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Review

Research Progress on Deep Eutectic Solvents and Recent Applications

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Abstract: In this study, the classification, composition, preparation methods, and performance parameters of deep eutectic solvents (DESs) and their recent applications in natural product extraction, drug delivery systems, trace metal determination, nanomaterial synthesis, and electrochemistry are systematically summarised through the literature of recent decades, using DESs and applications as keywords. The hydrogen bond acceptors (HBA) of DESs are mainly quaternary ammonium salts (e.g., choline chloride) or amphoteric ions (e.g., betaine); the hydrogen bond donors (HBD) are mostly compounds such as urea, polyols, and sugars. Their melting points are related to hydrogen bonding, their polarities are higher than most ionic liquids, and their viscosities are generally in the range of 0.01–5 Pa·s. Compared with traditional organic solvents and conventional ionic liquids, DESs have higher solubility, with their ability to dissolve metal oxides and insoluble drugs, and have good biodegradability. DESs have high extraction rates in flavonoids and phenols, can increase drug solubility in drug delivery systems, can effectively extract and perform pre-concentration of metals in trace metal determination, can synthesise new nanomaterial, and can be used as electrolytes for electrochemical reactions in electrochemistry. This paper collates the relevant literature on the physicochemical properties and multi-field applications of DESs, which provides a deeper understanding of DESs and looks forward to the future development of DESs

Keywords: deep eutectic solvents; properties; applications

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1. Introduction

With the introduction of the concept of "green chemistry", green solvents have attracted the attention of researchers. Compared with green solvents, traditional organic solvents (e.g., methylene chloride and ethyl acetate) have disadvantages such as high volatility, toxicity and difficulty in recycling, and improper use causing pollution or even endangering people's health, which is not in line with the concept of green chemistry.

To find a "green and designable" chemical reaction medium that can replace traditional organic solvents, ionic liquids have gradually become a research hotspot [1]. Ionic liquids have high thermal and chemical stability [2], strong electrical conductivity, low vapour pressure, and low flammability. Ionic liquids are safe compared to traditional organic solvents, yet they are difficult and more expensive to prepare. Most ionic liquids have high viscosity and density, and high viscosity ionic liquids are not conducive to the mass transfer process of the target substances during the extraction and separation of traditional Chinese medicine [3].

To address the shortcomings of organic solvents and ionic liquids, Abbott et al. [4] first proposed, in 2003, that choline chloride (hydrogen bond acceptor, HBA) and urea (hydrogen bond donor, HBD) could be co-blended in a 1:2 ratio to form "deep eutectic solvents (DESs)" with a melting point below that of the two single components [5]; this mixture could effectively solve the problems associated with conventional organic solvents. Therefore, DESs have replaced traditional organic solvents and ionic liquids and have been called the new green solvents. Analogous to ionic liquids, the physical and chemical properties of DESs depend on the selection of HBD and HBA components and their ratio [6], yet DESs are superior to ionic liquids in some parameters. For example, DESs have the properties of low vapour pressure, solubility, and electrochemically stable plasma liquid, and have the unique properties of simple preparation, non-toxicity, and biodegradability [5]. The viscosity of DESs is lower than that of ionic liquids, mainly because DESs rely on hydrogen bonding, while ionic liquids rely on ion interaction. Therefore, DESs are widely used in the extraction of active ingredients from natural products, the preparation of nanomaterials, the determination of trace metals, and electrochemistry.

This paper describes the latest research results on the classification, composition, preparation, physical and chemical properties, and application of DESs.

2. Classification of DESs

DESs are a novel eutectic hybrid solvent formed by the complexation of HBAs and HBDs. HBDs include urea, carboxylic acids, polyols, amino acids, and sugars. HBAs are mainly quaternary ammonium salts (e.g., choline chloride), amphoteric ions (e.g., betaine), or their hydrochloride salts. So far, DESs are roughly divided into the following five types: (1) The combination of quaternary ammonium salts with metal chlorides, such as choline ferric chloride or choline chloride–aluminium chloride [7]; (2) The combination of a quaternary ammonium salt and hydrated metal chloride, such as choline chloride–cobalt chloride [8] in aqueous solution; (3) A mixture of quaternary ammonium salts and small organic molecules, such as choline chloride–urea; (4) Mixtures of metal chloride hydrates and an organic HBD, such as copper chloride–fructose [9]; (5) A mixture of non-ionic, molecular HBA and an HBD, such as 4-nitrophenol–menthol [10,11].

