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A REVIEW ARTICLE ON DEEP EUTECTIC SOLVENTS – AN APPROACH TO DRUG DELIVERY SYSTEM

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ABSTRACT

Deep eutectic solvents comprising or acting as solvents of active pharmaceutical ingredients (API – DES) emerged as promising alternatives to improve therapeutic efficiency, with additional possibility to integrate them in biopolymer-based system to enhance their delivery. These strategies avoid a current major concern related to drugs and APIs, i.e. polymorphism, and increase the solubility and bioavailability of the target API which leads to increased bioavailability. Owing to their composition versatility, polymerizable API-DES can also be prepared.

KEYWORDS: Eutectic solvents, Ionic liquids, drug delivery system.

INTRODUCTION

In the past 20 years, room temperature ionic liquids (RTILs) have attracted considerable attention especially in the fields of catalysis, electrochemistry, material chemistry, and more recently for the pre-treatment of biomass.[1] At the early stages of these research studies, scientists mainly focused on the formation of ionic liquids by mixing metal salts, mostly zinc, aluminium, tin and iron chlorides, with quaternary ammonium salts.[2-3] Although both salts have very high melting points, their proper mixing leads to the formation of a liquid phase, the so-called eutectic mixture. These eutectic mixtures are generally characterized by a very large depression of freezing point, generally higher than 150°C. With the introduction of the concept of green chemistry in the early 1990's, the search for metal-free ionic liquids (ILs) has become of growing interest. The possibility to chemically modify the cationic moiety almost infinitely in combination with a very large choice of anions offers chemists a broad range of ILs exhibiting different physical properties such as melting point, solubility, viscosity, density, conductivity, and refractivity, among others.[4-5] For instance, in 2009, Seddon and co-workers have reported that 1018 different ILs can be theoretically produced, 250 of them being already commercialized. Owing to their low vapour pressure and high boiling point, which facilitates their recycling, ILs were qualified as green solvents. However, the ‘‘green affiliation’’ of these neoteric solvents is now largely contested in the current literature.[6] Indeed, many reports pointed out the hazardous toxicity and the very poor biodegradability of most ILs. ILs with high purity are also required since impurities, even in trace amounts, affect their physical properties. Additionally, their synthesis is far to be environmentally friendly since it generally requires a large amount of salts and solvents in order to completely exchange the anions. These drawbacks together with the high price of common ILs unfortunately hamper their industrial emergence and new concepts are now strongly needed in order to utilize these systems in a more rational way. To overcome the high price and toxicity of ILs, a new generation of solvent, named Deep Eutectic Solvents (DES), has emerged at the beginning of this century. Formation of these DESs can be obtained by simply mixing together two safe components (cheap, renewable and biodegradable), which are capable of forming a eutectic mixture. One of the most widespread components used for the formation of these DESs is choline chloride (ChCl).[7] ChCl is a very cheap, biodegradable and non-toxic quaternary ammonium salt which can be either extracted from biomass or readily synthesized from fossil reserves (million metric tons) through a very high atom economy process.[8] In combination with safe hydrogen bond donors such as urea, renewable carboxylic acids (e.g. oxalic, citric, succinic or amino acids) or renewable polyols (e.g. glycerol, carbohydrates), ChCl is capable of rapidly forming a DES.[9-10] Although most of DESs are made from ChCl as an ionic species, DESs cannot be considered as ILs because,

1. DESs are not entirely composed of ionic species and
2. Can also be obtained from non- ionic species.

As compared to the traditional ILs, DESs derived from ChCl gather many advantages such as;

1. Low price
2. Chemical inertness with water (i.e. easy storage),
3. Easy to prepare since DESs are obtained by simply mixing two components, thus by-passing all problems of purification and waste disposal generally encountered with ILs.
4. Most of them are biodegradable,8 biocompatible and non-toxic, reinforcing the greenness of these media.

Physico-chemical properties of DESs (density, viscosity, refractive index, conductivity, surface tension, chemical inertness, etc.) are very close to those of common ILs. For this reason, DESs derived from ChCl are also familiarly named ‘‘biocompatible’’ or ‘‘bio renewable’’ ionic liquids in a few studies. Thanks to their low ecological footprint and attractive price, DESs have now become of growing interest both at academic and industrial levels and the number of publications dedicated to the use of DESs is now rapidly increasing in the current literature, further demonstrating the attractiveness of these media.

