using synthetic ILs, especially their multistep synthesis, toxicity and environmental hazards [51]. Thus, it seems that DESs could be considered in many cases to overcome the limitations of aqueous solubility of CDs. However, investigations are still in their infancy, with only promising results for dry and hydrated ChCl:urea (1:2) DES, with a focus on the importance of urea.

In the case of DESs, the focus has been on uncovering the theoretical forces involved in the solvation of CDs and modeling the accumulation of DES components around and inside the macrocycle [35,74]. There has been little motivation to experimentally determine the factors that influence the solubilization process. Various physicochemical parameters such as viscosity, surface tension, excess partial molar volume, electrical conductivity, acidity/alkalinity and so on can affect the solubilization process and also help to identify the applicability of a DES/CD combination. In addition, for a beneficial increase in solubility, CDs should ideally retain their complexation ability in this new solvation medium. However, unlike in water and organic solvents, this task is not straightforward. For example, the addition of water to DES can lead to the dissociation of the solvent into free components that compete with the guest for the CD cavity. Also, depending on the hydration level, water can be incorporated as a component of the DES or disturb the eutectic composition. No in-depth investigations have been made to optimize the molar ratio of DES for better solubilization of CDs instead of only considering the eutectic point. Last but not least, no study has explored the effect of DES composition nor evaluated the long-term stability under different conditions. All these gaps need to be filled in order to rationalize the use of (deep) eutectic mixtures for the solubilization of CDs, as these media hold great promise not only for CD solubilization but also for the broadening of their application.

CRediT authorship contribution statement

Miriana Kfoury: Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation, Conceptualization. **Sophie Fourmentin:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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