REVIEW ARTICLE

Deep Eutectic Solvents: Green Alternative for Bioactive Compound Solubilization, Properties for Sustainable Utilization

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Abstract

The novel class of environmentally friendly solvents, known as deep eutectic solvent (DES), was introduced, which has several differences from conventional solvents. DES is an easier and less costly option to ionic liquids (ILs) a mixture of two or three solid materials in a liquid form at normal temperature is known as a DES. DES has various properties like low volatility and high solvation ability. DES consists of eutectic mixture of components, one of the components being hydrogen bond acceptor such as salts like choline chloride, trimethylammonium chloride, and alanine and the other hydrogen bond donor such as ammonium or phosphorous containing compounds urea, glycerol, and oxalic acid in a specific molar ratio (1:1, 1:2, 2:1, 1:3, 3:1). DES is less toxic, biodegradable, easy to synthesize and low-cost starting material. In this paper, the examination of DES in various areas is carried out, such as in chromatography, medicine, and environment. A new class of environmentally friendly solvents (DES) is discussed in terms of its special features and applications, paying attention to its extraction, separation and solubilization capabilities of bioactive materials. The low toxicity, low cost and ease of production are attractive alternatives to conventional solvents. The article is about the synthesis and properties of DES and provides valuable information regarding the possible applications of DES in various fields, such as chromatography. In addition, it presents an in-depth review of works which have been successfully applied to DES in different applications in bioactive compounds and other samples. The paper emphasizes the significance of DES in the field of green chemistry and the intriguing avenues for future research.

Key words: Bioactive compound, chromatography, deep eutectic solvent, hydrogen bond acceptor, hydrogen bond donor

INTRODUCTION

In the past two decades, ionic liquids (ILs) have attracted interest as a potential solvent due to their unique properties, such as low vapour pressure, low melting point and chemical and thermal stability. The properties of ILs make them commonly used in the chemical, medical and nanotechnology industries. In fact, ionic solutions are also used in medicine administration and for the production of pharmaceutical active substances (active pharmaceutical ingredient). Research shows that ILs can provide a way to increase the solubility of medications and to enhance the transport of biologically active compounds. ILs, however, often are expensive and tend to be toxic.[1]

For these reasons, the deep eutectic solvent (DES), can be created by mixing two or three molecules of hydrogen donor (HBD) and hydrogen acceptor (HBA) [Figure 1] it was proposed by Abbot *et al.*[2]. HBD and HBA will be brought into contact with each other by hydrogen bonding after mixing.[3]

The theories of Verpoorte *et al*. and Choi *et al*. suggest that urea, ethylene glycol, D-sorbitol, etc., are HBD, while choline chloride, betaine, alanine, etc., are the most frequently used HBA.[4-6] One of the unique features of the DES solution is its

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low melting point compared to its two constituents, HBD and HBA. Besides the advantages of IL, DES is relatively cheap, harmless, abundantly available and often biodegradable. Moreover, the physicochemical properties of DES can easily be changed to suit a wide range of possible applications.[7-9]

Choi *et al*. have prepared a novel class of solvents, natural deep eutectic mixtures, using two or more natural chemicals.[7] The ingredients of natural DES (NADES) are of natural origin, making them safe and suitable for food, pharmaceutical and cosmetic formulation. These properties made it widely accepted that these solvents would be used to solubilize bioactive compounds; therefore, the number of papers utilizing these solvents to solubilize bioactives was increasing rapidly. Based on this research, NADES are very effective to increase the dissolution of bioactive substances, and can be used to enhance the solubilization for drug delivery system development.[10,11]

