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NATURAL DEEP EUTECTIC SOLVENTS IN EXTRACTION PROCESS

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Abstract. Developing new, eco-friendly solvents which would meet technological and economic demands is perhaps the most popular aspects of Green Chemistry. Natural deep eutectic solvents (NADES) fully meet green chemistry principles. These solvents offer many advantages including biodegradability, low toxicity, sustainability, low costs and simple preparation. This paper provides an overview of knowledge regarding NADES with special emphasis on extraction applications and further perspectives as truly sustainable solvents.

Keywords: natural deep eutectic solvents, green chemistry, extraction.

1. Introduction

Without any doubt the awareness of the human impact on the environment increases day by day. This has pushed environmentally friendly extraction (green extraction) as an alternative process with respect to scientific and industrial research and development. The requirements for green extraction are based on the design and discovery of extraction processes which offer an optimal utilization of solvents, raw materials, and energy [1, 2]. In addition, one of the EU environmental policy and legislation issue is the decreased usage of petrochemical solvents as well as volatile organic compounds (VOCs), due to the fact that most of these chemicals are volatile, flammable and often toxic. Furthermore, the industrialists applying organic solvents in different type of processes have to fulfill rigorous safety requirements, prove that risk for workers during the extraction process not exist and demonstrate safety of the final product regarding solvent traces [1]. Therefore, developing new, environmentally friendly and tunable solvents which would meet both technological and economic demands is perhaps the most active area of Green Chemistry and Green Analytical Chemistry (GAC). Indeed, several principles of green chemistry and GAC refer to this problematic aspect (directly or indirectly) [3-5].

Taking into account the new solvents introduced in last decades, ionic liquids (ILs) have gained much attention from the scientific community, thus the number of published data concerning these solvents has grown exponentially. It is well known that the main advantage of ILs is their unique physicochemical properties which depend on the structure, as well as size of their cationic and anionic constituents. To be useful in microextraction process, ILs should be characterized by high thermal stability, hydrophobicity, negligible vapour pressure, solvent miscibility and tunable viscosity and many of ILs meets these requirements [6, 7]. Furthermore, ILs can be structurally designed to extract target analytes selectively based on unique molecular interactions, leading to highly efficient extraction procedures. Nevertheless, IL "greenness" is often challenged, mainly due to their poor biodegradability, biocompatibility, and sustainability [8, 9]. Moreover, ILs appear to be highly toxic towards organisms from different trophic levels [10].

An alternative to ILs are deep eutectic solvents (DES) introduced in 2003 [11]. Deep eutectic solvents are defined as a mixture of two or more components, which may be liquid or solid and that at a particular composition present a high melting point depression becoming liquids at room temperature. Deep eutectic solvents have comparable characteristics to ILs but are cheaper to produce due to lower cost of the raw materials, less toxic, and often biodegradable [10]. However, the high viscosity and solid state of most DES at room temperature restrict their application as extraction solvents [12]. To overcome these drawbacks, natural deep eutectic solvents (NADES) were introduced [13].The milestones of DES are schematically presented in Fig. 1.