Deep eutectic solvents comprising or acting as solvents of active pharmaceutical ingredients (API – DES) emerged as promising alternatives to improve therapeutic efficiency, with additional possibility to integrate them in biopolymer-based system to enhance their delivery.[11] These strategies avoid a current major concern related to drugs and APIs, i.e. polymorphism, and increase the solubility and bioavailability of the target API which leads to increased bioavailability. Owing to their composition versatility, polymerizable API-DES can also be prepared.[12]

The relatively easy preparation of API- DES and their capacity to tune the API’s release profile when incorporated in (bio) polymer-based systems represent an effective alternative to improve the APIs therapeutic action and to develop controlled drug delivery systems. They have versatility in the design of these new liquid forms, by the proper selection of the hydrogen bond-donor (HBD) and hydrogen bond-acceptor (HBA) species, dictate their role in drug delivery and thus their pharmacological action.[13-14]

API-DES has vast applications in drug delivery and ability to overcome some drawbacks of solid drugs by increasing the drug’s stability, solubility, permeation, bioavailability and therapeutic action.[15] It has many advantages than other solvents that are used for pharmaceutical formulations because they may have less solubility and least permeability more over that they may be incompatible with the active ingredient.

Deep eutectic solvents are sometimes refers as a mixture of two components, in which one component at a particular molar composition become liquid at room temperature and the another one of them is an active pharmaceutical ingredient (API). Now we can consider one example that is the DES based on menthol complexed with three different APIs, ibuprofen (ibu), BA (BA) and phenyl acetic acid (PA), are prepared. The interactions between the components that constitute the DES were studied by NMR, confirming that the eutectic system is formed by H-bonds between menthol and the API. The mobility of the DES components was studied by PFGSE NMR spectroscopy. Now by considering the self-diffusion of the species follows the same behaviour as observed as in ionic liquids, in which the components migrate via jumping between voids present in the supra structure created by punctual thermal fluctuations. After evaluating the solubility and permeability of the systems in an isotonic solution then made a comparison with the pure APIs and establish the diffusion and permeability studies carried out in a Franz cell. The solubility of the APIs when in the DES system can be seen that is improved up to 12-fold.[16]

Deep eutectic solvents are composed of components which are able to establish hydrogen bond interactions with each other to form an eutectic mixture, that is liquid melting at the desired temperature (most of them are liquid between room temperature and 70°C) with a melting point lower than that of the each individual.

COMPREHENSIVE STUDY ON EUTECTIC SOLVENTS

DEFINITION OF DEEP EUTECTIC SOLVENTS

A DES is generally composed of two or three cheap and safe components which are capable of associating with each other, through hydrogen bond interactions, to form a eutectic mixture. The resulting DES is characterized by a melting point lower than that of each individual component. Generally, DESs are characterized by a very large depression of freezing point and are liquid at temperatures lower than 150 1C. Note that most of them are liquid between room temperature and 70 1C. In most cases, a DES is obtained by mixing a quaternary ammonium salt with metal salts or a hydrogen bond donor (HBD) that has the ability to form a complex with the halide anion of the quaternary ammonium salt. Scheme 1 summarizes the different quaternary ammonium salts that are widely used in combination with various HBDs in the formation of DESs.[17]

Owing to its low cost, biodegradability and low toxicity, CHCl was widely used as an organic salt to produce eutectic mixtures generally with cheap and safe HBDs such as urea, glycerol, carbohydrate-derived polyols or renewably sourced carboxylic acids. These DESs are attractive since they exhibit similar physicochemical properties to traditional imidazolium based ILs and thus can advantageously replace them in many applications. As compared to traditional organic solvents, DESs are not considered as volatile organic solvents and not flammable, making their storage convenient. From the view point of green chemistry, these DESs are even more attractive since some of them have been proven to be biodegradable and compatible with enzymes further increasing their interest. Additionally, synthesis of DESs is 100% atom economic, easy to handle and no purification is required, thus making their large-scale use feasible.[18] In the following sections, we wish to present an overview of the recent advances made in the field of DESs. Through selected examples, we will show that DESs are particularly promising for the design of innovative catalytic processes, the preparation of new materials and novel structures, the dissolution of valuable substrates and also in the field of electrochemistry.[19] In all these DES-based processes, we will try to demonstrate that use of DESs not only allows the design of safer processes but also provides a straightforward access to new chemicals and materials.

