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Combination of DES and macrocyclic host molecules: Review and perspectives

Sophie Fourmentin, Miriana Kfoury, David Landy

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10 **Abstract**

11
12 Solvation in Deep Eutectic Solvents (DESs) and encapsulation in macrocycles are efficient
13 strategies for molecule's solubilization. Recently, new systems combining DES and
14 macrocycles are being constructed using two approaches: *a*) solubilizing hosts in preformed
15 DES or *b*) using hosts as a DES component. This strategy could evolve in new outcomes in
16 DES properties, more precisely provide the solvents with supramolecular capacity, and
17 translate into interesting performances. In the present review, we will give the reader an
18 overview of the studies accomplished in this growing research area, with a focus on the
19 experimental perspectives that we consider to be the most important in order to enlarge
20 knowledge on the properties and behavior of these neoteric systems.

21
22 **Keywords:** cucurbituril, crown ether, cyclodextrin, deep eutectic solvents, low melting
23 mixtures.

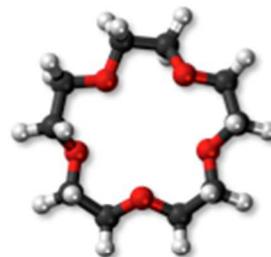
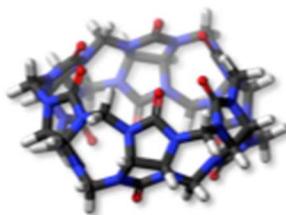
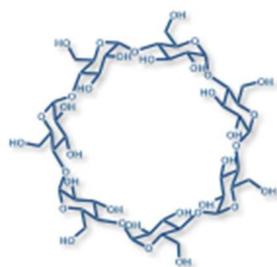
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27 **Introduction**

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29 Within the perspective of green chemistry, Deep Eutectic Solvents (DESs) are gaining a
30 rapidly growing interest and popularity as sustainable substitutes to organic solvents and ionic
31 liquids [1,2]. DESs are considered for their negligible vapor pressures, nonflammability,
32 thermal stability, chemical inertness, recyclability and high solubilizing ability. Such a class
33 of emerging solvents has many desirable applications in analytical chemistry, catalysis,
34 extraction, biomass pretreatment and conversion and gas separation. DESs are low melting
35 mixtures (LMMs) characterized by a large depression of the melting temperature of the
36 mixture at the eutectic point compared to the melting temperature of the separated pure
37 constituents and their ideal liquid mixture. DESs are classified according to the constituents
38 used in their preparation. Type I and II are formed from quaternary ammonium salts and
39 either metal chloride or metal chloride hydrate, respectively. Type III and IV are obtained by
40 combining either quaternary ammonium salts or metal chloride hydrate, respectively, with
41 hydrogen bond donors. More recently, type V eutectics have been proposed. They are
42 obtained using non-ionic hydrogen bond acceptors (HBA) and hydrogen bond donors (HBD)
43 [3].

44 The most commonly studied DES is a blend of choline chloride and urea (1:2 molar ratio)
45 called reline [3]. The huge panel of cheap, safe, sustainable, renewable and biodegradable
46 materials (*e.g.* carbohydrates, polyalcohols, amino acids) that are able to form eutectic
47 mixtures makes the possibility of creating new DESs exceedingly large. However, changing
48 the nature and ratio of the components can influence the physical properties and behavior but
49 do not grant the solvents with additional functionalities. Hence, it is crucial to find a new base
50 to reinforce DESs with new features.

51 Supramolecular chemistry is one of today's main growing research areas, with great
52 application potential in various domains (*e.g.* food, medicine, environment) [4]. It is the
53 chemistry beyond the molecule that deals with the association of two or more chemicals
54 through non-covalent interactions [5]. This leads to organized entities of higher complexity
55 [6]. Host/guest chemistry, a branch of supramolecular chemistry, allows the construction of
56 inclusion complexes with improved physicochemical properties compared to those of the free
57 guest. Host molecules are various [7]. Their efficient functioning was traditionally
58 accomplished in conventional media *i.e.* water or organic solvents.



