University of Thi-Qar Journal of Science (UTJsci)
E-ISSN: 2709-0256, P-ISSN: 1991-8690, Vol. 11, No. 1, Jun. 2024

A review of deep eutectic solvents (DESs), Preparation, Classification, Physicochemical properties, Advantages and disadvantages

Sajda .S. Affat
Department of Chemistry, College of Science, University of Thi-Qar, Thi-Qar, Iraq

Email: sajida.j_mschem@sci.utq.edu.iq

Received: 2024-03-18, Revised: 2024-04-18, Accepted: 2024-04-22, Published: 2024-06-19

***Abstract*— Since deep eutectic solvents (DESs) are readily available, inexpensive, highly biodegradable, and easy to synthesize, they are gaining popularity as a green alternative to hazardous organic solvents and traditional ionic liquids (ILs). DES is a mixture of hydrogen bond donor (HBD) and acceptor (HBA) that is viscous and non-water soluble. There are two main penalty areas of DES fabrication. The first is to reduce its operation temperature to lower that of these components. The second is to produce a molten salt with a melting point lower than its components. Therefore, DESs are being utilized more and more in a range of analytical chemical applications. Different extraction techniques have been used for this kind of salt. In this review, production methods, and classification of DESs were discussed. The most physical properties of DESs were demonstrated, including melting point, viscosity, density, surface tension, phase changes in behavior, analyte solubility, instrumental compatibility, and toxicity. It also included the main advantages and disadvantages of DES production.**

***Keywords*— DESs, HBD, HBA, Hydrogen bonding, Van der-Waals.**

I. INTRODUCTION

Deep eutectic solvents (DESs) are molten salt solvents made of HBD and HBA bound by hydrogen bonds in particular proportions and at suitable temperatures, making DES [1-3]. In ecological analytical chemicals, this new class of green solvents has received a lot of interest lately. This is due to its desirable properties like low-cost industrial, biocompatible, biodegradable, and ease of use compared to ionic liquids and hazardous organic solvents. Due to these benefits, DESs are now widely used instead of traditional organic solvents in the extraction and prior concentration of a wide range of both inorganic and organic compounds [4,5]. DESs are becoming one of the most desirable alternatives to toxic chemical solvents [6,7]. These are interactions, or solvent eutectic combinations, of several substances connected by hydrogen bonds and their van der Waals forces [8, 9]. This causes eutectic temperatures that are lower than the melting points of all the compounds that make up EDS [10]. The most of these chemicals are nontoxic, eco-friendly extraction solvents [11,12]. According to traditional methods, which use harmful organic solvents, an increasing number of advanced, eco-friendly analytical techniques use this new solvent family. Because of its wide range of applications and structural flexibility, DES a rise in interest has recently seen in micro-extraction techniques [13]. Depending on the applications, the solvent's hydrophilic / hydrophobic properties can be changed [6].DESs are also referred to as inexpensive ionic liquid substitutes [14,15]. An increasing number of novel analytical techniques that are less harmful to the environment than conventional procedures that rely on hazardous organic solvents are using this family of newly developed solvents [11].

II. AN OVERVIEW OF DESs IN BRIEF

Initially, the term "eutectic" was used in 1884 to characterize metal alloys with melting temperatures lower than those of their parts [16]. This idea led to the definition of a eutectic mixture as a combination of two or three compounds that, in the corresponding phase diagram, show a minimal melting point at a certain molar ratio [17]. In 2003, Abbott and colleagues reported the introduction of novel eutectic combinations that have interesting solvent characteristics and are liquid at room temperature [18]. Entitled "deep eutectic solvents (DESs)," these solvents were prepared by eutectic amide and quaternary ammonium salt combinations [18]. They are frequently a eutectic combination of a hydrogen bond (HBD) donor and an HBA molecule. The point of melting of the DESs decreased in relation to the melting point for each of their individual components as a result of the charge dislocation driven on by hydrogen bonding [19]. In addition, combinations maintain their liquid state because of the bonds of hydrogen and van der Waals forces that prevent the original components from crystallizing [20]. One of the most significant aspects of these novel solvents is the range of DESs that can be generated by altering their components [20]. Because of their low structural energy, and massive nonsymmetic ions, DESs how

https://doi.org/10.32792/utq/utjsci/v11i1.1208

low melting temperatures. To create DES, tetra ammonium salt is typically mixed with a HBD or metal salt. The reduction in the melting point of the combination relative to the melting points of its constituent parts can be attributed to charge delocalization resulting from hydrogen bonding, such as that between a hydrogen-donor moiety and a halide ion [21]. Abbott et al. investigated the freezing points of various quaternary ammonium compounds by heating them with $ZnCl_2$ in 2001. It was discovered that using choline chloride as the ammonium salt produced the lowest melting point, 23–25 °C [21]. Depending on this original study, other liquids consisting of eutectic salt combinations and donors of hydrogen bonds have been produced since. The phrase "deep eutectic solvent" was used to distinguish these liquids from ionic liquids, different anions.