3. Composition of DESs

In recent years, DESs have been successfully used in natural material extraction, drug delivery, metal determination, nanomaterial preparation, electrochemistry and other fields. Choline chloride is a cheap, biodegradable (more than 93% in 14 days) compound with very low acute toxicity, making it the most widely used HBA while facilitating the recycling of DESs. There are many types of HBDs, and the exploration of DESs prepared by different HBDs still needs to be deepened. Some common DES compositions are shown in Table 1.

Table 1. Common deep eutectic solvents (DESs) components.

HBA	HBD	Mole Ratio (HBD:HBA)	References
Choline chloride	Ethylene glycol	1:2	[12]
Choline chloride	Oxalic acid	1:1	[13]
Choline chloride	Lactic acid	1:2	[14]
Choline chloride	Formic Acid	1:2	[15]
Choline chloride	Urea	1:2	[16]
Choline chloride	Citric Acid	1:1	[16]
Choline chloride	Malic acid	1:2	[14]
Choline chloride	Fructose	1:1	[14]
Tetrabutylammonium bromide	Imidazole	3:7	[16]
Methyltriphenylphosphonium bromide	Glycerol	1:3	[16]
Methyltriphenylphosphonium bromide	Triethylene glycol	1:5	[16]
Methyltriphenylphosphonium bromide	Ethylene glycol	1:4	[16]
Ethylamine chloride	Urea	1:1.5	[16]
Ethylamine chloride	Acetamide	1:1.5	[16]
Betaine	Ethylene glycol	1:2	[14]
Betaine	Fructose	1:1	[14]
Betaine	Malic Acid	1:1	[13]
Betaine	Maleic acid	1:2	[13]
Betaine	Xylitol	1:1	[13]

4. Preparation of DESs

DESs can be obtained by the following six methods of preparation:

(1) Heated and stirred method refers to mixing an HBA and an HBD to form a homogeneous liquid. This method is fast, simple to operate, does not require additional solvents, and does not produce by-products. Fernandes et al. [17] prepared several acidic DESs by the heating and stirring method and screened out the DESs for lignin extraction from sea pine wood chips. From the screening results of DESs, the extraction performance of chloro-based DESs is significantly better than that of betaine- or urea-based DESs. In addition, the molar ratio of HBAs and HBDs in DESs was tested and optimised, and it was found that DESs containing a higher molar fraction of HBD had a higher extraction rate.

(2) Microwave irradiation method has green advantages such as short synthesis time and low energy consumption compared with the traditional heating and stirring process. Gomez et al. [18] used microwave-assisted synthesis of several natural DESs. The microwave radiation method shortened the synthesis time to 20 s and reduced the energy consumption by 650 times.

(3) Freeze-drying method refers to mixing two or more ingredients and dissolving them in water, pre-freezing them at low temperatures, and then freeze-drying them. This method is widely used for its ease of production and speed. Liu et al. [19] mixed choline chloride with an aqueous urea solution and freeze-dried it to obtain viscous and transparent DESs. Chen et al. [20] mixed glycerol and amino acids and dissolved them in water, pre-froze them at low temperature for 0.5–1 h, and then freeze-dried them for 8–12 h to obtain glycerol–amino acid DESs.

(4) Grinding method refers to mixing HBAs and HBDs and then grinding them to form a clear liquid. Florindo et al. [21] used two different synthetic methods, heating and grinding, to prepare DESs using choline chloride as the HBA and several carboxylic acids (levulinic acid, glutaric acid, malonic acid, oxalic acid, and glycolic acid) as HBDs.

(5) Vacuum evaporation method involves dissolving a component with a known molar ratio in water, evaporating it under reduced pressure at 50 °C, and storing it in a silica gel desiccator to obtain constant weight DESs. This method can handle thermosensitive materials that tend to decompose at high temperatures and can use a low-temperature heat source to reduce energy consumption. Huang et al. [22] dissolved the HBD fraction and the HBA fraction in proportion to each other in water, evaporated under reduced pressure at 50 °C, and then stored in a desiccator until a constant weight liquid was obtained, after which 22 different natural deep eutectic solvents (NADESs) were systematically screened for ultrasound-assisted extraction of active ingredients from the widely used Chinese herbal plant salvia miltiorrhiza.