| Macrocycle | Cyclodextrins | Cucurbiturils | Crown ethers |
|--------------|---|---|---|
| Origin | Natural | Synthetic | Synthetic |
| Structure | Hydroxyl groups rims and hydrophobic cavity | Hydrophobic cavity and two identical carbonyl-lined portals | Macrocyclic polyethers with hydrophobic external ring |
| Guests | Hydrophobic guests | Hydrophobic guests | Cations |
| Interactions | Size complementarity | Size complementarity | Coordination with oxygen atoms |
| Media | Aqueous media | Aqueous media | Non polar solvents |

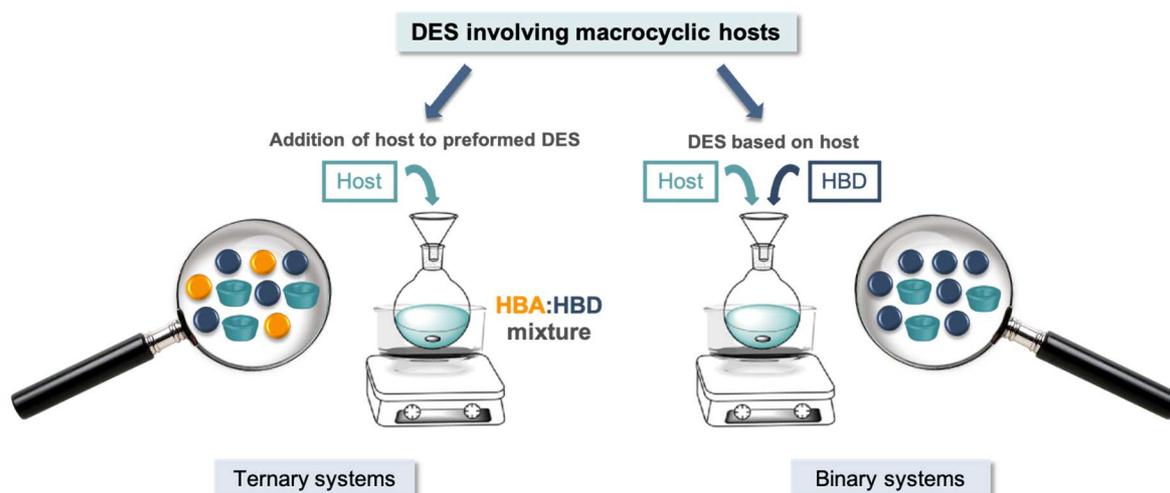
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60 **Figure 1. General features of the macrocycles used in the literature for the construction**
 61 **of ternary or binary systems.**

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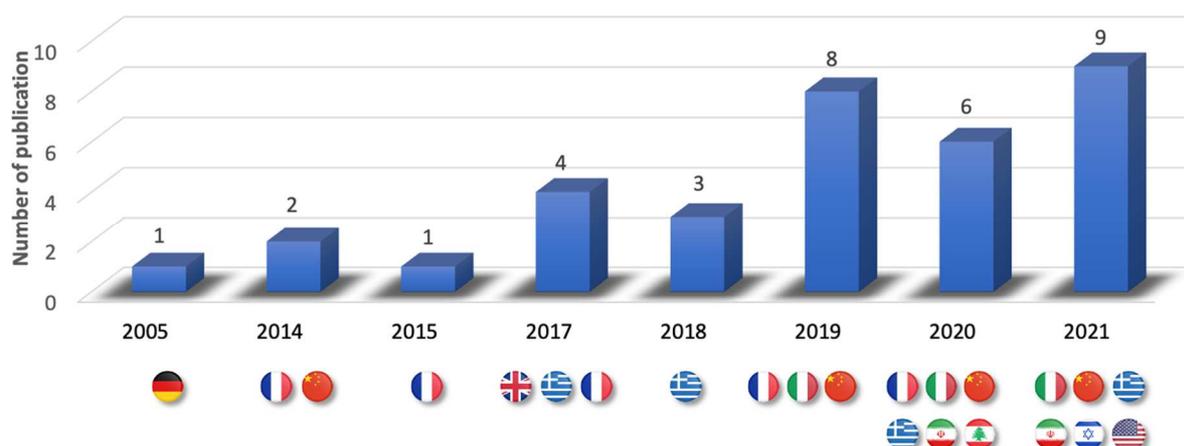
63 Transition to sustainable chemistry conducted researchers to attempt studying the solubility of
 64 macrocyclic hosts in green solvents such as DESs or to prepare LMMs using macrocyclic
 65 hosts where theoretically these molecules can act as both functional monomers and cage
 66 molecules. Figure 1 shows the general features of host molecules studied in or used for the
 67 design of eutectics. The two strategies for the combination of DESs and macrocycles are
 68 illustrated in Figure 2. Ternary systems refer to HBA + HBD + host while binary systems
 69 refer to HBA (host) + HBD . A literature overview of the field can be summarized in Figure
 70 3, showing a climbing interest over the last five years (keywords used: eutectic and either
 71 macrocycle or host or cyclodextrin or crown ether or cucurbituril or calixarene).

