WORLD JOURNAL OF PHARMACEUTICAL RESEARCH

SJIF Impact Factor 8.084

Volume 12, Issue 6, 557-572. Review Article ISSN 2277– 7105

BRIEF REVIEW ON DEEP EUTECTIC MIXTURE AND ITS APPLICATION

Rajesh Ramrao Suryawanshi*, Dr. Pravin S. Kawtikwar, Ankita P. Kawtikwar, Shivani M. Suryawanshi, Vaibhav P. Patange

Department of Industrial Pharmacy, Sudhakarrao Naik Institute of Pharmacy Pusad, Nagapur Road Dist. Yavatmal, Maharashtra-445204.

Article Received on 01 March 2023,

Revised on 22 March 2023,
Accepted on 12 April 2023

DOI: 10.20959/wjpr20236-27896

***Corresponding Author**
Rajesh Ramrao Suryawanshi
Department of Industrial Pharmacy, Sudhakarrao Naik Institute of Pharmacy Pusad, Nagapur Road Dist. Yavatmal, Maharashtra-445204.

ABSTRACT

Deep eutectic solvents (DES) are a type of liquid mixture composed of solid components that exhibit remarkable properties, including high solvent capacity, biodegradability, low volatile organic compound content, and relatively low toxicity. The wide range of DES available, formed from different components and ratios, has resulted in numerous studied applications. This review focuses on the applications of DES in the health field. DES have shown promise in the development of oral liquid formulations for poorly soluble active pharmaceutical ingredients, although this area is still in its early stages. We assess the potential and limitations of DES in this regard. Additionally, DES have been used as synthesis media, and we explore their use in the synthesis and extraction of bioactive natural products. Finally, we examine other exciting applications of DES in promoting health, such as their use in genomics studies, as nano-carriers for the encapsulation of anticancer drugs, or in the stabilization of medical samples.

KEYWORDS: Deep eutectic solvent, Hydrogen bond acceptor, Hydrogen bond donor, drug delivery systems.

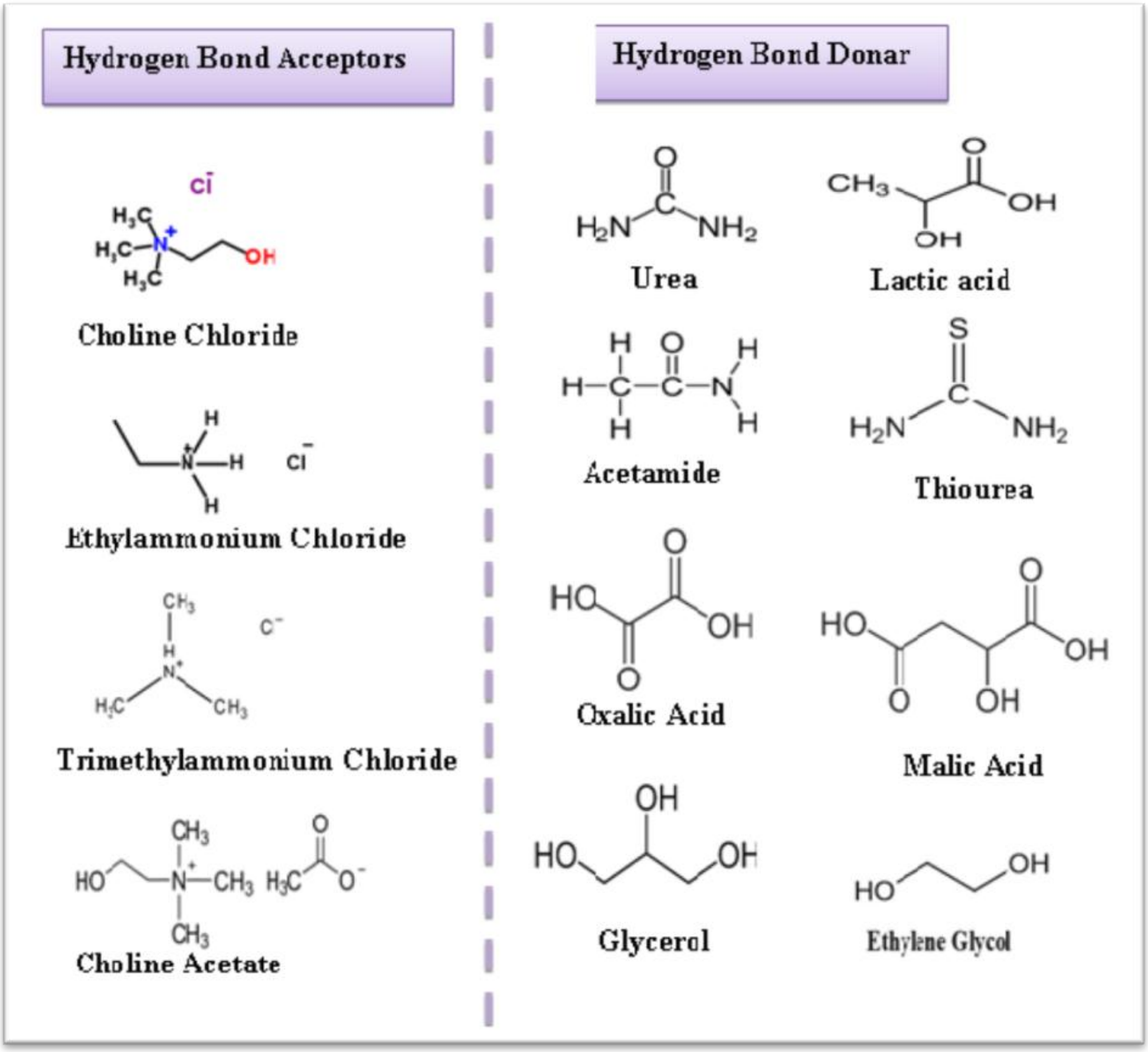
INTRODUCTION

Deep eutectic solvents (DESs) are a type of green solvent that has gained attention in the past two decades as an emerging class related to ionic liquids (ILs).[1] This interest was sparked by a study conducted by Abbott et al, who observed an unusual deep melting point depression at the eutectic composition of certain hydrogen bond donors (HBDs) and acceptors (HBAs).

