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Natural designer solvents for greening analytical chemistry

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ABSTRACT

Developing new green solvents is one of the key subjects in Green Chemistry. Ionic liquids and deep eutectic solvents were discovered as an option to replace organic solvents. However, ionic liquids and deep eutectic solvents (DES) have still some limitations to be applied to real chemical industry. In this sense, a new generation of designer solvents have emerged in the last decade as promising green media. When the compounds that constitute DES are primary metabolites, namely, aminoacids, organic acids, sugars, or choline derivatives, DES are called Natural Deep Eutectic Solvents (NADES). NADES fully represent green chemistry principles. These solvents offer many striking advantages including biodegradability, low toxicity, solute stabilization, sustainability, low costs and simple preparation. Thus, interesting applications in health-related areas can be proposed. This review presents an overview in order to up-to-date knowledge regarding NADES with special emphasis on their analytical applications and further perspectives as truly green solvents.

Contents

1. Introduction

Developing sustainable solvents is perhaps the most active area of Green Chemistry. This represent an important challenge because the use of them often represent for the vast majority of mass wasted in syntheses and processes [1]. In this context, finding green solvents as replacements for nongreen ones became a prior target. In fact, several principles of green chemistry and green analytical chemistry directly or indirectly refer to this problematic issue [2].

The implementation of solvent-free processes would be ideal; however, they are almost unavoidable due to their crucial role in dissolving solids, mass and heat transfer, influencing viscosity and in separation and purification steps. Accordingly, two main strategies for green solvent development have been proposed: the substitution of solvents derived from petroleum with others obtained from renewable resources, and the substitution of hazardous solvents with ones that show better environmental, health and safety properties [3,4].

Over the past two decades, ionic liquids (ILs) have gained much attention from the scientific community, and the number of reported articles in the literature has grown exponentially. Nevertheless, ILs "greenness" is often challenged, mainly due to their poor

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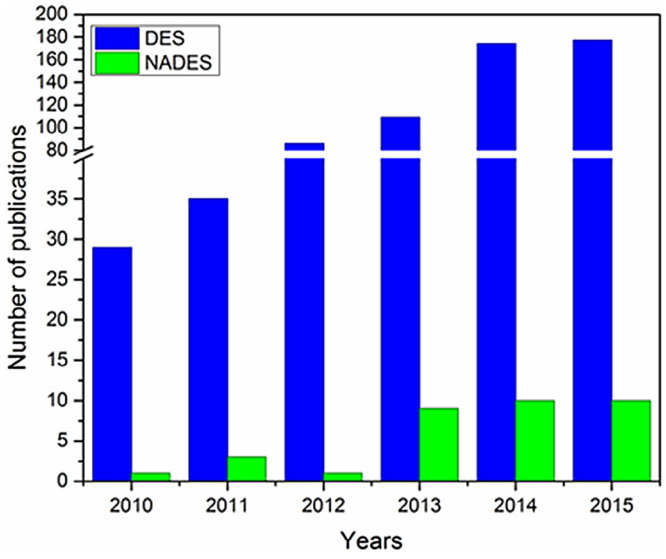

Fig. 1. Number of publications using the keywords *deep eutectic solvents* and *natural deep eutectic solvents* in the past five years (source www.scopus.com; date of search: 09.10.15).

biodegradability, biocompatibility, and sustainability [5]. In 2003 Abbott and co-workers [6] introduced a new type of solvents, called Deep Eutectic Solvents (DES). The mixture was formed by urea and choline chloride, both solid starting materials with high melting points. These mixtures form a eutectic system with a wide liquid range and interesting properties to be used as a solvent. Hydrogen bonding and Van der Walls interactions are the main driving force of this phenomenon. The study on hydrogen-bond (HBD) donor–acceptor (HBA) combinations enables tailoring the chemical nature, physical properties, and phase behavior of this new family of designer solvents [7]. When the compounds that formed DES are abundant cellular constituents such as sugars, alcohols, amino acids, organic acids, and choline derivatives, they are called Natural Deep Eutectic Solvents (NADES).

NADES fully represent green chemistry principles. This term was postulated by Choi et al. [8] considering that in living organisms there is an alternative medium to water and lipids. If there were only this two mediums it would be difficult to explain a great number of biological processes that occur in all organisms, such as biosynthesis of poorly water soluble metabolites and macromolecules in the aqueous environment of cells, also survival of organisms in extreme drought and cold conditions.

As this is a recent growing area of research contrasting information could be found. In this sense DESs are also known as low-transition-temperature mixtures (LTTMs) [9]. Moreover, as the definition of NADES is novel, it is possible to find reported mixtures described as DES which fits in the definition of NADES. Their recent appearance is reflected in the search of the term NADES comparing with DES (Fig. 1).

This review presents an overview in order to up-to-date knowledge regarding NADES and clarify the classification of this solvents with special emphasis on their analytical applications and further perspectives as truly green solvents.

2. NADES preparation

A major advantage of NADES is the facility to prepare these solvents and the large number of combinations that could be made (around 10^6) [7]. Considering this, the possibilities that arise from the ability of tailor-made new solvents with the most adequate properties for a given application are outsize [5].

There are three methods which are most commonly used for preparing NADES:

a) *heating and stirring method* described by Dai et al. [10]: the two-component mixture with calculated amounts of water is placed in a bottle with a stirring bar and cap and heated in a water bath below 50°C with agitation till a clear liquid is formed (about 30–90 min) [10–13] or, following the conditions used by Abbot and co workers 2003 [6], heating and stirring at 80°C [11,14,15];
b) *evaporating method* described by Dai et al. [10]: components are dissolved in water and evaporated at 50°C with a rotatory evaporator. The liquid obtained is put in a desiccator with silica gel till they reach a constant weight;
c) *freeze drying method* described by Gutierrez et al. based on the freeze-drying of aqueous solutions of the individual counterparts [16]. However, it is not used as frequent as the others. These three methods are used in different works with suitable modifications (time of heating, temperature, etc.) according to the nature of the compounds.

