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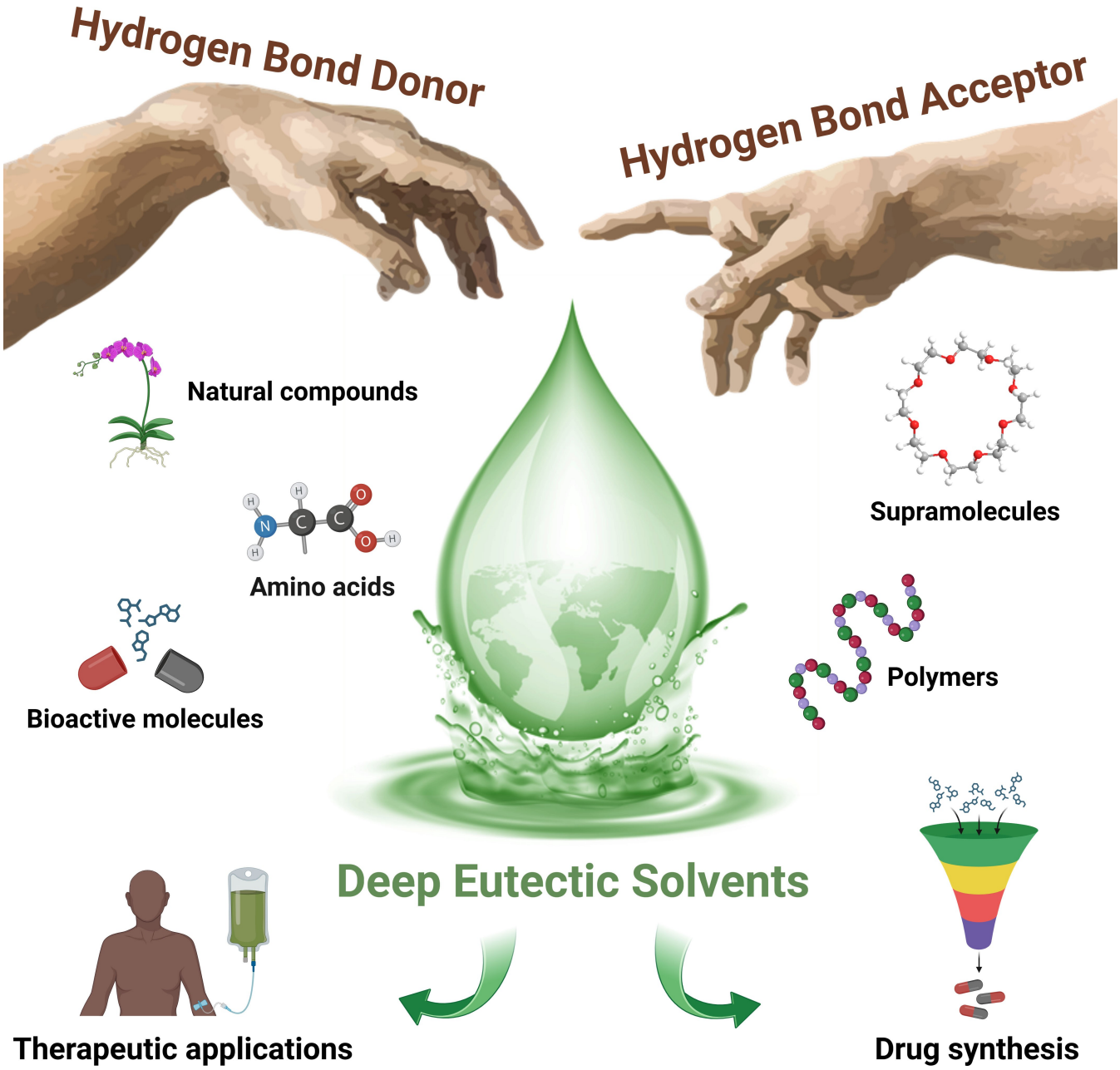
Deep Eutectic Solvents: An Eco-friendly Design for Drug Engineering

Feras Oyoun,[a, b] Antoniya Toncheva,[b] Luis Castillo Henríquez,[a] Raphael Grougnet,[c] Fouad Laoutid,[b] Nathalie Mignet,[a] Khair Alhareth,[a] and Yohann Corvis*[a]



In the spirit of circular economy and sustainable chemistry, the use of environmentally friendly chemical products in pharmacy has become a hot topic. In recent years, organic solvents have been the subject of a great range of restriction policies due to their harmful effects on the environment and toxicity to human health. In parallel, deep eutectic solvents (DESs) have emerged as suitable greener solvents with beneficial environmental impacts and a rich palette of physicochemical advantages related to their low cost and biocompatibility. Additionally, DESs can enable remarkable solubilizing effect for several active pharmaceutical ingredients (APIs), thus forming therapeutic DESs (TheDESs). In this work, special attention is paid to DESs, presenting a precise definition, classification, methods of preparation, and characterization. A description of natural DESs (NaDESs), i.e., eutectic solvents present in natural sources, is also reported. Moreover, the present review article is the first one to detail the different approaches for judiciously selecting the constituents of DESs in order to minimize the number of experiments. The role of DESs in the biomedical and pharmaceutical sectors and their impact on the development of successful therapies are also discussed.

1. Introduction

Solvents are generally employed in about 85% of pharmaceutical processes. In this domain, water is the most convenient solvent due to its safety and eco-friendliness. However, organic solvents are used the most for poorly water-soluble active pharmaceutical ingredients (APIs) employed in formulation development and manufacturing. Many conventional organic solvents are harmful to the environment or toxic to human health. Consequently, many regulations have limited their use, especially for the ones classified as carcinogenic or toxic for reproduction.[1,2]

Two main categories of solvents can be considered of great interest as eco-friendly alternatives: Ionic liquids (ILs) and deep eutectic solvents (DESs). ILs emerged as outstanding green alternatives to conventional organic solvents due to their negligible vapor pressures and good chemical/thermal inertness.[3,4] However, some limitations are still encountered regarding their biotoxicity and biodegradability.[5] On the other hand, Abbott et al. described in 2003 a fascinating class of nonaqueous solvents, which is called deep eutectic solvents, representing eutectic mixtures of ammonium salts (e.g., choline chloride, ChCl) and hydrogen bond donors (HBD) (e.g., urea and glycerol).[6] This class of solvents has some IL-like solvent properties such as low melting point and volatility, high thermal stability and solubility, and finetuned physicochemical properties by choosing appropriate DES components.[7–9] Interestingly, a great range of DESs components are present in nature and are easily prepared by several approaches. DESs can be considered as a greener alternative compared to ILs, accompanied with interesting advantages: Low cost, higher purity and biodegradability, and potential low toxicity. Consequently, such DESs have been extensively employed in different pharmaceutical applications, including solubilization of poorly water-soluble drugs, permeability enhancement, stability improvement, and designing polymeric and self-assembled nanocarriers.[10–12] Furthermore, they have attracted a great attention in many academic and industrial fields, such as inorganic synthesis, organic (bio)catalysis and synthesis, dissolution and extraction processes, material chemistry, bioengineering, and biotechnology.[13–17] The evolution of the DESs and their involvement in various research areas during the last years are summarized in Figure 1.

This review aims to clarify some misconceptions about DESs, unveiling the main difference between eutectic and deep eutectic mixtures, which has been misused in several published articles. Also, we highlight the importance of natural deep eutectic solvents (NaDES) to avoid the potential environmental hazards of traditional solvents. Moreover, the main criteria involved in the selection process of DESs components is illustrated in addition to the methods of preparation and characterization tools of these systems. Finally, we discuss the role and the potential activity of DESs in pharmaceutical applications, also providing a brief future perspective for using this eutectic system in drug discovery and formulation development.

2. Definition and Classification of Deep Eutectic Solvents

In 1884, Frederick Guthrie coined the term *eutectic* by combining the Greek words "ευ"–meaning good/easy–with "τηκτική"–which means melting. He defined it as systems consisting of two or more components, which are in such proportion to one another, giving the resultant system with a lower temperature of liquidus at a given composition (i.e., the eutectic point) compared to any other proportion.[18] Nowadays, the International Union of Pure and Applied Chemistry (IUPAC) gold book defines eutectics as an isothermal and reversible reaction between two (or more) solid phases that produce a single liquid phase during the heating of the system.[19] Nevertheless, the latter definition is inconsistent with a previously published article by Pereira et al., where a eutectic solvent was prepared using limonene as one of the constituents, which is

[a] F. Oyoun, L. C. Henríquez, Dr. N. Mignet, Dr. K. Alhareth, Prof. Y. Corvis
CNRS, Inserm, Chemical and Biological Techniques for Health (UTCBS)
Université Paris Cité, School of Pharmacy
4 avenue de l'Observatoire, F-75006 Paris (France)
E-mail: yohann.corvis@u-paris.fr
[b] F. Oyoun, Dr. A. Toncheva, Dr. F. Laoutid
Laboratory of Polymeric & Composite Materials
Materia Nova – Research and Innovative Center
Avenue Copernic 3, B-7000 Mons (Belgium)
[c] Dr. R. Grougnet
Natural products, Analysis, Synthesis, UMR CNRS 8038 CiTCoM, Université Paris Cité, School of Pharmacy, F-75006 Paris (France)

liquid at room temperature (rt).[20] In addition, the IUPAC definition does not include the importance of molar ratio to obtain eutectic systems. Therefore, Guthrie's definition is more accurate because it considers the melting points and the molar ratio of the constituents regardless of their initial physical state.