III. Methods of Preparation

DESs are made using the 100% atom economy method, as was covered in the beginning. This method only requires combining HBA and HBD; waste disposal and purification were either omitted or not necessary.

(I) The most common method for preparing DESs involved heating and constantly stirring HBA and HBD in an inert environment until uniform liquids were created [18].

(II) First, the components of DES were dissolved in water in the second process, known as the evaporating method. The water then evaporated at 323 K in a vacuum. The mixture that was produced was maintained in the desiccator until a stable weight was reached.

(III) Solid HBA and HBD were injected using a mortar housed in a glove box with an inert nitrogen environment. After that, the mortar was continuously broken down until a clear, uniform liquid was produced [22].

(IV) Prior to processing by the freeze-drying procedure, HBD and HBA were dissolved in five weight percent of water. The two aqueous solutions are mixed and then frozen. The mixture was then freeze-dried to yield a consistent, clear liquid [23].

IV. Classifications of Deep Eutectic Solvents (DESs)

The general formula Cat^+X^-zY can be used to characterize deep eutectic solvents, where X is a Lewis base, usually a halide anion, and Cat^+ is, in theory, any ammonium, phosphonium, or sulfonium cation. Between X^- and a Lewis or Brønsted acid Y, complex anionic species are generated (z denotes the number of Y molecules that interact with the anion). Imidazolium and quaternary ammonium cations have been the subject of most research, with an emphasis on simpler systems that include choline chloride [ChCl, $HOC_2H_4N^+(CH_3)_3Cl^-$][24]. The most common combinations of halide salts and hydrogen-bond donors used to create DESs are shown in Fig. 1 [25].

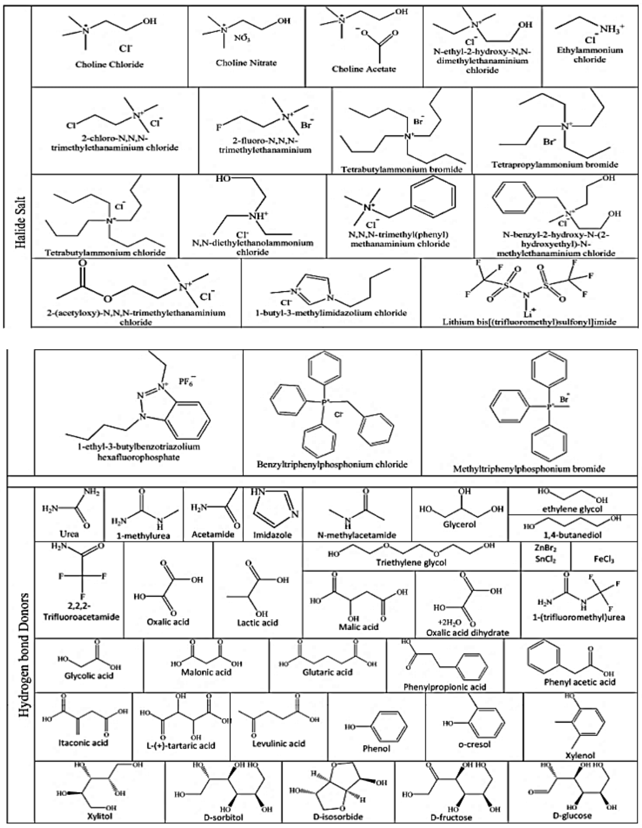

Fig. 1. The DES synthesis procedure utilizes the most common combinations of hydrogen-bond donors and halide salts

As shown in Table 1, the DESs are separated according to the characteristics of their constituents [20]. There have been reports of four primary DES types. There has been some discussion of the potential existence of a fifth kind of DES, but not enough research has been done on it.

Type I: Anhydrous metal chlorides and quaternary salts are used to make this kind of DES. Since fewer low-melting-point non-hydrated metal halides are used to create type I DESs, there are fewer HBD combinations available for them.

Type II: These DESs are made with hydrated metal chlorides and quaternary salts.

Type III: These DESs, also known as HBA and HBD compounds, are created from quaternary salts. Due to the wide variety of HBD and HBA components that are available, there is a possibility of creating a huge number of these distinct DES types with varying chemical and physical characteristics [26]. Therefore, by changing one or both of its components, the properties of this family of DESs can be changed [26].