This behavior was first observed in a combination of powdered choline chloride (2-hydroxyethyl)-trimethylammonium chloride) and crystalline urea in a 1:2 mole fraction, named "reline," which resulted in a liquid at room temperature with a melting point of 12°C (see Figure 1). This discovery opened the door to the exploration of DESs and their unique properties, which include being environmentally friendly and exhibiting high solvent capacity, biodegradability, low volatile organic compound content, and low toxicity.[2]

Figure 1: Deep Eutectic Mixture of Choline Chloride + Urea.

According to Abbott et al. the liquid was termed a "deep" eutectic mixture (DEM) to explain the phenomenon. These DEMs melt at low temperatures, which make them cost-effective solvents and electrolytes for various chemistries. As their properties are of primary interest, the term "deep eutectic solvent" (DES) has become the commonly used term for this diverse class of materials.[3] These eutectic fusions are generally characterized by a veritably large Depression of freezing point, generally advanced than 150 °C. With the preface of the Concept of green chemistry in the early 1990 s, the hunt for essence-free ionic liquids (ILs) Has come of growing interest. The possibility to chemically modify the cationic half nearly infinitely in combination with a veritably large choice of anions offers druggists a broad Range of ILs flaunting different physical parcels similar as melting point, solubility, density, viscosity, conductivity, and refractivity, among others.[4-5] Almost DESs are double or ternary fusions of at least one hydrogen bond patron and at least one hydrogen bond acceptor that are tightly linked by hydrogen bond interactions. This contributes to drop the chassis energy of the system, and therefore the melting point. Some DESs don't parade clear melting points, rather glass transitions, and are also known as low- transition- temperature fusions.[6] In a recent review, Abbott and coworkers have revisited the term DES so as to include eutectic mixtures of Lewis or Bronsted acids and bases which can contain a variety of anionic and cationic species and classified them into four types according to their constituents.[7] Although the concept of DESs is quite different from that of ionic liquids (ILs, liquids entirely composed of weakly coordinated ionic species with melting points below 100 °C), DESs share many physico-chemical properties with traditional ILs (e.g. low vapour pressures, excellent thermal stability, nonflammability, conductivity, and ease of recycling). Furthermore, normal DES components are derived from renewable sources [e.g. choline chloride (ChCl), urea, glycerol (Gly), lactic acid, carbohydrates, polyalcohols, amino acids, vitamins].



Therefore, their biodegradability is extraordinarily high and their toxicity is non-existent or very low. In view of their minimal ecological footprint, cheapeness of their constituents, tunability of their physico-chemical properties, and easy of preparation, DESs are successfully and progressively replacing often hazardous and organic volatile compounds in many fields of science.[8–10] Several years back, Choi et al. identified a novel type of DES after observing that certain combinations of natural products such as choline, amino acids, and sugars exhibited comparable properties to that of a DES when mixed in the right proportions. These natural deep eutectic solvents (NADESs) were coined by the authors.[11] To date, more than 174 DESs have been documented in various literature sources.[12] The versatility and unique properties of DESs have garnered the interest of both academic and industrial sectors. These mixtures have been proven to have numerous applications, such as synthesis, extraction, separation processes, biocatalysis, electrochemistry, biotechnology, nanomaterials, cosmetics, food, pharmaceuticals, and even as biofuels. One notable application of DESs is as excipients for delivering hydrophobic drugs, as well as a medium for poorly soluble drugs in the pharmaceutical industry. DESs hold much promise in this area as they can potentially serve as a promising alternative to organic solvents. This study focuses on the applications of DESs in the health field, specifically exploring the properties, important DESs, and main applications of these mixtures.[13]