Over the last two decades, eutectic solvents have been extensively studied in various research areas leading to different denominations according to the field. These are named phase change materials (PCM) in the field of thermal energy storage devices or building materials,[21,22] eutectic alloys for metallurgy,[23] and low transition temperature mixture in green chemistry.[24,25] As mentioned before, the term "Deep Eutectic Solvents" was first used by Abbott et al.[6] The authors refined later the definition of DESs as systems elaborated from a eutectic mixture of Lewis or Brønsted acids and bases which can include a wide range of anionic and/or cationic species.[26] However, the previous definitions do not satisfy the requirements of a stricter definition to distinguish between eutectic and deep eutectic solvents. The crucial factor relies in the comparison of the predicted (ideal) and the experimental (real) eutectic temperatures of these solvents.[27] The ideal solid-liquid phase (SLP) diagram, i.e., the solidus and liquidus equilibria, is obtained from the Schröder – van Laar equation [Eq. (1)] and allows predicting the eutectic point for an ideal mixture ($T_{eutectic(ideal)}$).[28] In contrast, the solidus and liquidus temperatures for real mixtures are determined experimentally and plotted against the molar ratio to show the experimental eutectic point, $T_{eutectic(real)}$, (Figure 2).

$$\ln(x_i \cdot \gamma_i) = \frac{\Delta_{fus}H}{R} \cdot \left(\frac{1}{T_{fus}} - \frac{1}{T_x}\right) \quad (1)$$

where γ_i is the activity coefficient of compound *i* at a given mole fraction composition x_i. $\Delta_{fus}H$ represents the heat of fusion (J mol^{-1}), and T_{fus} represents the melting point (in Kelvin) of the pure compound *i*. T_x is the melting point of the binary mixture at a specific x_i composition. R is the gas constant (8.314 J K^{-1} mol^{-1}).

Prof. Dr. Yohann Corvis holds an engineering doctorate in physical chemistry, material sciences and process (Lorraine University, 2005). He currently works at the Faculty of Pharmacy of Paris (Université Paris Cité), in the CNRS/Inserm group "Chemical and Biological Techniques for Health". His research expertise deals with the state of matter of raw pharmaceutical materials, interactions characterization, and formulation of final products such as nanomedicines for anesthetic, anti-tumor, and anti-inflammatory therapies, from pre-formulation to in vivo evaluation. To date, he has authored 53 publications, 3 patents, 1 book chapter, etc. He has supervised 65 interns and 3 PhD students and his work has been presented at 78 international symposia, 42 national symposia, and 30 invited talks.

Based on the ideal and real melting points, DES is defined as a mixture of pure compounds whose real eutectic point is lower than the ideal eutectic point at a specific molar ratio due to the formation of supplementary hydrogen bonding in the liquid state. On the contrary, the mixture of pure components is simply called "eutectic solvent" if the real eutectic point is identical, or higher than the ideal one but remains below the melting points of the pure constituents (Figure 2).

Furthermore, DESs can be classified according to the nature of the constituents into i) NaDES, ii) therapeutic deep eutectic solvent (TheDES), iii) amino acid deep eutectic solvent (AADES), and iv) poly deep eutectic solvent (PDES), which contain plant origin compounds, active pharmaceutical ingredient (API), amino acids, and polymers, respectively (Table 1). Additionally, supramolecular deep eutectic solvents (SupraDES) appeared in 2020 as a new DES subclass incorporating macrocycle-based supramolecular molecules as one of the DES components.[29,30]

Another classification system is used to sort the DESs into five categories based on the chemical structures of the constituents, as shown in Table 2. Type I DESs include non-hydrated metal halides having relatively high melting temperatures, which limit their application for biomass processing.[36] On the other hand, Type II DESs are more convenient for industrial processes due to the lower cost of the hydrated metal halides. The most commonly used DESs are Type III given their low toxicity and easy preparation.[37,38] Type IV DESs combine Type II and Type III by incorporating metal halide hydrate and organic HBD.[39] Type V DESs are of recent emergence and comprises the eutectic systems composed of only non-ionic HBDs and hydrogen bond acceptors (HBAs).[40]

3. Safety of Deep Eutectic Solvents

Every year, around 20 million tons of solvents are liberated from the chemical and pharmaceutical industries into the nature.[41] Consequently, one of the important objectives of green chemistry is to reduce classical organic solvents use or move toward alternative solvents with lower impact on the environment and human health, and with cost-effective use. Recently, the safety of DESs has been a controversial topic due to the variation of natural and molecules that can be included in their formation. Therefore, several studies have been conducted to compare the physicochemical properties of DESs with organic solvents and ILs. The main features addressed in the literature of these three solvents classes (DESs, ILs, and organic solvents) are summarized in Table 3. However, it is still possible to find some variations in the sub-classes depending on the nature of the constituents.[42–47] For example, DESs and ILs usually have common properties (e.g., highly tunable, low flammability, and low volatility) which make them considered as potential alternatives to organic solvents.[48] Moreover, various eutectic systems have been considered more biodegradable compared with ILs, and are foreseen as greener solvents with a wide range of biomedical applications.[49,50] In addition, the recyclability of DESs is considered another important feature which allows the researchers to reuse the eutectic systems and decrease the

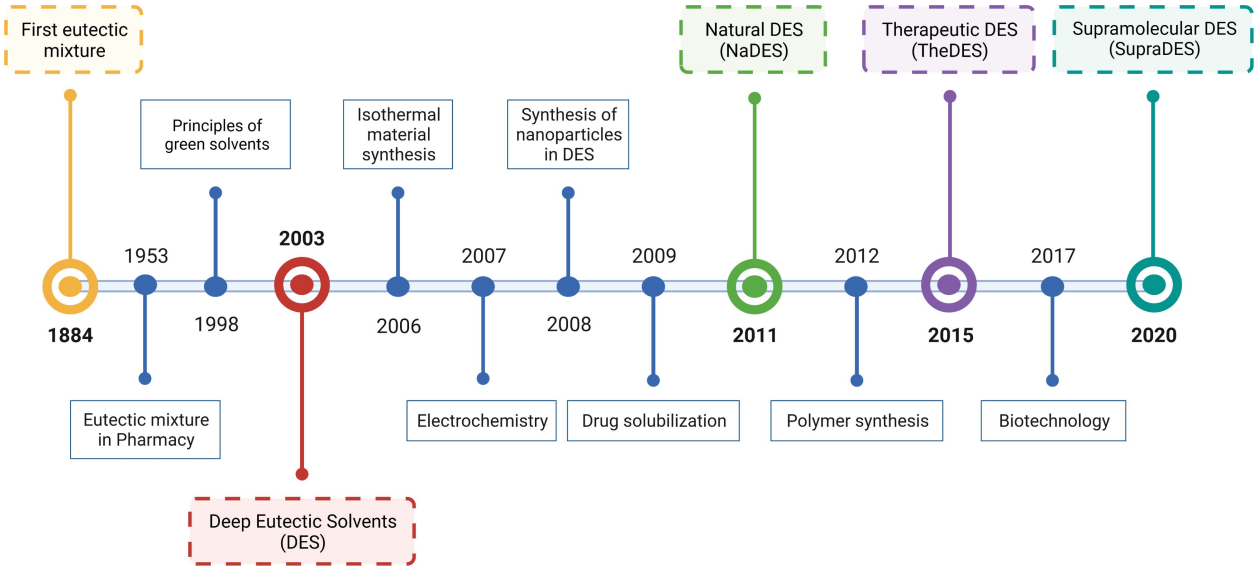


Figure 1. Deep eutectic solvents timeline: From discovery to research applications.

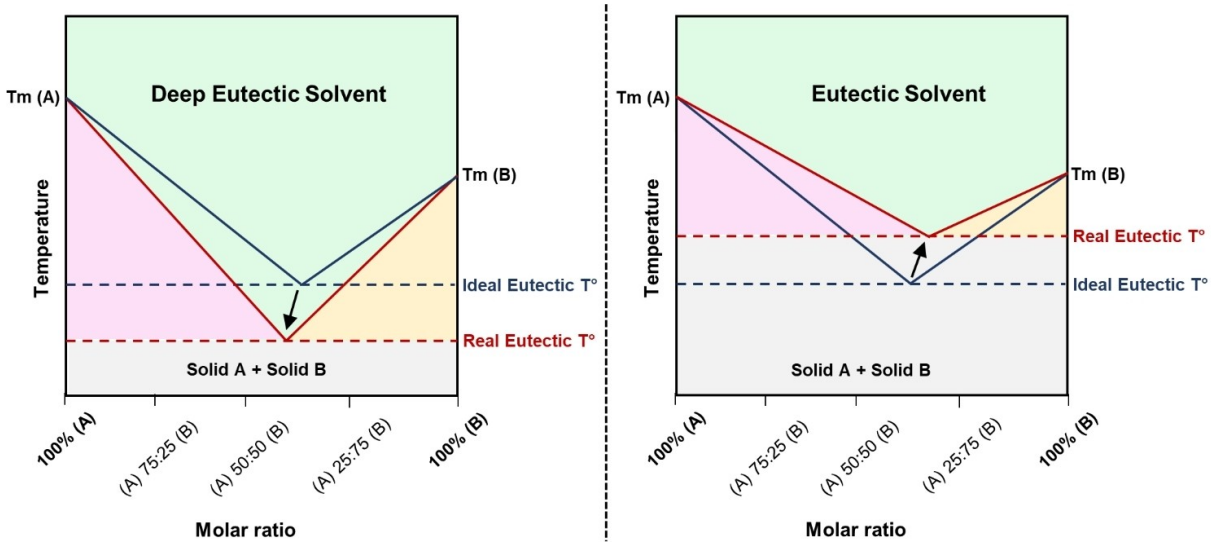


Figure 2. Solid-liquid phase diagram representing the difference in real and ideal eutectic temperatures between DESs (left panel) and eutectic solvents (right panel). The physical state of the mixture at various temperatures and molar ratios is represented by the following colors: white (solid A + solid B), pink (liquid + solid A), yellow (liquid + solid B), and light green (DESs "left" and eutectic solvent "right"). NB: For the eutectic solvent solid-liquid phase diagram (left panel), the real eutectic temperature can also be equal to the ideal one.