Of these findings, the natural deep eutectic solvent was composition developed by Silva *et al*. was seen to be intriguing since ascorbic acid and choline chloride, the components utilized to manufacture the NADES, are considered green from a green chemistry perspective.[12] Therefore, in the opinion of council directive, choline chloride is considered to be, when used as a nutritional addition, a non-toxic addition well recognised as having dietary antioxidant properties, as ascorbic acid, commonly referred to as Vitamin C, is well recognised for its dietary antioxidant properties. The main functions of ascorbic acid are to prevent scurvy, to modulate neurological processes and to be easily scavenged by reactive oxygen species. The NADES, which contain ascorbic acid and choline chloride, are obviously a novel and promising approach to the solubilization of bioactive substances.[11,13]

Definition

Two or more chemicals, when mixed in a specific molar ratio, can often show a significantly lowered melting point, after which they are transformed to liquid at room temperature and become a DES.[3] The first step in doing this is to examine and rectify some common misconceptions: DES are not "new" or "innovated" pure substances. It is recommended to avoid the use of commercially-sounding names for these mixes, such as reline, glycerine, ethylene, and urea because they are not the same as cheap ILs, and in fact, at most, they are not homogeneous compounds but rather can be an ion solution. These are characteristics that are dependent on the starting materials used and the mixing process, so they should not be generally described as non-toxic, environmentally friendly, green, easy to simulate, or economical. A great deal of these generalizations has been used incorrectly in the study of ionized fluids, and in the literature on DES, they are used again incorrectly. Any mixture of chemicals that is completely or partially insoluble in the solid state is a DES.[14]

The otherwise excellent research by Hunt et al. on the chemical reactions that take place between the combination [Ch]Cl and urea is a fine illustration of this type of assessment, which avoids a full understanding of the system, and thus renders a rejection of the notion that a dominating 2:1 ratio of HBA to hydrogen bond donor complex is the driving force behind the DES nature.[15] In many cases, the lack of enthalpy of fusion data will prevent comparisons with the ideal mixture behavior, but other approaches to establishing the irrationality of the liquid phase may be possible, especially for one of the component chemicals of the combination.[16] In addition to its temperature depression, the composition of a DES is another important consideration in its definition. Although they used a fixed proportion of the ratio 1:2 for the definition of the [Ch] Cl+ urea, which they determined to be the eutectic point of the system, they tried to develop a solid-liquid phase diagram for several of the systems they investigated, to determine the liquid phase region, and the point of the stereometric eutectic mixture.[17] The testing of mixes containing stated different ratios of HBD to HBA (the most commonly used ratios—3:1, 2:1, 1:1, 1:2 and 1:3, but others are also common, such as intermediate or more intense ratios) quickly became a widely accepted method, whereas most other writers did not do so. This assumes that the eutectic composition is directly related to the complex formation, which is not true. Nowadays, it is typical to find in the literature that the complex's creation is demonstrated by a eutectic composition that approaches a definite stoichiometric proportion.[18]

The main benefit of this is that it increases the flexibility of the DES specification, making parameters of the eutectic solvent composition not the only ones limiting the DES characteristics. The composition of DES can be optimized to achieve a further customized physical and phase behavior of DES by carefully adjusting its composition. In addition, by selecting the right precursor mix, DES's structures and properties can be changed. According to us, a combination of two or more pure chemicals is considered a "deep eutectic solvent" if the temperature is decrease of eutectic point than that of an ideal combination of liquids, and it exhibits notable negative departures from ideality ($\Delta T2 > 0$).[19] In addition, the mixture should be fluid within a certain composition range at room temperature. If not, any two solids that cause to form liquid at a particular melting point reduction can be called "eutectic solvents." As far as these two characteristics are concerned, we consider the results for several combinations and compounds in the following sections, as well as the modeling of the non-idealities of the liquid phase and the eutectic coordinates.[20]

PROPERTIES OF DES

They share similar physical properties, such as the ability to be adjusted as solvents to meet specific chemical requirements, are non-flammable, have a relatively wide

liquid range and have a reduced vapor pressure. The DESs are less chemically inert than the conventional ILs, but they offer the following advantages over the latter: They are easily prepared; They are readily available from low-cost chemicals (The chemicals required to prepare the DESs are well known and are toxicologically safe).[21]

