Recent Advances in Hydrophobic Deep Eutectic Solvents for Extraction

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Abstract: In the over 1,800 articles published since their inception in 2001, most deep eutectic solvents (DES) synthesized have been hydrophilic. The low cost, low toxicity, and bioavailability of DES make the solvent 'green' and sustainable for diverse applications. Conversely, the hydrophilicity of DES limits their practical application to only polar compounds, which is a major drawback of the solvent. For the past three years, hydrophobic deep eutectic solvents (HDES) have emerged as an alternative extractive media capable of extracting non-polar organic and inorganic molecules from aqueous environments. Due to the infancy of HDES, for the first time, this mini-review summarizes the recent developmental advances in HDES synthesis, applications, challenges, and future perspectives of the solvent. In the future, it is believed HDES will replace the majority of toxic organic solvents used for analytical purposes.

Keywords: deep eutectic solvents; hydrophilic; hydrophobic; liquid-liquid extraction; transition metals

1. Introduction

Chemists and process engineers continue to search for greener solvents capable of replacing conventional toxic organic solvents in their daily activities [1–4]. Due to the environmental, health, and safety implications of some organic solvents, the impetus in solvent replacement is growing globally. The challenge stems from the difficulty to acquire more sustainable and greener alternatives to toxic volatile organic chemicals with the desired chemical and physical properties [2]. The increasing demand for solvents has been forecasted to reach 9.6 billion pounds by 2020 in the United States (US Solvent Market Projection; last accessed on 14 January 2019). This growth is driven by a strict US Environmental Protection Agency (EPA) regulations toward more eco-friendly and biodegradable solvent alternatives with reduced emissions and toxicity. A little over a decade ago, deep eutectic solvents (DES) emerged as a new generation of ionic liquids (ILs) synthesized by combining a hydrogen bond acceptor (HBA) and a hydrogen bond donor (HBD) [5–7] with remarkably low volatility. Since most DES are synthesized by combining naturally occurring proton donors like fatty acids, urea, glucose, and glycerol with acceptor molecules like choline chloride, the combined eutectic mixture is environmentally benign, safe, and sustainable [5,6,8–12]. The advantages of using DES for extraction goes beyond their simple preparation procedures, greener nature, and easy tunability [11,13,14], as they are bioavailable and have low toxicity. DES chemical and physical properties are flexible, as they can be adjusted by either changing the constituents or by adding other compounds to form a ternary or a complex mixture. It is worth understanding the phase behavior of the DES in order to tune their physicochemical properties. Despite the numerous publications about DES since their first inception in 2001 [12,15], most of the research work has

concentrated mainly on hydrophilic DES, which limits the solvents utilization to polar environments [12,16].

In an application that requires hydrophobic media, the common truth is that most chemists and process engineers still resort to toxic organic chemicals due to the scarcity of greener hydrophobic alternatives. This is a major drawback to the call for environmental sustainability. The availability of greener solvents in all of the four solvent categories, high basicity-low polarity, low basicity-low polarity, high basicity-high polarity, and low basicity-high polarity, is pivotal to ensuring sustainability [17]. A hydrophobic ILs involving [NTf2] anion, ([Bmim][NTf2]), was reported to be more efficient in the enzymatic synthesis of biodiesel compared to the hydrophilic [PF6] and [BF4] anionic counterparts [18]. A review of the application of hydrophobic ILs in biodiesel synthesis is available [19]. To date, nearly all deep eutectic solvents are hydrophilic and are limited in applications that require high basicity and low water content such as liquid–liquid extraction (LLE). The concept of DES in extraction is still in its infancy [20] compared to ionic liquids, nonetheless, the increasing number of yearly publications make the field very promising. In Figure 1, a web of science search of the phrase "deep eutectic solvents" shows an increasing number of publications since 2004. Out of the 1860 hits, over 88% of DES articles are from 2013 to 2018. In addition, over 175 articles are considered as DES reviews for the past 5 years. The skyrocketing numbers have been biased towards hydrophilic DES rather than their hydrophobic counterparts. The concept of hydrophobic DES (HDES) was introduced by van Osch and co-workers [21] in 2015 when they combined diverse quaternary ammonium salts (QAS) with decanoic acid (DecA). The water-immiscible solvent was applied to extract water-insoluble volatile organic compounds, which reported a high extraction yield and efficiency [21]. Since then, active research is ongoing to investigate how HDES are synthesized and its application in diverse fields.

This mini-review gives an overview of HDES synthesis and provides up-to-date insight into their various applications in the extraction and separation of biomolecules and inorganic metals. It should, however, be emphasized that detailed discussion on HDES synthesis, extraction techniques, and instrumental analysis of the analytes are beyond the scope of this article. Since the majority of reviews on DES captures only hydrophilic DES (DES with high water miscibility), this mini-review gives a brief and concise account on hydrophilic DES. This article differs from available DES reviews on extraction by offering a new overview of what HDES are, and further goes beyond to summarize the sporadic HDES applications in literature.
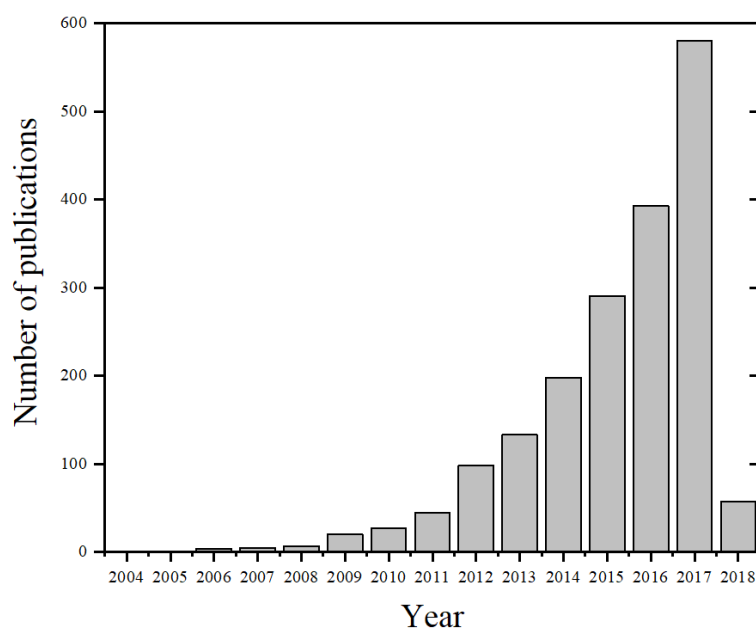