PHYSICOCHEMICAL PROPERTIES OF DEEP EUTECTIC SOLVENTS

Similar to ILs, DESs are chemically tailorable solvents since they can be designed by properly combining various quaternary ammonium salts (e.g. CHCl) with different hydrogen bond donors (HBD). Hence, task- specific DESs with different physicochemical properties such as freezing point, viscosity, conductivity, and pH, among others, can be prepared. Owing to their promising applications, many efforts have been devoted to the physicochemical characterization of DESs. In this section, the main physicochemical properties of DESs will be described and discussed.[20]

Freezing Point (Tf)

As mentioned above, DESs are formed by mixing two solids capable of generating a new liquid phase by self- association via hydrogen bonds. This new phase is generally characterized by a lower freezing point than that of individual constituents. For instance, when CHCl and urea are mixed together in a molar ratio of 1: 2, the freezing point of the eutectic is 12°C, which is considerably lower than that of CHCl and urea (melting point of CHCl and urea are 302 and 133°C, respectively). The significant depression of the freezing point stems from an interaction between the halide anion and the hydrogen bond donor component, here urea. For all reported DESs, their freezing points are below 150°C. Generally, DESs with a freezing point lower than 50°C are more attractive since they can be used as inexpensive and safe solvents in many fields. Tables 5.1 list the freezing points of various DESs described in the literature.[21]

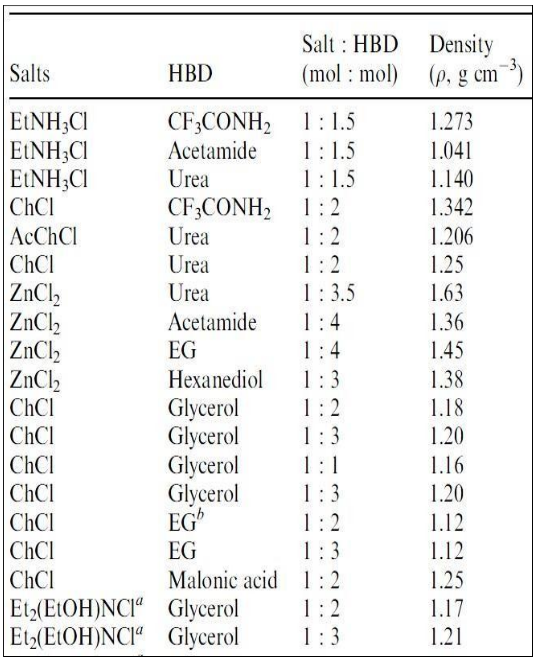
Table. Freezing point (Tf) of the reported DESs (Tm): melting point of pure HBD.

Hydrogen Bond Donor (HBD)	CHCl : HBD (Molar Ratio)	Tm / °C	Tf / °C
Urea	1: 2	134	12
Thiourea	1: 2	175	69
Acetamide	1: 2	80	51
Benzamide	1: 2	129	92
Ethylene glycol	1: 2	-12.9	-66
Glycerol	1: 2	17.8	-40
Imidazole	3:7	89	56
Benzoic acid	1:1	122	95
Citric acid	1:1	149	69
Oxalic acid	1:1	190	34
Phenylacetic acid	1:1	77	25
Succinic acid	1:1	185	71
Resorcinol	1:4	110	87

Density

The density is one of the most important physical properties for a solvent. Generally, densities of DESs are determined by means of a specific gravity meter. Table 5.2 lists the density data of common DESs. Most of DESs exhibit higher densities than water. For instance, type IV $ZnCl_2$– HBD eutectic mixtures have densities higher than 1.3 g cm^3. Among them, density of $ZnCl_2$–urea (1: 3.5) and $ZnCl_2$–acetamide (1 : 4) are different (1.63 and 1.36 g cm3, respectively). This notable difference of density might be attributed to a different molecular organization or packing of the DES.[22] Note that densities of both DESs are higher than those of pure HDBs (acetamide: 1.16 and urea: 1.32 g cm^3). This phenomenon may be explained by the hole theory. Similar to imidazolium-based ILs, DESs are composed of holes or empty vacancies. When $ZnCl_2$ was mixed with urea for instance, the average hole radius was decreased, resulting in a slight increase of the DES density as compared to that of neat urea.[23-24]

Table. Densities of common DESs at 25°C.



Salts	HBD	Salt : HBD (mol : mol)	Density (ρ, g cm^{-3})
$EtNH_3Cl$	CF_3CONH_2	1 : 1.5	1.273
$EtNH_3Cl$	Acetamide	1 : 1.5	1.041
$EtNH_3Cl$	Urea	1 : 1.5	1.140
ChCl	CF_3CONH_2	1 : 2	1.342
AcChCl	Urea	1 : 2	1.206
ChCl	Urea	1 : 2	1.25
$ZnCl_2$	Urea	1 : 3.5	1.63
$ZnCl_2$	Acetamide	1 : 4	1.36
$ZnCl_2$	EG	1 : 4	1.45
$ZnCl_2$	Hexanediol	1 : 3	1.38
ChCl	Glycerol	1 : 2	1.18
ChCl	Glycerol	1 : 3	1.20
ChCl	Glycerol	1 : 1	1.16
ChCl	Glycerol	1 : 3	1.20
ChCl	EG^b	1 : 2	1.12
ChCl	EG	1 : 3	1.12
ChCl	Malonic acid	1 : 2	1.25
$Et_2(EtOH)NCl^a$	Glycerol	1 : 2	1.17
$Et_2(EtOH)NCl^a$	Glycerol	1 : 3	1.21

The organic salt/HBD molar ratio also has an obvious effect on the densities of DES. Figure 5.1 shows the density of a glycerol/CHCl DES as a function of the molar composition.