Taking into account that NADES could be found in nature, the multiple component mixtures described are formed by metabolites that are naturally present in all types of cells and organisms [10]. The common components of NADES are sugars (glucose, sacarose, fructose, etc.); organic acids (lactic, malic, citric acids, etc.); urea and choline choride (Fig. 2).

Different combinations of NADES reported as stable liquids were classified, in four groups: Derivatives from organic acids, Derivate from choline chloride, Mixtures of sugars and others combinations (Table 1). The major mixtures are made of choline chloride with differents metabolites, being the combination with Lactic Acid the most studied in different molar ratio (1:1;1:2;1:3;1:4;1:5;1:9;2:1 and 3:1) and extraction of phenols and flavonoids their principal applications. Choline chloride is an essential nutrient, it is also known to be nontoxic and biodegradable and former of vitamin B4 [17,18].

3. The structure of NADES

The nature of the interactions that take place in the eutectic behavior depends on the type of the components where hydrogen bonds or Van der Waals forces are involved. Different techniques have been used to explore the structure of NADES. Nuclear Magnetic Resonance (NMR) spectroscopy, Crystallographic data, Fast Atom Bombardment-Mass Spectrometry (FAB)-MS and Fourier Transform Infrared Spectroscopy (FT-IR) have been used [7,10,11].

As an example, the study of the mixture proline:malic acid suggested that the proper ratio to form an adequate eutectic mixture is 1:1 [11]. All the research up to date showed an extensive hydrogen-bonding network between the components of NADES [11,16]. Moreover, in some mixtures, such as different sugars with choline chloride, water can be present as part of the solvent. This water is strongly retained in the liquid and cannot be evaporated [8].

Even though NADES could be prepared by different methods, studies of ^{1}H NMR spectra showed the same chemical profile for NADES with the same composition [16]. The number of HBD or HBA, the spatial structure of those groups and the position of the bonds appeared to have significantly influence on the formation and stability of NADES [10]. The strength of the hydrogen bonds can be correlated with the phase-transition temperature, stability, and solvent properties of the respective mixture. In general, the higher the hydrogen-bonding ability of the counterparts, the deeper the decrease in the freezing point [16].

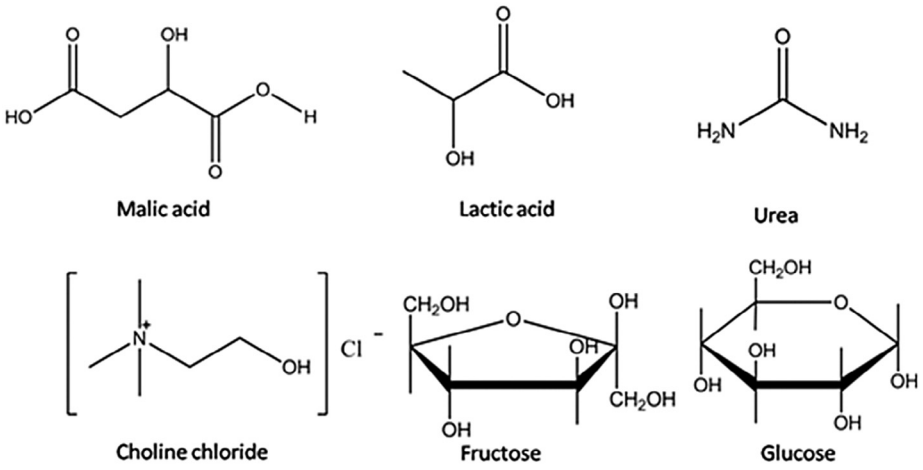

Fig. 2. Common components of NADES.

The supermolecular structure of NADES changes after dilution with water because a progressive rupture of the hydrogen bonding; physicochemical properties such as viscosity, conductivity, density, water activity, and polarity vary to some extent depending on chemical nature of the components [11].

4. Analytical applications

Achieving the general aims and objectives of Analytical chemistry in today's changing world requires producing tangible (reagents, sorbents, solvents, instruments, analyzers) and intangible means (strategies, calibration procedures, advances in basic science) to facilitate the development of new analytical methods or improvement of existing ones [26]. In this sense, analytical chemistry is the science that goes "one-step-ahead", producing "revolutionary" applications in order to contribute to "evolutionary" advances in Science and Technology in areas such as health, industry and environment.

NADES offer endless opportunities at method development, with enhancement perspectives at different steps and sub-steps of the Entire Analytical Process. They can be applied in different research fields, particularly as solvents for extraction and synthesis, biocatalysis, gas separations, materials science and electrochemistry. NADES are truly designer solvents that can be utilized as sustainable and safe extraction media. In the biomedical or pharmaceutical field, the possibility to prepare drug delivery systems was reported by Scott and coworkers who described the preparation of a bioactive eutectic system [13].

A deeper understanding of the chemical structures and physical properties of NADES, the intermolecular interactions between NADES and target analytes, and their efficiency and selectivity are necessary. Studies about their ability to solubilize and stabilize biomolecules provide the basis for the developing of tailor-made NADES for specific applications. In order to gain more insight into the solubilizing mechanism of NADES, Dai et al. [10] studied by high-resolution magic angle spinning (HR-MAS) NMR a saturated solution of quercetin in Xilitol-Choline chloride-Water. Cross peaks between quercetin and NADES were observed in the HR-MAS-NOESY spectrum indicating that the interaction forces, might result from hydrogen bonding between NADES molecules and solutes, providing an explanation of the high solubilizing capacity of NADES. However, the authors have not presented any graphical information. Much is still unknown about the structure and interaction of NADES with target analytes, and this is definitely an interesting topic to explore in order to unravel these questions.