Table 1. Classification of deep eutectic solvents based on the nature of the constituents.

Type	Combination	Example	Ref.
TheDES	API + co-former	lidocaine + camphor	[31]
AADES	amino acid + co-former	l-proline + ethylene glycol	[32]
NaDES	natural compound 1 + natural compound 2	betaine + sucrose	[33]
PDES	polymer + co-former	polyethylene glycol + tetra-butyl ammoniumbromide	[34]
SupraDES	component 1 + component 2	*N*,*N*′-dimethylurea + cyclodextrins	[35]

waste produced.[51] For instance, Annes et al. synthesized 2H-chromene (structural motif in many bioactive compounds) in good yields using DESs, which were recycled for five times.[52]

Due to the presence of various data gaps for DESs properties and their components, the claims about the DESs greenness are sometimes exaggerated. In general, many studies showed

Table 2. Classification of deep eutectic solvents based on their chemical structures.

Type	Combination	Formula	Example
I	organic salt + metal salt	$Cat^+ X^- + zMCl_x$ (M = Zn, Sn, Fe, Al, Ga, In)	$ChCl + ZnCl_2$
II	organic salt + metal salt hydrate	$Cat^+ X^- + zMCl_x \cdot yH_2O$ (M = Cr, Co, Cu, Ni, Fe)	$ChCl + CoCl_2 \cdot 6H_2O$
III	organic salt + HBD	$Cat^+ X^- + zRZ$ (Z = $CONH_2$, COOH, OH)	ChCl + urea
IV	metal salt (hydrate) + HBD	$MCl_x + RZ$ (M = Al, Zn; Z = $CONH_2$, OH)	$ZnCl_2$ + urea
V	nonionic HBA + HBD	$R'Z' + RZ$ (Z and Z' = $CONH_2$, OH, COOH)	citric acid + glucose

that DESs are greener solvents compared to organic solvents and ILs, but some eutectic mixtures are less than initially thought, probably due to the nature of their constituents.[43,48] Therefore, a comprehensive assessment of commonly used DESs as well as their constituents was performed by TOPSIS (Technique for Order Performance by Similarity to Ideal Solution) algorithm to clarify their greenness status.[53] The multi-criteria decision analysis (TOPSIS ranking) was applied with combination of biological effect modeling for DESs to rank them according to greenness criteria, which includes safety, biodegradability, and toxicological aspects. The results showed that DESs constituted of sugars, straight-chain alcohol, sugar alcohol, and amines can be promising green solvents, in contrary to eutectic systems containing organic acids and metal ions. In addition, these findings are consistent with another study conducted by analyzing 572 DESs and their constituents using in silico modeling approach for the assessment of their environmental toxicity (Figure 3).[54]

In the light of recent works, natural molecules-based eutectic systems are potentially greener solvents and more sustainable compared with conventional organic solvents and ILs. In 2011, Choi et al. paid attention to NaDESs, a special class of DESs.[55] Originally, the assignment of "natural" is related to the important class of primary plant metabolites, such as polysaccharides, amino acids and others, that can form non-toxic DES-like liquids. Nowadays, the general trend is to substitute the terms primary and secondary metabolites for biosynthetically primordial metabolites (PRIM) and biosynthetically more highly evolutionary metabolites (HEVO), respectively.[56] Indeed, these reflect better the slight distinction between both groups of compounds and the potential turnover as exemplified for cyanogenic glycosides, such as linamarin and linustatin.[57] Additionally, these terms also take into account other physiological functions beyond the long deciphered allelopathic or cooperative ecological roles.

Among hundreds of up-to-date described NaDES systems, most are mode of PRIM. Highly polar and hydrophilic combinations, mainly in ternary/quaternary mixtures, are able to integrate and strongly retain the necessary water molecules for plants growth. Nevertheless, some HEVO, such as the ubiquitous flavonoids, quercetin, kaempferol and their glycosides may be present at ample concentrations that cannot be explained only by allelopathy or interspecific cooperation purposes (e.g., pollination). Thus, a putative membership as NaDES components should be considered as likely. Moreover, their occurrence in adaptogen plants such as Sedum, Rhodiola, Kalanchoe/Bryophyllum belonging to the botanical family Crassulaceae, able to survive in arid climates, is noticeable.[58] In those species characterized by the Crassulacean Acid Metabolism, malic acid

Table 3. Comparison of the main properties of DESs with ILs and organic solvents.

	Organic solvents	DESs	ILs
composition	organic compounds[a]	HBA + HBD	cation + anion
volatility	high	low	low
flammability	usually flammable	usually non-flammable	usually non-flammable
viscosity	low	± high	± high
hazard level	high	low	high
solubility of chemicals	mainly organic compounds	organic and inorganic compounds	organic and inorganic compounds
tunability	–	high	high
biodegradability	non-biodegradable	± biodegradable	± non-biodegradable
toxicity to the environment	high	low	low
cost	± expensive	± less expensive	± expensive

[a] Aliphatic or aromatic hydrocarbons, amines, esters, ethers, ketones, and nitrated or chlorinated hydrocarbons.

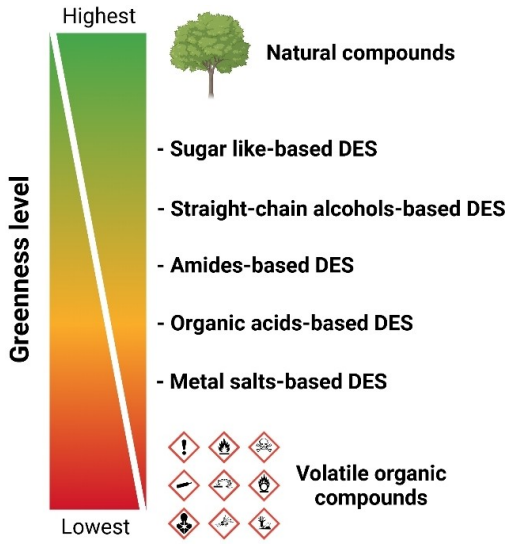


Figure 3. Likelihood for greenness level of different types of DESs.

plays a key-role in an original photosynthetic process. As this small organic acid is known as a NaDES component, an association with HEVO aglycon and/or glycosides seems plausible.

Currently, NaDESs are of great interest as evidenced by numerous recent research papers with a great range of applications. Indeed, due to their potential lack of toxicity, NaDESs can be used not only for food extraction and nutraceuticals, but also in pharmaceutical and cosmetic formulations.[59]

4. Tools and Criteria to Design Deep Eutectic Solvents

One of the advantages of DESs is the ability to be "designable" solvents, which means that constituents with different structures and characteristics can be screened to customize DESs for specific applications. Precursors selection to form eutectic systems is challenging due to the vast number of possible compounds. Performing the screening process without relying on specific tools and criteria might be time-consuming and very expensive. Therefore, the following sections describe the main parameters used in the literature to choose suitable DES components.

4.1. Molar ratio and solid-liquid phase diagram

The molar ratio is strongly linked to the eutectic point, which corresponds to the lowest melting temperature at a particular composition for a given multicomponent system. The selection of an optimal molar ratio has been proven to produce DESs with a reasonable strength of hydrogen bonds.[60] Moreover, altering the molar ratio of a DES having the same constituents can change its physicochemical and functional properties such as density, viscosity, pH, and the extraction effect.[61–64] For example, the properties of the ChCl/D-glucose eutectic system were analyzed at different molar compositions by Hayyan et al. The authors reported that the lowest viscosity obtained at the ideal eutectic composition and the other properties such as refractive index, pH, and surface tension were significantly modified with varying molar compositions.[65] Hence, choosing a suitable molar ratio is crucial for obtaining DESs with appropriate properties. Indeed, as most eutectic systems have a relatively wide liquid composition window, which allows them to be used as solvents for temperatures comprised between a temperature above the eutectic point and rt (Figure 4), these may present a range of stoichiometric ratios for the latter temperature range.