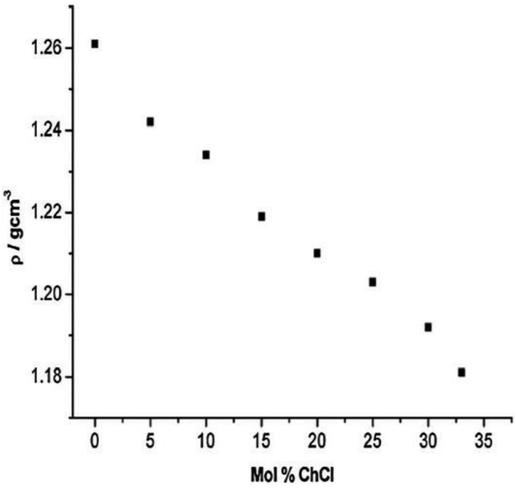


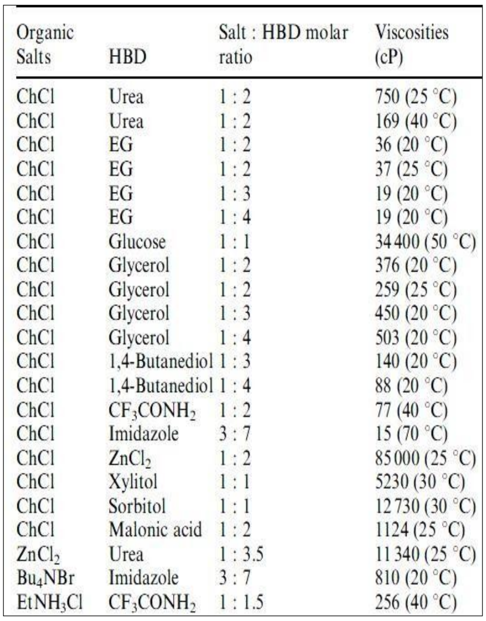
Figure. Densities of Glycerol/ CHCl DESs.

Viscosity

Like most of the ILs, viscosity of DESs is an important issue that needs to be addressed. Except for CHCl–ethylene glycol (EG) eutectic mixture, most of the DESs exhibit relatively high viscosities (>100 cP) at room temperature. The high viscosity of DESs is often attributed to the presence of an extensive hydrogen bond network between each component, which results in a lower mobility of free species within the DES. The large ion size and very small void volume of most DESs but also other forces such as electrostatic or van der Waals interactions may contribute to the high viscosity of DES.[25]

Owing to their potential applications as green media, the development of DESs with low viscosities is highly desirable. In general, viscosities of eutectic mixtures are mainly affected by the chemical nature of the DES components (type of the ammonium salts and HBDs, organic salt/HBD molar ratio, etc.), the temperature, and the water content. As discussed above, viscosity of DES is also dependent on the free volume. Hence, the hole theory can also be used to design DESs with low viscosities. For instance, use of small cations or fluorinated hydrogen- bond donors can lead to the formation of DES with low viscosity. Viscosity of binary eutectic mixtures is essentially governed by hydrogen bonds, van der Waals and electrostatic interactions. Table 5.3 lists the viscosity data of common DESs at different temperatures.

Table. Viscosities of selected DESs at different temperatures.