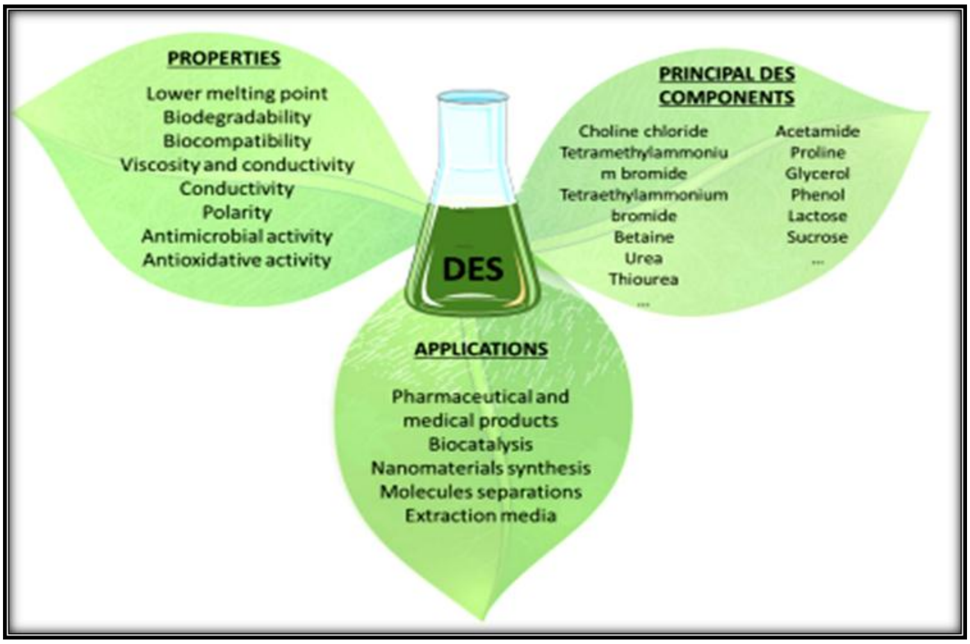


Figure 2: Properties and Application of DES.

DEFINATION AND TYPE OF DES

DES are commonly defined as systems composed of a mixture of at least two or more substances in particular molar ratio, a hydrogen bond acceptor (HBA) and a hydrogen bond donor (HBD), which are able to self-associate to form a new eutectic phase characterized by a melting point (below 100 ˚C) lower than that of each individual component. These individual components should also be inexpensive, biodegradable, renewable, and secure in addition to having these qualities. Figure 1 provides a graphic illustration of how a deep eutectic solvent forms. DES have often been described by the formula Cat^+X^-zY, in which Cat^+ is the cation of any ammonium, sulfonium, or phosphonium salt, and X^- is a Lewis base, generally the halide anion of the salt.[14] Y can be a Lewis or Bronsted base, and z represents the quantity of Y molecules. Between X and Y, complex anionic species develop. The main interactions between the halide salt or HBA and HBD are essentially hydrogen bonds, although occasional electrostatic forces and van der Waals interactions are also likely to be established.[15] Experimental and theoretical studies have shown that, in general, the highest fraction of hydrogen bonds in DES are intramolecular and occur between the HBD and the halide anion. The anion-HBD hydrogen bond network is the basis for the fundamental properties of DES (see Section 3 below). A comprehensive discussion of these features has been provided in a recent review.[16] DESs are largely classified depending on the nature of the complexing agent used, see figure 3.

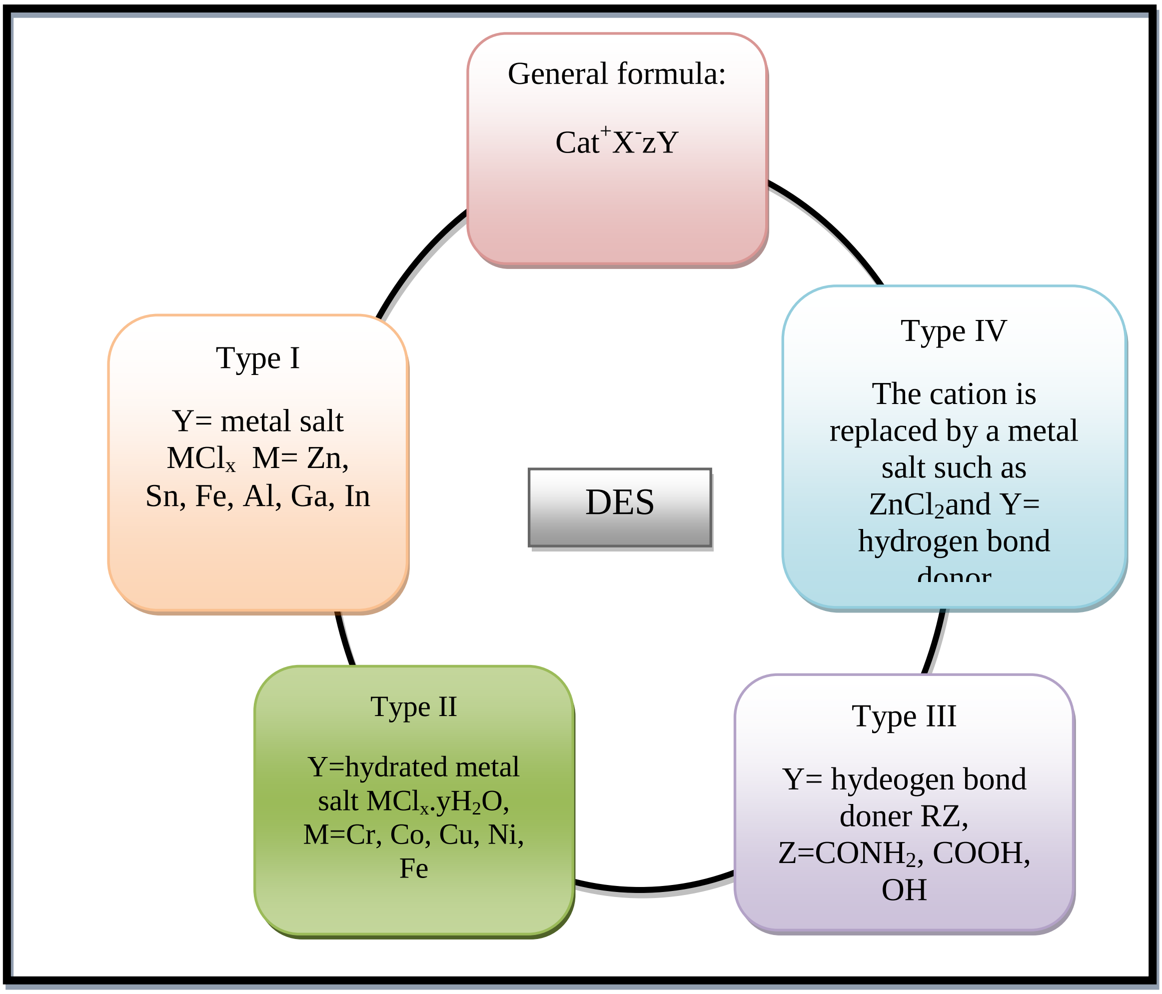


Figure 3: Types of Deep Eutectic Solvents.