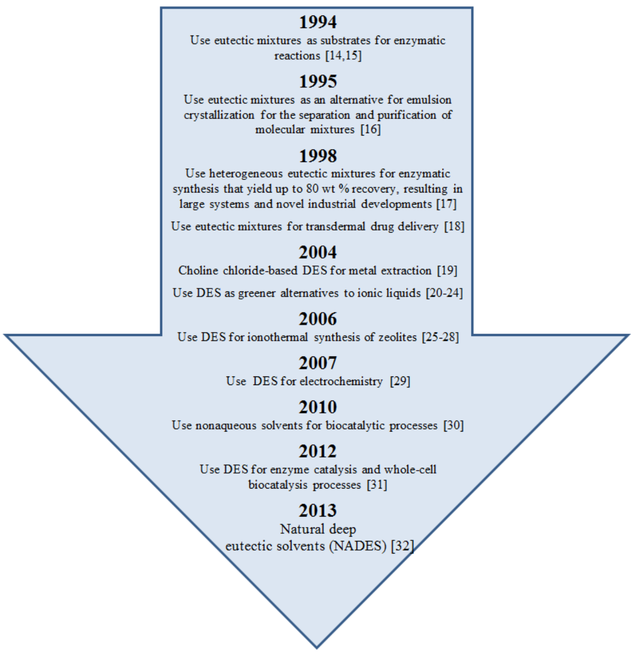

Fig. 1. Milestones of deep eutectic solvents development

Representing a new generation of liquid salts, NADES are based on mixtures of cheap and readily available components: naturally-derived uncharged hydrogen-bond donors (*e.g.* amines, sugars, alcohols and carboxylic acids) and non-toxic quaternary ammonium salts (*e.g.* cholinium chloride) [1]. NADES fully represent green chemistry principles and offer many advantages, including readily available components, low costs, simple preparation, a low toxicity profile and sustainability. These solvents are characterized by very good physicochemical properties: negligible volatility, a liquid state even at temperatures far below 273 K, adjustable viscosity, a wide polar range and a high degree of solubilisation strength for different compounds. Taking into account the numerous structural possibilities of NADES and the potential for designing their physicochemical properties to accommodate different purposes, without any doubt they may be considered as “designer solvents” [1]. Large combinations of NADES could be envisaged, and the possibilities that arise from the ability of tailor-made new solvents with the most adequate properties for a given application are enormous. It is no wonder that they also gained recognition in analytical chemistry. Currently, the use of NADES as extraction solvents for phenolic compounds is the most studied application by far. Because NADES are greener and safer alternatives, it is not surprising that they have also been employed in extraction of natural products for pharmaceutical applications. NADES present good properties to be used as alternative extraction solvents, such as being liquid at room temperature (and sometimes even below 273 K), having a viscosity that can be adjusted easily, and being sustainable and safe. Because NADES can dissolve both polar and nonpolar metabolites, this envisages that they can serve as a solvent for the extraction of many types of natural compounds, depending on the physicochemical properties of each NADES.

This paper provides an overview of knowledge regarding NADES with special emphasis on their extraction applications and further perspectives as truly sustainable solvents.

2. Preparation, Structure and Properties of NADES

Without any doubt, one of the most important advantages of NADES is the facility to prepare these solvents and the large number of combinations that could be made [33]. Recently, a large number of stable NADES based on natural compounds, particularly primary metabolites such assugars (glucose, fructose, *etc*.), organic acids (lactic, malic acids, *etc*.), urea and quaternary ammonium salts such as choline chloride [1, 33-34] are reported. Chemical structure of different compounds with the ability to form natural deep eutectic solvents is presented in Fig. 2.

NADES are capable of donating or accepting electrons or protons to form hydrogen bonds. This property gives them excellent dissolution properties [35]. Table 1 lists literature information on most commonly methods used for preparing NADES. These preparation methods are used in the literature with various modifications about *e.g.* time of heating or temperature, depending on the nature of the substances which are ingredients for preparing NADES.

Due to the large number of combinations in the selection of components for the preparation of this new type of green and sustainable solvents, different purposes media for various applications can be create.

It is well known that the interactions nature that takes place in the eutectic behavior depends on the components type where hydrogen bonds or Van der Waals forces are involved. Many reports concerning different techniques applied for the exploring of the NADES structure exist. These techniques are: Crystallographic data, Nuclear Magnetic Resonance (NMR) spectroscopy, Fourier Transform Infrared Spectroscopy (FT-IR) and FastAtom Bombardment-Mass Spectrometry (FAB)-MS [34, 36, 37].