(6) Ultrasonication method refers to forming a homogeneous mixture of HBAs and HBDs after a mixed ultrasonication reaction. Wang's team synthesised choline chloride–glycerol using ultrasonication-assisted and stirring–heating methods, and used choline chloride–glycerol combined using ultrasonication for efficient extraction of glycosides from lilac [23].

5. Properties of DESs

5.1. Melting Point of DESs

The melting point (mp) of DESs is the temperature at which the solid raw material melts to form DESs, and the melting point determines the minimum temperature of DESs [24]. After mixing an HBA with an HBD, the melting point of the component mixture is lower than that of the single component. The lower melting point is mainly due to the hydrogen bonding between the HBD and HBA, which inhibits the precipitation of solids. Abbott et al. [4] found that a eutectic occurs when choline chloride and urea are mixed at a ratio of 1:2. The melting point of the eutectic mixture is 12 °C, which is much lower than that of any single component (choline chloride mp = 302 °C, urea mp = 133 °C). Abbott et al. found that the decrease in the melting point was related to anions and cations; the symmetry of the cation decreases, and the melting point of the mixture decreases. When combined with urea, the melting point of monovalent anion choline salt and urea decreased in the order of $F^- > NO_3^- > Cl^- > BF_4^-$, which was related to the strength of the hydrogen bond. The lower the melting point of the liquid used in the extraction or separation process, the more favourable the mass transfer process of the target substance. Pang et al. [25] found that quaternary ammonium salts can combine with phenolic compounds in oil at room temperature to form DESs that are insoluble in the oil phase, thereby achieving the separation of phenolic compounds from oil. DES separation methods avoid the disadvantages of using strong acid and strong alkali aqueous solutions in the traditional method (alkali washing method) and mutual dissolution in the organic solvent method; additionally, the extraction efficiency is high and the extractant can be reused. Therefore, DESs have a wide range of application prospects in the extraction and separation of substances. Common DES melting points are shown in Table 2.

Table 2. Melting point of DESs.

No.	DESs Type	Melting Point/°C	References
1	Choline chloride: Urea (1:2)	12.00	[26]
2	Choline chloride: Ethylene glycol (1:2)	−66.00	[27]
3	Choline chloride: Imidazole (3:7)	56.00	[26]
4	Choline chloride: Malonic acid (1:1)	10.00	[26]
5	Choline chloride: Acrylic acid (1:1.6)	Liquid (25.00 °C)	[26]
6	Choline chloride: 1,4-butanediol (1:3)	−32.00	[26]
7	Choline chloride: Trifluoromethylamide (1:2)	51.00	[26]
8	Choline chloride: 2,2,2-trifluoroacetamide (1:2)	Liquid (25.00 °C)	[26]
9	Methyltriphenylphosphonium bromide: Glycerol (1:3)	−5.55	[28]
10	Methyltriphenylphosphonium bromide: Ethylene glycol (1:4)	−49.34	[28]
11	Methyltriphenylphosphonium bromide: Triethylene glycol (1:5)	−21.00	[28]

5.2. Polarity and Viscosity of DESs

Polarity is an important parameter of solvents. The polarity of a solvent can be assessed by the empirical parameter of solvent polarity (ET(30)), which is the electron leap energy of the fluorescent probe in the solvent (Rechard Fluorescence 30), which can be measured by using a Rechard Fluorescence 30 with UV–Vis technology. DESs have higher polarity values than most ionic liquids, with glycerol-based DESs being the highest, followed by ethylene glycol, and then urea [29]. The types of HBD and HBA components are important factors affecting the polarity of DESs. For example, the DESs of choline chloride are less polarised than those of betaine [30].

