Postprint of: Vilková M., Płotka-Wasylka J., Andruch V., The role of water in deep eutectic solvent-base extraction, Journal of Molecular Liquids, Vol. 304 (2020), 112747, DOI: 10.1016/j.molliq.2020.112747

The role of water in deep eutectic solvent-base extraction

Mária Vilková, Justyna Płotka-Wasylka, Vasil Andruch

[a] *Department of Analytical Chemistry, Institute of Chemistry, Faculty of Science, Pavol Jozef Šafárik University in Košice, SK-04154, Košice, Slovakia*

[b] *Department of Organic Chemistry, Institute of Chemistry, Faculty of Science, Pavol Jozef Šafárik University in Košice, SK-04154, Košice, Slovakia*

[c] *Department of Analytical Chemistry, Faculty of Chemistry, Gdańsk University of Technology, PL-80-233 Gdańsk, Poland*

Corresponding author: Mária Vilková maria.vilkova@upjs.sk

Abstract

Deep eutectic solvents (DESs) are currently being used in different sectors, such as electrochemistry, electrodeposition, organic synthesis, nanoparticle preparation, bioactive compound separation, etc. Their use in analytical chemistry has only recently begun to expand. Despite the publication of a sufficient number of DES-based analytical extraction procedures, some details, such as interaction of DES with the sample and target analytes as well as with water are insufficiently explored and theoretically explained. Here we discuss the role of water in DES-based extraction in terms of analytical chemistry, especially for the pre-treatment of solid samples. We believe that this review will benefit those who have linked their research with DESs and will enable them to speed up their work.

Keywords: deep eutectic solvent, physicochemical properties, effect of water, solid-liquid extraction, liquid-phase microextraction

Introduction

In the past decade, deep eutectic solvents (DESs) (introduced by Abbott et al. [1]) have arisen as a new group of organic solvents promising environmentally friendly alternatives to conventional solvents and have found use in various areas. DESs have been getting a lot of attention mainly due to

their versatility and their easy and speedy preparation, as they need no further purification. In addition, the vast array of compounds to choose from for their preparation has led to the full tailoring of their relevant properties as solvents [2]. The premise that natural deep eutectic solvents (NADES) can play a role as an alternative medium to water in living organisms was also presented [3- 5].

Since their advent in 2003, DESs have found application in various areas where their solvent properties, which enable the dissolution of a large variety of solutes, and their "green" characteristics, give them advantages over more conventional solvents [6]. Recently, the application of DESs has been extended to the field of analytical chemistry [7-10] in general, and to the extraction, separation and quantification of target analytes in particular (**Figure 1**). DES-based extraction procedures for both solid [11, 12] and aqueous [13, 14] samples have been reported. However, the procedure for extracting analytes from organic liquid samples or organic solvents and solid samples differs somewhat. It should also be mentioned that a relatively large volume of DES is required for solid sample analysis to provide a reproducible extraction.

In developing extraction procedures, analysts most often focus on the analytical procedure itself and its characteristics, such as selectivity, sensitivity, recovery, linear range, detection limit, etc. and spend less time and effort investigating the processes that take place in the solution. Since DESs are prepared by mixing a hydrogen bond acceptor (HBA) and a hydrogen-bond donor (HBD) and are formed through hydrogen bond interactions, the presence of a high polar solvent such as water can probably affect not only their physicochemical properties but also their extraction capability. Therefore, with the increasing interest in DES-based extraction procedures, due attention should be paid to study of the structure of DESs, interactions between the DES and a sample, the DES and the target analytes, as well as between DESs and water (or a polar organic solvent). This information may be useful in understanding the essence of the processes taking place during analytical extraction and thereby assist in the targeted design of a DES for a specific analyte and sample [15].

Herein we try to analyze and systematize published papers which discuss the role of water in a DES-based extraction. We focus mainly on the applicability of DESs in the direct pretreatment of solid samples, especially various plants and herbs. Therefore, the paper may be useful for those who are working with these kinds of samples, but also for those who are applying DESs in extraction processes generally.