4.1. Sample preparation

4.1.1. Solvent talents

NADES skills as green smart solvents together with their capacity as stabilization agents, offer interesting perspectives for sample preparation, including extraction, synthesis, dilution and/or preconcentration. They show appropriated physicochemical properties as solvents: negligible volatility, liquid state even far below 0°C, adjustable viscosity, sustainability, biodegradability combined with acceptable toxicity profiles, and high solubilization power of both polar and non-polar compounds [12,27]. All those properties imply their great potential in the extraction of valuable secondary metabolites of plants for their direct application in pharmaceutical, cosmetics and food industries [3,8].

There is limited information concerning NADES toxicity. Paiva et al. [5] tested the cytotoxicity of 11 different NADES. However, the analysis of the results obtained does not indicate a clear trend concerning the cytotoxic effect and the constituents of the NADES. In this work, the authors conclude that the viability depends on the concentration. Hayyan et al. [28] studied the toxicity and cytotoxicity of choline chloride (ChCl) based DESs with four hydrogen bond donors including glycerine, ethylene glycol, triethylene glycol and urea. It was found that there was no toxic effect for the tested DESs. DESs are expected to serve as selective chemicals which may have the potential to be destructive for certain types of cells, e.g. any abnormal cells (tumor cells) and non-destructive for other cells.

NADES show high solubilization ability of both non-polar and polar compounds, and some metabolites are significantly more soluble in NADES than in water [27]. The solubility of poorly soluble molecules such as benzoic acid, griseo-fulvin, danazol, and itraconazole was reported to be 5 to 22,000 times higher in NADES composed by a mixture of choline choride:urea and choline choride:malonic acid, than in water [5]. NADES have been reported for the dissolution of carbohydrates and ionic metal oxides [29]. The dilution of NADES changes their polarity affecting the solubilization capacity. This solubility is also correlated with the solutes' polarity. Nonpolar compounds have the highest solubility in pure NADES, while a 5–10 v% of water dilution allows the highest solubility of medium polar compounds [10]. The ability of NADES formed by a mixture of carboxylic acids and trimethylglicine to solubilize L-amino acids was evaluated. The amino acids with an aromatic portion in their structures (phenylalanine, tryptophan and tyrosine) showed higher solubility in NADES than in water [21].

Table 1
Mixtures of compounds reported as stable liquids forming NADES

Composition of NADES	Molar ratio	Dilution (% v/v)	Application	Method of preparation	Ref.
Derivatives from Organic Acids					
malic acid:proline	1:1	25;50;75	stabilisation ability for phenolic compounds	heating and stirring at 50°C	[12]
	1[a]:1[b,c]		formation and stability of NADES	vacuum evaporating	[10]
	n.s		analysis of physicochemical properties	heating with stirring at 70°C	[11]
DL-malic acid:L-serine	2:3/1:1		formation and stability of NADES	vacuum evaporating	[10]
DL-malic acid:β-alanine	2:3/1:1		formation and stability of NADES	vacuum evaporating	[10]
malic acid:sucrose	1:1		preparation of NADES and NMR measurements	freeze-dried	[10]
	1[a]:1/2[a]:1		formation and stability of NADES	vacuum evaporating	[10]
malic acid:fructose	1:1		preparation of NADES and NMR measurements	freeze-dried	[8]
malic acid:glucose	1:1				
DL-malic acid:D-mannose	1:1		formation and stability of NADES	vacuum evaporating	[10]
DL-malic acid:D (+)trehalose	2:1				
DL-malic acid:lactose	2:1/1:1				
DL-malic acid:betaine	1:1	30	flavonoid extractions from Flos sophorae	freeze-drying	[19]
DL-malic acid:D-sorbitol	1:1		formation and stability of NADES	vacuum evaporating	[10]
DL-malic acid:D(+)glucose:D(−)fructose	1:1:1				
DL-malic acid:D(+)glucose:glycerol	1:1:1				
DL-malic acid:sucrose:glycerol	1:1:2				
DL-malic acid:betaine:D(+)glucose	1:1:1				
DL-malic acid:betaine:proline	1:1:1				
malic acid:proline:water	1:1:3	0–100	analysis of physicochemical properties	heating with agitation in a water bath at 50°C[i]	[11]
			physical properties of NADES	heating with stirring at 50°C	[10]
malic acid:β:alanine:water	1:1:3		analysis of physicochemical properties	heating with agitation in a water bath at 50°C[i]	[11]
			physical properties of NADES	heating with stirring at 50°C	[10]
maleic acid:glucose	4:1		preparation of NADES and NMR measurements	freeze-dried	[8]
maleic acid:sucrose	1:1				[8]
L (+)tartaric acid:betaine	1:2		formation and stability of NADES	vacuum evaporating	[10]
tartaric acid:glucose	1:1	7,5	use as polymers plasticizing agents	vacuum evaporating at 50°C[i]	[13]
	1[e]:1[d]		formation and stability of NADES	vacuum evaporating	[10]
lactic acid:sucrose	1:2	20	phenolic extraction from Cajanus cajan leaves	heating and stirring at 80°C	[14]
			flavonoid extraction from Radix Scutellariae	heating and stirring at 80°C	[15]
lactic acid:glucose	1:2	20	phenolic extraction from Cajanus cajan leaves	heating and stirring at 80°C	[14]
	5:1		stabilisation ability for phenolic compounds	heating and stirring at 50°C	[12]
	5:1[d]		formation and stability of NADES	vacuum evaporating	[10]
lactic acid:β-alanine	1:1				
lactic acid:betaine	2:1/5:1	5;10;15;20;50	pretreatment of lignocellulosic biomass rice straw	shaking water bath at 60°C 100 rpm	[20]
lactic acid:D/L-proline	1:1		formation and stability of NADES	vacuum evaporating	[10]
lactic acid:glucose:water	5:1:3	0–100	analysis of physicochemical properties	heating with agitation in a water bath at 50°C[i]	[11]
			physical properties of NADES; solubility of small molecules and macromolecules	heating with stirring at 50°C	[10]
citric acid:sucrose	1:1	6,4	use as polymers plasticizing agents	vacuum evaporating at 50°C[i]	[13]
			formation and stability of NADES	vacuum evaporating	[10]
			preparation of NADES and NMR measurements	freeze-dried	[8]
	1:2	20	phenolic extraction from Cajanus cajan leaves	heating and stirring at 80°C	[14]
			flavonoid extraction from Radix Scutellariae	heating and stirring at 80°C	[15]
citric acid:glucose	1:1	8.2	use as polymers plasticizing agents	vacuum evaporating at 50°C[i]	[13]
	1:1[d]		formation and stability of NADES	vacuum evaporating	[10]
		30	flavonoid extractions from Flos sophorae	freeze-drying	[19]
	1:2	20	phenolic extraction from Cajanus cajan leaves	heating and stirring at 80°C	[14]
			flavonoid extraction from Radix Scutellariae	heating and stirring at 80°C	[15]
	2:1		preparation of NADES and NMR measurements	freeze-dried	[8]