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Figure 2. The two existing combination strategies of DESs and macrocyclic hosts.



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Figure 3. Number of papers related to the combination of DESs and macrocyclic host molecules associated to the countries (source: Scopus, October 2021).

80 However, two main questions arise from these forerunner studies; what are the main driving
81 forces of the solubilizing mechanisms of these hosts in such non-conventional solvents? Do
82 these macrocycles still preserve their peculiarity to form host/guest inclusion complexes? In
83 this brief opinion, we will not simply summarize the published results related to the
84 combination of DESs and macrocycles but also try to answer these questions. We will
85 additionally attempt to gain a better understanding of what is required to get desired
86 formulation characteristics and good performance and to point out the gaps which need to be
87 filled by further investigations.

88
89

Solubilization of macrocycles in DESs: Ternary systems

90 In 2016, a patent described for the first time the efficiency of solubilizing CDs in reline in
91 order to improve the ability of this DES to solubilize Volatile Organic Compounds (VOCs)

92 [8]. Then, experimental investigations conducted in 2017 focused on the solvation of native
93 CDs and CB[n]s in reline. These two host families are insoluble in organic solvents and suffer
94 from a moderate solubility in water limiting their application to a specific concentration range
95 [9]. Interestingly, the solubility of the most widely used CD, β -CD, was increased 55 times
96 compared to water [10]. The absence of β -CD aggregates or clusters in reline was later
97 demonstrated, proving that β -CDs are maintained as isolated entities even at elevated
98 concentrations [11].

99 DESs possess a highly ordered liquid structure comprising strong hydrogen-bonding
100 interactions [12,13]. This network might have the ability to include and stabilize high amount
101 of macrocycles *via* extra hydrogen bonding. Molecular dynamics results showed that all reline
102 moieties (choline, chloride, and urea) favorably interact with β -CD, with urea developing the
103 most favorable dispersive interactions by extenuating inter-CD hydrophobic interactions,
104 while still maintaining the potency to establish strong hydrogen bonds with both the
105 constituents of DES and β -CD itself [11]. In other terms, urea is able to accumulate inside the
106 hydrophobic β -CD cavity as well as its exterior forming two solvation layers. Since urea
107 exerts the best solubilizing potential why not only using urea aqueous solution to enhance β -
108 CD concentration? It is true that urea has much more strongly solubilizing effect towards β -
109 CD in comparison to choline chloride when tested alone. But, the solubility of urea in water is
110 limited and the very high concentration of urea found in reline cannot be attained in aqueous
111 solutions. Replacing water with choline chloride enhances β -CD's stabilization by urea,
112 leading to overall much higher β -CD solubility in reline at low hydration [11]. The dissolution
113 process of β -CD in reline was shown to be an exothermic process, meaning that interactions
114 between the DES and CD are highly favorable and raising temperature does not facilitate the
115 dissolution [14].

116 However, results obtained with a macrocycle in a defined DES could not be projected to
117 another system. If β -CD was perfectly soluble in choline:urea (1:2), it was insoluble
118 in choline chloride:ethylene glycol (1:2), choline chloride:glycerol (1:2) and
119 tetrabutylammonium chloride:lactic acid (1:2) DESs [11,15]. Thus, each system should be
120 considered separately. Additionally, a panel of urea-based DESs should be tested in order to
121 strengthen the role of urea in the solvation process and evaluate the potential influence of the
122 DES partner.