Recently published review papers

More than fifty review papers dedicated to the application of DESs in various fields of science, research and technology have been published in last five years. Here we can mention only a few

selected articles which are far from covering all the existing areas of using DES. The application of DESs in nanotechnology [16], for the production of new materials [17], in gas separation [18]; in organic transformation [19], in biotechnology and bioengineering [20]; to intensify biotransformations [21] and for redox biocatalysis [22] have been recently reviewed. One can also easily find several reviews discussing the application of DESs in analytical chemistry for NADES- mediated extractions [23], for the extraction of organic and inorganic analytes from aqueous environments [24], for the extraction and separation of natural products [25] and in chromatography [26], in extraction techniques [27] and in dispersive liquid-liquid microextraction [28].

Recently published review papers discussing the role of water

Recently, Ma et al. published a review "*The peculiar effect of water on ionic liquids and deep eutectic solvents"*. They collected, analyzed and discussed the experimental data and theoretical results for IL/DES–H_2O systems at various water concentrations [29]. In the Conclusion section they stated that DES–H_2O binary systems are more complex than IL–H_2O systems, and detailed researches are needed to reveal the differences between aqueous DES solution and the aqueous solution of individual DES components [29].

Very recently El Achkar et al. [15] in their review "*Deep eutectic solvents: An overview on their interactions with water and biochemical compounds*" analyzed few selected papers [30-32], and stated that water can be a part of the a supramolecular DES complex. On the other hand, above a certain water content, this complex may disintegrate with formation of an aqueous solution of the individual components. Nevertheless, adding water can be used for tailoring the physicochemical properties of DESs in a controlled way [30]. Recently a review paper "*New horizons in the extraction of bioactive compounds using deep eutectic solvents*" was published [33]. Among other things, the authors discuss the physicochemical properties of DESs, such as melting point, density, conductivity and viscosity and viscosity, which may vary depending on the structure of the DES. One short section is devoted to *Effect of the addition of water on extraction efficiency* [33].

Physicochemical properties of DES in the presence of water

The properties of DESs can be adjusted by changes of the type of HBA and/or HBD, the molar ratio between components and water content (**Figure 2**). Herein we focus only on the influence of water on the properties of DESs. Researchers are most often interested in the following features of DESs: viscosity, density, conductivity, surface tension, and polarity. From the point of view of analytical chemistry, viscosity and polarity are probably the most important of these.

High viscosity is one of the major obstacles in DES analytical application because it limits the mass transfer between the sample and the extraction phase. In addition, the resulting viscous phase containing the target analytes is not compatible with most analytical instruments. The addition of water leads to a decrease in the viscosity of the reaction media, enhancing the mass transfer and improving the extraction efficiency [36].

Besides affecting the properties mentioned above (viscosity, density, conductivity, etc.), the addition of water can lead to a change in the polarity of a DES, which in turn can significantly affect their ability to dissolve target compounds according to the principle of *like dissolves like*. Matched polarity between a DES and an analyte could increase their solubility in the DES and thus promote the extraction process [37]. The extraction is more efficient in a DES-water system than in a pure DES probably due to water's ability to form hydrogen bonds with a great variety of analytes. However, the similarity of solvent and analyte polarities does not guarantee the highest extraction efficiency [38]. Other interactions can also play an important role [39]. Therefore, based only on the physicochemical parameters of DESs, it is difficult to predict which DES is most suitable for the extraction of a particular analyte or group of analytes. Consequently, experimental studies have to be conducted to find the appropriate DES and extraction conditions [37].

Water may be used as a cosolvent to modify the physicochemical properties of some DESs. On the other hand, an excessive amount of water can lead to a significant weakening of the interactions between DES components and consequently to complete disruption of the DES. Studies of the influence of water on the DES supramolecular structure are commonly performed by FTIR and NMR experiments. The addition of water gradually weakens the bonding between the DES components and ultimately destroy the supramolecular structure of the DES [30]. It should also be mentioned that water, as a part of supramolecular structure, can be strongly retained in the solvent and it cannot be evaporated, as was shown by Choi et al. [3].