The viscosity of DESs is similar to that of ionic liquids, mainly due to the presence of sufficiently large ions in their structure, the small pore volume, and the effect of forces such as van der Waals and electrostatic forces. The viscosity of DESs is generally in the range of 0.01–5 Pa·s and is higher than that of the molecular solvent ethanol [31]. Abbott et al. [4] found that the viscosity of DESs is influenced by the mobility, free volume, and surface tension of the ions, while the type of HBD, temperature, and moisture content also affect the viscosity of DESs. The Eyring and Vogel–Fulcher–Tamman (VFT) models were used to describe the temperature dependence of the dynamic viscosity of aqueous solutions of choline chloride as quaternary ammonium salt in the temperature range from 293.15 K to 363.15 K [32]. For instance, the viscosity of DESs depends closely on the nature of the HBD, and an increase in temperature increases the distance between anions and cations, making their interaction forces and vscosity decrease [33]. In the temperature range of 293.15–333.15 K, using choline chloride–ethylene glycol and choline chloride–1,2-propanediol as raw materials, with the molar ratio of HBA/HBD being 1:2 to 1:6 at 101.3 kPa, the viscosity decreases with the increase in temperature and the addition of HBD (ethylene glycol). The substitution of the HBD in DESs by HBDs with longer carbon chains increases their viscosity at constant temperature [34]. Therefore, hydrophilic DESs usually reduce their viscosity by decreasing surface tension, increasing temperature, and adding a certain amount of water. The polarity and viscosity of 10 groups of DESs are shown in Table 3, as verified by the preliminary experiments of our group.

Table 3. Polarity and viscosity of DESs.

No.	DESs Type	Water Content	Polarity	Viscosity (Pa·s)
1	Choline chloride: Lactic acid	20%	48.09	0.02530
2	Choline chloride: Ethylene glycol	20%	48.54	0.01270
3	Choline chloride: Fructose	20%	58.17	0.04800
4	Choline chloride: Xylitol	20%	48.41	0.03500
5	Betaine: L-proline	20%	60.44	0.03720
6	Betaine: L-ascorbic acid	20%	48.37	0.15400
7	Betaine: Fructose	20%	58.70	0.01890
8	Betaine: Malic acid	20%	48.29	0.01490
9	Betaine: Maleic acid	20%	59.56	0.00940
10	Betaine: Xylitol	20%	60.57	0.01710

5.3. Surface Tension of DESs

So far, there are few studies on the surface tension of DESs. Surface tension also follows a similar trend to viscosity because it strictly depends on the intermolecular forces that control the formation of DESs, and the presence of hydroxyl groups leads to greater surface tension. The longer the alkyl chain in HBD, the greater the surface tension of DESs. The surface tension of DESs shows a linear correlation with temperature, and the surface tension decreases with the increase in temperature. With the increase in salt mole fraction, the surface tension decreases and the viscosity also decreases, which is due to the added ammonium salt breaking the hydrogen bond network structure. Abbott et al. [4] reported the surface tension of some DESs based on choline chloride and zinc chloride. At room temperature, the surface tensions of choline chloride/malonic acid (1:1) and choline chloride/phenylacetic acid (1:2) are about 65.68 and 41.86 mN/m, respectively. The surface tension of zinc chloride/urea (1:3.5) is 72 mN/m, and zinc chloride/acetamide (1:4) has a smaller surface tension of 53 mN/m. These values are higher than the surface tension of most molecular solvents and imidazole ionic liquids at room temperature, but lower than the surface tension of high-temperature molten salts at 441–1395 K [35,36].

5.4. Solubility of DESs

Solubility refers to the ability of a solute substance to form a solution with another substance. DESs have high solubility and can dissolve metal oxides, insoluble drugs, carbon dioxide, cellulose, low-carbon alkanes, etc. Jin et al. [37] found that the solubilities of low-carbon alkanes C_3H_8 and CH_4 in ionic liquids was 0.408 mmol·g^{-1} and 0.029 mmol·g^{-1}, while the solubilities of C_3H_8 and CH_4 in 12 DESs (e.g., choline chloride–glycerol, choline chloride–ethylene glycol, choline–2,2,2-trifluoroacetamide chloride, etc.) were 0.308–0.516 mmol·g^{-1} and 0.024–0.035 mmol·g^{-1}, respectively, which are higher than that of all reported ionic liquids (e.g., 1-ethyl-3-methylimidazolium bis (trifluoromethanesulfonyl)imide salt, butylimidazolium tetrafluoroborate, etc.). The solubility of some DESs is shown in Table 4.

Table 4. DESs improve the solubility of substances.