(*continued on next page*)

Table 1 (*continued*)

Composition of NADES	Molar ratio	Dilution (% v/v)	Application	Method of preparation	Ref.
citric acid:D(−)fructose	1:1		formation and stability of NADES	vacuum evaporating	[10]
citric acid:D-mannose	1:1				
citric acid:maltose	2:1				
citric acid:raffinose	3:1				
citric acid:trehalose	2:1		formation and stability of NADES	vacuum evaporating	
	2:1		preparation of NADES and NMR measurements	freeze-dried	[8]
citric acid:adonitol	1:1		formation and stability of NADES	vacuum evaporating	[10]
		30	flavonoid extractions from Flos sophorae	freeze-drying	[19]
citric acid:D-sorbitol	1:1		formation and stability of NADES	vacuum evaporating	[10]
citric acid:xylitol	1:1				
citric acid:ribitol	1:1				
citric acid:proline	1:1[b]/1:2[b]/1:3[b]				
	1:1/1:2/ 1:3		preparation of NADES and NMR measurements	freeze-dried	[8]
citric acid:β alanine	1:1		formation and stability of NADES	vacuum evaporating	[10]
citric acid:betaine	1:1				
	2:1		evaluation of the solubility of amino acids	mixing at 90°C	[21]
glycolic acid:betaine	2:1				
oxalic acid:betaine	2:1				
oxalic acid:betaine:D(+)glucose	1:1:1		formation and stability of NADES	vacuum evaporating	[10]
Mixtures of Sugars					
fructose:sucrose	1[f]:1		formation and stability of NADES	vacuum evaporating	[10]
	1:1		preparation of NADES and NMR measurements	freeze-dried	[8]
glucose:sucrose	1:1				
glucose:fructose	1:1				
glucose:sucrose:fructose	1:1:1				
fructose:glucose:sucrose:water	1:1:1:11		analysis of physicochemical properties	heating with agitation in a water bath at 50°C[i]	[11]
			analysis of physical properties of NADES	heating with stirring at 50°C	[10]
Derivate from choline chloride					
choline chloride:D(−)fructose	5:2		formation and stability of NADES	vacuum evaporating	[10]
choline chloride:xylose	2:1	7	use as polymers plasticizing agents	vacuum evaporating at 50°C[i]	[13]
	3:1	5,6			
	2:1[g]/3:1[g]		formation and stability of NADES	vacuum evaporating	[10]
choline chloride:A-L rhamnose	2:1				
choline chloride:D(+)trehalose	4:1				
choline chloride:(D)-mannose	5:2				
choline chloride:sorbose	5:2/1:1				
choline chloride: D(+)galactose	5:2				
choline chloride:raffinose	11:2				
choline chloride:maltose	1:1/1:2/ 1:3/1:4	0,20,40,60	phenolic extraction from Cajanus cajan leaves	heating and stirring at 80°C	[14]
	1:2	20	flavonoid extraction from Radix Scutellariae	heating and stirring at 80°C	[15]
	4:1		formation and stability of NADES	vacuum evaporating	[10]
choline chloride:sorbitol	1:2	20	phenolic extraction from Cajanus cajan leaves	heating and stirring at 80°C	[14]
			flavonoid extraction from Radix Scutellariae	heating and stirring at 80°C	[15]
	3:1[h]/5:2[h]		formation and stability of NADES	vacuum evaporating	[10]
choline chloride:glucose	1:1[d]	30	flavonoid extractions from Flos sophorae	freeze-drying	[19]
	1:2	20	phenolic extraction from Cajanus cajan leaves	heating and stirring at 80°C	[14]
			flavonoid extraction from Radix Scutellariae	heating and stirring at 80°C	[15]
	5:2	90	stabilisation ability for phenolic compounds	heating and stirring at 50°C	[12]
	5:2[d]		formation and stability of NADES	vacuum evaporating	[10]
choline chloride:xylitol	4:1		stabilisation ability for phenolic compounds	heating and stirring at 50°C	[12]
	5:2		formation and stability of NADES	vacuum evaporating	[10]
		30	flavonoid extractions from Flos sophorae	freeze-drying	[19]
choline chloride:ribitol	5:2		formation and stability of NADES	vacuum evaporating	[10]

(*continued on next page*)

Table 1 (*continued*)