The SLP diagram elaboration is a feasible method to predict the melting temperature of DES mixture and the application range of its molar ratio. As mentioned before, the diagram is made using the Schröder – van Laar equation based on three molecular descriptors, namely, the melting point, the heat of fusion, and the activity coefficient of the pure compounds. The latter is equal to one for molecules that have ideal thermodynamic behavior. Consequently, plotting the calculated "theoretical" melting temperatures versus the mole fraction composition of the binary system allows to predict the feasibility of obtaining a DES before doing any experiments. Many articles in the literature showed a compromise between the predicted melting temperatures of DESs and the experimentally determined eutectic points, confirming the importance of this method.[27,66,67]

4.2. Melting properties of the pure components

Several chemical and physical factors can interfere in mixture's ability to hit its eutectic point, such as the melting temperature

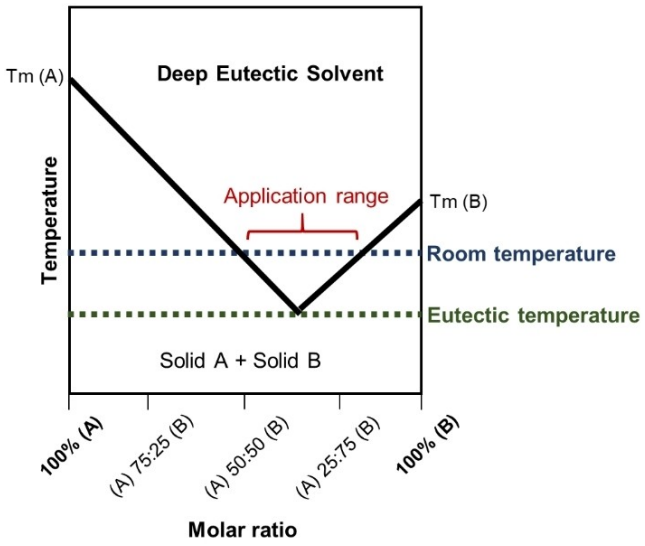


Figure 4. Solid-liquid phase diagram for the assessment of the theoretical application range to obtain deep eutectic solvents at rt.

of the HBD and the HBA. The melting point is defined as the ratio between the enthalpy of fusion ($\Delta_{fus}H$) and entropy of the component ($\Delta_{fus}S$) [Eq. (2)]. The enthalpy of fusion is the heat required to transform a substance from a solid state to a molten state, and it depends on the crystal form of the solid phase and the force of interactions between the molecules.[68] On the other hand, the entropy of fusion is the increase in the degree of disorder upon melting, depending on the molecular geometry (e.g., symmetry) and flexibility.[69,70] Based on the previous definitions, we can notice that the thermal properties of a molecule are strongly related to its structure and the degree of interactions, which are discussed in the next section.

$$T_m = \frac{\Delta_{fus}H}{\Delta_{fus}S} \quad (2)$$

Wolbert et al. evaluated and used three APIs and six excipients to prepare 11 combinations of eutectic systems. They showed that the excipient's melting point should be similar to that of the API, and the excipient melting enthalpy should be as low as possible to obtain the most suitable API/excipient TheDES.[71] Moreover, Alhadid et al. demonstrated that components with a lower melting enthalpy would give eutectic mixtures with a larger depression in the melting temperature.[28] This is actually coherent with the Schröder–van Laar equation. Similarly, the diminution of the melting temperature of the constituents with comparable melting enthalpies increases the eutectic temperature depression. Consequently, the alteration in eutectic temperature of DESs aligns with changes in the melting point and the enthalpy of fusion of their constituents. However, predicting whether the eutectic temperature will increase or decrease becomes challenging when these two factors shift in opposite directions. In summary, the assessment of the thermal properties of DES components can efficiently be used to find a worthy option for conceiving proper eutectic solvents.

4.3. Intermolecular interactions

The melting and boiling points of a substance are critical physical properties that are related to the intermolecular forces established between its basic constituents. DESs are formed due to a hydrogen bonding network that leads to a significant melting point depression compared to the parent compounds. The latter indicates higher force of interactions between HBA and HBD than the intermolecular interactions of the parent compounds.[72] Moreover, the magnitude of the interaction between HBA and HBD is affected by several factors, such as the molecular structure of pure components and their functional groups.

4.3.1. Functional groups of pure components

The usually involved atoms in hydrogen bonds are nitrogen, oxygen, and fluorine. The presence of certain functional groups can influence the interactions between HBA and HBD. For instance, Migliorati et al. studied the structural properties of two DES systems, namely urea/ChCl (reline) and urea/butyltrimethyl ammonium (UBTMAC), and the effect of hydroxyl group on their behavior. They showed that the hydrogen bond interactions between chloride ions and urea molecules are more favored in the absence of hydroxyl group in UBTMAC, which has a lower melting point depression. Moreover, the presence of hydroxyl group in reline induces the three-dimensional rearrangement in the mixture, which hinders the hydrogen bond formation between the cation and hydroxyl group.[73] Consequently, the functional groups influence the melting point of the DES either by participating in the hydrogen bonding network, or by changing the structural arrangement of the eutectic mixture.

Although the formation of hydrogen bonding is crucial for preparing DESs, it is insufficient if the resulting interactions are not enough substantial. Silva et al. determined SLP diagrams of several binary systems containing sugar alcohol to check the suitability of forming DESs.[72] They found that the intermolecular interactions between the molecules' hydroxyl groups are insufficient to obtain a eutectic system with a melting point significantly lower than the melting points of its constituents. They also designed another two eutectic systems composed of ChCl and sugar alcohols, namely, mannitol and maltitol. A significant melting temperature depression for these two eutectic solvents was obtained. This depression in melting temperature was explained by the formation of hydrogen bonds between the hydroxyl groups of mannitol or maltitol and the chloride anion of ChCl, which is stronger than the O–···O hydrogen bonding established in the pure phases of sugar alcohols. In addition, the melting temperature of the maltitol/ChCl eutectic mixture is lower than the one comprising mannitol/ChCl since maltitol has a much larger number of hydroxyl groups than mannitol, which means that the former can establish more Cl–OH hydrogen bonds. Moreover, Wang et al. prepared various DESs containing ChCl as HBA and polyols (e.g., Butanediol) as HBD and demonstrated the key role of the hydrogen bond interactions between the chlorine atom of ChCl and O–H group in the polyols to obtain DESs. They found that the strength of the hydrogen bonds between the DESs components increases with both the decrease of length of hydrocarbon chain between the two hydroxyl groups in butanediol, and the increase of hydroxyl number in polyols.[60] Therefore, the number and position of the functional groups on the starting compounds have a strong influence on the strength of hydrogen bond interactions, and thus, on the eutectic melting temperature.[60,72,74]

4.3.2. Molecular structure of pure components

The molecular structure of DES constituents can affect the strength of interactions, and hence, the melting properties. One of the molecular descriptors is the flexibility and rigidity of the molecules. The longer the chain in a simple linear

molecule, the higher flexibility. On the other hand, the presence of some functional groups, or the aliphatic and aromatic cyclic compounds can contribute to the molecular flexibility. Some molecules are presented in Table 4 with their flexibility number, which increases with the chain length.[70]

Alhadid et al. found that the melting enthalpy of two compounds having similar melting temperature is lower for the molecule with rigid molecular structure compared to the other with a flexible one.[75] Therefore, the molecular structure of the DES components may be closely linked with the eutectic temperature, presenting an avenue to streamline the screening process for formulating eutectic systems.

5. Preparation and Characterization of Deep Eutectic Solvents

5.1. Preparation of deep eutectic solvents

One of the main reasons why DESs have been deeply studied is due to the existence of different preparation methods. To date, seven approaches have been used to prepare these types of solvents. The majority of DESs are prepared by the **heating and stirring method**. This is defined by a continuous mixing with gentle heating of the constituents at a specific stoichiometric ratio until a homogeneous mixture is obtained. Despite its wide use and simplicity, the temperature and the duration of mixing should be controlled during the process of preparation to avoid the risk of decomposition and formation of by-products in case of using high temperature, or the risk of crystal formation when preparing at low temperatures and/or too short heating and stirring times.[76,77] Other eutectic systems can be easily prepared by stirring at rt without heating or any additional external energy.[78,79] The second approach, called **the grinding method**, is used for thermosensitive molecules to prepare DESs at rt. This mechanochemical process produces eutectic systems by mixing and crushing the constituents using a mortar and a pestle until a clear liquid is obtained.[80] However, the lack of temperature control during the mixing step is considered as a drawback. Another mechanochemical approach, the **twin screw extrusion (TSE) method**, is described in the literature by its continuous mixing and crushing of the constituents using twin screw extruder that consists of two co-rotating or counter rotating identical screws encased in a barrel. This method can be easily scaled-up and unlike the grinding method, temperature control is possible during the mixing process. Moreover, the thermal degradation can be avoided due to the short heat exposure time.[81,82] A fourth approach is the **freeze-drying method**, which is considered as a good choice for thermosensitive reagents. It is described by the dissolution of stoichiometric amounts of HBA and HBD with distilled water. The obtained solution is frozen using a freezer or liquid nitrogen, and then freeze-dried by lyophilization.[83] Noteworthily, this method is not suitable for volatile reagents due to the low-pressure exposure. A similar method reported in the literature, called **vacuum evaporation method**, is illustrated by dissolution of the constituents in water followed by water elimination using rotary evaporation to get the DES. A desiccator with silica gel is used to dry the DES until obtaining a constant weight but complete water elimination can be difficult and time consuming. In this approach, lower temperatures are used compared to the heating and stirring method.[84] Another faster, cheaper and easier method was used in a few works, called **microwave irradiation method**. It is defined by the addition of stochiometric amounts of HBA and HBD into a vial and then putting it in a microwave for a specific duration and at a particular radiation power. This technique requires less energy compared to the previously mentioned ones, and it is highly eco-friendly.[85,86] The last method is called **ultrasound-assisted preparation** and it is used to prepare DESs by mixing stoichiometric amounts of HBA and HBD in a vial, followed by treatment in an ultrasonic bath for a specific time and at a particular temperature. After preparation, the DESs are kept for 24 h at rt to ensure the formation of a homogenous mixture.[87] A list of DESs prepared by the different methods are listed in Table 5. Regardless of the selected approach, considering the stoichiometric ratio between the HBA and the HBD is essential in order to obtain DES systems at temperatures where they exhibit a complete molten state.

The choice of method depends on the characterization of the HBA and HBD that constitute the DESs. The use of heat-free methods to prepare DESs containing thermosensitive components is a major concern. Previous studies showed that the method of preparation can influence the physical and chemical properties of DESs. For instance, Florindo et al. used the heating/stirring and grinding methods to prepare five DESs composed of ChCl as the HBA and different carboxylic acids as the HBDs. The DESs obtained by the grinding method were pure, whereas the heating method produced DESs with impurities in variable amounts ranging from 5% to 30%. This difference was explained by the esterification reaction between ChCl and carboxylic acid taking place upon heating.[80] Moreover, esterification can increase the water content in the obtained mixture by producing water molecules as by-product.[91] Consequently, chemical reactions between some HBDs

Table 4. Examples of some molecular flexibility numbers obtained from ref. [70].