Selected examples of papers devoted to the investigation of adding water on the physicochemical properties and supramolecular structure of DESs are given below. Dai et al. (**2015**) investigated several NADESs and their mixtures with water in terms of their supramolecular structures, physicochemical properties (viscosity, conductivity, density, water activity, and polarity) and solubilizing capacity for two poorly water-soluble compounds (quercetin and carthamin) [30]. Aroso et al. evaluated the NADES-forming ability of mixtures of choline chloride or betaine with 3 sugar molecules (glucose, xylose and sucrose) and 2 carboxylic acids (citric and tartaric acids). The conductivity and rheological properties and their variation with water content and temperature were evaluated [40]. We may also mention a few other recently published articles on this topic. Gabriele et al. studied the effect of water on the physicochemical properties and structural features of three DESs formed by choline chloride and glycols with a different number of oxyethylene units [41]. Alcalde et al. recently published an experimental and theoretical investigation of the physicochemical properties on choline chloride–lactic acid based NADES. Moreover, they explored the ability of the prepared NADES of several molar ratios for capturing atmospheric water [42]. Similarly, as Maugeri and Domínguez de Marıa [43] reported, DESs are highly hydrophilic and upon exposure to atmospheric moisture, the amount of water increases

quickly. The rate of water absorption decreases in an almost linear manner with increasing HBA:HBD molar ratio. This is in accordance with findings that water interacts competitively with chloride anion. More than one molecule of HBD results in considerable steric hindrance, and this prevents the interaction between water and chloride anion.

One of the advantage of DESs as green solvents is the possibility of their regeneration, which is mainly performed by precipitation of either the solute[44] or the solvent[43] in an anti-solvent. Very often water, which is applied for this purpose. In order to recover the DES, the anti-solvent forming a homogeneous mixture with the DES has to be evaporated from the DES. However, this step is very energy intensive. Thus, alternative separation techniques are being sought and will aid in the industrial applicability of DESs. For example, resins were used to recover phenolic compounds from a DES; however, this process required large solvent volumes to elute the extractants from these resins [45]. In another work [46] , flavonoids were recovered from a DES by sorption. Electrodialysis membranes was another method applied to recover DESs after biomass fractionation [47]; however, high dilution of DES in water was needed to achieve an effective result.

DES-based solid–liquid extraction

The most commonly analyzed solid samples are various plants and herbs. Generally speaking, in optimization of solid–liquid extraction procedures, the effect of the following variables should be investigated: extraction solvent type and amount, co-solvent type and concentration, solid/liquid ratio, temperature, extraction time, auxiliary energy type and parameters. Most commonly, solid–liquid extraction assisted by microwave, ultrasound, heating, stirring or shaking is used to analysis of various plant and herb samples. The auxiliary energy mainly helps break down cell walls, resulting in the release and dissolution of the target compounds [48]. A DES can play the role of absorbing medium for microwave radiation, the destroyer of cell walls and a solvent for dissolving the released compounds [49]. In addition, at higher temperatures, the solvent viscosity decreased [50]. When choosing a DES in solid–liquid extraction, besides the factors mentioned above, the physicochemical properties of the DES, such as viscosity and polarity, must also be taken into account. However, authors often do not investigate and discuss these influences in detail and limit themselves only to a simple statement of these facts and influences and verbal descriptions of the obtained results. Selected examples of DES-based solid–liquid extraction are given below and their main characteristics are shown in Table 1.

Cui et al. investigated the extraction efficiency of eleven DESs (9 based on choline chloride and 2 based on glucose) with different polarity, viscosity, composition and solubility and developed a DES-based microwave-assisted extraction (MAE) method for extracting the three major active compounds, genistin, genistein and apigenin, from pigeon pea roots. A mixture of 1,6-hexanediol/ChCl with a 7:1 molar ratio and 30% water content proved to be the most efficient extraction solvent, and optimal conditions for DES–MAE were a liquid/solid ratio of 14 mL/g, microwave power 600 W, temperature 80 °C and time 11 min. The authors compared the extraction efficiency of three DES-based extraction methods, namely microwave-assisted extraction, ultrasound-assisted extraction and heat-refluxing extraction, and concluded that DES–MAE have noticeable advantages over other extraction methods, including higher extraction yields and shorter extraction time [51].

Yao et al. reported the polyols-based deep eutectic solvents (PDES) microwave assisted extraction of five phenolic compounds (hyperin, 2'-O-galloylhyperin, quercetin-O-rhamnoside, quercitrin and chimaphilin) from *Pyrola incarnata* Fisch. followed by HPLC–UV determination. A variety of PDES prepared from choline chloride and different polyols (ethyl glycol, glycerol, 1,2-butanediol, 1,3-butanediol, 1,4-butanediol and 1,6-hexanediol) with various molar ratios were studied. The optimized PDES–MAE conditions were an extraction solvent of 30% water in ChCl/1,4-butanediol (1:4), liquid/solid ratio of 10 mL/g, an extraction temperature of 70 °C and an extraction

time of 20 min. The authors compared the developed procedure with heat-stirring extraction and ultrasound-assisted extraction with PDES and found MAE to be a more efficient extraction method for plant samples [38].