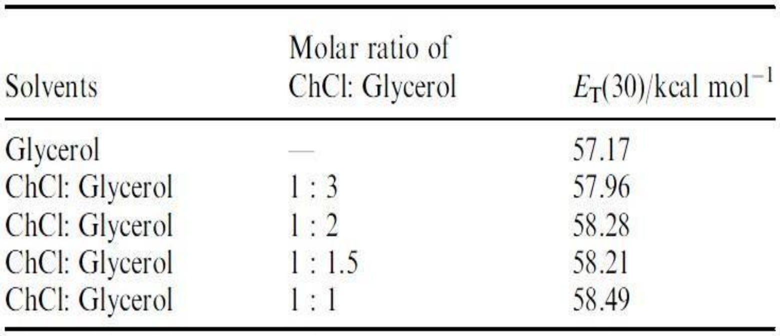


Organic Salts	HBD	Salt : HBD molar ratio	Viscosities (cP)
ChCl	Urea	1 : 2	750 (25 °C)
ChCl	Urea	1 : 2	169 (40 °C)
ChCl	EG	1 : 2	36 (20 °C)
ChCl	EG	1 : 2	37 (25 °C)
ChCl	EG	1 : 3	19 (20 °C)
ChCl	EG	1 : 4	19 (20 °C)
ChCl	Glucose	1 : 1	34 400 (50 °C)
ChCl	Glycerol	1 : 2	376 (20 °C)
ChCl	Glycerol	1 : 2	259 (25 °C)
ChCl	Glycerol	1 : 3	450 (20 °C)
ChCl	Glycerol	1 : 4	503 (20 °C)
ChCl	1,4-Butanediol	1 : 3	140 (20 °C)
ChCl	1,4-Butanediol	1 : 4	88 (20 °C)
ChCl	CF_3CONH_2	1 : 2	77 (40 °C)
ChCl	Imidazole	3 : 7	15 (70 °C)
ChCl	$ZnCl_2$	1 : 2	85 000 (25 °C)
ChCl	Xylitol	1 : 1	5230 (30 °C)
ChCl	Sorbitol	1 : 1	12 730 (30 °C)
ChCl	Malonic acid	1 : 2	1124 (25 °C)
$ZnCl_2$	Urea	1 : 3.5	11 340 (25 °C)
Bu_4NBr	Imidazole	3 : 7	810 (20 °C)
$EtNH_3Cl$	CF_3CONH_2	1 : 1.5	256 (40 °C)

Polarity

Generally, polarity of a solvent can be evaluated by its polarity scale, ET 30), which is the electronic transition energy of a probe dye (e.g. Reichardt's Dye 30) in a solvent. By means of UV-visible technology and using Reichardt's Dye 30. In Table 5.4, the polarity data of various CHCl$^-$glycerol eutectic mixtures using the Reichardt's Dye method are summarized.

Table 5.4 Solvent polarity parameters of various CHCl– glycerol mixtures.



Solvents	Molar ratio of ChCl: Glycerol	$E_T(30)$/kcal mol^{-1}
Glycerol	—	57.17
ChCl: Glycerol	1 : 3	57.96
ChCl: Glycerol	1 : 2	58.28
ChCl: Glycerol	1 : 1.5	58.21
ChCl: Glycerol	1 : 1	58.49

These results show that CHCl/glycerol DESs exhibit similar polarity to those of $RNH_3{}^+X\_$ and $R_2NH_2{}^+X\_$ ILs bearing discrete anions. Clearly, an increase in the CHCl/glycerol molar ratio results in an increase of the ET (30) of the DES.

Additionally, a roughly linear increase of ET (30) with the CHCl concentration was observed.[26]

Acidity or alkalinity

The Hammett function has been widely used to evaluate the acidity and basicity of nonaqueous solvents by determining the ionization ratio of indicators in a system. For a basic solution, the Hammett function measures the tendency of the solution to capture protons. When weak acids are chosen as indicators, the Hammett function H_ is defined by the following equation.[27]

$H\_=pK(HI)+\log([I^-]/[HI])$

Where pK(HI) is the thermodynamic ionization constant of the indicator in water, $[I^-]$ and [HI] represent the molar concentrations of anionic and neutral forms of the indicator, respectively. A medium with large H_ value has strong basicity.

When 4-nitrobenzylcyanide was used as indicator, the H_ value of the CHCl/urea (1: 2) DES was 10.86, suggesting that this DES is weakly basic.[28-29]

Surface Tension

Up to now, studies related to the surface tension of DESs have been very scarce.

Abbott et al. reported some data about the surface tension of CHCl-based and $ZnCl_2$-based DESs. Surface tensions of CHCl/malonic acid (1:1) and CHCl/phenylacetic acid (1:2) DESs were about 65.68 and 41.86 mN $m^{-}1$, respectively.[30]

Surface tension is also expected to follow a similar trend to viscosity since it strictly depends on the strength of intermolecular interaction that governs the formation of DESs. In particular, the surface tensions of various CHCl/glycerol DESs showed a linear correlation with temperature.[27] Additionally, surface tension of the CHCl/glycerol DES decreases as the CHCl concentration increases, supporting that addition of CHCl to glycerol disrupts the extensive hydrogen bond network of glycerol, as previously discussed for viscosity.[31]

APPLICATIONS OF DES

Dissolution and Separation in DESs

1. CO2 solubility

It is now well established that many ILs have strong ability to dissolve CO2. Similar to ILs, DESs consist predominantly of ionic species, and thus also have interesting solvent properties for high CO2 dissolution.[32] Considering that combination of CO2 with green DES systems has a great potential for a variety of chemical processes (separation and purification of gas, chemical fixation of CO2, catalysis, etc.), studies on the CO2 solubility in DESs are of prime importance.[33]