Type IV: These DESs are made of HBD compounds and metal chloride.

DESs types III and IV may be either water-immiscible or water-miscible based on the makeup of their constituents, whereas DESs types I and II are all water-miscible [27]. 2019 saw the proposal by Coutinho et al. for a type V DES composed of non-ionic substances like menthol and thymol

[28]. Table 1 contains examples of several DES kinds as well as a general formula.

TABLE 1. Examples and a general formula for DES classification

Types of DESs	DESs components	Formula	Terms	Examples
I	Quaternary salts + anhydrous metal chloride	$Cat^+ X^- zMCl_x$	M=Zn, Sn, Fe, Al, Ga, In	Choline chloride + $ZnCl_2$
II	Quaternary salts + hydrated metal chloride	$Cat^+ X^- zMCl_x .y H_2O$	M= Cr, Co, Cu, Ni, Fe	Choline chloride + $CoCl_2.6H_2O$
III	Quaternary salts + HBD compounds	$Cat^+ X^- zRZ$	Z=OH,COOH, $CONH_2$	Choline chloride + Urea
IV	Metal chloride + HBD compounds	$MC1x + RZ = MCl^{+}_{x-1} RZ + MCl_{x+1}$	M= Al, Zn, and Z= OH, $CONH_2$	Urea +$ZnCl_2$
V		HBD + HBA	HBD = hydrogen bond donor HBA= hydrogen bond acceptor	Thymol + Menthol

V. Physicochemical Properties of DESs

A. *Melting Point*

Its melting point is the lowest temperature at which DES may be used as a liquid, and it is far lower than the melting point of the components that make it up. The main factors affecting a DES's melting point are the hydrogen bonds, or van der Waals forces, between the HBD and HBA. The HBA and HBD interacted throughout the eutectic phase due to changes in entropy and lattice energy, resulting in this large melting point drop [29]. The alkyl chain structure of HBD and HBA plays a major role in determining the melting point of DESs, according to a study cited by van Osch et al. Most ionic and non-ionic hydrophobic DESs melt at increasing temperatures as the fatty acid HBD's alkyl chain length increases. Furthermore, the melting point of ionic, hydrophobic DESs is significantly influenced by both anions and cations in the ionic components (HBA) [30].

B. *Viscosity*

In the extraction process, solvent viscosity is thought to be a crucial factor, especially for large-scale applications [31]. However, When DESs are compared to organic solvents like heptane as an extraction medium; there are still a lot of problems with their viscosity. For instance, the DES solvent viscosity will decrease when moisture is present [32]. Typically, the hydrophilic DES system's HBD components are responsible for the largest variations in its viscosity. The viscosity of hydrophilic DESs, including phenol, glycols, and ethylene glycol, is reduced. On the other hand, the hydrophilic DESs based on choline chloride and composed of urea, polycarboxylic acids, or sugars have a medium to high viscosity [29].

C. *Density*

Density has a big impact on how extraction operations are prepared and which solvents are selected. The degree of interaction between its constituent parts and the molecular packing has a significant impact on the density of DES. This is why the majority of hydrophobic DESs are preferred in the sample pre-treatment procedure since their densities are either the same or less than that of water [29]. Ibrahim et al.'s research shows that temperature affects the density of the DESs. [33]. Martins et al. found that when the alkyl chain length of the monocarboxylic acid grows, the density of DESs containing menthol and monocarboxylic acid drops. Compared to menthol-based DESs, thymol-based DESs have a greater density based on the length of the alkyl chain of monocarboxylic acid [34]. Furthermore, Guo et al.'s study discovered that the density of the generated DES was influenced by the HBA to HBD mole ratios [35].

D. *Surface Tension*

As the energy needed to increase the surface area per unit area, surface tension is a basic fluid property. This energy is produced at the contact by intermolecular forces [36]. Surface tension affects DES impact in mass transfer interfacial processes [37]. Temperature and the intensity of DES intermolecular interactions both have an impact on surface tension [38]. Most DESs have a surface tension that is higher than that of traditional solvents [39]. The interactions between HBD and HBA play a significant role in DES surface tension. The strength of the connections between HBD and HBA affects the surface tension of DESs [40]. Table 2 shows a few examples of physical characteristics for several DES types at the eutectic composition at 298 K, in addition to a comparison to ionic liquids containing discrete anions and certain molecular solvents. Conductivities compared to other ionic liquids and molecular solvents, DESs have relatively high viscosities and low. The large ion sizes and relatively free volume in the ionic systems are thought to be the cause of this discrepancy. The big ion sizes and comparatively huge free volume in the ionic systems have been proposed as the causes of this discrepancy. The viscosities of ionic liquids are substantially higher than those of the most common molecular solvents. It demonstrates that the activation energy of viscous flow has vast values and that the viscosity exhibits an Arrhenius tendency with temperature.