No.	DESs Type	Mole Ratio	Solubility	References
1	Choline chloride: Glycolic acid: Oxalic acid	1:1.6:0.4	The solubility of itraconazole increased by 53,600 times.	[38]
2	Choline chloride: Ethanoic acid	1:1–1:4	The solubility of itraconazole increased by 7600 times.	[38]
3	Choline chloride: Ethanoic acid	1:1–1:4	The solubility of piroxicam increased by 430 times.	[38]

Table 4. *Cont.*

No.	DESs Type	Mole Ratio	Solubility	References
4	Choline chloride: Ethanoic acid	1:1–1:4	The solubility of posaconazole increased by 28 times.	[38]
5	Choline chloride: Ethanoic acid	1:1–1:4	The solubility of lidocaine increased by 6400 times.	[38]
5	Choline chloride: Ethylene glycol	Mixed	The solubility of coumarin increased by 80 times.	[39]
6	Lactic acid: Propyleneglycol	Mixed	Could dissolve spironolacton and trimethoprim at a concentration up to 50 and 100 mg/mL, respectively	[40]
7	Choline chloride: Glycerol	1:1	Compared to aqueous solutions, it is increased by 12,000 times	[41]

5.5. Biodegradability of DESs

DESs, known as "green solvents", are mostly biodegradable. Because most of the components that make up DESs are natural products, they can be degraded by different kinds of organisms in nature. Mbous et al. [42] found that glycerol was used as DESs, which can complete the final metabolism through glycolysis or glial cell formation. Pei et al. [43] found that the biodegradabilities of *N*,*N*-diethyl ethanol ammonium chloride (EAC): zinc nitrate hexahydrate (ZnN) and EAC: zinc chloride were different (about 80% vs. 62%) by studying the biodegradability of a metal salt and a hydrated metal salt. The biodegradability of the former is better than that of the traditional ionic liquid (77%). The study also found that the inherent structure sof the HBA and the HBD are critical factors in determining the biodegradability of different DESs.

6. Application of DESs

6.1. Application of DESs in Natural Product Extraction

The common natural products in nature are flavonoids, phenols, polysaccharides, lignins, alkaloids, volatile oils, etc. Research has confirmed that natural products have a wide range of pharmacological effects, such as anti-viral, anti-cancer, and slowing down aging, and have been widely used in many fields such as drug research and new drug development. Flavonoids have anti-oxidation, anti-cancer, anti-tumour, anti-allergy, liver protection, and other medicinal values, so the extraction of flavonoids has always been a research hotspot. The application of DESs in the extraction of flavonoids is shown in Table 5.

Table 5. Application of DESs in the extraction of flavonoids.

No.	DESs Type	Mole Ratio	The Sample	Extraction of Substances	References
1	80% Acetylcholine: Lactic acid aqueous solution	1:1	Green Tea	Total flavonoids	[44]
2	Choline chloride: 1,4-butanediol aqueous solution	1:5	*Cyclocarya paliurus (Batal.) Iljinskaja* Leaves	Kaempferol, quercetin	[45]
3	30% Choline chloride: Propylene glycol aqueous solution	1:4	*Pollen Typhae*	Quercetin, naringenin, kaempferol	[46]
4	55% Choline chloride: Malonic acid aqueous solution	1:2	*Ginkgo biloba* leaves	Proanthocyanidins	[47]
5	Choline chloride: Glucose	4:1	*Ampelopsis grossedentata* Leaves	Total flavonoids	[48]

Table 5. *Cont.*

No.	DESs Type	Mole Ratio	The Sample	Extraction of Substances	References
6	10% Choline chloride: Urea	1:2	*Moringa oleifera* leaves	Hyperoside, vitexin, quercetin, cynaroside, quercetin 3-β-D glucoside, kaempferol, luteolin, and taxifolin	[49]
7	Choline chloride: Malic acid	1:1	*Perilla* Leaves	Apigenin 7-*O*-caffeoylglucoside, scutellarein 7-*O*-diglucuronide, luteolin 7-*O*-diglucuronide, and scutellarein 7-*O*-glucuronide	[50]
8	Choline chloride: Lactic acid	2:1	*Ziziphi Spinosae*	Total flavonoids	[51]
9	Citric acid: Urea	1:2	*Lotus*	Astragalin, hyperoside, and isoquercitrin	[52]
10	Choline chloride: p-Toluenesulfonic acid	1:2	*Lycium barbarum* L. fruits	Prunetin, mulberry pigment, rutin	[53]

Phenolic compounds have been reported to have pharmacological effects such as antioxidant, antibacterial, anti-inflammatory, and antidiabetic. Ali [54] found that DESs/NADESs have high extraction efficiency for phenolic compounds and can replace toxic organic solvents. The solvent composition, component structure, molar ratio, extraction temperature, solid–liquid ratio, and water content of DESs/NADESs all had significant effects on the extraction of phenolic compounds. The application of DESs in phenolic extraction is shown in Table 6.

