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Research on the Design and Application of Natural Deep Eutectic Solvents

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ABSTRACT

Green technology actively seeks new solvents to replace common organic solvents. Over the past two decades, ionic liquids (ILs) have gained enormous attention from the scientific community, and the number of reported articles in the literature has grown exponentially. Nevertheless, IL “greenness” is often challenged, mainly due to their poor biodegradability, biocompatibility, and sustainability. An alternative to ILs are deep eutectic solvents (DESs). DESs are defined as a mixture of two or more components, which may be solid or liquid and that at a particular composition present a high melting point depression becoming liquids at room temperature. When compounds that constitute the DESs are primary metabolites, the DESs are so called NADESs. NADESs fully represent green chemistry principles. The current state of the art concerning the advances made on these solvents in the past few years is reviewed in this paper, and future perspectives on the major directions toward which the research on NADESs is envisaged are here discussed, and these comprised undoubtedly a wide range of chemically related subjects.

KEYWORDS

NADESs; Ionic liquids; Green chemistry; Choline chloride; Physical−chemistry properties

1. INTRODUCTION

Green chemistry actively seeks new solvents to replace common organic solvents that have inherent toxicity and high stability, leading to the evaporation of volatile organic compounds into the atmosphere. In the past two decades, ILs have attracted significant attention from the scientific community, with the number of reported articles in the literature growing exponentially. ILs are molten salts that are liquid at room temperature. The great potential stems from their unique properties, namely their physicochemical properties (viscosity, density, hydrophilicity, and solubility), which can be adjusted by combining different cations and anions. ILs have been applied in very different fields and have very different uses. For example, they can be used as solvents in biocatalytic processes [1], extraction solvents [2, 3], and in electrochemical applications. Recently, the ability of ILs to dissolve and improve the processability of renewable biopolymers has been discovered, and this ability can be applied in the biomedical field [4]. However, the "greenness" of ILs often varies, mainly due to their poor biodegradability, biocompatibility, and sustainability.

An alternative to ILs is eutectic solvent, which may also have ionic properties but consists of a mixture of organic matter that has a much lower melting point than either of its components.

The most common eutectic solvents are based on choline chloride, carboxylic acids, and other hydrogen bond donors such as urea, citric acid, succinic acid, and glycerol. Eutectic solvents have similar properties to ionic solutions, but are cheaper to produce (from cheaper raw materials), less toxic, and often biodegradable. Dai and colleagues recently reported a large number of stable

NADESs based on natural compounds, especially primary metabolites such as organic acids, amino acids and sugars.

DESs or NADESs are formed by the complex between hydrogen acceptor and hydrogen bond donor. The emergence of electron displacement is responsible for the subsequent reduction in the melting point of the mixture relative to the raw material. The main advantage of DESs over ionic solutions is that they are easy to prepare. DESs can be prepared from a concentrated aqueous solution containing each compound, heated to a predetermined value from a melt dissolved in one component of another or from a solid mixture of two components. A large number of combinations of DESs can be envisaged and are likely to arise from the ability to design new solvents with characteristics most suitable for the given application.

2. HISTORICAL PROSPECT AND APPLICATION OF DESS

Until the early 21st century, DESs were rarely reported in the literature. Some manuscripts reported in the 1990s were related to specific applications of these liquid mixtures.

In 1994 Gill and colleagues [5, 6] reported eutectic mixtures as substrates for enzymatic reactions. This pioneering work demonstrated that the enzyme can remain active when dissolved in eutectic mixtures, providing a better reaction medium than conventional organic solvents. It may only be four years before more scientific progress in this area is reported. In their work, Erbeldinger et al. reported the application of eutectic mixtures of radically different components in enzyme-catalyzed synthesis with yields up to 80% by weight, and these discoveries have since had a well-known impact on large-scale systems and new industrial developments. The biocatalytic process in eutectic solvent is more advanced than the enzyme reaction. Results published by Gutierrez in 2010 describe the possibility of maintaining the viability of whole organisms such as bacteria in non-aqueous solvents [7]. Clouthier reviewed enzyme-catalyzed and whole-cell biocatalytic processes. Plenty of results have been reported on this topic due to the need to improve biocatalyst immobilization, stability and recycling to reduce processing costs. In this sense, DESs have been developed as green alternatives to ILs and have been widely used in the field of biocatalysis.