DESs formed from MClx and quaternary ammonium salts of type I can be viewed as equivalent to extensively studied metal halide/imidazolium salt systems. The well-studied chloroaluminate/imidazolium salt melts are examples of type I eutectics, as are less common ionic liquids produced using imidazolium salts and various metal halides such as FeCl2. Furthermore, Scheffler and Thomson investigated EMIC and the metal halides AgCl, CuCl, LiCl, CdCl2, CuCl2, SnCl2, ZnCl2, LaCl3, YCl3, and SnCl4. . The selection of non-hydrated metal halides that have a sufficiently low melting point to form type I DESs is restricted, but the range of deep eutectic solvents can be using hydrated metal halides and choline chloride, widened (type II DES). Due to their inherent air/moisture insensitivity and affordability, the use of many hydrated metal salts in large-scale industrial processes is feasible. Type III eutectics, created from choline chloride and hydrogen bond donors, are of interest due to their ability to solvate a wide range of transition metal species, including chlorides and oxides.[17,18] A variety of hydrogen bond donors have been examined, resulting in the development of deep eutectic solvents utilizing amides, carboxylic acids, and alcohols. These liquids are simple to create and are relatively unreactive with water, with many being biodegradable and low-cost. This group of deep eutectic solvents is highly adaptable due to the wide range of hydrogen bond donors available. The physical properties of the liquid are influenced by the hydrogen bond donor and can be tailored to fit specific applications easily. Despite the electrochemical windows being narrower than those of some imidazolium salt-discrete anion ionic liquids, they are still wide enough to enable high current efficiency metal deposition such as Zn. This type of deep eutectic solvent has proven to be extremely versatile, with various potential applications being explored, including glycerol removal from biodiesel, metal oxide processing, and cellulose derivative synthesis.[19]

PREPARATION OF NADES

Hydrogen bonding acceptor (HBA) and hydrogen bonding donor (HBD) were combined at the proper molar ratio to create NADES. The mixture was heated at 100 ◦C for 2 h through a vacuum evaporation method until a homogeneous, transparent NADES liquid was produced. Then NADES was stored before use.[20]

Methods use in DES preparation

For components in equal proportions, there is no need to apply heat to produce a clear DES. If the ratio of any one component is kept constant and the other component ratio is increased, even mixing for a long time without heating results in no formation of clear DES. At that condition, if the temperature is increased (slight to more) depending upon the ratio, it results in a formation of clear DESs. DESs can also be made using the freezing process, which involves mixing the ingredients and freezing them to produce a transparent liquid. The vacuum evaporating method can also be used to prepare DES. It is difficult to stir highly viscous sugar based DESs; however, this problem can be solved by adding water to the mixture. The water in the DESs can then be vaporised in a vacuum-evaporating procedure using a rotary flash evaporator at 323K/49.85°C.[21]

Technique/Method	Procedure	Endpoint
Mortal and pestle	Mix two components in the mortar and pestle	Until formulation of clear liquid
Mixing in magnetic stirrer without heat	Mix two component in a magnetic stirrer without heat	Until formulation of clear liquid
Mixing in the magnetic stirrer with slight/more heat	Mix two component in a magnetic stirrer with slight/more heat	Until formulation of clear liquid
Freezing	Mix the components and freeze it	Until formulation of clear liquid
Vacuum evaporating	Highly viscous sugar-based DESs are difficult to stir. This problem can be overcome by adding extra water into the mixture. Then evaporate the water at 323 K using a rotary flash evaporator. Keep the obtained DEEs in a desiccators containing silica gel until uniform weight is attained	

PROPERTIES OF DESs

Although DESs and conventional ILs have distinct chemical properties, they share similar physical properties such as their ability to act as tunable solvents that can be tailored to suit a specific type of chemistry. Both exhibit a low vapor pressure, wide liquid-range, and non-inflammability. Unlike traditional ILs, DESs offer several advantages such as ease of preparation and ready availability from relatively inexpensive components that are toxicologically well-characterized, making them suitable for large-scale processing. However, they are generally less chemically inert. DESs can be produced through simple mixing of two components with moderate heating, which is more cost-effective than conventional ILs (e.g., imidazolium-based liquids) and allows for large-scale applications. Although the individual components of DESs are well-characterized for toxicity, there is limited information available about the toxicological properties of eutectic solvents themselves, and further research is needed. The term "deep eutectic solvent" was first used to describe type III eutectics but has since been applied to all eutectic mixtures. While this approach encompasses early work on haloaluminates, this will not be discussed here other than for comparative purposes as it has been the subject of numerous reviews.[22-24]