TABLE 2. Physical properties of DESs and molecular solvents at 298 K

Salt	**HBD**	**Molar ratio**	**Viscosity (cp)**	**Conductivity (ms cm^{-1})**	**Density/gc(m^{-3})**	**Surface tension (mN m^{-1})**
ChCl	Glycerol	1:3	450	1.05	1.20	50.8
$ZnCl_2$	Urea	1 : 3.5	11 340	0.18	1.63	72
$ZnCl_2$	Acetamide	1 : 4			1.36	53
ChCl	CF_3CONH_2	1:2		0.286	1.342	
ChCl	Ethylene glycol	1:3	19		1.12	45.4
C_4mimCl	$AlCl_3$		19	9.2	1.33	

E. Phase Changes in Behavior

The difference, ΔTf, between the freezing point at the eutectic composition of a binary mixture of A and B and that of a theoretical ideal mixture is independent of the degree of interaction between A and B. ΔTf will be larger, the greater the interaction. Fig.2 depicts this schematically. Let's begin with type I eutectics: Different metal halides will interact with the halide anion from the quaternary ammonium salt to make identical halometallate classes with related enthalpies of production. ΔTf values, therefore, ought to be in the range of 200 and 300 °C. It has been discovered that for a eutectic to occur at ambient temperature, a metal halide's melting point often needs to be 300 °C or below. Thus, it is simple to understand why metal halides like $AlCl_3$ (mp=193°C) [42], $FeCl_3$ (308) [24], $SnCl_2$ (247) [42], $ZnCl_2$ (290) [43], $InCl_3$ (586) [44], CuCl (423) [45], and $GaCl_3$ (78) [46] produce eutectics at ambient temperature. Even though they haven't been studied yet, metal salts like $SbCl_3$ (mp = 73°C), $BeCl_2$ (415), $BiCl_3$ (315), $PbBr_2$ (371), $HgCl_2$ (277), and $TeCl_2$ (208) may also be expected to produce ambient temperature eutectics. Conversely, fewer symmetrical cations, which have a lower melting point cause lower melting point eutectics in quaternary ammonium compounds. To add more metals to the DES formulations, type II eutectics were created. It was discovered that the related anhydrous salt had a melting point higher than that of metal halide hydrates. It is apparent that the waters of hydration lower the melting point of metal salts by lowering the lattice energy. A lower melting point of the pure metal salt (ΔTf) will result in a lesser depression of the freezing point (ΔTf), as Fig. 2 illustrates [47].

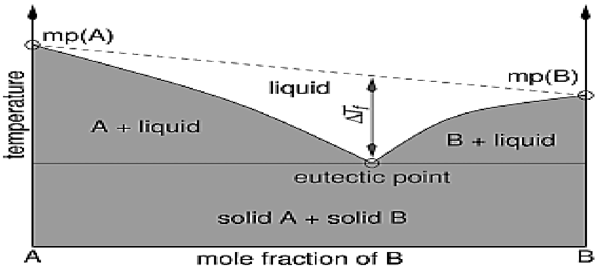

Fig. 2. Schematic representation of a eutectic point on a two-component phase diagram

TABLE 3. Temperatures of freezing point on a variety of DESs

Halide salt	**mp (°C)**	**HBD**	**mp (°C)**	**Salt:HBD (molar ratio)**	**Tf (°C) of DES**	**Ref.**
ChCl	303	adipic acid	153	1:1	85	41
ChCl	303	1-methyl urea	93	1:2	29	48
ChCl	303	1,3-dimethyl urea	102	1:2	70	48
ChCl	303	1,1-dimethyl urea	180	1:2	149	48
ChCl	303	acetamide	80	1:2	51	48
ChCl	303	banzamide	129	1:2	92	48
methyltriphenylphosphonium bromide	231−233	glycerol	17.8		- 4.03	49
methyltriphenylphosphonium bromide	231−233	ethylene glycol	−12.9		- 49.34	49
methyltriphenylphosphonium bromide	231−233	2,2,2-trifluoro acetamide	73−75		−69.29	49
methyltriphenylphosphonium bromide	345−347	glycerol	17.8		50.36	49
$ZnCl_2$	293	urea	134		9	50
$ZnCl_2$	293	acetamide	81		-16	50
$ZnCl_2$	293	ethylene glycol	-12.9		-30	50
$ZnCl_2$	293	hexanediol	42		-23	50

F. *Analyte Solubility*

For an increased in commercial activity, especially in the pharmaceutical and drug analytical fields, solubility is a crucial physicochemical feature [51]. DES solvents have better solubilizing properties than traditional solvents [52]. According to published reports, these solvents have potent solubilization properties for both polar and weak-polar materials, including pharmaceuticals, metal oxides, carbon dioxide, and elemental species including cadmium, lead, and mercury [53].