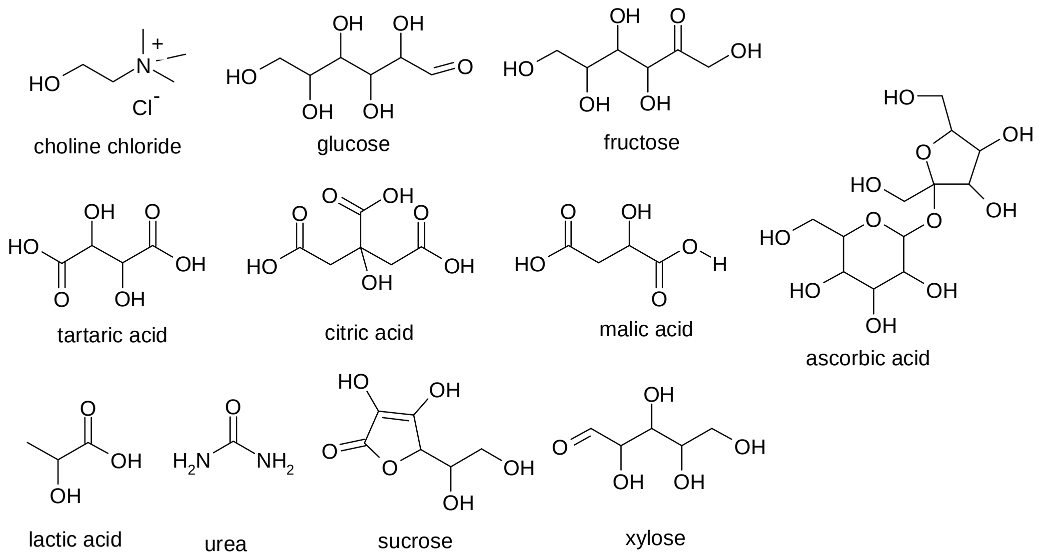

Fig. 2. Chemical structure of different compounds with the ability to form natural deep eutectic solvents

Table 1

The most commonly methods used for preparing natural deep eutectic solvents in analytical chemistry

Method	Preparation	Ref.
Heating and stirring	Stir two-component mixture and water and heat in a water bath below 323 K until a clear liquid is formed (30–90 min).	[36-38]
	Heat the two-component mixture to 353 K under constant stirring until a homogeneous liquid is formed.	[11, 39-40]
Vacuum evaporating	Dissolve components in water and evaporate at 323 K using rotatory evaporator. The obtained liquid put in a desiccator with silica gel until constant weight is reached.	[36]
Freeze drying	Mix components. Freeze the obtained aqueous solution and subsequently freeze-dried for the achievement of clear viscous liquids.	[41]

Despite the fact that different methods are used for the preparation of NADES, studies of ^{1}H NMR spectra showed the same chemical profile for NADES with the same composition [33]. The significant influence on the formation and stability of NADES have several parameters including the number of hydrogen-bond donors (HBD) or hydrogen-bond acceptors (HBA), the position of the bonds appeared and the spatial structure of those groups [36]. The strength of the hydrogen bonds can be correlated with the phase-transition temperature, stability and solvent properties of the respective mixture [33]. Taking this into account, the corresponding dependence exists, namely the higher the hydrogen-bonding ability of the counterparts, the deeper the decrease in the freezing point [41].

It has been proved that the supermolecular structure of NADES changes after dilution with water due to the progressive rupture of the hydrogen bonding. In addition, physicochemical properties such as conductivity, viscosity, density, polarity and water activity vary to some extent depending on chemical nature of the components [33]. Moreover, NADES is made of components that are abundant in our daily food, being thus cheap, sustainable, and safe. Interestingly, some NADES show a very high solubilization ability of both nonpolar and polar compounds, and some metabolites are significantly more soluble in NADES than in water [12]. Furthermore, it has been proved that NADES are able to dissolve even macromolecules [42]. This predicts a great potential for NADES as solvents in the extraction of valuable secondary metabolites for their application in the food or pharmaceutical industry [12].

3. NADES Applied in Extraction Process

Green technology and green analytical chemistry are nowadays very important scientific issues. Green analytical chemistry involves developing non-hazardous and environmentally friendly substances such as solvents, extraction and reaction media. Growing awareness of human impact causes that clean and green extraction to be one of the most important and highlighted subjects.

Ionic liquids are considered to be so called green solvents due to their unique properties (mentioned above). So far ILs are applied in various branches of chemistry, like organic synthesis, electrochemistry, as extraction solvents or reaction media and in catalytic processes [8, 39]. Regardless their versatility and broad spectrum of possible applications, recently the issue of high toxicity of ILs is drawing attention [43, 44].