PHASE BEHAVIOR

As previously mentioned, deep eutectic solvents (DESs) are not pure compounds but instead are mixtures of two or more pure compounds, and their system is represented by a solid-liquid phase diagram that shows the melting temperature as a function of the mixture composition. For instance, in a binary mixture of compounds A and B, the eutectic point indicates the composition and the minimum melting temperature at which the melting curves of both compounds converge (as shown in Figure 4). According to Martins et al., DESs should only be referred to as "deep" if their melting point is lower than the ideal eutectic temperature, as otherwise, they cannot be differentiated from other mixtures.[25] Moreover, for a mixture to be considered a DES, it must remain in a liquid state at the operating temperature, even if this requires a different composition than the eutectic point. Therefore, having a phase diagram is crucial, and knowing the melting properties of the pure compounds is necessary to determine the ideal solubility curve. However, little has been reported on the thermodynamic behavior of DESs to date. Most DESs have freezing points that fall between -69°C and 149°C, but all of them have a freezing point below 150°C.[26] The choice of the hydrogen bond donor,[17] the nature of the organic salt and its anion.[17] and the organic salt/ hydrogen bond donor molar ratio can all affect the freezing point of the mixture. The method of preparation can also influence the value of the freezing point, but not the eutectic composition which must remain unchanged no matter the method used[18] On the other hand, no correlation was found between the freezing point of a deep eutectic solvent and the melting points of its pure components The hydrogen bond donor did, however, affect the freezing point depression ΔT. For instance, Abbott et al. discovered that the freezing point depresses more when the molecular weight of the hydrogen bond donor is lower.[3,27] But unlike Abbott and coworkers who considered the temperature depression as the difference between the linear combination of the melting points of the pure components and the real eutectic point (ΔT1), Martins et al. thought it would be more appropriate to define the temperature depression as the difference between the ideal and the real eutectic point (ΔT2); otherwise, any mixture of compounds would be referred as a deep eutectic solvent.[25]

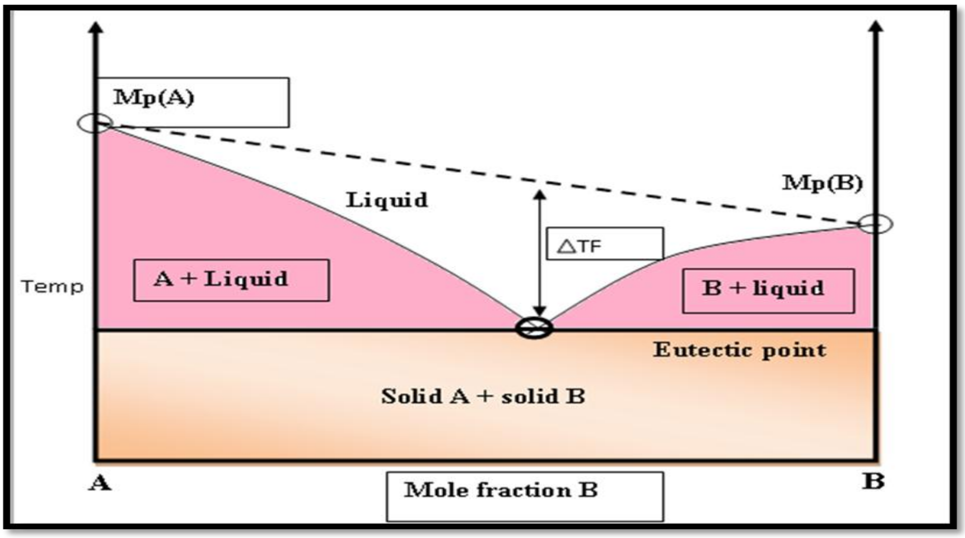


Figure 4: Phase Behavior.

FREEZING POINT (TF)

deep eutectic solvents, are formed when two solids capable of self-association via hydrogen bonds are mixed together to create a new liquid phase. This new phase is characterized by a lower freezing point than that of the individual constituents. For example, a mixture of CHCl and urea in a 1:2 molar ratio results in a eutectic with a freezing point of 12°C, which is significantly lower than the melting points of CHCl and urea (302°C and 133°C, respectively). The depression of the freezing point is due to an interaction between the halide anion and the hydrogen bond donor component, which is urea in this case. The freezing points of all reported DESs are below 150°C, and DESs with a freezing point lower than 50°C are particularly attractive because they can be used as safe and inexpensive solvents in various fields. Table 1 provides the freezing points of different DESs described in the literature.[28]

Table No. 1: Freezing Point of The Reported DESs: Melting Point of Pure HBD.

Hydrogen Bond Donor (HBD)	CHCl : HBD (Molar Ratio)	Tm / °C	Tf / °C
Urea	1: 2	134	12
Thiourea	1: 2	175	69
Resorcinol	1: 4	110	87
Succinic acid	1:1	185	71
Phenylacetic acid	1:1	77	25

Oxalic acid	1:1	190	34
Citric acid	1:1	149	69
Benzoic acid	1:1	122	95
Imidazole	3:7	89	56
Glycerol	1: 2	17.8	40
Ethylene glycol	1: 2	12.9	66
Benzamide	1: 2	129	92
Acetamide	1: 2	80	51

DENSITY

One of the most significant physical properties of a solvent is its density. DES densities are typically measured using a specific gravity meter. The majority of DESs have greater densities than water. Type IV ZnCl2- HBD eutectic compounds, for example, have densities greater than 1.3 g cm3. The densities of ZnCl2-urea (1: 3.5) and ZnCl2-acetamide (1: 4) vary. (1.63 and 1.36 g cm3, respectively). This significant difference in density could be ascribed to the DES's different molecular organisation or packing.[22] It should be noted that the densities of both DESs are greater than those of pure HDBs. (acetamide: 1.16 and urea: 1.32 g cm3). The hole the theory could explain this phenomenon. DESs, like imidazolium-based ILs, are made up of holes or empty spaces. For instance, for example, when ZnCl2 was combined with urea, the average hole radius was reduced, leading in a small increase in DES density over neat urea.[29]