123 The ability of DESs to dissolve macrocycles at higher concentrations opens up additional
124 interesting exploitations of such hosts. Nowadays, innovative extraction techniques and
125 catalysis are substituting well-known organic solvents with green, environment-friendly DESs

126 [16]. Researchers took profit from the ability of DESs to solubilize CDs to dope extraction
127 media with these macrocycles aiming to boost the extraction efficiency [17–21] or use them
128 as supramolecular catalysts in the green reaction medium [22]. Others synthesized water-
129 soluble β -CD-based nanosponges in natural DESs [23,24].

130 The usefulness of the use of a macrocycle resides in its peculiar encapsulation ability. In this
131 context, the new hybrid systems combining DES and CD would be mutually armed with the
132 beneficial properties of each component. Deeper queries were conducted trying to answer the
133 question: Is the high added value from CDs flow from their complexing ability? A positive
134 answer was given in 2019 by two different techniques (static-headspace gas chromatography
135 and NMR) [14,25]. Another experimental evidence of the formation of inclusion complexes
136 with native CDs and derivatives in reline was obtained later [26]. However, a drastic decrease
137 of formation constants (K_f) values of inclusion complexes was observed in DES compared to
138 water [14,25]. No correlation was observed between K_f values obtained in reline neither with
139 K_f in water nor with the decrease magnitude. This indicates that several mechanisms, that
140 should be revealed, affect the complexation in reline.

141 Adding water to DESs could modify their physicochemical properties (*e.g.* viscosity, polarity)
142 [27]. While high amount of water jeopardizes the integrity of DES hydrogen bond network, it
143 seems like adding some water to reline preserves a residual molecular network while offering
144 CD an aqueous-like environment with an increase in molecular rotational motion allowing it
145 to form inclusion complexes [28]. Since the integrity of DES is still preserved in the presence
146 of moderate amount of water, this leads to the apparition of the appellation of hydrated reline.
147 Interestingly, it seems like the integration of water in the system is full of benefits; *a)* at low
148 amounts it does not threaten the DES self-organization, *b)* it gives CD enough mobility to
149 form inclusion complexes and *c)* it decreases the high viscosity of DES, permitting
150 consequently an easy use of traditional NMR for quantitative measure of binding strength.
151 ROESY spectrum showed that β -CD cavity protons interact with protons of several guests in
152 hydrated reline such as piroxicam [28], VOCs (aniline and toluene) [25] and drugs
153 (amitriptyline and cyclobenzaprine) [29]. NMR results also proved that β -CD retained its
154 enantiorecognition ability in hydrated DES [29].

155 Yes, strong experimental findings evidenced that CDs maintain their encapsulation ability in
156 hydrated reline. K_f values for β -CD/toluene in water 287 M^{-1} [30], hydrated reline 79 M^{-1} [25]
157 and pure reline 11 M^{-1} [14] seem to support a linear correlation between the K_f and the
158 amount of water in the system. However, to undoubtedly elucidate this tendency more

159 investigations need to be undergone with stable inclusion complexes (with higher K_f values in
160 water) in order to increase the accuracy.

161 Electron paramagnetic resonance and spin probe studies underlined that β -CD and γ -CD did
162 not show the same tendency to encapsulate probe molecules in DESs [26]. This indicated that
163 one could not generalize from findings of data collected for one CD in one DES.
164 Additionally, caution should be taken when dealing with other host molecules, more precisely
165 CB[7]. Results showed that a small amount of DES in water ($H_2O:DES$ 20:1, V:V) was
166 sufficient to completely obstruct guest inclusion even at a relatively large amount of
167 macrocycle [26].

168 From an application point of view, formulation with improved solubilizing ability should also
169 ensure sustained and controlled release. Literature lacks any data about the release profiles of
170 entrapped guest in DES/macrocycle systems. Table 1 summarizes the topical areas of ternary
171 systems research fields.