Table 6. Application in phenolics (or polyphenols) extraction.

No.	DESs Type	Mole Ratio	Extraction Site	Extraction of Substances	References
1	Choline chloride: Fructose/Organic acid/Urea	1:2	*Chokeberry*	Total phenols	[55]
2	Choline chloride: Malic acid	1:1	*Carya cathayensis Sarg*	Phenolic compounds	[56]
3	Choline chloride: Glycerol	1:2	Tea Seed Oil	Free phenol, bound phenol	[57]
4	Choline chloride: Malic acid	1:1	Cherry crumbs	Polyphenols	[58]
5	Choline chloride: Urea: H_2O	1:2:4	*Allium cepa* L. Skin	Phenolic compounds	[59]
6	α-Terpineol:1-octanoic acid	1:4	Environmental water samples	Phenolic substances	[60]
7	Choline chloride: Malic acid	1:2	*Carya cathayensis Sarg.* peels	Catechins, prunetin, etc.	[61]
8	Choline chloride: Xylitol	1:1	Virgin Olive Oil	Phenolic compounds	[62]
9	Choline chloride: Caffeic acidCholine chloride: Lactic acid	Mixed	Olive pomace	Phenolic compounds	[63]

In addition to the two major categories of natural products above, DESs have applications in the extraction of other classes of natural products. As the most abundant natural aromatic polymer on earth, lignin has great potential to produce value-added products. Fernandes et al. [17] prepared, characterised, and screened novel acidic DESs for lignin extraction from maritime pine sawdust, evaluating the use of co-solvents and the development of new DESs for their extraction and selectivity properties. The results showed that 95% of the total lignin in pine biomass could be recovered with a purity of 89% using new DESs consisting of lactic acid, tartaric acid, and choline chloride, named Lact:Tart: ChCl, in a molar ratio of 4:1:1, in a one-hour extraction process at 175 °C. The excellent purity of lignin extraction using a "green" solvent system makes this process very attractive for future large-scale applications.

A study by Rodriguez et al. [64] demonstrated an alternative method for the recovery of chitin from brown crab shell biomass using a low phytotoxicity ChCl/organic acid DES-based method with the potential to be competitive on a commercial scale. Chloroform: lactic acid (1:1) at 130 °C is the best system for chitin recovery, with the highest demineralisation and deproteinisation efficiency. In addition, other authors have demonstrated that DESs can be recycled and reused when used as solvents, which is a very "green" approach from an environmental and economic point of view [65].

6.2. Application of DESs in Drug Delivery Systems

Improving drug efficacy can be achieved by changing the route of administration, using different doses of administration, modifying the drug structure, compounding the drug, and increasing the solubility, which is one of the goals of the pharmaceutical industry today. About 40% of drugs approved for marketing and 90% of drugs under development have poor water solubility, which leads to low bioavailability and poor permeability. This is especially true for bio-pharmacological delivery system (BCS) class II substances, which have low solubility and high permeability, necessitating improvement of their bioavailability by altering the solubility of the drug in the gastrointestinal tract. DESs have been extensively studied as solubilisers, and, since the components in DESs are pharmacologically acceptable, they have the potential to be used as carriers for oral drug delivery in rats during early pharmacokinetic studies. In addition, nucleic acids can form reversible denaturing secondary structures when heated in DESs, broadening the scope of DES research in the life sciences [66]. The application of DESs in drug delivery systems is shown in Table 7.

Table 7. Application of DESs in drug delivery systems.