Two components are merely blended together, typically with some heating, to create DESs. This makes it possible for extensive applications while maintaining a relatively cheap manufacturing cost as compared to typical ILs. Although single DES components are well-documented toxicologically, more work is needed in the scientific community regarding the toxicological characteristics of the eutectic solvents.[22] The term DESs were coined from the term Type III eutectics, but it is now used to describe all the eutectic combinations mentioned above. This is a sensible approach and, although it includes all the initial studies on halo-aluminates, it has been reviewed extensively and will not be discussed here apart from in comparison.[23]

Phase behaviors

The binary mixture A+B is a difference between the freezing point at the eutectic content and ΔTf is a theoretical ideal mixture, which is dependent on the interaction degree of A and B. If there is a lot of interaction between the components, it will show a maximum ΔTf. Figure 2 shows a graphic representation of this.

A eutectic point in the phase diagram of two components is highlighted in Figure 2 by emphasizing the point of thought. Type I eutectic. Different metallic halogens will react with different salt of quaternary ammonium halogens to form equivalent halogenated metallate compounds, having similar formation energies. Based on this, the optimum range for the values of ΔTf is 200–300°C. The melting point of the metal should be 300°C or lower if a eutectic is to be produced at ambient temperature.[24]

Type II eutectics were created to introduced more metals into DES compositions. The melting temperature of the anhydrous salt of the metal halides was found to be lower than that of the corresponding hydrates. From this, it is apparent that the melting point of the metal salts' fluids is lowered due to the process of hydration, which reduces the lattice energy. The freezing point depression (ΔT) will be less for a pure metal salt with a lower melting point, as shown in Figure 2.

When the salts of halogen ions have more than one function and are capable of hydrogen bonding, eutectic mixes of type III cannot be formed until the hydrogen bond donor function is complete, which is more like a 1:1 molar ratio of salt to HBD. In the same experiment, it was shown that the decrease in freezing point and the mass percentage of HBD in the combination was correlated.[3,4,8]

Surface tension, density, viscosity, and conductivity

The density of DESs was predicted using a technique presented by Shahbaz *et al*. and the typical proportional percentage difference for each of the tested results for DESs was calculated as 1.9% between the actual and predicted. densities.[25] In addition, the effect of the ratios of donor group of salt to hydrogen bonds at the predicted densities of DES was investigated. In addition, the same group has studied DESs based on salts of phosphorus and other HBDs. The dissolved oxygen, density, viscosity, pH, conductivity, and melting point were observed at various temperatures. The authors found that each of the following factors had a significant effect on the attributes studied: type of salt, mole ratio, and HBD of each chemical. Compared with other substances such as ionic fluids and molecular solvents, DESs have relatively high viscosities and low conductivities. This difference is attributed to ionic regimes because the large ions are suggested by the both the large ions and the relative freedom space in the ionic regimes are suggested to cause this difference. The viscosities of the ILs are much larger than those of most common molecular solvents. It is discovered that the viscosity changes with temperature in an Arrhenius way, with huge amounts of energy needed for activation for viscous flow. This was shown to be experimentally equal to the average radius of the voids in the liquid and the ratio of the number of ions to the number of conducing molecules in it. The molar conductivity (λ) and fluidity (η, inverse of viscosity) of the anionic liquid have been considered to be linearly related often. With DESs, a similar association is shown. This has traditionally been incorrectly associated with the applicability of the Walden law, which is $\Lambda\eta$ = constant. This applies to a particular electrolyte in an infinite dilution of a solvent system. Abbott demonstrated that the holes, which exhibit infinite dilution, are what restrict charge transmission as a result of the holes rather than the ions.[26]

Hole theory and ionicity

In comparison with aqueous electrolytes, deep eutectics' greater viscosity and hence lower conductivity have occasionally prevented their usage.