172

173 **Formation of DESs with macrocycles as a partner: Binary systems**

174 Development of binary systems that are efficient requires less assay development, less time,
175 and less consumption of reagents than optimizing ternary formulations. However, totally
176 shifting to binary systems could present some inconvenience. This could mainly reduce the
177 number of possible combinations that could be made to control the properties of the medium
178 (*e.g.* the concentration of the host) as compared to ternary systems.

179 Hydrogen bonding is one of the most important requirements to create a DES, macrocycles
180 possessing functional groups that can be involved in hydrogen bonding could be used as
181 DESs components. Additionally, the host/guest recognition is a kind of non-covalent
182 interaction that could be applied to form DESs [31]. Even if the first attempts have started as
183 early as 2005 when α -CD was considered among other sugars used to prepare LMMs [32], the
184 use of macrocycles as host partners in LMMs have not blow up before 2014 [33,34]. In 2020,
185 the era of SUPRADES (supramolecular DES) was officially launched [35,36]. Table 2
186 summarizes all DESs or LMMs based on macrocycles.

187

188 **Table 1. The topical areas of ternary systems research fields.**

| Research field | Macrocycle | DES | Reference |
|---|--|---|------------------|
| Absorption process of gaseous effluents by combining macrocycles and DESs | β -CD, RAMEB | Choline chloride:urea | [8] |
| Solubilization of macrocycles in DESs | α -CD, β -CD, γ -CD CB[6], CB[7], CB[8] | Choline chloride:urea | [9] |
| Experimental and computational structural study of the dissolution mechanism of macrocycles in DESs | β -CD | Choline chloride:urea | [10,11] |
| Investigation of the thermodynamic properties of macrocycles dissolution in DESs | β -CD | Choline chloride:urea | [14] |
| Study of the complexation mechanism with or without water | α -CD, β -CD, γ -CD, HP- β -CD, and CRYSMEB | Choline chloride:urea | [14,25,26,28,29] |
| | Methyl- β -CD | Glycine:glycerol | [17] |
| | β -CD | Ammonium acetate:L-lactic acid | [18] |
| | HP- β -CD | Sodium acetate:glycerol | [19] |
| New extraction media combining macrocycles and DESs | β -CD | Nicotinamide:L-lactic acid Choline chloride:L-lactic acid Ammonium acetate:L-lactic acid Sodium acetate: L-lactic acid L-alanine:L-lactic acid Glycine:L-lactic acid | [20] |
| New catalytic media combining macrocycles and DESs | α -CD, β -CD, γ -CD, HP- β -CD, and MCD | 17 NADES | [22] |
| Synthesis of macrocycles-based polymers in DESs | β -CD | Choline chloride:citric acid | [23] |

Table 2. DESs or LMMs prepared using macrocycles.

| Macrocycle | % (wt) | Partner | % (wt) | Liquid at RT | Reference |
|---|--------|----------------|--------|--------------|-----------|
| α -CD | 30 | DMU | 70 | No | [32] |
| β -CD/ CRYSMEB/ RAMEB/ TRIMEB/ HP- β -CD/ HTMAP- β -CD | 30 | DMU | 70 | No | [33] |
| α -CD/ β -CD/ γ -CD HP- α -CD/ HP- β -CD/ HP- γ -CD/ TRIMEB/ TRIAC- β -CD/ CRYSMEB/ RAMEB | 30 | | 70 | | |
| β -CD/ CRYSMEB/ RAMEB | 20 | DMU | 80 | No | [34] |
| β -CD/ CRYSMEB/ RAMEB | 50 | | 50 | | |
| β -CD/ CRYSMEB/ RAMEB | 70 | | 30 | | |
| CRYSMEB/ RAMEB | 80 | | 20 | | |
| HP- β -CD/ CRYSMEB/ RAMEB/ Captisol® | 30 | Levulinic acid | 70 | Yes | [36] |
| β -CD/ RAMEB/ TRIMEB / HP- β -CD | 20 | L-lactic acid | 80 | Yes | [15] |
| | 3 | PEG 200 | 97 | | |
| 15-crown-5:NaOH | 1.5 | PEG 400 | 98.5 | | |
| | 1 | PEG 600 | 99 | Yes | [37] |
| | 3.5 | PEG 200 | 96.5 | | |
| 18-crown-6:KOH | 2 | PEG 400 | 98 | | |
| | 1 | PEG 600 | 99 | | |