2. Dissolution of metal oxides

DESs are capable of donating or accepting electrons or protons to form hydrogen bonds which confers them excellent dissolution properties. More interestingly, DESs are also capable of dissolving various metal oxides, thereby opening a ‘green’ strategy for the separation and recycling of metals, a key point in electrochemistry technology. The dissolution and solubility of metal oxides in DESs still remain poorly explored due to the lack of data in comparable systems. Abbott et al. first demonstrated the possibility of using DESs for the dissolution of metal oxides. Oxides such as aluminates or silicates are, however, insoluble in tested DESs. This difference of solubility of metal oxides in DESs can be used for the selective recovery of metals. Note that metals such as copper can be recovered electrochemically from the DES with high current efficiencies using bulk electrolysis.[34]

3. Drug Solubilization

To date, explorations of the solubility properties of DESs were mainly focusing on the dissolution of metal oxides. Studies on the dissolution of organic macromolecules in DESs are very scarce. Morrison et al. investigated the dissolution of several poorly soluble drugs including benzoic acid, griseofulvin, danazol, itraconazole and N-[4-[[6-[4-(trifluoromethyl)phenyl]- 4pyrimidinyl]oxy]-2- benzothiazolyl]acetamide (AMG517) in ChCl/urea and ChCl/malonic acid DESs. In the case of aqueous solution of DES, solubility of drugs was also enhanced as compared to neat water. Owing to their low toxicity, DESs are now emerging as promising vehicles for oral dosing of rats during the early development of pharmacokinetic investigations. Moreover, it is noteworthy that recently the DESs have also been proven to be promising anhydrous solvents for nucleic acids. Hud and coworkers39 showed that the nucleic acids can form several secondary structures that are reversibly denatured upon heating in DESs. In our opinion, this work definitely provides a new concept to widen the scope of DESs for life science.[35]

4. Catalysis in DESs

In the field of catalysis, the choice of the solvent is crucial. The solvent not only allows a better contact between reactants and catalysts but also determines the choice of work-up procedures and recycling (including the catalyst) or disposal strategies. In this context, the search of cheap and safe media for catalysis has become a very important topic. Recently, ILs have received considerable attention, especially for the stabilization of nanoparticles, the immobilization of homogeneous catalysts, the catalytic conversion of renewable raw materials (i.e. biomass, CO2), among others. Comprehensive reviews covering this topic can be found in the current literature. Although fascinating results have been reported, ecological and economical footprint of these ILs- based processes still remains at an unacceptable level for an industrial application. As mentioned earlier, DESs exhibit similar properties to ILs.

Hence, much effort is devoted to the use of DESs as cheap and safe solvents for catalysis.[36]

5. Organic Synthesis in DESs

In the field of organic synthesis, the search for a green solvent is also of great interest and aims at reducing the use of toxic chemicals. In this context, Gore et al. reported the multicomponent synthesis of valuable biologically active dihydropyrimidinone (DHPM) in acidic DESs.

Multicomponent reaction can also take place in other carbohydrate- derived melts. In this context, Zhang et al. reported the synthesis of quinazoline derivatives via a one-pot three component reaction of 2- aminoaryl ketones, aldehydes and ammonium acetate in various carbohydrate-derived melts.[37]

6. Electrochemistry in DESs

The earliest research studies on ionic fluids started with the purpose of electrochemical application, viz. Humphrey Davy's pioneering works on the electrodeposition of simple molten salts. Due to their unique properties, ILs found a wide range of applications in various electrochemical devices including for instance lithium ion batteries, fuel cells, super capacitors, dye sensitized solar cells, etc. Similar to ILs, DESs were also used in electrochemistry as electrolytes for electrodeposition of metal, as solvents for electrochemistry reaction and for electropolishing (metal dissolution), etc.[38]

7. Preparation of materials in DESs Conventional preparation of inorganic materials often takes place in water or organic solvents, using in many cases the thermal step for crystallization and structure formation. The 'solvothermal synthesis' then consists in growing single crystals from a non-aqueous solution, by thermal treatment under pressure. Recently, the ionothermal synthesis, a new synthetic strategy involving predominantly ILs or deep eutectic solvents (DESs) as solvent, has been developed. In these syntheses, ILs or DESs can be used as both solvent and template (also called structure-directing agents).[39] In solvothermal reactions where solvents are predominantly volatile molecules, the high temperature required for crystallization or pore structure formation needs the use of autoclaves. Contrarily, ionothermal synthesis can be readily conducted in a lowpressure environment (e.g. under ambient pressure) due to the low volatility of ILs or DESs. The use of such solvents thereby reduces all security risks arising from the use of low boiling point solvents and simplifies the synthesis process. More importantly, the possibility to tune the ionic nature of DESs provides modulating reaction environments under which novel materials with useful structures (surface properties and porosity) may be produced. Nowadays, the iono thermal synthesis is gaining considerable attention. In this context, a newly emerging trend of this field consists in the replacement of ILs by cheap and safe DESs.[40]