$$\frac{3.5\ kT}{\gamma} = 4\ \pi r^2$$

Very few investigations have been carried out to gain the full picture of the fluid properties of DESs or other ILs in general. However, since the volume of the liquid and the free volume increase with its melting point, a number of models have been developed to describe the ion mobility in molten salts (also called high-temperature ILs). The ion mobility in DESs physical properties has been explained using hole theory. The hole hypothesis states that ionic materials, which melt, contain voids created by density variations within the

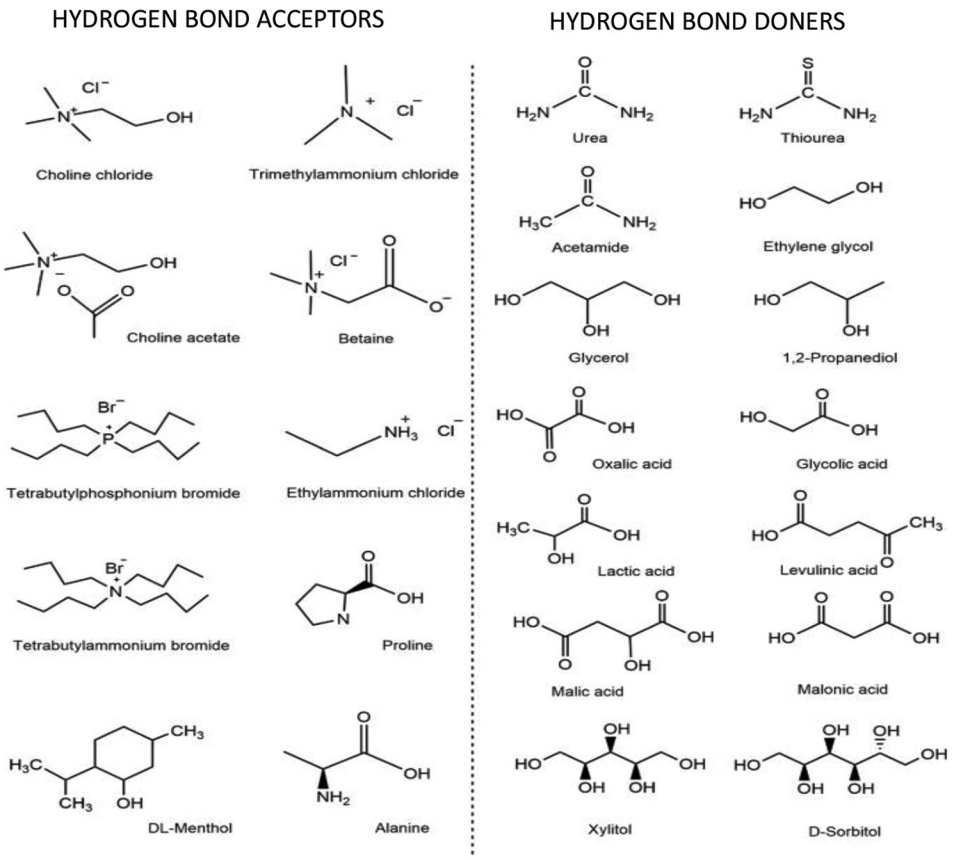

Figure 1: Various commonly used hydrogen bond acceptor and hydrogen bond donor

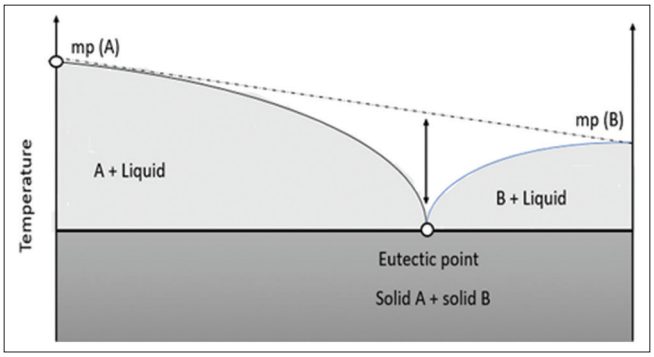

Figure 2: Schematic diagram of the eutectic point on a two-component phase

material from the heat. The holes are constantly moving and have variable dimensions and locations. The relationship between the average void's radius (r) and the liquid's surface tension (γ) is as follows:

- k is the Boltzmann constant, and T is the absolute temperature.
- The latter's size may be greater in the molted salt, and the average size of the hole will be smaller in a lower temperature system, making the ion mobility high.
- The low viscosity is due to the ease with which a mallion can be injected into an empty space, and the size of the puncture in salt is roughly the same as that of the ion in the molten state. The viscosity rates can be as high as 101–103 Pa in systems with lesser few degrees Fahrenheit due to a smaller hole diameter and larger ion size, which makes ion mobility challenging.[27,28]

Speciation

Many ionic species, including metal salts, are quite soluble due to the ionic nature of DESs and their relatively high polarity. The considerations that come to mind when considering the reactivity of a metal in a species that forms during dissolution are one of the most important questions. Metal ions are generally Lewis's acids and so can complex with Lewis or Brønsted bases. The H+ and OH chemistry – in aqueous fluids dominates the solubility of metals, redox properties, and species formed in solution. Although the DESs are more complex than water-soluble ones due to the eutectic composition and the diversity of the ions' Lewis basicity, the investigation of Metal Ion differentiation in DESs is relatively new. To understand the mechanisms by which nucleation and growth of metallic coatings occur, speciation in DESs is important because the number of ligands and their binding coefficients determine the exact mechanisms of electrochemical reduction. One problem with the lack of understanding of speciation is that quantitative structural data is hard to come by. The majority of metals create complexes of ions which are hard or not possible to form crystals from a mixture of solute and solvent, and the

solvent cannot evaporate. It takes a number of in situ methods to digest metallic ligation in solution. The X-ray absorption fine structure (EXAFS), which results from the phenomenon of Interference changes the wavelength of the absorption edge of X-rays when the photoelectrons are backscattered by neighboring atoms. The Fourier conversion provides a circumferential distribution function with a radius of about 600 pm, which is valid in real space. Element-specific EXAFS provides information on the local structure surrounding the excited element, even at low concentration.[29]

UTILIZATION OF DESFOR SEPARATION AND EXTRACTION TECHNIQUE

The utilization of chromatography

Designed to be an environmentally friendly solvent, DESs are increasingly being used to separate target molecules from natural materials in chromatography. In 2015, Tang *et al.* self-prepared DES-based silica as impermeable absorbent. [30]. Three polysaccharides, namely, fucoidan, laminarin and Arabic acid, have been isolated with high-performance size-exclusion chromatography (HP-SEC) using these dextran epitopes as a support. A steel and stainless columns of 250 × 4.6 mm were used to do the wet-packing of the mesoporous silicone dioxide spheres with DES base. The test displayed the individual results obtained from each of the three substances of interest from the three HP-SEC investigations based on DES. The chemical column was eluted at 40°C and 1.0 mL/min with the eluent being fresh water. Furthermore, the compounds of interest on the SEC columns were eluted at a high resolution on the DES- 1, 2, 3-based SEC columns. Li *et al*. published a study on the use of five different types of DES-based mesoporous silicon dioxide material in HP-SEC in 2015 and 2016. For the study of the characteristics of their packing columns, different dextran units, with molecular weights of 5, 50 and 670 kD, were used. The silica used was a DES-based silica and was used as an absorbent in an HP-SEC column. Clear shifts of Dextran-1 (5 K) to Dextran-2 (50 K) were observed for the ChCl/B- and ChCl/AA-based columns. The column can also be used to separate the three different kinds of dextran when using the ChCl/AA-based column. Furthermore, a key element in assessing an HP-SEC column's efficiency is resolution (R). The separation efficiency of the chromatograph for the two target chemicals is called R.