VISCOSITY

Viscosity is a crucial issue that needs to be addressed for most ILs, including DESs. With the exception of CHCl-ethylene glycol (EG) eutectic mixtures, most DESs have relatively high viscosities (>100 cP) at room temperature. The extensive hydrogen bond network between each component is often attributed to the high viscosity of DESs, which lowers the mobility of free species within the DES. Additionally, the high viscosity of DESs may be attributed to large ion size, very small void volume, and other forces like electrostatic or van der Waals interactions. Low-viscosity DESs are highly desirable due to their potential applications as green media. Eutectic mixtures' viscosities are influenced by various factors, including the chemical nature of DES components, temperature, and water content. As was previously mentioned, the free volume affects the viscosity of DESs, and low-viscosity DESs can be designed using the hole theory. For example, small cations or fluorinated hydrogen-bond donors can lead to the formation of DES with low viscosity. The viscosity of binary eutectic mixtures is primarily governed by hydrogen bonds, van der Waals and electrostatic interactions provides viscosity data for common DESs at various temperatures.[30]

POLARITY

The polarity of a solvent can be measured by its polarity scale, such as the ET 30 scale, which is determined by the electronic transition energy of a probe dye (e.g., Reichardt's Dye 30) in the solvent. The polarity of various CHCl-glycerol DESs has been evaluated using Reichardt's Dye method, and the results are summarized in Table 5.4. These results indicate that CHCl-glycerol DESs have similar polarities to those of ILs bearing discrete anions, such as RNH3+X_ and R2NH2+X_. The polarity of the DESs increases with an increase in the CHCl/glycerol molar ratio and a roughly linear increase of ET (30) with CHCl concentration has been observed.[31]

SURFACE TENSION

In comparison to other physicochemical properties, research on the surface tension of deep eutectic solvents are quite limited. It is, however, an important property because it is highly reliant on the intensity of the intermolecular forces occurring between the hydrogen bond donor and the corresponding salt. However, highly viscous liquids have significant surface tensions. At 25 °C, the values related to the reported deep eutectic solvents range between 35 and 75 mN m^{-1} Remarkably high values were once again recorded for sugar-based deep eutectic solvents, such as choline chloride :D-glucose and choline chloride:D-fructose, reflecting their extensive hydrogen-bond networks. Furthermore, the surface tension is affected by both the salt mole fraction and the cation type. A quaternary ammonium salt with an additional hydroxyl group or a longer alkyl chain results in higher surface tensions. Additionally, the surface tension decreases linearly with increasing temperature.[32]

IONIC CONDUCTIVITY

The main factor controlling the conductivity of deep eutectic solvents is viscosity, and as a result, most of these solvents have poor ionic conductivities at room temperature ($\kappa<2$ mS cm^{-1}). However, increasing the temperature decreases viscosity and leads to an increase in conductivity. The hydrogen bond accept or/hydrogen bond donor molar ratio, as well as the nature of the organic salt and hydrogen bond donor, also affect the conductivity property. The solvents' anion and water addition also play a role.[32]

APPLICATION OF DES

1. Related to Peculiar Solubility Properties of DES

There is a growing interest in the use of solvents that can improve solubility in health applications, and deep eutectic solvents (DESs) appear to be a promising alternative.[33] This is particularly relevant for drugs with poor water solubility, for which a solution is necessary. Various mechanisms have been used to address this problem, including the use of new dosage forms, alternative chemical structures such as salts and esters, prodrugs, active metabolites, and different routes of administration.[34] In fact, finding adequate media for active pharmaceutical ingredients (APIs) with poor water solubility is one of the most important challenges facing the pharmaceutical industry, as solubility has a direct impact on a drug's therapeutic effect.[35] In recent years, several studies have focused on the use of eutectic mixtures in the pharmaceutical field to improve drug solubility and bioavailability.[36]

2. Gas Adsorption

One of the most well-known applications of deep eutectic solvents is their ability to adsorb gases like carbon dioxide, which makes them a potential solvent for reducing global warming, much like traditional ionic liquids. For example, choline chloride and urea are a well-known deep eutectic solvent that has been discovered to be a good gas adsorbent by Han et al. They not only discovered this fact but also conducted research on the properties and factors that affect its ability to adsorb CO2. CO_2 solubility is affected by choline chloride content and environmental changes such as pressure and temperature, similar to how the eutectic point is achieved at a liquid with certain ratio of HBD and HBA. In this case, the solubility of CO2 is maximized at a ratio of 1:2 of choline chloride to urea. Furthermore, the ability of choline chloride/urea DES to dissolve CO2 is inversely proportional to temperature (the lower the temperature, the greater the solubility) and positively proportional to pressure. (the high pressure and high solubility). Many different DESs formed with various combinations of HBD and HBA have been discovered by various research teams or facilities, indicating their potential in this area.[37]