Composition of NADES	Molar ratio	Dilution (% v/v)	Application	Method of preparation	Ref.
choline chloride:glycerol	1:1/1:2		measure of limiting activity coefficients values	heating and stirring at 80°C	[17]
	1:1	30	flavonoid extractions from Flos sophorae	freeze-drying	[19]
	1:2		extraction of astaxanthin	heating and stirred at 80°C	[22]
		20	flavonoid extraction from Radix Scutellariae	heating and stirring at 80°C	[15]
			phenolic extraction from Cajanus cajan leaves	heating and stirring at 80°C	[14]
			saponin extraction of from Ziziphus joazeiro and Agave sisalana	heating and stirring at 100°C	[23]
	1:1/3:2		formation and stability of NADES	vacuum evaporating	[10]
choline chloride:sucrose	1:1	6,4	use as polymers plasticizing agents	vacuum evaporating at 50°C[i]	[13]
			formation and stability of NADES	vacuum evaporating	[10]
	1:2	20	phenolic extraction from Cajanus cajan leaves	heating and stirring at 80°C	[14]
			flavonoid extraction from Radix Scutellariae	heating and stirring at 80°C	[15]
	4:1	25;50;75	phenolic compounds stabilisation	heating and stirring at 50°C	[12]
		8,1	use as polymers plasticizing agents	vacuum evaporating at 50°C[i]	[13]
			formation and stability of NADES	vacuum evaporating	[10]
choline chloride:acetic acid	1:2		saponin extraction from Ziziphus joazeiro and Agave sisalana	heating and stirring at 100°C	[23]
choline chloride:lactic acid	1:1		formation and stability of NADES	vacuum evaporating	[10]
	1:2	20	phenolic extraction from Cajanus cajan leaves	heating and stirring at 80°C	[14]
			saponin extraction of from Ziziphus joazeiro and Agave sisalana	heating and stirring at 100°C	[23]
	1:1/1:2/ 1:3/1:4/ 2:1/3:1	20;40;60;80	flavonoid extraction from Radix Scutellariae	heating and stirring at 80°C	[15]
	1:2/1:5/ 1:9	5;10;15;20;50	pretreatment of lignocellulosic biomass rice straw	shaking water bath at 60°C and 100 rpm	[20]
choline chloride:citric acid	1:1	7,7	use as polymers plasticizing agents	vacuum evaporating at 50°C[i]	[13]
	1:2	2020	phenolic extraction from Cajanus cajan leaves	heating and stirring at 80°C	[14]
			flavonoids extraction from Radix Scutellariae	heating and stirring at 80°C	[15]
	1:1/2:1		formation and stability of NADES	vacuum evaporating	[10]
	2:1/3:1		preparation of NADES and NMR measurements	freeze-dried	[8]
choline chloride:malic acid	1:1		preparation of NADES and NMR measurements – solubility of compounds	freeze-dried	
	1:2	20	phenolic extraction from Cajanus cajan leaves	heating and stirring at 80°C	[14]
			flavonoid extraction from Radix Scutellariae	heating and stirring at 80°C	[15]
	1:1[a]/1,5:1[a]		formation and stability of NADES	vacuum evaporating	[10]
	2:1/3:1		preparation of NADES and NMR measurements	freeze-dried	[8]
choline chloride:malonic acid	1:1		formation and stability of NADES	vacuum evaporating	[10]
	1:2		saponin extraction from Ziziphus joazeiro and Agave sisalana	heating and stirring at 100°C	[23]
choline chloride:maleic acid	1:1/2:1		formation and stability of NADES	vacuum evaporating	[10]
	1:1/2:1/ 3:1		preparation of NADES and NMR measurements	freeze-dried	[8]
choline chloride:oxalic acid	1:2		saponin extraction from Ziziphus joazeiro and Agave sisalana	heating and stirring at 100°C	[23]
choline chloride:propionic acid	1:2		saponin extraction from Ziziphus joazeiro and Agave sisalana	heating and stirring at 100°C	
choline chloride:L(+)tartaric acid	2:1		formation and stability of NADES	vacuum evaporating	[10]
choline chloride:urea	1:2		synthesis of 4-thiazolidinones	heating and stirring at 100°C	[24]
			synthesis of aurones	heating and shaking at 80°C, 150 rpm	[25]
			saponin extraction from Ziziphus joazeiro and Agave sisalana	heating and stirring at 100°C	[23]
choline chloride:fructose:water	1:1:1		preparation of NADES and NMR measurements	freeze-dried	[8]
	5:2:5		analysis of physicochemical properties of NADES	heating with agitation in a water bath at 50°C[i]	[11]
			physical properties of NADES	heating with stirring at 50°C	[10]

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Table 1 (*continued*)

Composition of NADES	Molar ratio	Dilution (% v/v)	Application	Method of preparation	Ref.
choline chloride:glucose:water	1:1:1		preparation of NADES and NMR measurements	freeze-dried	[8]
	5:2:5	0–100	analysis of physicochemical properties	heating with agitation in a water bath at 50°C[i]	[11]
			physical properties of NADES – solubility of small molecules and macromolecules	heating with stirring at 50°C	[10]
choline chloride:sucrose:water	1:1:1		preparation of NADES and NMR measurements	freeze-dried	[8]
	4:1:4	0–100	analysis of physicochemical properties	heating with agitation in a water bath at 50°C[i]	[11]
			physical properties of NADES	heating with stirring at 50°C	[10]
choline chloride:lactic acid:water	1:1		analysis of physicochemical properties	heating with agitation in a water bath at 50°C[i]	[11]
choline chloride:malic acid: water	1:1:2		analysis of physicochemical properties	heating with agitation in a water bath at 50°C[i]	
			physical properties of NADES	heating with stirring at 50°C	[10]
choline chloride:DL-malic acid:proline	1:1:1		formation and stability of NADES	vacuum evaporating	[10]
choline chloride:DL-malic acid:xylitol	1:1:1				
choline chloride:glycerol:water	1:2:1		analysis of physicochemical properties	heating with agitation in a water bath at 50°C[i]	[11]
			physical properties of NADES	heating with stirring at 50°C	[10]
choline chloride:sorbitol:water	5:2:6		analysis of physicochemical properties	heating with agitation in a water bath at 50°C[i]	[11]
			physical properties of NADES	heating with stirring at 50°C	[10]
choline chloride:xylitol:water	2:1:3		analysis of physicochemical properties	heating with agitation in a water bath at 50°C[i]	[11]
			physical properties of NADES – solubility of Small molecules and Macromolecules	heating with stirring at 50°C	[10]
choline chloride:xylose:water	2:1:2		analysis of physicochemical properties	heating with agitation in a water bath at 50°C[i]	[11]
			physical properties of NADES	heating with stirring at 50°C	[10]
Others Combinations					
betaine:sucrose	2:1		formation and stability of NADES	vacuum evaporating	[10]
betaine:D(+)trehalose	4:1				
betaine:D-mannose	5:2				
betaine:sucrose:proline	1:1:1;5:2:2				
betaine:D-(+) glucose:proline	1:1:1				
D/L-proline:sucrose	2:1/3:1				
D/L-proline:D-sorbitol	1:1				
proline:D(+)glucose	1[b,c]:1/5[b,c]:3				
	5[b]:3	30	flavonoid extractions from *Flos sophorae*	freeze-drying	[19]

[a] DL-malic acid.
[b] L-proline.
[c] D-proline.
[d] D(+)-glucose.
[e] L(+)-tartaric.
[f] D(−)fructose.
[g] D-xylose.
[h] D-sorbitol.
[i] Mixed with certain amount of water.