W1 and W2 are the peak apertures of the substances measured, 1 and 2; tR2 and tR1 are the periods of retention of the target molecules 2 and 1, respectively. These DES-based materials have been found using their mesoporous architectures (pro size and HBD at the interface) in an HP-SEC column to assess their extraction efficiencies. DESs are also a special type of mobile phase element that can be used in separating basic chemicals on the opposite side of the spectrum. Tan *et al*. used in 2016, DESs were used as innovative mobile phase additives to enhance the chromatographic purification of four quaternary alkaloids on a C18 column.: sunnarine, coptisine chloride, berberine chloride, etc.[31] Significant benefits were acquired the separation of alkaloids using DESs added in modest amounts to the mobile phase on a C18 column. These benefits included decreased tailing and improved resolution, and it was discovered that the extraction hydrogen-bond donors' and acceptors' combined effects were the samples' mechanism.[32,33]

Application in aromatics

Aromatic hydrocarbons are one of the main components of the large no of organic substance industry, and are used in the production of chemicals, plastics, textiles, pharmaceuticals, preservatives, explosives, and more. However, most of the aromatic hydrocarbons are harmful to human health. Removing or reducing the volatile hydrocarbons in chemical compounds is beneficial to human health. Due to their carcinogenic and mutagenic properties, a broad class of chemical molecules known as polycyclic aromatic hydrocarbons (PAHs), or the European Union and the US Environmental Protection Agency, have designated PAHs as priority pollutants. Usually, food is used as the source for the extraction of these PAHs, particularly seafood. The amount of toluene, benzene, and ethylbenzene (BTE) is sufficient to enable tracking of PAH in ambient waters, and their low solubility allows for their detection. These chemicals thus require pre-concentration/purification before their identification by chromatographic methods. The liquid-liquid extraction (LLE) method is simple, useful, and widely applicable. LLE is an easy, useful, and versatile pre-concentration method for aqueous matrices. Helalat-Nezhad *et al.* succeeded in separating eight aromatic polycyclic hydrocarbons (PAHs) in a small amount of cyclohexane by using ChCl/oxalic acid (ChCl/Ox).[34] The PAHs were extracted, purified, and quantified using fluorescence detection and high-performance liquid chromatography after extraction. The optimum conditions were 55°C for 30 min, ChCl/Ox (1:2), which is much lower than that of the conventional and contemporary techniques. The excellent extraction efficiency of the approach, along with a short analysis time, low cost, and safe use of the components make it an attractive solution for routine PAH analysis of biological materials. However, Khezeli *et al.* used a really good microwave-assisted extraction (MAE) technique and a microwave-assisted extraction, or ultrasound-assisted extraction, with an emulsifying liquid-liquid microextraction method depending on the DES to substitute the traditional solvents in their extraction with an extract of the mixture of BTE, and 7 PAHs.[35]. These results indicated that the inclusion of DESs could have a significant effect on the extraction efficiency and selectivity. Second, DESs were stable at the study temperature and showed a short equilibration time.[36]

Application in bioactive compounds

The extraction of bioactive chemicals from plants using traditional techniques requires the use of considerable

quantities of organic solvent and longer extraction times. The aim was to find an environmentally friendly chemical extraction and separation method, and DESs as a special, environmentally friendly alternative to conventional solvents. The extraction of various phytochemical constituents is carried out to analyse the efficacy of the compound.[37]

Application in fuel

Over the past few years, crude feed's sulfur concentration has grown, making it harder to break down liquid fuels. The existence of the aromatic N molecule has further reduced the effectiveness of hydrodesulfurization (HDS) process due to its simultaneous adsorption as well as catalyst deactivation. This is why it is necessary to replace the desirable nitrogen compounds that are formed by crude oil before it reaches the HDS unit for better process efficiency.