Wei et al. investigated 14 different NADES systems for the MAE of phenolics with diverse polarity in *Cajanus cajan* leaves. They found that the NADES composed of choline chloride and maltose (1:2) containing 20% water is a suitable extraction media for both polar and weak polar compounds. Optimized parameters (extraction temperature 60 °C, liquid/solid ratio of 30:1 mL/g and irradiation time of 12 min.) were used to develop a UPLC method for comprehensive analysis of 14 phenolics in *Cajanus cajan* leaves with LODs less than 0.15 µg/mL [50].

In addition to microwave energy, DES-based extraction is also often supported by ultrasound energy. Here are a few examples: Jiang et al. investigated a range of different DESs and selected choline chloride–levulinic acid (1:2) with 30% water content for UAE (200 W, 40 kHz, at 50 °C for 30 min) of bioactive alkaloids from herbal medicines followed by HPLC–UV quantification. The authors stated that the most critical parameter for alkaloids extraction was the water content in the DESs [52]. Ali et al. studied 11 choline chloride-based DESs for UAE of flavonoids from *Lycium barbarum* L. fruits followed by HPLC–UV detection. The effect of various water content (5, 15, 25, 40%, w/w) on the selected DES, choline chloride/*p*-toluene sulfonic acid (1:2) was investigated. The highest extraction efficiency was achieved in pure DES, while increasing the water content (5–40%) resulted in a decrease in the extraction efficiency [53]. Selected examples of DES-based UAE are given in Table 1.

Bi et al. tested several DESs with different alcohols to choline chloride mixing ratios to extract flavonoids (myricetin and amentoflavone) from *Chamaecyparis obtusa* leaves, followed by HPLC–UV analysis. In addition to viscosity and polarity, they also proposed considering the effects of other factors, such as diffusion, solubility, surface tension and physicochemical interactions in solid–liquid extraction. Various modes of the extraction were tested, including stirring, heating and ultrasonic irradiation. The optimized conditions were found to be 35% of water in ChCl/1,4-butanediol (1:5) at 70 °C for 40 min. Good linearity was obtained from 0.1×10^{-3} to 0.1 mg/mL [54].

Most articles on DES-based solid–liquid extraction procedures describe the determination of organic analytes, and only a few articles are about the determination of inorganic analytes. NADESs based on xylitol, citric acid, and malic acid were investigated as solvents in the UAE of plant samples prior to elemental analysis by ICP–MS and ICP–OES for the determination of As, Ca, Cd, Cu, Fe, K, Mg, Mn, Na, P and Zn in the extracts [55].

DES-based liquid–phase microextraction

The applicability of hydrophobic DESs in conventional liquid–liquid extraction as well as their miniaturized modalities, such as DLLME, SDME and HF–LPME was recently reviewed by Lee et al. [24] and Makoś et al. [56]. Despite the fact that DES-based LPME is beyond the scope of this review we would like mention here one recently reported approach based on decomposition of a DES in an aqueous sample solution [57-59].

The authors established that DESs synthesized from tetrabutylammonium bromide (TBABr) and long-chain alcohols (amyl alcohol, heptanol, octanol, decanol and dodecanol) decomposed in aqueous phase resulting in the *in situ* dispersion of the organic phase and extraction of hydrophobic analytes [57]. The decomposition of a DES was studied in detail and applied for the separation and preconcentration of 17β-estradiol from transdermal gel samples. Higher extraction efficiency and better repeatability were obtained for the DES based on TBABr and heptanol at a 1:2 molar ratio [57]. To demonstrate the features, the developed procedure was compared with the DLMME procedure using a mixture of heptanol and various polar water-miscible solvents. Higher extraction efficiency was obtained for the DES when compared with the mixtures of heptanol with various dispersive solvents, probably because polar organic dispersive solvents can increase analytes solubility in aqueous phase [57]. As a continuation, an automated in-syringe DLLME using a DES as the disperser for determination of chromium(VI) in beverages was presented [58]. In this procedure a homogeneous mixture of 1-octanol as the extraction solvent and a DES composed of TBABr–formic acid containing 1,5-diphenylcarbazide as complex-forming reagent was used. The decomposition of the DES in aqueous phase leads to dispersion of the extraction solvent, the formation of a colored chromium(III) complex with 1,5-diphenylcarbazone and its extraction [58]. A procedure for the extraction and HPLC-FLD quantification of bisphenol–A in beverage samples was also reported [59].