3. Synthesis of Metal Nanoparticles

A promising application of DESs is their use as a solvent for the shape-controlled synthesis of metal nanoparticles, which could have a significant impact on the science of electrocatalysts. Researchers have successfully synthesized gold nanoparticles to produce Au-based catalysts without using surfactants or seeds, but with a DES as the solvent. Star-shaped nanoparticles were obtained directly from the reduction of HAuCl4 by L-ascorbic acid at room temperature in the DES. By adjusting the water content of the DES, nanoparticles of various shapes and surface structures, including snowflake-like and nanothorns, were also obtained. The electrocatalytic characteristics of the gold nanoparticles were investigated using H2O2 electroreduction as a probe reaction. The star-shaped nanoparticles exhibited much higher catalytic activity than other shaped nanoparticles and polycrystalline Au. In another study, the electrochemically shape-controlled synthesis of Pt nanocrystals with high surface energy was demonstrated in a 1 ChCl:2 urea DES. Concave tetrahexahedral nanocrystal growth was readily controlled without the use of seeds, surfactants, or other chemicals. This demonstrates the potential of DESs as a solvent for the synthesis of metal nanoparticles with desired shapes and properties.[38]

4. Pharmaceuticals and Medical Research

In addition to solubilization, DESs have also been investigated as potential drug delivery vehicles due to their ability to form gels and nanoparticles. Gels can be formed by mixing DESs with polymers, such as chitosan or alginate, and can be used to deliver drugs locally at a specific site. This has been demonstrated in several studies, including the delivery of an anti-inflammatory drug using a choline chloride-based DES-gel in a rat model of arthritis. Nanoparticles can also be formed using DESs as the solvent, and these can be used for systemic drug delivery. For example, DESs have been used to prepare chitosan-coated nanoparticles for oral delivery of insulin, and choline chloride-based DESs have been used to prepare gold nanoparticles for targeted delivery of anticancer drugs. However, more research is needed to fully understand the potential of DESs in drug delivery, and to optimize their properties for specific applications.[39]

CONCLUSION

The pursuit of environmentally friendly solvents is a growing field that contributes to the principles of green chemistry. Currently, deep eutectic solvents are being widely considered and investigated due to their intriguing properties that make them potential substitutes for conventional solvents in various academic and industrial fields. In this review article, we have provided a comprehensive overview of the fundamentals and characteristics of deep eutectic solvents. We have elucidated their updated definition, classification, and preparation methods. Furthermore, we have summarized their main physicochemical properties, such as their phase behavior, density, viscosity, ionic conductivity, surface tension, and polarity, highlighting the ten ability of these systems through different parameters, such as the choice of hydrogen bond donor and acceptor, their molar composition, temperature, and water content. Additionally, we have emphasized the impact of water on the physicochemical properties and structure of deep eutectic systems, considering the ubiquity of water and the extensive use of binary mixtures of deep eutectic solvents and water in many applications. It is worth noting that the presence of water significantly affects the properties of deep eutectic solvents, and several studies have recently emerged to investigate the behavior of aqueous mixtures of deep eutectic solvents. Although the addition of water can have some beneficial outcomes, it may also disturb the supramolecular network of eutectic mixtures. Further studies are needed to gain a deeper understanding of deep eutectic solvents, especially considering the countless combinations that can lead to their formation.

REFERENCES

1. Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice; Oxford University Press: New York, 1998.
2. Abbott, A. P.; Capper, G.; Davies, D. L.; Rasheed, R. K.; Tambyrajah, V. Novel Solvent Properties of Choline Chloride Urea Mixtures. Chem. Commun, 2003; 0: 70−71.
3. Abbott, A. P.; Boothby, D.; Capper, G.; Davies, D. L.; Rasheed, R. K. Deep Eutectic Solvents Formed Between Choline Chloride and Carboxylic Acids: Versatile Alternatives to Ionic Liquids. J. Am. Chem. Soc, 2004; 126: 9142−9147.
4. G. T. Kim, S. S. Jeong, M. Z. Xue, A. Balducci, M. Winter, S. Passerini, F. Alessandrini, G. B. Appetecchi, J. Power Sources, 2012; 199: 239–246.
5. J. L. Shamshina, S. P. Kelley, G. Gurau, R. D. Rogers, Nature, 2015; 528: 188–189.
6. M. Francisco, A. Van Den Bruinhorst, M.C. Kroon, Low-transition-temperature mixtures (LTTMs): a new generation of designer solvents, Angew. Chem. Int. Ed, 2013; 52: 3074–3085.
7. E.L. Smith, A.P. Abbott, K.S. Ryder, Deep eutectic solvents (DESs) and their applications, Chem. Rev, 2014; 114: 11060–11082.
8. A. Paiva, R. Craveiro, I. Aroso, M. Martins, R.L. Reis, A.R.C. Duarte, Natural deep eutectic solvents – solvents for the 21st century, ACS Sustainable Chem. Eng, 2014; 2: 1063–1071.