191 DMU: *N,N'*-dimethylurea; PEG: Polyethyleneglycol; Captisol®: Sulfobutylether- β -cyclodextrin; CRYSMEB: Low methylated- β -cyclodextrin;
 192 HP- α -CD: 2-Hydroxypropyl- α -cyclodextrin; HP- β -CD: 2-Hydroxypropyl- β -cyclodextrin; HP- γ -CD: 2-Hydroxypropyl- γ -cyclodextrin;
 193 HTMAP- β -CD: 2-Hydroxy-3-(trimethylammonio)propyl- β -cyclodextrin; RAMEB: Randomly methylated- β -cyclodextrin; TRIMEB: Trimethyl-
 194 β -cyclodextrin; TRIAC- β -CD: Triacetyl- β -cyclodextrin.

195 A series of LMMs based on native CDs (α -CD, β -CD and γ -CD) as well as β -CD derivatives
196 and *N,N'*-dimethylurea was successfully evaluated as inert catalytic solvents [33,34].
197 Interestingly, the yield of 1-decene hydroformylation varied significantly according to the
198 nature of CD incorporated in the LMMs [33]. This proved that CDs are not a dump partner in
199 the green solvent. Surprisingly, the values of conversion did not follow the size of the cavity
200 but were affected by the type and degree of CD substitution as well as solute solubility and
201 solvent viscosity [34]. Still, the aim was not reached since all these new solvents have a
202 melting point higher than 67 °C, thus they are not liquid at ambient temperature.

203 SUPRADES, DESs with supramolecular properties were then introduced [35]. Interestingly,
204 the new RAMEB:levulinic acid system was liquid at room temperature. 2D ROESY (Rotating
205 frame Overhauser Enhancement Spectroscopy) and DOSY (Diffusion ordered spectroscopy)
206 experiments confirmed the interaction between the studied guest and the CD cavity protons
207 while no interaction was detected with levulinic acid. This constituted the first experimental
208 evidence that the solubilized guest is embedded within the host cavity. Then, in addition to
209 this SUPRADES, three other LMMs, HP- β -CD:levulinic acid, CRYSMEB:levulinic acid and
210 Captisol®:levulinic acid, were successfully obtained [36]. They showed distinct storage and
211 thermal stability as well as physicochemical properties (density, viscosity) depending on the
212 type of CD. The viscosity of levulinic acid based SUPRADES were around 200, 400, 600 and
213 1400 mPa s at 30 °C when respectively using RAMEB, CRYMEB, HP- β -CD and Captisol®
214 for the construction of the solvents. Interestingly, these viscosity values were shown to
215 significantly decrease with temperature [34]. The effect of the host molecule on the viscosity
216 of the solvents was also observed when using dimethylurea as a partner for LMM formation
217 [31]. Authors showed that adding water efficiently decreases the viscosity of these solvents.

218 On the other hand, El Achkar et al. reported for the first time the ability of a CD-based LMMs
219 to delay the release of a solute over time. Other SUPRADES, comprised of CDs and lactic
220 acid were obtained and tested for their efficacy to extract aromatic organic pollutants from
221 aqueous solutions [15].

222 Beside CDs, crown ethers took also their share in the preparation of DESs [31,37]. Crown
223 ether based DESs showed desirable characteristics, more precisely low viscosity and melting
224 point. They were evaluated for their ability to extract *N*-compounds from fuel oils. Active
225 hydrogen-bonding interaction was shown to be formed between the macrocycle and solute
226 while no evidence proved the encapsulation of extracts in crown ethers [37].

227 Generally, titration experiments, where the concentration of the host is varied, are applied to
228 obtain K_f for host/guest inclusion complexes. When incorporated in DESs, hosts are available

229 in large amounts in the medium (>20%) but their concentration cannot be varied. Thus, new
230 methods should be envisioned allowing the evaluation of the complexing ability of a
231 macrocycle incorporated in a LMM. Additionally, a systematic and clear comparison of the
232 performance of host-based DESs and host solubilized in DESs should be realized. This would
233 clarify whether all the advantages deriving from the increased amount of hosts achieved in
234 DESs could be or not counterbalanced by a decrease in the host properties of macrocycles. In
235 host-based DES, macrocycles may be more toughly engaged in a strong hydrogen bond
236 network that might further reduce their encapsulation performance. Also, the effect of water
237 addition should be investigated.