In addition to the features as solvents, the stabilization ability is important for their further applications. Studies have demonstrated that natural pigments from safflower were more stable in sugar-based NADES than in water or 40% ethanol solution [11]. In NADES, an enhanced solubility of the flavonoids rutin, which is only slightly soluble in water, was observed. The solubility was 50- to 100-fold higher in glucose:fructose or aconitic acid:choline choride mixtures than in water [8]. Notably, the stabilization capacity of NADES can be adjusted by reducing water content with increasing viscosity. The formation of hydrogen bonding interactions between compounds, as happens with phenolic compounds and NADES provides a strong ability to stabilize molecules [11].

Selected studies concerning the use of NADESs to extract compounds from natural sources by different methods are shown in Table 2. NADES have been mainly applied for the extraction of phenolic compounds. Pigments, carotenoides and flavonoids of different polarity have been studied. The data obtained show that NADES increase the efficiency of existing extraction solvents [5,12,14,15,19,22], being choline chloride and acids the major choice for their preparation. Their potential for the extraction could be ascribable to their great capacity to form hydrogen bonds with the analytes. Considering the drawbacks of traditional methodologies, mainly due to the extensive use of organic solvents, NADES are a green option in this area. An additional advantage is the possibility to produce tailor-made solvents compatible with the chemical nature of the analytes under study. Physical properties of NADES, such as polarity, viscosity and temperature have a great influence in the extraction. The optimization of all the parameters by multivariate analysis, and also the extraction parameters, is a powerful tool to obtain the suitable results [14,15]. Moreover it has been reported for the extraction of this compounds the use of NADES in combination with other green techniques as ultrasound-assisted method [22] and microwave-assisted extraction (MAE) [14,15].

Table 2
NADESs as extraction solvents

Class	Compounds	Sample	NADES	Method of extraction	Ref
Phenolic compounds	-Hydroxysafflor yellow A -Cartormin -Carthamin -Tri-p-coumaroyl Spermidines -Quercetin glycosides Total phenolic compounds	Carthamus tinctorius L.	sucrose:choline chloride:water fructose:glucose:sucrose:water proline:malic acid:water glucose:choline chloride:water lactic acid:glucose:water sorbitol:choline chloride:water	-0.1 g of plant material in 1.5 mL NADES -mechanical agitation, 40°C, 60 min -centrifugation: 10,968× g, 20 min -filtration: 0.45 μm cellulose acetate filter -water dilution -HPLC-DAD analysis	[27]
		Green coffee beans	choline choride:xylose 3:1 choline choride:tartaric acid 1:1 choline choride:citric acid 1:1	-0.1 g of plant material in 1.5 mL NADES -mechanical agitation, 40°C, 60 min -centrifugation: 10,968× g, 20 min -filtration: 0.45 μm cellulose acetate filter -water dilution -HPLC-DAD analysis	[5]
	Flavonoids: -baicalin -wogonoside -baicalein -wogonin	Radix Scutellariae	choline chloride:glycerol 1:2 choline chloride:citric acid 1:2 choline chloride:malic acid 1:2 choline chloride:lactic acid 1:2 3:1, 2:1, 1:1, 1:3, 1:4 choline chloride:glucose 1:2 choline chloride:sorbitol 1:2 choline chloride:sucrose 1:2 choline chloride:maltose 1:2 citric acid: sucrose 1:2 citric acid:glucose 1:2 lactic acid:sucrose 1:2, 2:4	-2.00 g of plant material in 30 mL NADES -microwave-assisted extraction (MAE), 10 min, 55°C, radiation power 500 W -filtration: 0.45 μm nylon membrane -HPLC analysis	[15]
	Flavonoids: -quercetin -kaempferol -isorhamnetin	Flos sophorae	choline chloride:glycerol 1:1 choline chloride:xylitol 5:2 choline chloride:D-(+)-glucose 1:1 L-proline:D-(+)-glucose 5:3 citric acid:D-(+)-glucose 1:1 citric acid:adonitol 1:1 betaine:DL-malic acid 1:1	-0.05 mg of plant material in 0.75 mL of NADES -mechanical agitation in vortex -ultrasound-assisted extraction (UAE): ambient temperature, 20 min -centrifugation:12,300 g, 30 min -acid hydrolysis:150 μL of the extract mixed with 500 μL of 4 M hydrochloric acid in methanol, 90°C , 60 min. -LC-UV analysis	[19]
	-orientin -vitexin -luteolin -apigenin -isorhamnetin -formononetin -pinostrobin chalcone -pinostrobin -longistyline C -cajaninstilbene acid -cajanuslactone -cajanol -apigenin-6,8-Di-C-α-L-arabinoside -apigenin-8-C-α-L arabinoside	Cajanus cajan leaves	choline chloride:glycerol, choline chloride:glucose, choline chloride:sucrose choline chloride:maltose choline chloride:sorbitol choline chloride:citric acid, choline chloride:malic acid choline chloride:lactic acid citric acid:glucose, citric acid:sucrose lactic acid:glucose lactic acid:sucrose	-2.00 g of plant material in 60 mL NADES -microwave-assisted extraction (MAE), 12 min, 60°C. -filtration -HPLC analysis	[14]
Saponins		Dried Sisal waste and Juá bark	cholinium chloride:glycerol cholinium chloride:urea cholinium chloride:acetic acid cholinium chloride:propionic acid cholinium chloride:lactic acid cholinium chloride:oxalic acid cholinium chloride:malonic acid	-material/solvent ratio: 1/20 for juá bark and 1/10 for sisal -stirring 2500 rpm using a vortex, 0.5 min -stirring 120 rpm, 90 min, 50°C	[23]
Carotenoids	astaxanthin	Shrimp byproducts	cholinium chloride:glycerol 1:2	-100 mg of shrimp shell powder in 1 mL of NADES -ultrasound-assisted extraction (UAE): at a frequency of 20 kHz and an output power of 200 W max -200 μL of the extract were mixed with an equal volume of the mobile phase -centrifugation -filtration: 0.2 μm -HPLC analysis	[22]
Lignin		Rice straw	lactic acid:betaine lactic acid:choline chloride (5, 10, 15, 20, and 50% of distilled wáter)	-10–20 g of dried residue in 200 mL of NADES -incubation at 60°C for 12 h with constant agitation at 100 rpm -centrifugation at 5000 rpm for 30 min at room temperature for separated NADES-treated solid biomass residue from the soluble lignin extract fraction -precipitation of soluble lignin from NADES extract by simple dilution method using distilled water at 4°C for 2–3 h. -centrifugation at 10,000× g for 10 min separation of precipitated lignin from NADES solution -washing of pellet two times with distilled water -drying to obtain powdered lignin.	[20]