In 1995, a work published in Nature revealed the possibility of using eutectic mixtures as an alternative to emulsified crystallization. Provides a more cost-effective strategy for the separation and purification of molecular mixtures [8].

In 1998 Stott and colleagues demonstrated for the first time the possibility of developing a device for drug delivery, particularly transdermal drug delivery [9]. In their results they successfully described a mixture of pharmaceutically active compounds and different terpenoids such as skin penetration enhancers. The possibility of combining a bioactive eutectic system after the preparation of an active compound and a second component opens a wide range of future developments involving pharmaceutical and biomedical applications.

The first hint that DESs could be used as substitutes for ILs began in 2004 [10]. Since that year, a considerable amount of literature has been published on DESs, especially physicochemical properties and thermodynamic systems. Knowledge of basic properties can lay a foundation for promoting the wide application of DESs.

Common minerals require the presence of organic matter to guide the formation of structures. Parnham and colleagues describe the possibility of following the path of ionic thermosynthesis using ILs and, or DESs. These reactions are characterized by the fact that organic matter acts as both solvent and template. DESs exhibit the advantage that during the reaction process, one of the components of the eutectic solvent breaks down to provide the organic template required for the reaction. The preparation of aluminium, zirconium or zinc phosphate zeolites following this reaction has recently been described in the literature.

The use of DESs based on choline chloride for cyclic voltammetry and chronoamperometry, reported in 2007, has broadened the scope of application of such solvents, i.e., electrochemistry. A particular application in this area of research is the electrodeposition of metals, thanks to the high solubility of metal salts in non-aqueous solutions and the high conductivity of ionic solutions and DESs.

DESs have gained increasing scientific interest, and the attention of the scientific community is now moving directly towards understanding the properties that make these liquids very special. A survey of the literature by the Institute for Scientific Information in the United States shows 380 references to DESs.

The main scientific areas studied under this subject address are chemistry, physics, materials science, and electrochemistry and these manuscripts are mainly concerned with basic and foundational research. This highlights the lack of knowledge in this subject to broaden the scope of new applications that remain to be elucidated. The worldwide distribution of these publications reveals an interesting phenomenon: Europe is the most actively studied region, followed by China, followed by other Asian countries, while the United States and Canada are only fourth.

3. FUTURE PROSPECT

The future development of DESs and NADESs relies on multiple factors. Firstly, characterizing their fundamental properties like viscosity, density, conductivity, and solubility is crucial, as these impact performance. Understanding how these properties change with temperature, pressure, and concentration unlocks potential. Secondly, grasping the phase behavior of components is essential. Since they're formed by mixing substances, knowing their phase transitions helps optimize synthesis and predict stability and compatibility. Also, deciphering intermolecular interactions within eutectic mixtures dictates overall behavior. By understanding these at the molecular level, we can customize solvents for specific uses. Similar to ionic solutions in the 1990s, significant contributions are expected in physicochemical and thermodynamic systems. Researchers will likely publish findings, from new synthesis routes to unique eutectic combinations, bringing DESs and NADESs closer to mainstream use.