SUMMARY AND CONCLUSION

This work reveals that the deep eutectic solvents have great significance in pharmaceutical preparations, the room temperature ionic liquids which are used in older days are highly expensive, toxic and are also incompatible with several active ingredients to overcome these problems a novel solvent system is derived from the ionic liquids known as deep eutectic solvents. Formation of these DESs can be obtained by simply mixing together two safe components (cheap, renewable and biodegradable), which are capable of forming a eutectic mixture.one of the most common DESs is choline chloride (ChCl). ChCl is a very cheap, biodegradable and non-toxic.

Deep eutectic solvents acting as solvents of active pharmaceutical ingredients (API – DES) emerged as promising alternatives to improve therapeutic efficiency, with additional possibility to integrate them in biopolymer-based system to enhance their delivery. These strategies avoid a current major concern related to drugs and APIs, i.e. polymorphism, and increase the solubility and to increased bioavailability. Owing to their composition versatility, polymerizable.

API-DES can also be prepared. The relatively easy preparation of API-DES and their capacity to tune the API's release profile when incorporated in (bio) polymer-based systems represent an effective alternative to improve the APIs therapeutic action and to develop controlled drug delivery systems. Here on this review also tries to reveal that the ILs and DES both have relation with each other but also DESs have different application and is prominent over the ILs, because of its high compatibility with active ingredients. From the above described results, it clearly appears that DESs exhibit close physico-chemical properties (viscosity, density, conductivity, among others) to those of traditional ILs. Additionally, like ILs, the physico-chemicals properties of DESs can be tuned almost infinitely by changing the nature of the quaternary ammonium salt and the hydrogen-bond donor, making possible the preparation of task-specific DESs. As compared to ILs, DESs have however notable advantages stemming from (1) their convenient synthesis (100% atom economy), (2) their very low price since most of DESs can be prepared from readily accessible chemicals and (3) their low toxicity, especially DESs derived from ChCl and renewable chemicals. Clearly, these notable ecological and economic advantages of DESs now open alternative routes for the emergence of ionic fluids at a larger scale.

This work also reveals that the excellent dissolution properties for CO2, inorganic salts, and organic molecules, many DESs can also selectively dissolve different metal oxides, which thus provide great potential for the selective recovery of pure metals, especially in electrochemistry. In the particular field of metal electro deposition, similar result those reported in conventional ILs where obtained in DESs.

These findings state that the DESs have much more application in the solubilization of active ingredients. It also acts as a new key that enables the access to the controlled release and targeted drug delivery systems.

Despite all these promising applications, much effort is still needed in order to widen the utilization DESs in chemistry. For instance, the in stability of DESs during electrochemical processes still represents an important issue that needs to be addressed in the future.

REFERENCES

1. L. A. Blanchard, D. Hancu, E. J. Beckman, J. F. Brennecke, Nature, 1999; 399: 28–29.
2. G. T. Wei, Z. Yang, C. Y. Lee, H. -Y. Yang, C. R. C. Wang, J. Am. Chem. Soc., 2004; 126: 5036–5037.
3. H. Itoh, K. Naka, Y. Chujo, J. Am. Chem. Soc., 2004; 126: 3026–3027.
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. Abbott, A. P.; Capper, G.; Davies, D. L.; Rasheed, R. K.; Tambyrajah, V. Novel solvent properties of choline chloride/ureamixtures. Chem. Commun, 2003; 70−71.
7. Kanchanomai, C.; Miyashita, Y.; Mutoh, Y. Strain-rate effects onlow cycle fatigue mechanism of eutectic Sn−Pb solder. Int. J. Fatigue, 2002; 24: 987−993.
8. Chen, N.; Morikawa, J.; Hashimoto, T. Effect of cryoprotectantson eutectics of NaCl·2H2O/ice and KCl/ice studied by temperaturewave analysis and differential scanning calorimetry. Thermochim. Acta, 2005; 431: 106−112.
9. Buckley, M. M.; Paul, B. Eutectic lidocaine/prilocaine cream. Areview of the topical anaesthetic/analgesic efficacy of a eutecticmixture of local anaesthetics (EMLA). Drugs, 1993; 46: 126−151.
10. Petrova E. Innovation in the pharmaceutical industry: the process of drug discovery and development. In Innovation and Marketing in the Pharmaceutical Industry. Ding M, Eliashberg J, Stremersch S, editors. chapter 2. NewYork: Springer Science+Business Media, 2014; 19-81.
11. Kalepu S, Nekkanti V. Insoluble drug delivery strategies: review of recent advances and business prospects. Acta Pharm Sin B., 2015; 5: 442–453.
12. Welton, T. Room-temperature ionic liquids. solvents for synthesisand catalysis. Chem. Rev., 1999; 99: 2071−2084.