No.	DESs Type	Mole Ratio	Applications	References
1	Choline chloride: Ascorbic acid	2:1	Improving the solubility of dapsone	[67]
2	Oxymatrine: Fatty acid	2:1	As novel penetration enhancers for transdermal drug delivery	[68]
3	Choline chloride: Malic acid	2:1	Enhancing the hypoglycemic effect of insulin through the nasal route	[69]
4	Choline chloride: Malic acid/Glucose/Sucrose	Mixed	Improved pharmacokinetics of orally administered flavopiridol hydrochloride	[70]
5	Amino acid: Citric acid	3:1	Novel DESs-hydrogel systems for synergistic transdermal delivery of Chinese herb medicine and local treatments for rheumatoid arthritis	[71]
6	Choline bicarbonate: Geranic acid	1:4–1:2	Effect of DESs ion ratio on insulin delivery	[72]
7	Choline bicarbonate: Geranic acid	1:2	Acts as a transdermal permeation enhancer to promote the passage of bioactive compounds	[73]
8	Fructose:Citric acid: Water	1:1:5	Achieving antibiotic solubilisation	[74]
9	Choline chloride: Urea, Choline chloride:Ethylene glycol, Choline chloride:Glycerol	1:2	Improving the solubility of betamethasone and meloxicam	[75]
10	Choline chloride: Xylitol/Citric acid/Sorbitol/Glucose	Mixed	Improving the solubility of caffeine and furosemide	[76]

6.3. Application of DESs in the Determination of Trace Metals

Trace metals in the soil pose a serious threat to food safety and the ecological environment. The sources of trace metals may be naturally occurring or excessive human use of metal-containing fertilisers, pesticides, etc. Therefore, the determination of trace metal content in soil is of particular importance to environmental safety and agricultural development. DESs can effectively extract Cu, Pb, Cd, As, Mn, and other heavy metals in various foods, water, and soil, with a removal rate higher than 90% [77]. Commonly used analytical methods include dry/wet digestion, ultrasonic-assisted extraction, microwave-assisted acid digestion, etc. [78,79]. The reagents used are mostly toxic chemical reagents such as sulfuric acid, hydrochloric acid, nitric acid, or oxidants containing halogen ions. Therefore, to avoid the use of toxic and harmful organic solvents, it is necessary to develop a green reagent preparation method. The application of DESs in trace metal determination is shown in Table 8.

Table 8. Application of DESs in the determination of trace metals.

No.	DESs Type	Mole Ratio	Applications	References
1	n-Butanol and choline chloride: Menthol: p-Aminophenol	Mixed	Extraction of Co, Zn, Ni, Cu, Pb, and Tl from honey samples	[78]
2	Choline chloride: p-Aminophenol	1:2	Extraction of Zn, Ni, Cu, Pb, and Hg from the sample solutions	[80]
3	Choline chloride: Phenol	1:4	Determination of Cd in food and water samples	[79]
4	Choline chloride: Oxalic acid	1:2	Determination of As and Se in edible mushroom samples	[79]
5	Choline chloride: Oxalic acid	1:2	Determination of As, Cr, Mo, Sb, Se, and V in agricultural soils	[80]
6	Choline chloride: Phenol	1:2	Determination of Pd in wastewater	[81]
7	Choline chloride: Oxalic acid	1:2	Determination of Se and As in fish samples	[82]
8	Choline chloride: Citric acid	1:2	Removal of Cd from the contaminated soil of coking plant.	[83]
9	Choline chloride: Ethylene glycol	1:2	Determination of biotoxic Hg^{2+}, Cd^{2+}, Pb^{2+}, and Cr^{6+}	[84]
10	Choline chloride: Phenol	1:3	Determination of prohibited trace Pb and Cd in hair dye and nail flower	[85]

6.4. Application of DESs in the Preparation of Nanomaterials

DESs, due to their thermal stability, good dispersion, large ionic conductivity, and wide electrochemical window, have been used as dispersants, exfoliants, and nanomaterial templates. The application of media for nanoparticles synthesised by chemistry and electrochemistry is similar to that of ionic liquids. The use of DESs in nanoscience instead of ionic liquids has been inevitable. The applications of DESs in nanomaterial synthesis are shown in Table 9.

Table 9. Application of DESs in the synthesis of nanomaterials.