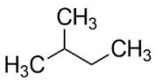
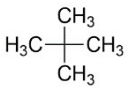
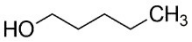
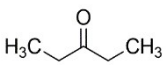
Name	Structure	Flexibility number
n-pentane		5.93
2-methylbutane		2.44
neopentane		1
1-pentanol		14.44
3-pentanone		3.8
cyclopentane		1

Table 5. Sustainable preparation of DESs by the different methods reported in the literature.

Method of preparation	DES components HBA	HBD	Molar ratio	Description	Ref.
heating and stirring	choline chloride	1,6-hexanediol	1 : 2	extraction of bioactive macamides from the roots of *Lepidium meyenii* Walp	[88]
	DL-menthol	thymol	1 : 4	production of therapeutic hydrophobic DES-based nanoemulsions for enhanced antimicrobial applications	[89]
grinding	choline chloride	glutaric acid	1 : 1	assessment of the impact of heating and grinding methods in the thermophysical properties of the prepared DES	[80]
twin screw extrusion	choline chloride	urea	1 : 2	assessment of the TSE as a method for the large-scale manufacture of DESs	[81]
freeze-drying	choline chloride	urea	1 : 2	incorporation of large unilamellar vesicles (Liposomes) in DESs	[83]
vacuum evaporation	choline chloride	DL-malic acid	1 : 1	a comparative study to understand the effect of some process parameters on the formation and the impurities of DESs prepared by freeze-drying, vacuum evaporation, and heating methods	[90]
microwave irradiation	glucose	lactic acid	1 : 5	DESs were successfully prepared using the microwave irradiation method with results demonstrating outstanding advantages such as a decrease in preparation time and energy consumption	[85]
ultrasound-assisted method	xylitol	citric acid	1 : 1	NaDESs were prepared according to heating and stirring, microwave irradiation, and ultrasound-assisted methods. The physicochemical characteristics of the prepared NaDESs were compared to distinguish the advantages and disadvantages of each method of preparation	[86]

and HBAs can occur when applying high temperatures or choosing inappropriate methods of preparation. Therefore, the selection of suitable preparation method is critical to obtain homogenous, pure, and stable DESs.

5.2. Characterization of deep eutectic solvents

Before using the DESs at early pharmaceutical research stages or at industrial level, several physicochemical properties should be explored to determine their applications. The most important properties of these solvents are the melting point, pH, density, and viscosity (Figure 5). However, studying other characteristics of the eutectic systems used for biomedical applications, such as biocompatibility, biodegradability, and toxicity, is also essential. Moreover, the scientific community studied other properties of these systems, such as ionic conductivity, polarity, and surface tension, because they have been employed in various research areas, including organic synthesis, extraction, and nanotechnology.[92–94] Therefore, to understand deeply and characterize DESs, abundant information is needed to fully map the pieces and understand the behavior of these systems. The

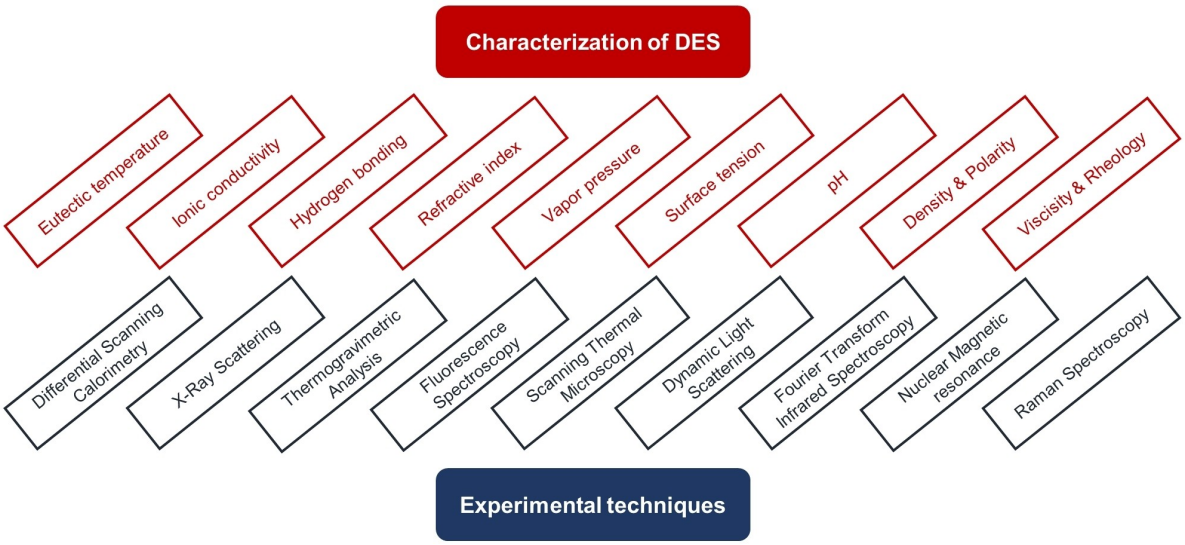


Figure 5. Physicochemical characterization of deep eutectic solvents by a comprehensive set of experimental techniques.

following sections highlight the main experimental techniques employed in the study of DESs.

5.2.1. Differential scanning calorimetry

Differential scanning calorimetry (DSC) is used to identify the thermal parameters such as the melting and crystallization temperatures, glass transition temperature (T_g), reaction enthalpy, and heat capacity when the sample undergoes a physical transformation from one state of matter to another. Determination of the thermal properties of the DESs is crucial for understanding their behaviors at different temperatures. DSC is a widely used thermal analysis method due to its flexibility in sample volume or form, high sensitivity, and speed. Moreover, it can be used at very high and low temperatures ranging from −180 to 700 °C.[95] For the aforementioned reasons, the DSC technique is addressed in the majority of the published papers dealing with DESs. For example, Martins et al. established the SLP diagram for various eutectic solvents composed of the terpenes thymol or L-(−)-menthol and monocarboxylic acids by monitoring the phase transitions at different molar compositions using DSC.[66] In addition, Craveiro et al. evaluated the thermal stability of several NaDESs using DSC by increasing the temperature up to 250 °C. They also showed the effect of water on the NaDES by measuring the T_g.[96] In summary, DSC is an indispensable technique for the characterization of DESs, and it is the principal method used to confirm their formation.

5.2.2. Nuclear magnetic resonance

Nuclear magnetic resonance (NMR) spectroscopy is a powerful analytical technique used in research to determine the presence and/or contributions of different functional groups in a sample for purposes ranging from verification of purity to identification of functional groups. Because this technique allows detecting a large number of elements, it is used to gain a baseline understanding of what functional groups are present, how they rearrange, and how they interact. Consequently, this tool allows researchers to elucidate the types of interactions between the HBD and the HBA forming DES system as well as the moieties of each counterpart involved, which permits to get insight into the hydrogen bond network. For example, Silva et al. used NMR spectroscopy to prove the establishment of hydrogen bonding for three different TheDESs composed of menthol as HBD and saturated fatty acids as HBAs. The hydroxyl group of the saturated fatty acids disappeared in the TheDES spectrum, while the spectrum of pure fatty acids showed sharp and defined signals. In addition, a well-defined doublet signal was observed in the menthol spectrum, which is ascribed to its hydroxyl group, whereas a larger singlet was obtained in the TheDES spectrum. The obtained results indicate that the hydrogen bonds are established between the carboxyl group of saturated fatty acids and the hydroxyl groups of menthol.[97] The NMR spectroscopy also helps researchers to assess the effect of water on DESs and to detect any impurities or byproducts generated during the preparation process.[80,98]

5.2.3. Infrared spectroscopy

Infrared (IR) spectroscopy is an essential tool for studying intermolecular interactions and detecting the presence of water or impurities in the DESs. The theory of this technique is based on the principle that molecules absorb specific frequencies of light that are characteristic of their structure due to the continuous vibration of their bonds. Consequently, the formation of intermolecular hydrogen bonds can lead to notable changes in the IR spectrum, such as shift of frequency and/or intensity, for bands related to vibrational modes of functional groups directly involved in the hydrogen-bond bridges.[99] Qu et al. used Fourier transform infrared spectroscopy (FTIR) to characterize the chemical structure of five hydrophilic and three hydrophobic DESs. The successful preparation of the eight DESs was proven due to the presence of a broad peak ascribed to the stretching vibration of the hydroxyl groups (–OH) and relatively wider than the peak of the pure components.[100] Moreover, Pires et al. used FTIR to verify the formation of hydrogen bonds in NaDESs and to evaluate the effect of water in these eutectic systems. They showed in the NaDESs spectra that the glycine peak, which corresponds to the symmetrical stretching of the CCN group, disappeared because of the destruction of the crystal structure of the pure components owing to the occurrence of the melting process. They also revealed that the addition of water did not cause changes in the vibrational modes of the NaDESs spectra.[101] Therefore, this technique is successfully used to quickly and accurately detect any alteration of structures that occurs in the DESs, with sufficient sensitivity to assess the formation of hydrogen bonds.[102]