3.1. Biodegradation and Toxicity

A major advantage of DESs over ionic solutions is the fact that these solvents can be synthesized from natural primary metabolites. This fact provides proof that these systems should be significantly less toxic than ionic solutions. Hayyan and colleagues evaluated the cytotoxicity and toxicity of three phospho-based eutectic solvents with harvest shrimp and two strains, gram-positive and gram-negative [11, 12]. With regard to the cytotoxicity of DESs to fertile shrimp, as expected, this study provides evidence that toxicity depends on the composition, viscosity and concentration of the eutectic solvent. In this work, the authors conclude that the eutectic mixture of the two components has a greater toxic effect than that of the aqueous solution of a single molecule. The toxicity of these eutectic solvents to bacteria indicates that these substances can be used as bacteriostatic agents. This can be explained by the fact that the presence of charge displacement in such liquids destroys the bacterial cell wall.

Another study reported by Hou and colleagues provides more insight into the toxicity and degradation of choline amino acid ILs [13]. In this study the authors provide information on the toxicity of DESs to acetylcholinesterase, a critical enzyme in the nervous system of almost all higher organisms. The inhibition of eutectic solvent is one order of magnitude lower than that of an imidazolyl ionic liquid. However, the effect varies with the amino acid composition of the eutectic solvent. The antimicrobial and antibacterial activities of different eutectic solvents prepared were also investigated.

In our work, we followed the ISO guideline ISO/EN 10.993 to detect the cytotoxicity of 11 different DESs and two different ILs. In this assay, the viability of cells in contact with a low eutectic solvent and a solution with a concentration of 25mg/mL of ionic liquid was measured. Different solutions were placed in contact with a template cell line inoculated on a polystyrene tissue culture plate with a concentration of 1.5×104 cells per ml of L929 and detected after MTS assay. The experiment was based on the biological reduction of a tetrazole compound, namely, the reduction of MTS to a water-soluble Brown mezan product that can be quantified by ultraviolet.

These results indicate that the presence of tartaric acid has an adverse effect on the metabolic activity of cells. However, the analysis of the results obtained did not show a clear correlation between cytotoxicity and composition of the eutectic solvent. Frade et al. followed this experiment to report the cytotoxicity of different magnetic ILs. In this work, the authors conclude that survivability depends on concentration, but that choline-based solvents prepared in general are not cytotoxic.

Biodegradability and environmental impact are key issues in the design of new solvents. Based on the biodegradability and environmental impact of the single component of the eutectic solvent, it can be expected that these solvents are more biodegradable and exhibit lower environmental impact than any common ionic liquid. Hou and colleagues, who have studied the degradation of low eutectic solvents by different microorganisms, looked at biodegradation, especially anaerobic degradation. After 21 days, most of the compounds studied had degraded by 80 percent, and this degradation was attributed to the presence of choline receptors.

3.2. Biocatalysis

Although DESs can be composed of known denaturants such as citric acid and urea, many esterases are also active in DESs such as CALB, which shows high activity and stability in acetylcholinyl DESs. Gorke et al. reported the use of such hydrolyzed acids in the ester group transfer of ethyl valerate to monobutanol. CALB showed 20 to 35 times more stability than aqueous solvents alone using DESs, i.e., acetylcholine and urea as co-solvents. Lindberg et al. described the use of acetylcholinyl eutectic solvents as co-solvents in the hydrolysis of chiral (1, 2) -trans-2-methylstyrene oxides with epoxides. The wide application of esterases in the pharmaceutical industry is mainly due to their high compatibility, regionality and chemical selectivity, however, there are still some problems in the downstream process of obtaining pure products. Reetz et al. proposed the combination of ILs and supercritical liquids such as supercritical carbon dioxide as a viable solvent. In a two-phase separation system, the reaction can be carried out in the ionic liquid phase, while the product of interest can be extracted by a higher supercritical phase. Because ionic solutions are extremely insoluble in supercritical carbon dioxide, no solvent is lost in the supercritical phase. Moreover, the presence of ionic solutions improves the selectivity of supercritical carbon dioxide to the components of interest. The downside of this strategy is the high cost and biodegradability of ionic solutions. NADESs like those previously mentioned are inexpensive and nature-based solvents that have similar properties to ionic solutions, and more specifically the high solubility of supercritical carbon dioxide in NADESs. Moreover, due to their low vapor pressure, NADESs are almost insoluble in supercritical carbon dioxide. This opens up the possibility of a cheaper and more environmentally friendly biocatalytic process in a two-phase system.