No.	DESs Type	Mole Ratio	Applications	References
1	Choline chloride: Oxalic acid dihydrate	1:2	Preparation of functionalised cellulose nanoparticle stabilised emulsion	[86]
2	Choline chloride: Oxalic acid	1:1	Fabricate starch nanoplatelets	[87]
3	Choline chloride: Lactic acid	Mixed	Preparation of cellulose nanofibers containing lignin	[88]
4	Choline chloride: Urea	1:2	Synthesis of anatase TiO_2 catalysts	[89]
5	Choline chloride: Ethanolamine	1:6	Preparation of multifunctional nanocomposites	[90]
6	Choline chloride: Lactic acid	1:9	Preparation of multifunctional nanocomposites	[90]
7	Choline chloride: Levulinic acid	1:2	As a hydrolysis medium for cellulose nanocrystal production	[91]
8	Choline chloride: p-Toluenesulfonic acid monohydrate	1:1	As a hydrolysis medium for cellulose nanocrystal production	[91]
9	Choline chloride: Oxalic acid dihydrate	1:1	Combined with ultrasonic treatment to produce nanocellulose	[92]
10	Choline chloride: Urea	1:1	Synthetic flexible and highly conductive cellulose nanofibers	[93]
11	Choline chloride: Lactic acid	Mixed	Lignin-containing cellulose nanomaterials produced DESsTreatment as rheology modifiers for fracturing fluids	[94]
12	Choline chloride: 1-propanol	1:3	DES-based graphene oxide solid-phase extraction chip preparation	[95]

6.5. Application of DESs in Electrochemistry

DESs have already attracted interest due to their favourable electrochemical properties. DESs can dissolve metal oxides and are used in electrochemical applications such as electrodeposition, electrochromism, and storage. DESs have the advantage of being safe, low-cost, green, and recyclable as electrolytes for electrochemical reactions. The applications of DESs in electrochemistry are shown in Table 10.

Table 10. Application of DESs in electrochemistry.

No.	DESs Type	Mole Ratio	Applications	References
1	*N*,*N*,*N*-trimethyl butylsulphonate ammonium hydrosulfate: Urea	1:2	Test the performance in fuel cells	[96]
2	Lactic acid: Glucose: H_2O	Mixed	Improved electrochemical detection of olive bitter glycosides in combination with graphene oxide.	[97]
3	Choline chloride: Urea	Mixed	Cobalt Electrochemical Recovery from Lithium Cobalt Oxides	[98]
4	Choline chloride: Ethylene glycol	Mixed	Formic Acid Electrochemical Oxidation	[99]
5	Choline chloride: Ethylene glycol	1:2	Preparation of lead powder from high-efficiency electrolytic recovery of waste lead paste	[100]
6	Choline chloride: Oxalic acid	1:1	X-ray structure and ionic conductivity studies	[101]
7	Choline chloride: Urea	Mixed	Gas-phase fragmentation of the supra-molecular ionic assemblies detected in CSI–MS	[102]
8	Choline chloride: Malonic acid	Mixed	Metallic bismuth films were prepared by electrodeposition	[103]
9	Choline chloride: Urea	1:2	Efficiently co-deposit In–Ga on Cu and Mo electrodes	[104]
10	Choline chloride: Lactic acid	Mixed	Ionic conductivity and structure of chitosan films	[105]
11	Choline chloride: Ethylene glycol	Mixed	Ni/cerium molybdenum oxide hydrate micro-flakes composite coatings electrodeposited	[106]

7. Outlook

At present, breakthroughs have been made in the study of DESs and have found applications in natural product extraction, drug delivery systems, trace metal determination, nanomaterial synthesis, and electrochemistry. However, there are still needs to continuously develop new HBAs and HBDs, to research and prepare new DES systems to provide references for exploring new application fields and expanding the application scope of DESs, and then to adapt to the demand of recovery and recycling applications in actual industrial production.

8. Conclusions

Replacing traditional toxic and harmful organic solvents with green solvents has become an important topic in modern research. Since the discovery of DESs in 2003, DESs have been continuously explored for their unique properties and have gradually become a research hotspot in various fields, mainly focusing on their use as solvents for the extraction of active ingredients from natural products. This study provides a comprehensive summary of the classification, composition, and properties of DESs and their applications in natural product extraction, drug delivery systems, trace metal determination, nanomaterial synthesis, and electrochemistry. Among them, DESs for extracting flavonoids and phenols were widely used as solubilisers to improve the bioavailability of drugs, which had a good enrichment effect on trace metal ions and prepared nanomaterials with good performance. This lays the foundation for exploring their different properties and broadening the scope into unknown fields.

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