9. D.A. Alonso, A. Baeza, R. Chinchilla, G. Guillena, I.M. Pastor, D.J. Ramón, Deep eutectic solvents: the organic reaction medium of the century, Eur. J. Org. Chem, 2016; 612–632.
10. C. Florindo, L.C. Branco, I.M. Marrucho, Quest for green solvents design: from Hydrophilic to hydrophobic (deep) eutectic solvents, ChemSusChem, 2019; 12: 1549–1559.
11. Yang, Z. Natural Deep Eutectic Solvents and Their Applications in Biotechnology. Adv. Biochem. Eng. Biotechnol, 2019; 168: 31–59.
12. Liu, Y.; Friesen, J.B.; McAlpine, J.B.; Lankin, D.C.; Chen, S.-N.; Pauli, G.F. Natural Deep Eutectic Solvents: Properties, Applications,And Perspectives. J. Nat. Prod, 2018; 81: 679–690.
13. Lomba, L.; García, C.B.; Ribate, M.P.; Giner, B.; Zuriaga, E. Applications of Deep Eutectic Solvents Related to Health, Synthesis, And Extraction of Natural Based Chemicals. Appl. Sci, 2021; 11: 10156.
14. E.L. Smith, A.P. Abbott, K.S. Ryder, Deep eutectic solvents (DESs) and their applications, Chem. Rev, 2014; 114: 11060–11082.
15. Q. Zhang, K.O. Vigier, S. Royer, F. Jérome, Deep eutectic solvents: synthesis, properties and applications, Chem. Soc. Rev, 2012; 41: 7108–7146.
16. Y.P. Mbous, M. Hayyana, A. Hayyan, W.F. Wong, M.A. Hashim, C.Y. Looi, Applications of deep eutectic solvents in biotechnology and bioengineering—promises and challenges, Biotechnol. Adv, 2017; 35: 105–134.
17. Abbott, A. P.; Capper, G.; Davies, D. L.; Rasheed, R. K.; Tambyrajah, V. Chem. Commun, 2003; 70.
18. Abbott, A. P.; Capper, G.; Davies, D. L.; McKenzie, K. J.; Obi, S. U. J. Chem. Eng. Data, 2006; 51: 1280.
19. Emma L. Smith, Andrew P. Abbott, and Karl S. Ryder Chemical Reviews, 2014; 114(21): 11060-11082.
20. Zhou P, Tang D, Zou J, Wang X. An alternative strategy for enhancing stability and antimicrobial activity of catechins by natural deep eutectic solvents. LWT, 2022 Jan 1; 153: 112558.
21. Kalhor, P.; Ghandi, K. Deep Eutectic Solvents for Pretreatment, Extraction, and Catalysis of Biomass and Food Waste. Molecules, 2019; 24.
22. Wilkes, J. S. ACS Symp. Ser, 2002; 818: 214.
23. Lin, I. J. B.; Vasam, C. S. J. Organomet. Chem, 2005; 690: 3498.

24. Wilkes, J. S. Green Chem, 2002; 4: 73.
25. Martins MAR, Pinho SP, Coutinho JAP (2019) Insights into the nature of eutectic and deep eutectic mixtures. J Solution Chem, 48(7): 962–982.
26. Zhang Q, De Oliveira Vigier K, Royer S, Jérôme F (2012) Deep eutectic solvents: syntheses, properties and applications. Chem Soc Rev, 41(21): 7108–7146.
27. Abbott AP, Capper G, Davies DL, Rasheed RK (2004b) Ionic liquid analogues formed from hydrated metal salts. Chem Eur J, 10(15): 3769–3774.
28. A. P. Abbott, J. C. Barron, K. S. Ryder and D. Wilson, Chem.–Eur. J, 2007; 13: 6495– 6501.
29. K. Shahbaz, F. S. Mjalli, M. A. Hashim and I. M. AlNashef, Thermochim. Acta, 2011; 515: 67–72.
30. PK, Vajid, and K. Jasna. "A Review Article On Deep Eutectic Solvents–An Approach To Drug Delivery System." World journal of pharmaceutical research, 2020; 9: 7: 215-230.
31. M. A. Kareem, F. S. Mjalli, M. A. Hashim and I. M. AlNashef, J. Chem. Eng. Data, 2010; 55: 4632–4637.
32. PK, Vajid, and K. Jasna. "A Review Article On Deep Eutectic Solvents–An Approach To Drug Delivery System." (2020).
33. Zainal-Abidin, M.H.; Hayyan, M.; Ngoh, G.C.; Wong, W.F.; Looi, C.Y. Emerging Frontiers of Deep Eutectic Solvents in Drug Discovery and Drug Delivery Systems. J. Control. Release, 2019; 316: 168–195.
34. Kumar, S.; Dilbaghi, N.; Rani, R.; Bhanjana, G.; Umar, A. Novel Approaches for Enhancement of Drug Bioavailability. Rev. Adv. Sci. Eng, 2013; 2: 133–154.
35. Sanphui, P.; Goud, N.R.; Khandavilli, U.B.R.; Nangia, A. Fast Dissolving Curcumin Cocrystals. Cryst. Growth Des, 2011; 11: 4135–4145.
36. Araya-Sibaja, A.M.; Vega-Baudrit, J.R.; Guillén-Girón, T.; Navarro-Hoyos, M.; Cuffini, S.L. Drug Solubility Enhancement through the Preparation of Multicomponent Organic Materials: Eutectics of Lovastatin with Carboxylic Acids. Pharmaceutics, 2019; 11: 112.
37. Isik M.; Ruiperez F.; Sardon H. Innovative Poly(Ionic Liquid)s by the Polymerization of Deep Eutectic Monomers Macromol. Rapid Commun, 2016; 37: 1135-1142.
38. Wei, L.; Fan, Y. J.; Tian, N.; Zhou, Z.-Y.; Zhao, X.-Q.; Mao, B.- W.; Sun, S.-G. J. Phys. Chem. C, 2012; 116: 2040.
39. Hansen BB, Spittle S, Chen B, Poe D, Zhang Y, Klein JM, Horton A, Adhikari L, Zelovich T, Doherty BW, Gurkan B. Deep eutectic solvents: A review of fundamentals and applications. Chemical reviews, 2020 Dec 14; 121(3): 1232-85.