5.2.4. Other experimental techniques

Additional types of equipment are used to determine other properties to deeply explore the characteristic of DESs, such as densimeter, viscometer, pH meter, and conductimeter. Density is a fundamental property for determining solvent diffusion and miscibility with other liquids. The majority of the reported DESs present higher densities than water with some exceptions such as hydrophobic deep eutectic solvents.[103,104] Another important and extensively studied characteristic of DESs is the viscosity. Similarly to the density, most of the studied DESs have a viscosity greater than that of water at rt, which is mainly attributed to the dense hydrogen bond network taking place between the DES components.[105–107] An inadequate viscosity would hamper the delivery of APIs by oral or intravenous routes of administration and can be a cause of toxicity. Contrarily, a highly viscous preparation would be an advantage for topical applications as long as it can be easily spread on the skin. As far as density and viscosity are concerned, the ionic conductivity and pH can also be an issue for DES.[108,109] Generally, the ionic conductivity of eutectic systems is low at rt due to their high viscosities.[110] Furthermore, the wide range of pH that can be obtained with DESs allows them to be used in various pharmaceutical and industrial sectors.[111] The aforementioned properties, in addition to others such as polarity, surface tension, and refractive index, must be explored for each eutectic system as these are influenced by the molecular structure

and the molar ratio of the DES components.[112–114] Moreover, the water content in DESs has an impact on their properties, so this factor may be used as a tool for controlling and tuning their properties to employ them for specific tasks and applications.[115,116]

6. Role of Deep Eutectic Solvents in Drug Engineering

DESs have found applications in different research areas, including organic synthesis, analytical chemistry, biotechnology, and metal processing applications (Figure 6A, 6B). Over the last decade, the use of DESs in the therapeutic (TheDES) and pharmaceutical fields has increased (Figure 6C) as they have been considered promising greener alternatives to traditional solvents, providing a wide variety of advantages.[117,118] However, selection of TheDES components ideally should satisfy the Generally Recognized as Safe (GRAS) requirements of the Food and Drug Administration (FDA). Several studies have demonstrated the role of TheDESs in the treatment of dermatological, infectious and metabolic related diseases, such as wound healing, diabetes mellitus, and atherosclerosis.[119,120] Moreover, some eutectic systems showed a cytotoxic effect against a wide range of cancer cell lines.[121,122]

The APIs must efficiently and specifically reach the site of action to achieve the desired therapeutic effect. However, the obstacles to drug delivery come in different forms and involve poor biopharmaceutical properties of the APIs such as chemical instability, low solubility, low permeability, and rapid metabolism and elimination from the body.[123] To overcome the mentioned barriers, numerous APIs are formulated as nanocrystals or encapsulated in different types of drug delivery systems, such as polymeric nanoparticles.[124–126] In the following sections, we highlight the interest of using TheDESs as solvents of APIs or as the active compound itself to improve their bioavailability. We also illustrate the involvement of DESs as reaction media or catalysts for the synthesis of various APIs. Moreover, we attempt to overview the potential of TheDESs to design (bio)polymeric-based systems and integrate the APIs to enhance their delivery.

6.1. DES as a solvent for active pharmaceutical ingredients

Low aqueous solubility and/or low permeability is a common dilemma encountering many active pharmaceutical molecules, where finding a green solvent is critical to enhance their dissolution and *in vivo* absorption. Consequently, the bioavailability of these molecules must be improved. DESs have been used in several studies as a new approach to dissolve different APIs due to their safety and biodegradability.[127] Their contribution as solvents involves a broad spectrum of known drugs ranging from small molecules used for therapeutic applications to high molecular-weight molecules such as proteins and nucleic acids.[128,129] For example, numerous molecules of interest to the pharmaceutical industry have been investigated by many researchers. Morrison et al. tested the ability of DESs to solubilize five poorly water-soluble compounds: Griseofulvin, benzoic acid, danazol, itraconazole, and AMG517. The results revealed that the solubility in DES improved 5 to 22,000-fold compared with water.[130] Other macromolecules, such as deoxyribonucleic acid (DNA), albumin, amylase and starch, showed a higher solubility in some DESs compared with water.[55,131] Moreover, Sanchez-Fernandez et al. investigated the solubility and stability of two proteins, namely, bovine serum albumin (BSA) and lysozyme, in ChCl/Glycol DES containing different amounts of water. The authors reported that the solubilization of BSA in DES prompts an increase in its stability against thermal degradation.[132] Furthermore, the use of peptides and other biological macromolecules for transdermal delivery is limited due to the poor skin permeability. Therefore, Banerjee et al. used choline/geranate DES to enhance topical delivery of BSA, ovalbumin, and insulin into the epidermis and dermis.[133] In addition, DESs were applied to improve the

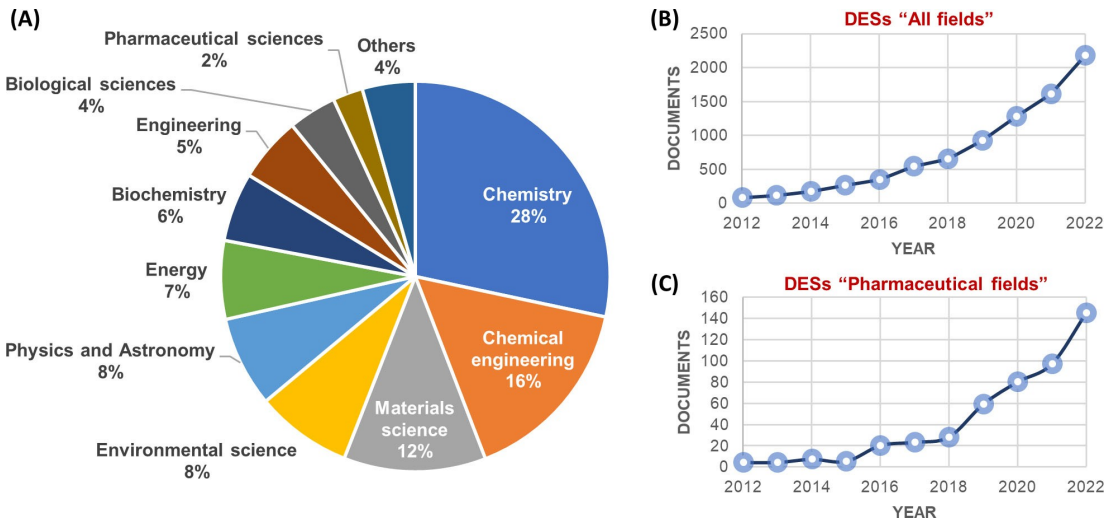


Figure 6. Relative distribution of deep eutectic solvents related publications in different fields (A), as well as number of publications per year for DESs used in all fields (B) and pharmaceutical domains (C). Data from Scopus.com in the last 10 years (2012–2022) for the keyword "deep eutectic solvents".

stability of immunoglobulin G (IgG) antibodies, which are used to treat immunodeficiency and a wide range of autoimmune diseases.[134] These biomolecules usually suffer from low stability, needing low temperatures and the use of excipients for storage. Dhiman et al. prepared cholinium-based eutectic systems for improving the conformational and colloidal stability of IgG antibodies without adding any excipients. Furthermore, the IgG exhibited a relatively long-term stability (20 days) at rt.[135] Altogether, these studies demonstrate that DESs are promising solvents for many therapeutic molecules and can serve as vehicles for transdermal delivery of therapeutic proteins. Table 6 gives some examples about the improvement of solubility, stability, and the therapeutic outcomes of several APIs and biomacromolecules dissolved in DESs.

Table 6. List of DESs tested for the solubilization of different APIs.

DES					
Component 1	Component 2	API	Indication	Description	Ref.
		itraconazole[a]	anti-fungal		
		posaconazole[a]	anti-fungal		
choline chloride	glycolic acid	piroxicam[a]	non-steroidal anti-inflammatory drug	solubility enhancement of itraconazole, piroxicam, lidocaine, and posaconazole by 6700, 430, 28, and 6400-fold, respectively, as compared to their water solubility	[136]
		lidocaine[a]	local anesthetic		
choline chloride	propylene glycol	dapsone[a]	FDA-approved for acne treatment. It also has therapeutic activities for a range of dermatological diseases	solubility enhancement and topical delivery of dapsone with solubility of 500 mg/mL in DES compared with its solubility in water (380 mg/L)	[137]
betaine	ethylene glycol	mesalazine[a]	treatment of Crohn's disease and ulcerative colitis	the mesalazine solubility in DES + water mixtures increased by increasing mass fractions of DES	[138]
choline (or acetyl choline)	glycolate, lactate, propionate, hexenoate, or geranate	insulin[a] and monoclonal antibodies	subcutaneous delivery of protein therapeutics	incorporation of insulin and monoclonal antibodies in DESs showed an improvement in the pharmacokinetics of insulin and the bioavailability of monoclonal antibodies	[139]
citric acid	arginine	mesoporous silica nanoparticles containing nanoceria and methotrexate	topical management of rheumatoid arthritis using DES-NPs hydrogel	DES-NPs hydrogel formulation resulted in sustained penetration and accumulation of NPs at rheumatoid arthritis sites	[140]
choline chloride	malonic acid	tadalafil[a]	wound healing and antimicrobial activity	tadalafil was dissolved in DES for topical application to avoid systemic exposure. Then, Lidocaine was added to the formulation to provide a local anesthetic effect. Propylene glycol was also included in the formulation to reduce the viscosity	[141]
proline + urea + malonic acid		ciprofloxacin[a]	antibacterial activity	solubility enhanced up to 430-fold while extending the antibiotic stability. The susceptibility of specific bacteria to the antibiotic improved by 2 to 4-fold	[142]
betaine	urea	imipenem[a]	antibacterial activity	stability improvement of imipenem in the DES formulation correlates with an increase in the antibacterial effectiveness	[143]
choline chloride	glycolic acid	cefixime trihydrate[a]	antibacterial activity	solubility of cefixime in the DES was enhanced by 2418-fold compared with its solubility in water	[144]
menthol	fatty acids	curcumin	anti-inflammatory effects on macrophage cells	DES increased the anti-inflammatory effects of curcumin without significant cytotoxicity	[145]
sucrose	citric acid	piroxicam[a]	non-steroidal anti-inflammatory drug	piroxicam dissolution in DES with 30% water content (w/w) increased more than 2420 times compared with pure water	[146]

[a] FDA-approved drug.