5-hydroxymethylfurfural is a valuable building block of biological origin. The esters produced by the biocatalytic esterification of 5-hydroxymethylfurfural have some industrial applications such as surfactants, fungicides and monomers. Krystof et al. studied the esterase-catalyzed transfer of hydroxymethylfurfural in the ester extraction of 5-hydroxymethylfurfural with a NADESs as the purification solvent.

NADESs based on glycerol may be a viable alternative to bio-catalytic production of biofuels. Esterases are widely used in the enzymatic catalytic production of bio-fuels. Zhao et al. published in 2013 the use of DESs in enzymatic catalytic production of bio-fuels, using DESs based on acetylcholine. In their work, the authors show that the high biocatalytic activity of CALB can be maintained in a reaction carried out in acetylcholine and glycerol and that these solvents can be used in enzyme-catalyzed transesteryl transfer of triglycerides and alcohol, obtaining high reaction yields.

It is envisaged that NADESs due to their low cost, biodegradability and biocompatibility will be widely used as solvents in biocatalytic reactions, especially in the pharmaceutical, nutritional food, and beauty industries where the biocompatibility of these products is a key issue. Moreover, as shown in Krystof et al., DESs have also been shown to be active extractants.

3.3. Extract

The potency of an extractant depends on its dissolving properties. DESs have the ability to provide and receive protons and electrons, thus giving them the ability to form hydrogen bonds, thereby increasing their ability to dissolve. In fact, DESs have been reported as extractants of chemical mixtures and as extractants and dissolvers of sugar enzymes.

Dai et al. [14] studied the extraction of phenols from safflower with different NADESs, such as lactic acid and glucose, glucose and acetylcholine, fructose, glucose and sucrose. In this work, it was found that NADES has a strong ability to extract phenols, which is related to the hydrogen bond interaction between phenolic compounds and NADES molecules. The physical properties of NADESs such as polarity and viscosity also have a great influence on extraction. By optimizing these parameters (viscosity, polarity, and temperature), the authors report higher phenolic compound extraction yields using NADESs compared to common solvents such as water and ethanol.

It is reported that the solubility of insoluble molecules such as benzoic acid, griseofulvin, Danazole, itraconazole and AMG517 is 5 to 2200 times higher in DESs such as acetylcholine and urea and acetylcholine and malonic acid than in water. This demonstrates the usefulness of DESs as extractants of bioactive molecules. Moreover, the DES can also dissolve more ionic transition metal oxides from minerals.

Since NADESs are a greener and safer alternative, it is not surprising that they have been used to extract natural substances for pharmaceutical applications. Natural eutectic solvents exhibit excellent properties when used as alternative extractants such as liquid at room temperature (sometimes even below zero), easy to adjust viscosity, sustainable and safe. Since natural eutectic solvents can dissolve both polar and non-polar metabolites, it can be envisaged that they can be used as extractants for many types of natural substances, depending on the physicochemical properties of each natural eutectic solvent.

In this work we also present preliminary results for the extraction of phenolic compounds from coffee beans using different natural eutectic solvents. These results were compared with traditional methods of phenolic extraction. The experimental procedure is based on the results of Dai et al. Results The method of gallic acid equivalent of total phenol content was compared with that of acetone and citric acid as solvent.

Biomedical applications. Due to their versatile, non-toxic and biodegradable properties, eutectic solvents have been used in the biomedical field. It is reported that the eutectic solvent can dissolve the model drug and improve solubility, permeability and absorption. Tuntarawongsa et al. reported the preparation and dissolution of ibuprofen as a low eutectic solvent with therapeutic properties made from menthol and camphor. Natural eutectic solvents dissolve a considerable amount of ibuprofen compared to water. With the addition of polymers, a polymer eutectic drug delivery system is formed. Other authors have also reported the ability of eutectic solvents to absorb drugs transdermal, using eutectic solvents composed of ibuprofen and terpenes.