Even though the authors continually label their methods as DLLME, we have to disagree with this designation, as a conventional dispersive solvent was not used, whereas dispersion is achieved by DES decomposition. The original DLLME method was designed using an extraction solvent heavier than water and a polar dispersive solvent [60]. In our opinion, the term DLPME, which more closely describes the essence of the procedure, is more appropriate here [61].

Concluding remarks

Water can be either present in a DES as an unavoidable impurity or can be added purposefully to change its physicochemical properties [62]. In terms of analytical chemistry, the viscosity and polarity are the most important parameters due to their possible influence on extraction capability. The addition of water leads to a decrease of viscosity and simultaneously to an increase of polarity.

Decreasing the viscosity of the reaction media enhances the mass transfer from solid samples to the solution, thus resulting in improved extraction efficiency. On the other hand, increasing water content can weaken the interactions between the DES and the target compounds, as well as the interactions between the components of the DES. Moreover, a high excess of water can lead to the complete disruption of the DES. It should be emphasized that the effect of increasing the polarity of the extraction media (as a result of adding water) on extraction efficiency depends on the polarity of the target analytes themselves.

Summarizing, despite numerous published papers devoted to this amazing and challenging topic, some details remain unclear, and existing studies have not been systematic. Therefore, due to growing interest in the application of DESs, further studies are necessary to better understand aqueous DES mixtures.

Acknowledgements

This work was supported by the Scientific Grant Agency of the Ministry of Education, Science, Research and Sport of the Slovak Republic (VEGA 1/0010/15).

Abbreviations

ChCl, Choline chloride;
DES, Deep eutectic solvents;
DLLME, Dispersive liquid–liquid microextraction;
DLPME, Dispersive liquid-phase microextraction;
ICP-MS, Inductively coupled plasma–mass spectrometry;
ICP-OES, Inductively coupled plasma–optical emission spectrometry;
FLD, Fluorescence detection;
FTIR, Fourier-transform infrared spectroscopy;
HAE, Heat-assisted extraction;
HBA, Hydrogen bond acceptor;
HBD, Hydrogen bond donor;
HF-, Hollow fiber-based;
HPLC, High-performance liquid chromatography;
HRE, Heat-refluxing extraction;
IL, Ionic liquids;
LPME, Liquid-phase microextraction;
MAE, Microwave-assisted extraction;
NADES, Natural deep eutectic solvents;
NMR, Nuclear magnetic resonance;
PDA, Photodiode array detector;
PDES, Polyols-based deep eutectic solvents;
SDME, Single-drop microextraction;
TBABr, Tetrabutylammonium bromide;

UAE, Ultrasound-assisted extraction;
UHPLC, Ultra-high-performance liquid chromatography;
UPLC, Ultra-performance liquid chromatography;
UV, Ultraviolet detection.