Table 7. Selected TheDESs containing FDA-approved APIs with different indications.

API	TheDES Co-former	Indication	Description	Ref.
ibuprofen	L-menthol, DL-menthol, thymol, or 1,8-cineole	anti-inflammatory drug	transdermal permeability enhancement	[152]
itraconazole	phenol	anti-fungal drug	permeability enhancement	[153]
irbesartan	nicotinic acid or ascorbic acid	anti-hypertensive drug	DESs increased the solubility and the intrinsic dissolution rate of irbesartan. They also showed an improvement in the therapeutic efficacy in the management of hypertension	[154]
ibuprofen	menthol	non-steroidal anti-inflammatory drug	the solubility of ibuprofen, when in the TheDES system, improved 12-fold, and the permeability increased 3-fold in comparison with the pure form	[155]
pirfenidone	n-acetylcysteine	treatment of idiopathic pulmonary fibrosis	development of stable DES nanoemulsion for pulmonary route of administration showed improvement in the bioavailability and lung distribution	[156]
risperidone	capric acid/lauric acid	antipsychotic drug	solubility improvement of risperidone was up to 70,000-fold compared with water	[157]

6.2. DES as an active ingredient for pharmaceutical applications

TheDESs have the ability to act as therapeutic agent by incorporating an active molecule as one of their constituents. Thus, they have been defined as a bioactive eutectic system containing at least one API as DES components. In 1998, Stott et al. prepared a number of eutectic systems by combining ibuprofen, a non-steroidal anti-inflammatory drug, with several terpenes molecules, including thymol and menthol to improve the transdermal penetration of the drug.[147] Nonetheless, it was not until 2015, when Aroso et al. referred to this type of systems as TheDESs.[148] The researchers studied the dissolution and the antibacterial activity of numerous TheDESs prepared by associating choline chloride or menthol with three different APIs that behave as HBDs, namely, acetylsalicylic acid, benzoic acid, and phenylacetic acid. The results showed an increase in the dissolution rate for the APIs forming TheDES with menthol compared to the APIs alone, while the antibacterial activity of the resulting TheDESs was maintained.[149] Currently, TheDES works as a delivery system while simultaneously improving the properties of the API(s) itself (themselves). Therefore, several TheDESs with different bioactivities have been studied in different therapeutic applications such as wound healing, inflammation, bacterial or fungal infections, and cancer treatment.[20,150,151] Some TheDESs containing FDA-approved APIs are gathered and summarized in Table 7.

In the last two decades, the European Medicinal Agency (EMA) and the FDA approved several TheDES-based formulations that are used as anesthetics or for the treatment of primary premature ejaculation (Table 8). The first FDA-approved drug is EMLA® (an abbreviation for Eutectic Mixture of Local Anesthetics) containing two anesthetic agents (lidocaine and prilocaine) for topical treatments. To the best of our knowledge, no data is available on FDA-approved TheDES used for other therapeutic applications. Currently, one eutectic system is in clinical trial: The choline bicarbonate/geranic acid (CAGE) mixture. It has been proposed for the treatment of rosacea, a common inflammatory skin disorder that typically affect the face. Ko et al. described the different phases for translational studies including, scale-up, characterization, stability test, mechanism of action, dose selection, toxicity study, and human clinical study.[158] The CAGE eutectic system was selected due to the ease of preparation, excellent stability under stressed storage conditions, inherent antimicrobial properties, low toxicity, and the ability to improve drug delivery through the skin.[159,133] After 12 weeks of treatment, the resulting formulation demonstrated a significant reduction in the lesion (~70%) with mild to moderate side effects. These results prove the significant potential of CAGE gel for the treatment of rosacea.[158] Finally, the previously mentioned example as well as the FDA-approved TheDESs demonstrated the potential of these eutectic systems to be used as therapeutic agents for various medical applications. However, filling the gaps of knowledge regarding the physicochemical properties of some eutectic systems and their therapeutic activities is mandatory to move toward clinical phases.

Table 8. FDA- and EMA-approved TheDES-based drugs with the year of the FDA approval.

Trade name	Composition	Dosage form	Indication	Year of approval
FORTACINTM	lidocaine/ prilocaine	spray	primary premature ejaculation	2019 (FDA)
PLIAGLISTM	lidocaine/ tetracaine	cream	topical analgesic	2006 (FDA)
SYNERA®	lidocaine/ tetracaine	topical patches	local anesthesia	2005 (FDA)
EMLA®	lidocaine/ prilocaine	cream	topical anesthesia	1992 (FDA)

6.3. DES for the synthesis of APIs and drug delivery systems

One of the main issues for the successful synthesis of a drug is choosing the optimal solvent for the chemical process. However, the choice becomes more limited when it comes to the industrial level due to toxicity, environmental, or cost-associate reasons. Consequently, several guides for the solvent selection process have been generated by pharmaceutical companies, helping researchers involved in early development to select suitable solvents that will be accepted in all production sites.[160,161] In the last two decades, the implication of DESs in the synthesis of APIs and bioactive compounds has gained a lot of attention due to their safety, sustainability and eco-friendliness compared to the volatile organic compounds (VOCs). In this section, we highlight the role of DESs in the APIs manufacturing and their involvement in designing polymer-based drug delivery systems by highlighting different examples from the literature.

6.3.1. DES for the synthesis of APIs

In organic chemistry, the molecular interactions between reagents and substrate species is highly influenced by the nature of conventional organic solvents. However, the use of DESs as reaction media showed many advantages in some chemical synthesis compared to the VOCs, such as improving yield of production, shortening reaction time, and milder reaction conditions (e.g., lower temperature). For instance, Cicco et al. proved the possibility of adding organolithium or Grignard compounds to chiral *N-tert*-butanesulfinyl imines in the biodegradable eutectic mixture D-sorbitol/ChCl. This chemical reaction was performed in milder conditions (at rt and under air for 2 min) compared with the conventional approach to give a mixture of diastereomeric sulfinamides in good yields (up to 98%) (Figure 7).[162,163]

The aforementioned methodology was applied to synthesize two APIs, namely (R,R)-Formoterol and (R)-cinacalcet, which are used as a bronchodilator in the management of respiratory diseases (e.g., asthma and chronic obstructive pulmonary diseases), and as calcimimetic to treat secondary hyperparathyroidism, respectively.[164,165] (R)-cinacalcet was synthesized in the presence of the D-sorbitol/ChCl DES in three steps only (Figure 8). First, a mixture of the two diastereomeric sulfinamides (S_S,R)-**2** and (S_S,S)-**2** was synthesized by reacting sulfinyl imine (S_S)-**1** with methylmagnesium bromide (MeMgBr). The auxiliary group of the obtained mixture was removed by acidifying the DES to obtain (R)-1-(1-naphthyl)ethylamine (**3**). Finally, the target drug (R)-cinacalcet (**5**) was obtained (98% overall yield) by *N*-alkylating the amine (R)-**3** with alcohol (**4**) in the presence of iridium catalyst at 60 °C under air for 12 h.[162] The alkylation step was also performed in toluene at 100 °C under argon for 17 h to give (R)-cinacalcet with an overall yield of 50% only.[166]

Indole ring is a heterocyclic compound and a versatile pharmacophore that can be chemically modified to obtain thousands of molecules with a broad range of pharmacological activities (e.g., anticancer, antihypertensive, antiviral, antibacterial and anti-inflammatory).[167] Imran et al. synthesized a key intermediate (thiazole–indole) using ultrasound and ChCl/urea (2:1) DES to obtain indoline-2-one derivatives (**10**) as final products (Figure 9).[168] The yield of the key intermediate (**9**) was increased to 95% after only 1 h of reaction in DES. On the other hand, a similar organic synthesis was performed using conventional organic solvents (e.g., dioxane) that gives a yield around 44%–68% after 3 to 4 h.[168] It was conceived that the hydrogen bonds of the DES may have played a role in catalyzing the transformation. The final compounds (**10**) were synthesized with a yield of 80%–88% and showed good anti-inflammatory and/or analgesic activities compared to the standard drugs.

DESs have also been incorporated for the preparation of quinazolinones, which have various pharmacological activities

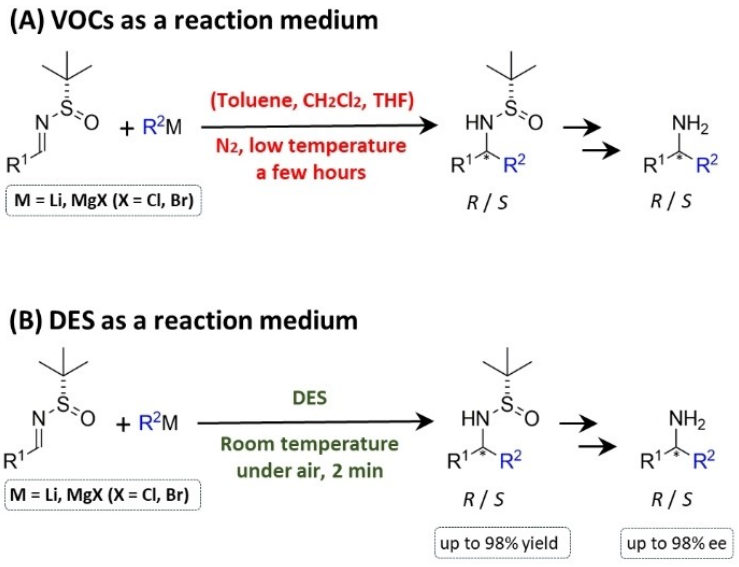


Figure 7. Addition of organometallic to sulfinyl imines using (A) VOCs at low temperature (up to −76 °C) and under inert gas or (B) DES at rt and under air.