The combination of natural eueutic solvents and bioactive molecules such as ibuprofen, menthol or phenylglycolic acid, as well as biodegradable natural polymers such as supercritical carbon dioxide, will be viable alternatives in drug delivery systems, bone therapy stents, and other biomedical applications. Biopolymers doped in natural eutectic solvents create structures for therapeutic delivery.

By subjecting the doped biopolymer to supercritical carbon dioxide, the foaming process occurs when the polymer is increased and thus the surface area is increased. And by using a template, the polymer can form any desired shape in the process. Our team also tested the potency of natural eutectic solvents in supercritical carbon dioxide foaming. These results reveal morphological changes involved in the porosity of the obtained samples. The presence of choline chloride and sucrose (1:1) is more pronounced than the example of citric acid and sucrose (1:1).

Green chemistry index. Natural eutectic solvents fully embody the principle of green chemistry. The preparation process of natural eutectic solvents is simply the mixing of two components. In some cases, either heating or liquefaction of the complex in water is required, meaning that the water is recovered through evaporation and condensation. This highlights the fact that there is no waste and no unwanted by-products formed during the production process. Since the natural eutectic solvent is in fact a mixture of the two components, the yield of this process can be considered to be 100%. These are some of the indicators that determine the continuity of the process, but the environmental factor is still the most useful one. Environmental factors are defined by the ratio of total waste to total production. In the case of natural eutectic solvents, an ideal zero environmental factor can be obtained. There are no chemical reactions involved in the production of natural eutectic solvents and therefore the atomic economy is 100%.

As for the carbon efficiency defined by the proportion of the total carbon of the product to the total carbon of the reactant, it can also be assumed to be 100% in cases where only two components are to be mixed. However, if heating and liquefaction of the original component is required, a more detailed calculation is required for the indirect use of carbon.

4. CONCLUSION

Low cost is one of the prominent features of NADESs. This is firmly based on the remarkable fact that they are composed of natural primary metabolites. These metabolites, being inherently sourced from nature, not only endow the solvents with an economical edge but also align them with the principles of green chemistry. In contrast to ionic solutions, the versatility of green NADESs truly stands out. Ionic solutions often have limitations in terms of their applicability due to factors like high cost, complex synthesis procedures, and potential environmental impacts. However, NADESs can adapt to a wide array of scenarios, whether it's in facilitating chemical reactions, enhancing extraction processes, or serving in electrochemical setups.

As the scientific community delves deeper, more and more insights into the basic principles and fundamental research aspects of NADESs are being unraveled. In the realm of biocatalysis, for example, these solvents have the potential to provide a more favorable microenvironment for enzymes, enabling them to function with enhanced efficiency and selectivity. This could revolutionize the production of bio-based chemicals and pharmaceuticals. In extraction processes, they can selectively extract valuable compounds from complex matrices, such as natural products, with higher yields and lower energy consumption compared to traditional solvents. Electrochemistry is another field where their unique properties, like tunable conductivity and stability, can open up new avenues for the development of advanced batteries and energy storage devices. Even in biomedical applications, the biocompatibility of natural eutectic solvents makes them promising candidates for drug delivery systems and tissue engineering scaffolds.

What began as a simple spark of scientific curiosity has now blossomed into a full-fledged area of research. NADESs are increasingly being regarded as the next generation of solvents that hold the key to a more sustainable industrial future. While it is undeniable that copious amounts of research still lie ahead, with challenges ranging from optimizing synthesis methods to understanding long-term stability and potential toxicity, there is no doubt that such solvents are poised to make a momentous and far-reaching contribution to the pursuit of more sustainable industrial development.

They offer a glimmer of hope in reducing the environmental footprint of industrial processes while maintaining or even enhancing productivity.

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