G. *Instrumental Compatibility*

DESs are advantageous in extraction operations since they don't come into contact with detection techniques, which are frequently reported for these solvents and their constituents. Numerous experimental detection techniques, including HPLC, have demonstrated high compatibility with many deep eutectic solvents [39]. Consequently, new combinations utilizing enhanced separation methods (such as HPLC) and employing a particular amount of DES in the mobile phase are being created [54,55].

H. *Toxicity*

Especially toxicity profiling is essential for finding new pharmaceutical compounds. Regarding this, the majority of research on the toxicity of DES has focused on in vitro studies in rats, bacterial cells, and cell lines from humans in culture; however, the literature also involves fungal cells, plants, fish, and invertebrates [56]. The results presented here clearly indicate that the statement of green DESs is not entirely accurate, and it is best to avoid drawing such broad inferences [57]. These chemical compositions, concentrations, and viscosities of DESs determine their cytotoxicity. For example, heavy metals make type III DESs less dangerous than type I, II, and IV DESs [58]. The toxicity of DESs is still up for disagreement. Furthermore, due to the absence of research on the topic, there have been disagreements on the biological properties of such solvents [57]. Theoretical and experimental understanding of DES toxicity will probably grow in the future.

VI. ADVANTAGES AND DISADVANTAGES OF THE DEEP EUTECTIC SOLVENTS (DESS)

Eutectic compounds, or DESs, are composed of two or more constituents joined by hydrogen bonds or other non-covalent bonds [59]. DES solvents are not considered unique compounds but rather mix in general [60]. DESs could be created at a minimal cost and with excellent biodegradability [61]. DESs can be easily designed while adjusted. Nevertheless, DESs' advantages over VOCs do not imply that they are faultless. In actuality, these substances possess numerous flaws, including high hygroscopicity, flammability, and low to average stability, and significant variability. These problems could not be disregarded, but the good design might allow us overcome or greatly improve them.

VII. ADVANTAGE OF DESS

- DESs have become known for their cost-effectiveness, accessibility, non-volatile, non-toxic, biocompatible, renewable, and biodegradable qualities.
- Because the constituents do not interact, materials that are renewable, biodegradable, and biocompatible can be employed directly to generate DESs without sacrificing their advantageous features [62,63].
- DESs are simple to prepare; often, just one step is required, and solvents and byproducts are left behind.
- Full atom economy in the synthesis of DES.
- DESs are also extremely adjustable due to the types of interactions between molecules and the broad range of components.
- DESs are more diverse than we predicted since they are mixtures rather than pure compounds [60].
- High reactivity, non-sensitive to water, non-flammability, and thermal stability.
- Widening the catalytic and reaction window in biomass valorization and biorefinery.
- Excellent natural compatibility, showing significant promise for DESs to be used with some enzymes, as well as being environmentally beneficial at the industrial level for biotransformation processes.
- Solubilization of bio-based components.
- Customizable new reaction media for bio catalysis.

VIII. DISADVANTAGE OF DESS

- Increased complexity of the reaction system.
- High viscosity
- Some types have toxicity
- Difficult separation from the reaction medium, catalysis and products.
- The presence of DES components in samples can hinder analytics.
- A vast array of possible pairings between HBD and HBA. The choice of the ideal HBD and HBA pair is frequently unpredictable and heavily influenced by the unique physicochemical characteristics of the component.

- Instability: The volatility influences the bulk loss of DESs from TGA and its thermal decomposition.
  • Hygroscopicity and air exposure: DESs must to contact to further absorb airborne substances such as O_2, N_2, water, CO_2, and SO_2.
  • Cost and synthesis: For a genuine industrial process, the DESs' cost is crucial. In general, the formation components determine the cost of DESs [64–66].
  •Usage of energy.
  • There is a chance the DESs will eventually include impurities. The sources of pollutants in DESs could be raw materials used in their synthesis. Owing to the air's solubility in water, oxygen, and other gases, as well as the breakdown of DESs in those elements, DESs may become contaminated by the atmosphere [67, 68].

CONFLICT OF INTEREST

Authors declare that they have no conflict of interest.

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