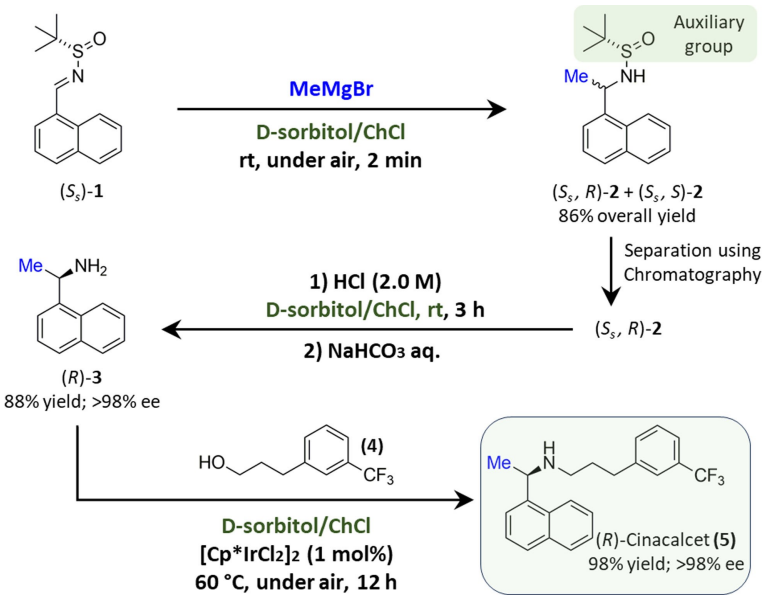


Figure 8. Chemical reaction for synthesizing (R)-cinacalcet (**5**) in D-sorbitol/ChCl eutectic system.

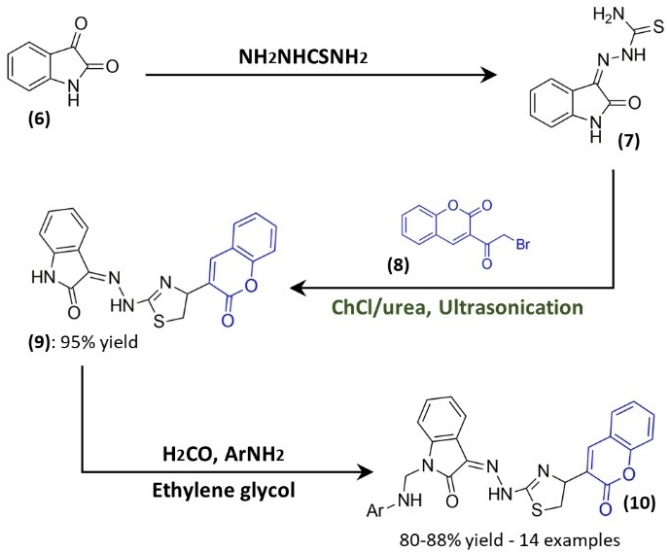


Figure 9. Synthesis of a key thiazole–indole derivative (**9**) by using ChCl/urea and ultrasound to obtain indolin-2-ones (**10**).

including antihypertension, antidepression, and antihyperglycemia.[169] The results showed that the process is cheaper regarding the starting materials and greener with good to excellent yield. The same protocol was successfully used for the synthesis of another alkaloid derivative such as penipanoid C.[170]

Interestingly, another key feature in the application of DESs for drug synthesis is the ability to use it as a solvent and catalyst at the same time. For instance, Sun et al. prepared a DES system combining ChCl and trifluoromethane sulfonic acid for the Beckmann rearrangement reaction. The eutectic mixture showed an outstanding catalytic activity with great stability. Moreover, the continuous medium was recovered and reused seven times without any significant decrease in the catalytic performance.[171] To summarize, DESs serve as environmentally friendly media in the field of green chemistry, and their use for drug synthesis can offer several benefits, including good yield, shorter reaction time, and the ability to reuse and decrease the waste produced.

6.3.2. DES for the synthesis of polymer-based drug delivery systems

Biocompatible polymers are widely used in regenerative medicine and drug delivery applications. However, the incorporation of APIs into polymeric materials is limited to polymers with relatively low processing temperatures, such as polycaprolactone (PCL), or some polysaccharides or proteins. Due to their properties reported in previous sections, DESs have attracted growing attention for designing polymeric drug delivery systems by directly incorporating the bioactive agents during the synthesis, providing green media for polymerization reactions and in mild conditions, acting not only as monomer but also improving the reactivity of the system and increasing the reaction yield. The development of polymeric-based DESs for drug delivery systems enables for improving the efficiency of the active agent release by protecting it from degradation, ensuring their secure transportation from the site of administration to the site of action, and providing cell- and tissue-specific targeted delivery. Using DES for polymer synthesis has been interestingly reviewed.[172–174]

DESs prepared from mixtures of 1,8-octanediol and lidocaine have been successfully used upon condensation with citric acid for the synthesis of a biodegradable and biocompatible poly(diol-*co*-citrate) (PDC) elastomers for temperature-controlled drug delivery applications.[175] In this example, the DESs provide most of

the ingredients necessary for the synthesis of PDC (one of the two monomers and the API) and also enable citric acid solubilization without using any additional solvent. It should be noted that the solubilization of the citric acid allows maintaining the temperature of the reaction below 100 °C and thus avoiding lidocaine thermal decomposition. In contrast, the routine synthesis of this elastomer needs higher temperature (several minutes at 160–165 °C followed by 60 min at 140 °C).

In some cases, using DES alone does not allow the dissolution of all the ingredients for the chemical synthesis, and the addition of a co-additive is required. This is the case for the free radical polymerization of the biobased building block, itaconic acid, used as HBD in blend with ChCl or tetraethylammonium chloride. The results demonstrated that the initiator of the polymerization reaction is not soluble in the DES (ChCl/itaconic acid) and that the addition of a small amount of water, and ammonium sulphate and *N*,*N*′-methylenebisacrylamide as initiator enable for increasing the yield of polymer conversion higher than 90%. In contrast, using only aqueous solution without the DES was able to reach a 50% only.[176] Indeed, the presence of DES allows increasing the reactivity of the carboxylic monomer owing to the interaction between quaternary ammonium salt and protic substances via hydrogen bonding.

Chandrakant et al. used NaDES (ChCl/fructose) for the preparation of drug loaded ion gel with indomethacin as anti-inflammatory drug by self-polymerization of 2-hydroxyethyl methacrylate (HEMA), a commonly used monomer for the development of biocompatible polymers.[177] The resulting gel demonstrates compatibility with human blood, does not inhibit mammalian cells growth *in vitro*, and presents pH-sensitive drug delivery property. Another NaDES (ChCl/glycerol) was used i/ to prepare curcumin suspensions in order to improve the solubility of the API, ii/ to preserve its therapeutic properties (anti-bacterial, anti-inflammatory and anti-cancer properties), and iii/ to ensure its safe storage. This eutectic system was also applied as an extraction medium for the generation of curcuminoids, while preventing curcumin from photo-degradation processes. Assisted by quantum chemistry computations, the bioavailability of curcumin was enhanced in simulated gastrointestinal fluids tests because of the occurred intermolecular interaction, leading to hetero-molecular pairs. In this research, choline chloride was a key element for the complex formation of the curcumin-based NaDES.[178]

NaDESs were also designed for the purpose of polymerization to synthesize drug carriers, using poly(HEMA) obtained by stoichiometric ratios of ChCl and xylitol. The obtained NaDES-poly(HEMA) loaded with 5-fluorouracil (5-FU) presented smooth interconnected porous morphology and encapsulation efficiency of 77%. The biodegradability of the drug carrier was determined by using esterase enzyme and the enhanced cytotoxicity of 5-FU-loaded NaDES-poly(HEMA) was found to be promising for cancer treatment with sustained release of the drug, as revealed by the *in vitro* experiments performed with the HeLa cancer cell line.[179]

Another example is β-cyclodextrin (β-CD)-based polymers that are widely used in pharmaceutics for the design of drug delivery systems. Pedrazzo et al. proposed an eco-friendly and efficient synthesis of β-CD polymers by combining β-CD with NaDES (ChCl/citric acid), using mechanical forces in order to drive and control chemical reactions via twin-screw extruder procedure. In this regard, the authors proposed a solution for the usually heavy procedures based on organic solvents or toxic reactants required for synthesis reactions involving β-CD.[180]

7. Summary and Outlook

Eutectic mixtures and deep eutectic solvents (DESs) containing active pharmaceutical ingredients (APIs) represent a novel approach in pharmaceutical sciences for generating liquid-based APIs subjected to a plethora of intra- and intermolecular interactions. The design versatility of these new liquid forms enables the possibility for an in situ release of the API owing to the stimuli-responsiveness of the materials upon endogenous or exogenous conditions (e.g., pH and thermal stimuli). As a new drug delivery system with high efficiency, TheDES is a promising new approach for drug development, where APIs requires relative stability and solubility for controlled release, accompanied by biocompatibility and theragnostic strategies. Moreover, various eutectic systems are employed as reaction media or catalysts for the synthesis of different APIs. An additional advantage of the TheDES systems is the possibility to combine them with (bio)polymer-based systems by direct loading or to explore a great range of polymerizable moieties while using "green chemistry", therefore, opening new horizons for chemistry and biomaterial applications.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Keywords: therapeutic deep eutectic solvents · green chemistry · polymers · drug design · drug delivery systems

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