4.1.2. Green organic reaction media

Many analytical procedures include a chemical reaction in order to enhance detection, modify polarity or avoid interferences. Moreover, on-line reactions are crucial in integrated approaches in Flow Injection Analysis (FIA) or microfluidic devices.

Organic reactions in green media have attracted considerable attention in recent years. NADES's application in organic synthesis has notable advantages. They can be used not only as a reaction media but also as a catalyst. A rapid procedure for green synthesis of 4-thiazolidinones was performed in choline chloride:urea. The general synthetic strategy employed is based on one-pot reaction of thiourea, chloroacetyl chloride and aromatic aldehydes [24]. Another application of this mixture was used in the synthesis of aurones through a simple and fast procedure [25]. It was also used for the bromination of 1-aminoanthra-9,10-quinone. The solvent was easily separated and reused without loss of activity [30]. The same NADES was reported for the synthesis of cinnamic acid and its derivatives via Perkin reaction. This process is efficient under mild conditions [31]. In other research the mixture carbohydrate:urea showed very good solvent properties compared to L-carnitine:urea mixture. It was successfully used for chemical transformations such as Diels–Alder reactions, Stille and Suzuki cross-couplings and for hydrogenation reactions [32]. Solvents are of essential significance in all synthetic processes. It is worth mentioning that the main role of these solvents is to homogenize all the reagents in the reaction media. Organic and non-organic solvents have been widely used, they are chosen depending on the reaction peculiarities and how the solvent may deal with them [27]. In this sense NADES are currently attracting significant attention as "greener" media for material synthesis and processing [17]. It has been demonstrated the possibility to use them as polymers plasticizing agents for the development of 3D porous architectures that have applications in a wide variety of scientific fields, particularly in analytical chemistry [13]. Other interesting promising area is nanotechnology, in particular nanoparticle synthesis. Recently, NADES have been the solvent of choice for the convenient synthesis of nanoparticles due to thermal stability, good dispersibility, large ionic conductivity and wide electrochemical window [27]. After synthesis, these materials are widely applied in the different steps of Analytical process like extraction, separation, and detection enhancement.

NADES are excellent solvents for many substrates, providing a promising bio-based and effective media for reactions [32]. In this respect, they have been efficiently used as an efficient media of reaction of enzymes such as hydrolases and lipases [33]. Taken together, the biocompatibility as well as the sustainability of a natural deep eutectic solvent makes it a good substitute for the aqueous media in studying biomolecules and they can be successfully applied to the fabrication of biosensors.

4.2. Detection

The excellent properties of NADESs, such as sustainability, ease of preparation, low cost, biodegradability, pharmaceutical acceptable toxicity and high extractability, highlight their potential as green solvents for their use at different steps of any analytical method. Nevertheless, is it possible to enhance detection when target analytes are part of the NADES supramolecular structure? Taking into consideration these solvents are like liquid crystals in which the solute molecules are fixed in the crystals, it is feasible to expect a detection improvement by means of a phenomenon similar to the micellar-enhanced spectrometry detection generated by surfactants [33,34].

There is scarce information concerning the study of detection enhancement provided by NADES. Karimi et al. [35] reported lower limits of detection in the presence of NADES with same detector (Electrothermal Atomic Absorption Spectrometry) and similar pretreatment technique (Dispersive Liquid-Microextracion). The enhancement factors, defined as the ratio of the slope of the calibration curves with and without preconcentration, were better in the presence of NADES for lead and cadmium.

Indeed, they Zhang et al. reported the application of NADES in an ultrasonic-assisted extraction prior to Liquid Chromatography for the analysis of astaxanthin from shrimp byproducts [22]. The amount of astaxanthin extracted using a traditional organic solvent was 50% lower than that obtained for the NADES-mediated extraction.

4.2.1. Electrochemical applications

In recent years, ILs have been broadly used in the electrochemical analysis due to its unique electrochemical properties, including higher ionic conductivity, wider electrochemical windows, low cost and environment-friendly [36]. ILs modified electrodes have a good prospect in electrochemical analysis. However, its preparation involves a complex procedure and the electrode modification is expensive, tedious and time consuming, which restricts its application in practical work. In recent times, DES have also been applied successfully in this field [6,37]. The physical–chemical properties of DES are similar to those of the ionic liquids [29,38]. Due to this, most of the reported applications of DES have been essentially in electrochemistry. Despite the large number of publications in electrochemistry with DES, no publications can be found with the keyword NADES. Taking in account that the term NADES has recently been proposed (2011), it has not been fully implemented yet. Therefore, some of the electrochemical applications reported as DES-based could be considered as NADES. Fig. 3 are shown NADES applications in electrochemistry.