Table 1. Selected examples of DES-based solid–liquid extraction

Analyte	Matrix	DES	Pretreatment	Method	LOD	Remarks	Ref.
Genistin, genistein and apigenin	Pigeon pea roots	Eleven DESs	MAE	HPLC-UV	0.03-0.10 μg/mL	30% of water in 1,6-HD/ChCl as the extraction solvent was used as the optimum. Higher water content in 1,6-HD/ChCl could reduce the viscosity of 1,6-HD/ChCl and increase the polarity of the solvent mixture. Excessive water in 1,6-HD/ChCl could decrease the hydrogen bond interconnection between 1,6-HD/ChCl and the target compounds, resulting in a decrease in extraction yields of the target compounds.	[51]
Phenolic compounds	*Pyrola incarnata* Fisch.	Six ChCl/polyols based-DESs	MAE	HPLC-UV	0.04-0.14 μg/mL	The extraction yields of analytes were highest at a water volume of 30% in the PDES–water mixture. The mixture of PDES and water can decrease the cost for extracting the target compounds compared to a normal PDES.	[38]
Fourteen phenolics	*Cajanus cajan* leaves	Fourteen different NADES	MAE	UPLC-UV	< 0.15 μg/mL	It was found that the water content in NADES had a significant effect on the extraction efficiencies. Although the addition of water can effectively reduce the viscosity, an excess of water caused a negative impact on the interactions between CCM and the target compounds and increased the polarity of extraction media; thus, 20% (v/v) water was used in the solvent mixture.	[50]
Bioactive alkaloids	Herbal medicines	Various DESs	UAE	HPLC-UV	-	It was found that the most critical parameter for alkaloids extraction was water content in the DESs.	[52]
Flavonoids	*Lycium barbarum* L. fruits	Eleven ChCl-based DESs	UAE	HPLC-UV	0.11-0.89 μg/g	It was shown that the addition of water to DESs resulted in increased dipolarity/polarizability. Increasing the water content (5–40%) in the DESs-6 led to a decrease in the extraction efficiency of flavonoids. The presence of water in DESs can disrupt the hydrogen bonds between the DES components and consequently destroy the supramolecular structure of DESs. Thus, limit the hydrogen bonding interactions between bioactive compounds and DES components. Water used as anti-solvent.	[53]
Phenolic compounds	Mulberry leaves	Twelve ChCl, betaine and L-proline based DESs	UAE	HPLC-UV	-	Water used as an anti-solvent could effectively recycle polyphenols from DES extracts. The utilization of ChCl-Ca with 90% water showed a similar efficiency of target compounds extraction in comparison with MeOH, with significantly decreased solvent consumption.	[48]
Isoflavones	Soy products	Seventeen different NADESs	UAE	UHPLC-UV	0.06-0.14 μg/g	In the case of low water concentrations (10, 15%), extraction efficiencies are also low, probably because the viscosity of NADES is very high, which is beneficial for the mass transport. The addition of 25–30% water significantly improved the extraction results. A further increase in water	[63]

						content (40–75%) led to a decrease in extraction efficiency. High concentrations of water can limit interactions between isoflavones and the NADES components.	
Rutin	Tartary buckwheat hull	Thirteen ChCl and glycerol based NADESs	UAE	HPLC-UV	-	Viscosity of NADES decreased by 1/5 when diluted with 5% water and decreased to 1/80 of its original viscosity with the addition of 20% water. The polarity of NADES increased with an increasing proportion of water. The presence of too much water (>20%, w/w) resulted in a decrease in the extraction efficiency of analyte, which may be attributed to a decrease of analyte solubility in the extraction media and to the interactions between the sample and ChGly. Excessive dilution of ChGly with water may result in the disruption of hydrogen bonds between the components of the NADES and consequent loss of supramolecular structure. Water was found to be the most efficient anti-solvent among tested solvents, with a recovery of 95.1%.	[64]
Flavonoids	*Chamaecyparis obtusa*	Seven ChCl/alcohol-based DESs	Heating	HPLC-UV	0.07-0.09 μg/mL	The DES-water mixture has stronger basicity and lower cost for extracting the target compounds compared to a normal DES solvent. The addition of water can decrease the viscosity, with increasing basicity, and an excessive concentration of water can decrease the interactions between the DES and flavonoids and increase the polarity of the mixture. It was shown that the water concentration had a larger effect on the amounts extracted than the extraction time did.	[54]
Natural pigments	*Curcuma longa* L.	NADESs formed by organic acids and glucose	Heating	HPLC-UV	0.25-0.37 mg/L	The viscosity of NADESs significantly changes with changes in water content. Adding a surplus of water weakens hydrogen-bonding interactions between the solvents and the target curcuminoids, leading to decreased extraction yields. Increasing the water content increases the polarity of the analytes, but this is not conducive to the extraction of weak polar compounds.	[65]
Phenolic compounds	Walnut leaves	ChCl-based DES	HAE	HPLC-PDA		The water content was clearly the most relevant extraction variable.	[66]

1,6-hexanediol, 1,6-HD; ChGly, Choline chloride-Glycerol

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Figures captions

Figure 1. Application of DESs in analytical chemistry

Figure 2. Information on the impact of the DES component on the DES solvent properties

Figure 2. Impact of the DES composition on the DES solvent properties