13. Wasserscheid, P.; Keim, W. Ionic liquids New “solutions” fortransition metal catalysis. Angew. Chem., Int. Ed., 2000; 39: 3772−3789.
14. Abbott, A. P.; Capper, G.; Davies, D. L.; Munro, H. L.; Rasheed, R. K.; Tambyrajah, V. Preparation of novel, moisture-stable, Lewis-acidic ionic liquids containing quaternary ammonium salts withfunctional side chains. Chem. Commun, 2001; 2010−2011.
15. Ana Rita, Alexandre Paiva: European journal of pharmaceutical and biopharmaceutics, 2017; 114: 296-304.
16. S. Tang, A. Gary, Baker and H. Zhao, Chem. Soc. Rev., 2012; 41: 4030– 4066.
17. Abbott, A. P.; Capper, G.; Swain, B. G.; Wheeler, D. A. Trans. Inst. Met. Finish, 2005; 83: 51.
18. Sk Saddam Hossain, Sneha Paul, Anunay Samanta. Liquid Structure and Dynamics of Tetraalkylammonium Bromide-Based Deep Eutectic Solvents: Effect of Cation Chain Length. The Journal of Physical Chemistry B, 2019; 123(31): 6842-6850.
19. S. Tang, A. Gary, Baker and H. Zhao, Chem. Soc. Rev., 2012; 41: 4030– 4066.
20. A. P. Abbott, D. Boothby, G. Capper, D. L. Davies and R. K. Rasheed, J. Am. Chem. Soc., 2004; 126: 9142–9147.
21. A. P. Abbott, J. C. Barron, K. S. Ryder and D. Wilson, Chem.–Eur. J., 2007; 13: 6495– 6501.
22. K. Shahbaz, S. Baroutian, F. S. Mjalli, M. A. Hashim and I. M. AlNashef, Thermochim. Acta, 2012; 527: 59–66.
23. K. Shahbaz, F. S. Mjalli, M. A. Hashim and I. M. AlNashef, Thermochim. Acta, 2011; 515: 67–72.
24. A. P. Abbott, G. Capper and S. Gray, Chem Phys Chem, 2006; 7: 803–806.
25. A. P. Abbott, R. C. Harris, k. S. Ryder, C. D’Agostino, L. F. Gladden and M. D. Mantle, Green Chem., 2011; 13: 82–90.
26. M. A. Kareem, F. S. Mjalli, M. A. Hashim and I. M. AlNashef, J. Chem. Eng. Data, 2010; 55: 4632–4637.
27. W. Li, Z. Zhang, B. Han, S. Hu, J. Song, Y. Xie and X. Zhou, Green Chem., 2008; 10: 1142–1145.
28. Z. Maugeri and P. Domı´nguez de Marı´a, RSC Adv., 2012; 2: 421–425.
29. A. P. Abbott, R. C. Harris and K. S. Ryder, J. Phys. Chem. B, 2007; 111: 4910–4913.
30. A. P. Abbott, R. C. Harris, k. S. Ryder, C. D’Agostino, L. F. Gladden and M. D. Mantle, Green Chem., 2011; 13: 82–90.
31. X. Li, M. Hou, B. Han, X. Wang and L. Zou, J. Chem. Eng. Data, 2008, 53, 548–550.

32. W. C. Su, D. S. H. Wong and M. H. Li, J. Chem. Eng. Data, 2009; 54: 1951–1955.
33. J. M. Rimsza and L. R. Corrales, Comput. Theor. Chem., 2012; 987(1): 57–61.
34. I. Mamajanov, A. E. Engelhart, H. D. Bean and N. V. Hud, Angew. Chem., Int. Ed., 2010; 49: 6310–6314.
35. S. B. Phadtare and G. S. Shankarling, Green Chem., 2010; 12: 458–462.
36. N. Azizi, E. Batebi, S. Bagherpour and H. Ghafuri, RSC Adv., 2012; 2: 2289–2293.
37. P. Cojocaru, L. Magagnin, E. Gomez and E. Valle´ s, Mater. Lett., 2011; 65: 3597– 3600.
38. E. R. Parnham, P. S. Wheatley and R. E. Morris, Chem. Commun., 2006; 380–382.
39. (a) L. Cammarata, S. G. Kazarian, P. A. Salter and T. Welton, Phys. Chem. Chem. Phys., 2001; 3: 5192–5200; (b) C. G. Hanke and R. M. Lynden Bell, J. Phys. Chem. B, 2003; 107: 10873–10878.