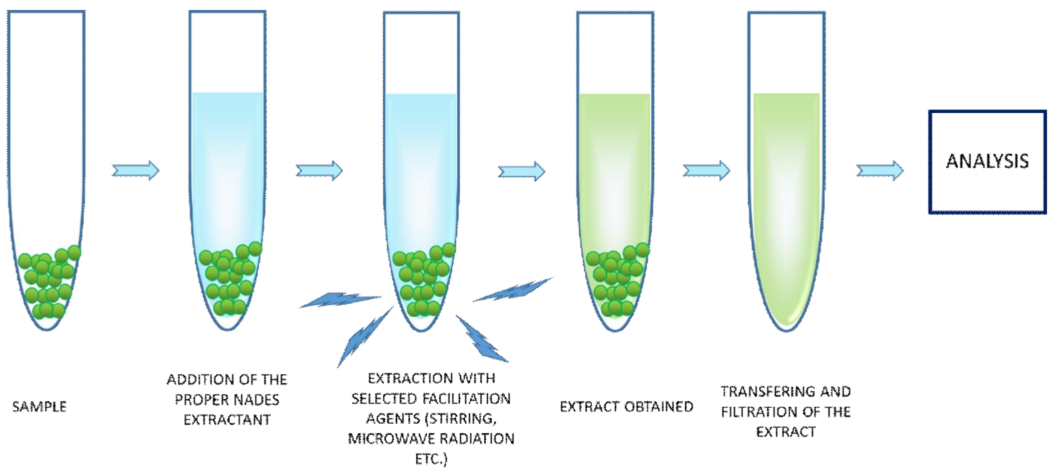

Fig. 3. General scheme of the extraction procedure using natural deep eutectic solvents as an extractant

Table 2

Information on application of NADES in sample preparation and as green reaction media

Composition of NADES	Water content, %	Application	Quantitaion method/ confirming method	Ref.
choline chloride: glycerol, choline chloride: 1,4-butanediol, choline chloride: maltose, choline chloride: sucrose, choline chloride: citric acid	0, 20, 40, 60	Extraction of polar phenolics from *C. Cajan* leaves	UPLC	[39]
lactic acid: glucose, sucrose: choline chloride, proline: malic acid, sorbitol: chlone chloride, fructose:glucose:sucrose	0, 10, 25, 50, 75	Extraction of phenolic metabolites from safflower	HPLC-DAD	[12]
choline chloride: glucose, choline chloride: xylose, choline chloride: glycerol	30	Extraction of the phenolic compounds from grape peel	HPLC-UV	[1]
proline: malic acid, malic acid: choline chloride, glucose: fructose: sucrose	–	Extraction of antocyanins from *Catharanthus roseus*	LC-MS	[45]
citric acid: glucose, L-proline: glucose, citric acid: adonitol, betaine: malic acid	–	Extraction of bioactive flavonoids from *Flos sophorae*	LC-MS, LC-UV	[46]
glucose: choline chloride, xylitol: choline chloride, proline: malic acid	25, 50, 75	Extraction of natural colorants from safflower	UV-VIS spectrometry	[38]
choline chloride: urea	–	Reaction of regioselective reduction of epoxides and carbonyl compounds	NMR	[47]
choline chloride: urea, choline chloride: ethylene glycol, choline chloride: glycol	–	Media in nanoparticle synthesis	–	[48]

Other types of novel environmentally friendly solvents are deep eutectic mixtures (DES). These solvents are composed of organic compounds and their melting point is below the melting points of each individual component [49]. DES show some advantages that overcome drawback connected with ionic liquids but the most important is that they are environmentally benign and show acceptable toxicity.

Natural Deep Eutectic Solvents in last few years have become more popular, especially for extraction of natural compounds from plants, food and other natural matrices. A great advantage of NADES is the possibility to prepare solvents in a large number of combinations. Moreover, they possess better extraction properties like liquid state below 273 K, tunable viscosity, cheap and easy preparation and very low toxicity [1, 12].

NADES have been reported for the dissolution a wide spectrum of both polar and non-polar compounds. The solubilization may be controlled by addition of water – nonpolar compounds are better soluble in pure NADES [32]. There have been some examples of using these green solvents.