Proposed a method for the evaluation of the efficiency of DESs for the removal of aromatic N-containing compounds from diesel fuel substitute. In this objective, they employed the model conductor-like assessment approach for a realistic solutions. To determine the selectivity and capacity when diluting indefinitely, the technique relied on forecasting the activity coefficient of the nitrogen-containing compounds in the DESs at a constant dilution and in simulated diesel. Depicts the chemical interaction that takes place between the anion, salt cation, HBD, and nitrogen molecule. The identical researchers denitrogenated diesel fuel in 2015 using DESs based on phosphorus and ammonium. The desulfurization of liquid fuels is another use for DES. Gano *et al*. reported the extraction desulfurization application of a simulation fuel containing S-containing compounds, namely, thiophene and dibenzothiophene (DBT), using ferric chloride-DES.[38] Commercial diesel was used as the fuel. The results indicated that the extraction efficiency for DBT reached as high as 64% in one stage of extraction, while that of thiophene was as high as 44% in one stage of extraction. Their tests proved the desulfurization and denitrogenating properties of DESs under various type fuels, including actual commercial diesel fuel containing sulfur content concentration which was eventually lowered to the ambient sulfur limit.[39,40]

Application in other samples

DES is a widely used extractive solvent in a few studies as an environment friendly solvent. In 2015, Kanberoglu *et al.* extracted iron from liver samples of sheep, cows and chickens using the DES made with ChCl.[41] Gjineci *et al.,* on the other hand, created two DESs and two ILs based on ethanolamine and ChCl, respectively, and assessed their effectiveness as entrainers as trainers for achieving extraction of an azeotropic mixture of ethanol and water.[41] The next year, Wang *et al*. used 3-(indolyl) methane modified silica that was nitro-substituted in ChCl/U in the ratio of 1:2 for SPE of organic acids, and the approach was more successful when compared with ILs in terms of separation ability and ability to be degraded.[42] The nitro-substituted modified silica absorbent had a strong adsorbed ability towards the specific organic compounds, as demonstrated by the results of rebinding studies. DESs were used in their research in an easy-to-use and precise extraction technique.[43]

CONCLUSION

DESs have become a promising class of green and sustainable solvent with many positive characteristics over conventional organic solvents and ILs. They are easy to make, inexpensive, biodegradable, non-volatile, and easily adjustable in terms of physicochemical properties, which is why they are so attractive for a multitude of industrial and pharmaceutical applications. This unusual combination of HBAs and HBDs leads to a very unique ability of very low melting point depression with increased solubilization ability, which is very advantageous for extraction, separation, and formulation processes.

This review focuses on the most relevant properties of DESs, such as viscosity, conductivity, density, phase behaviour, and ionic properties that make DESs versatile. DESs have shown great potential in chromatography, bioactive compounds extraction, denitrogenation, and desulfurization for fuels, removal of aromatic hydrocarbons, and sample preparation methods. NADES have been particularly highlighted due to their biocompatibility and their use in pharmaceutical, cosmetic, and food applications.

Moreover, DESs could be a green alternative for the extraction and solubilization of phytochemicals and other biologically active compounds, and decrease the amount of toxic organic solvents. The dissolution-enhancing and stabilizing properties of bioactive molecules suggest their great potential for drug delivery and pharmaceutical applications.

Although these benefits exist, more research is needed to fully characterize the toxicological properties, environmental fate, thermodynamics, and the applicability of DESs to large-scale industrial applications. Optimization of DES compositions, extension of its physicochemical properties, and exploration of newer applications in green chemistry, nanotechnology, medicine, and analytical sciences should be the focus of future research.

Overall, DEDs emerge as an innovative and sustainable tool in current chemistry and are likely to be of great value for the development of eco-friendly technologies and the processing of bioactive compounds in the future.

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