238

239 **Conclusions and future perspective**

240

241 The combination of novel deep eutectic systems and historical supramolecular chemistry
242 fields is currently an exciting scientific challenge. While pursuing the development and
243 optimization of innovative ternary and binary systems with promising and various application
244 fields, it will be important for future work to address deeper fundamental issues. Despite
245 numerous efforts executed in order to solubilize and elucidate the solubilization mechanism of
246 macrocycles in DESs or to prepare new host-based systems, the factors needed to elaborate
247 the optimal formulation are still not fully discovered.

248 Authors are encouraged to reveal the requirements needed to develop any binary system
249 because it becomes clear that hydrogen bonding is not the only must; a DES could not be
250 obtained using all hydrogen bond acceptor and donor couples. Various characteristics of the
251 building blocks should be considered (structure, mesomeric effect, hygroscopy, etc.).
252 Additionally when using macrocycles, like CDs for example, for the construction of eutectics,
253 different hosts do not form a DES with a same partner. Also, authors should give more
254 insights on the interaction mechanisms between hosts and DESs components and different
255 factors that influence the encapsulation properties (binding strength, isomers discrimination,
256 release) of macrocycles either when they are dissolved in DESs or used as partners.

257 On the other hand, these systems are growing in order to achieve safety and sustainability.
258 However, information on their storage stability, environmental degradation and toxicity is still
259 missed. Even if researchers take critical care in the selection of the building blocks, the
260 system safety statement should be proved. Completing fundamental and toxicological
261 investigations would boost the scaling up of DES/macrocycle systems.

262

263

264 **Conflict of interest statement**

265 Nothing declared.

266

267 **References**

268

269 Papers of particular interest, published within the period of review, have been highlighted as:

270 * of special interest

271 ** of outstanding interest

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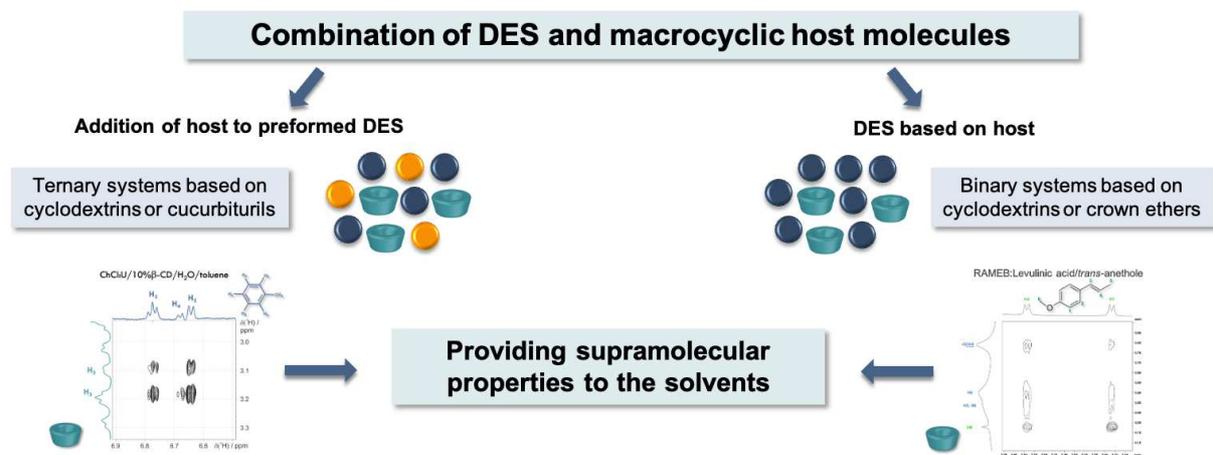
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306 concentrations with no clustering or aggregations. β -CD was maintained as isolated
307 entities as proved by the SAXS (Small angle X-ray scattering) technique.
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313 of DES are necessary as a) they synergistically enhance each other's stabilization effect
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429 **Graphical abstract**
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