Cyclic voltammetry and chronoamperometry measurements, reported in 2007, for choline chloride-based have broadened the application spectra of these class of solvents [39]. One particular application within this field of research is electrodeposition of metals (the major application field, Fig. 3), which may benefit from the high solubility of metal salts in nonaqueous solutions and the high conductivity of ionic liquids and deep eutectic solvents [5,40]. In fact, choline chloride based NADES have been successfully assessed for electrodeposition of different metals (Cr, Mn, Cu, Ag, etc.) [41,42], alloys (Zn/Cr, Zn/Sn, etc.) [43,44], in electrowinning of metals from complex oxide matrices [38,45,46] and enhancing electrochemical properties [37].

5. Conclusions and future perspectives

In the last decades, the concept "green" acquired a new significance in chemistry. The definition of sustainable development and green chemistry changed the way of thinking processes and methods. A critical issue is to look for an alternative to traditional solvents due to their low biodegradability, high toxicity and cost. After years of intense research, trying different mixtures with diverse compounds, a spark of light emerged from nature: in 2011 Choi coined the term Natural Deep Eutectic Solvents for this mixtures.

NADES have a large number of the advantages such as those already discussed in this review. Also as already specified, the preparation is simple, environmental friendly and low cost. Studies of 1H NMR spectra, FT-IR, crystallographic date and FAB-MS have demonstrated that NADES are supermolecules with hydrogen-bonding interactions between the components. Neverthless, there is still a lack of information about their structure, interactions between their components and with the target analytes.

The huge potential of NADES opens interesting perspectives for further research and industrial applications. Currently, the use of

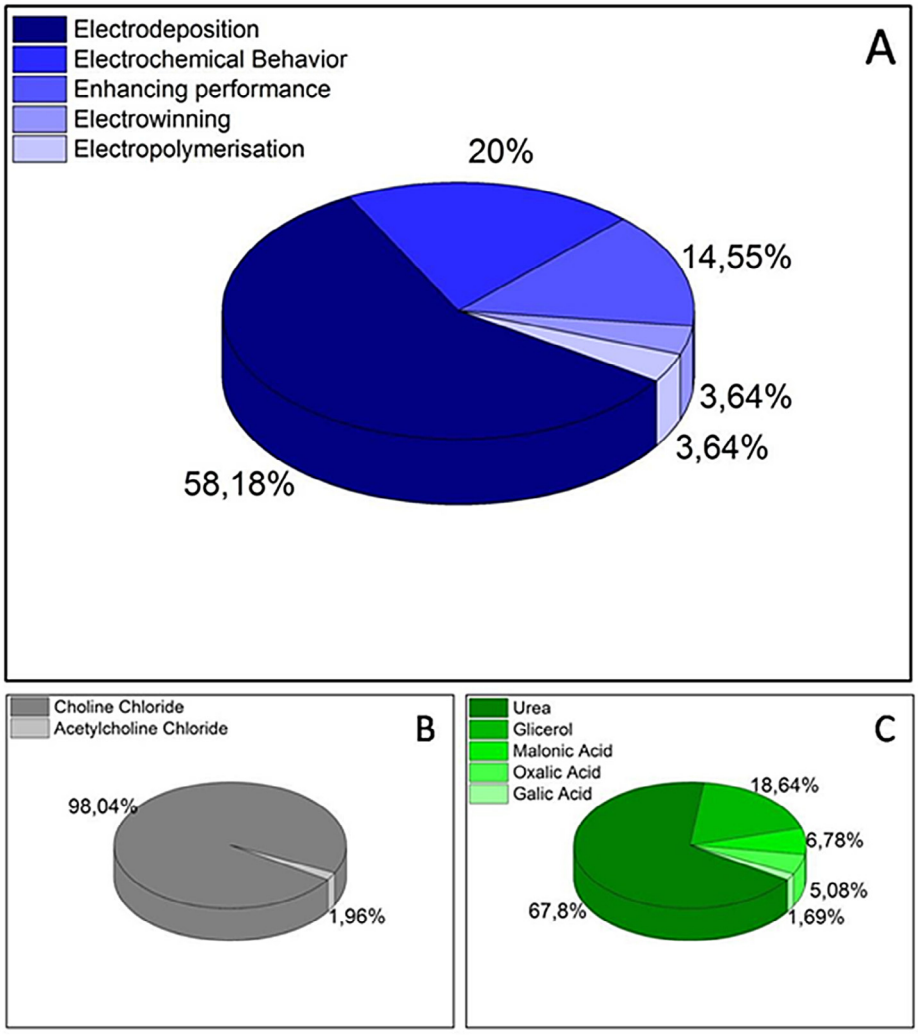

Fig. 3. NADES applications in electrochemistry (A) and the most common HBD (B) and HBA (C).

NADES as extraction solvents for phenolic compounds is the most studied application by far. Therefore, considering their stabilization skills 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.

Although recently analytical applications of NADES have appeared in literature, the full potential of these green solvents is still unexplored. There are no reports about the application of these solvents in separation processes. Concerning the toxicity, low biodegradability, high cost of the organic reagents commonly used in this step, efforts should be made in evaluating this new smart solvents. Considering their possibility of being tailored-made, there is great potential to modify the interaction between stationary phase and target analytes as it has been previous reported for ILs. Moreover, NADES could be used modifiers for the background electrolyte in Capillary Electrophoresis (CE) and may improve relevant parameters (acid-base dissociation behavior pH, separation efficiency, resolution, and electroosmotic flow).

The challenge of Analytical Chemistry is to develop techniques and methods aligned with Green Chemistry. In this sense NADES represents an excellent opportunity as a new generation of green solvents. They could be a great contribution to develop sustainable industrial process.

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