One of the applications of NADES in analytical chemistry is using these solvents as extraction medium. The procedure usually used for the extraction with NADES is schematically presented in Fig. 3. The first step is preparation of the proper deep eutectic mixtures by simple mixing, stirring and heating the ingredients. Then the biological matrix was mixed with different deep eutectic mixtures and extraction was assisted with microwave radiation. The extraction process was optimized by changing the water content in the extracting solvent. Then the extracts were filtered and analyzed with UPLC method. The recoveries gained by application of properly selected NADES with optimized water content were good or even better than these gained with ethanol as an extracting solvent [39]. This procedure was used to extract polar and weak polar phenolic compounds from *Cajanuscajan* leaves [39].

Another example of NADES applications is extraction of phenolic metabolites from *Carthamus tinctorius* [12], various phenolic compounds from grape peel [1], anthocyanins from *Catharanthus roseus* [45], flavonoids from *Flos sophorae* [46] and natural colorants from safflower [38]. In all cases, properly optimized conditions of the extraction (water content, temperature, time, good NASED selection) provided high recoveries and better stability of the extracts obtained.

In the literature issues of using NADES as reaction medium also are found. These solvents were successfully applied in simple and environmentally friendly procedure of regioselective reduction of epoxides and carbonyl compounds [47]. The information on application of NADES as reaction media and in extraction procedures is given in Table 2.

4. Conclusions and Future Perspectives

Due to such properties of traditional solvents as low biodegradability, high toxicity and cost, a growing research area in the development of green extraction is devoted to designing new and eco-friendly solvents which would meet technological and economic demands. Natural Deep Eutectic Solvents finally meet these requirements. As discussed in this review, NADES have a large number of advantages including low costs, readily available components, simple preparation, a low toxicity profile and sustainability. Moreover, these solvents feature very good physicochemical properties: negligible volatility, a liquid state even at temperatures far below 273 K, adjustable viscosity, a wide polar range and a high degree of solubilisation strength for different compounds. Based on these advantages, numerous structural possibilities of NADES and the potential for designing their physicochemical properties to accommodate different purposes it can be state that, NADES may be considered as “designer solvents”.

Without any doubt, due to the huge potential of NADES, interesting perspectives for further research and industrial applications are opened. Considering the application of NADES in analytical chemistry, the use of NADES as extraction solvents for phenolic compounds is the most studied application by far. Taking into account stabilization skills of NADES and their extraction talents, a very promising field for research in the next years is the extraction of biocompounds such as alkaloids, hormones and peptides. In addition, these solvents will certainly be one of those chosen for sustainable and green extraction, which will lead to the novel application of NADES in food and pharmaceutical industry. In sum, considering the possible combinations of NADES are enormous, roughly estimated to 10^8, NADES appear to offer huge possibilities for use as solvents in the future, along with their potential and promising health promoting activities.

However, the full potential of these green solvents is still unexplored. First of all, there are no data on the application of these solvents in separation processes. Therefore, efforts should be made in evaluating this new smart solvents because it could be very good alternatives to toxic, low biodegradable and expensive reagents used in this step of analytical process. Considering their possibility of being tailored-made, a potential to modify the interaction between stationary phase and target analytes exist (what has been reported for ILs).

Despite the fact that extensive research on NADES are still going on, there is still a lack of information on practical issues related to their application as an extraction solvent, such as their efficiency, optimal water content, and the recovery of extracted compounds from NADES extracts. The latter is particularly challenging considering the inherent low vapor pressure of NADES that makes it difficult to recover solutes from the NADES solution.

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ПРИРОДНІ ГЛИБОКОЕВТЕКТИЧНІ РОЗЧИННИКИ В ПРОЦЕСІ ЕКСТРАКЦІЇ

Анотація. *Показано, що розроблення нових, екологічно чистих розчинників, які відповідали б технологічним та економічним вимогам, є найпопулярнішим аспектом зеленої хімії. Природні глибоко евтектичні розчинники (NADES) повністю відповідають принципам зеленої хімії. Ці розчинники мають багато переваг, в тому числі біодеградабельність, низьку токсичність, стійкість, низьку вартість та простоту приготування. У статті приведено огляд відомостей про NADES з особливим акцентом на застосуванні у процесах екстракції і подальших перспектив як дійсно стійких розчинників.*

Ключові слова: *природні глибокоевтектичні розчинники, зелена хімія, екстракція.*