Figure 1. Number of publications based on a web of science search for the phrase "deep eutectic solvent". Date accessed: 10 February 2018.

2. Formation, Classification, and Types of DES

Deep eutectic solvents are formed by mixing a hydrogen bond acceptor with hydrogen bond donor at a specific molar ratio resulting in melting point (mp) depression of the solvent. Deep eutectic solvents are classified into 4 categories (Table 1) with type III as a focus of attention in most research. The Cat^+ in DES is usually quaternary ammonium, phosphonium, or sometimes sulfonium salt [12]. The X^- is the anionic moiety often involved in hydrogen bonding with protons from the donor RZ group (R = alkyl group and Z = $CONH_2$, COOH, or OH). Choline chloride is the most used QAS for DES synthesis due to its low cost, availability, biocompatibility, and low toxicity.

Table 1. General Formula for deep eutectic solvents (DES) classification. Adapted from [12].

Type	General Formula	Terms
type I	$Cat^+X^-zMCl_x$	M = Zn, Sn, Al, Ga, In
type II	$Cat^+X^-zMCl_x \cdot YH_2O$	M = Cr, Co, Cu, Ni, Fe
type III	Cat^+X^-zRZ	Z = $CONH_2$, COOH, OH
type IV	$MCl_x + RZ = MCl_{x-1}^+ \cdot RZ + MCl_{x+1}^-$	M = Al, Zn and Z = $CONH_2$, OH

The chloride anion is readily available to interact with diverse proton donors through hydrogen bonding. Abbott and co-workers [12] found that choline chloride (mp = 302 °C) and urea (mp = 133 °C) interact to form a liquid at room temperature with a freezing point of 12 °C at 1:2 molar ratio. DES physicochemical properties like conductivity, viscosity, polarity, and thermal properties can easily be tuned by varying the constituent raw materials. Most of the synthesized DES reviewed [10,12,22] are hydrophilic. The type III DES are categorized into low-transition-temperature mixtures (LTTMs), natural deep eutectic solvents (NADES), carboxylic acid-based deep eutectic solvents [5,13,23], and therapeutic deep eutectic solvents (THEDES) [24,25].

3. Hydrophilic DES and Applications

The LTTMs are synthesized mostly by mixing natural high-melting-point starting materials, which form a liquid by hydrogen-bond interactions with notable applications in organic synthesis [26–28], biofuel processing [29,30], and catalysis [10,31]. Some of the underexplored fields of DES include biomass processing and liquid–liquid extractions or extractive distillation [22]. Nonetheless, a few reviews on DES for LLE have surfaced recently [7,20,32–36]. Hizaddin et al. [37] screened 94 DES by applying a conductor-like screening model for realistic solvents (COSMO-RS) and evaluated their potential usage for extractive denitrification of diesel. A comprehensive review of deep eutectic solvents and their application in modifying electrode surfaces for electrochemical sensing and biosensors has been published [38,39]. The use of DES as media for *Candida antartica* B lipase transesterification reactions is explained in detail [40]. Apart from LTTMs, other forms of DES from natural raw materials have evolved over the past decade in the form of natural deep eutectic solvents (NADES).

NADES were introduced when cellular constituents like fructose, glucose, citric acid, proline, and other metabolites formed a viscous liquid at defined molar ratios [41]. NADES synthesis, types, characterization and applications including their use in extraction and lignocellulosic biomass pretreatment have been previously reviewed elsewhere [36,42–47]. A recent review by Vanda et al. [48] looked into the evolution of NADES from ionic liquids and DES, and further expanded on the applications of NADES in pharmaceuticals, cosmetics, food, and agricultural settings. NADES can be used as solubilization agents for macromolecules and as media for enzymatic reactions [48].

Unlike LTTMs and NADES, THEDES are another subgroup of DES with one of their components as a pharmaceutically active ingredient (API). Commonly used API include acetylsalicylic acid, benzoic acid, ibuprofen, and phenylacetic acid [24,25]. In some instances, THEDES might be classified under NADES when both the active ingredients and the other raw materials are from natural sources. Developmental research is currently ongoing to develop THEDES which will be effective for drug

delivery. Compared to water, choline chloride-urea and choline chloride-malonic acid DES improved their solubility with benzoic acid, danazol, griseofulvin, AMG517, and itraconazole by 5 to 22,000 folds [49]. This notable feature of DES makes them promising for pharmaceutical applications and in drug delivery. In view of this, developing HDES is eminent not only for liquid–liquid extraction but also as vehicles for drug solubilization.

4. HDES Synthesis (Common HBA and HBD)

The synthesis of HDES is similar to hydrophilic DES. As shown in Figure 2, HDES can be synthesized by mixing DL-menthol (HBA) and DecA (HBD) at 1:1 molar ratio followed by heating, stirring, and/or vortexing. The cosmo polarity surface of both the donor and the acceptor molecules show three regions; blue = proton donating region with negative charge density, red = proton acceptor region with positive charge density, and green = hydrophobic region.
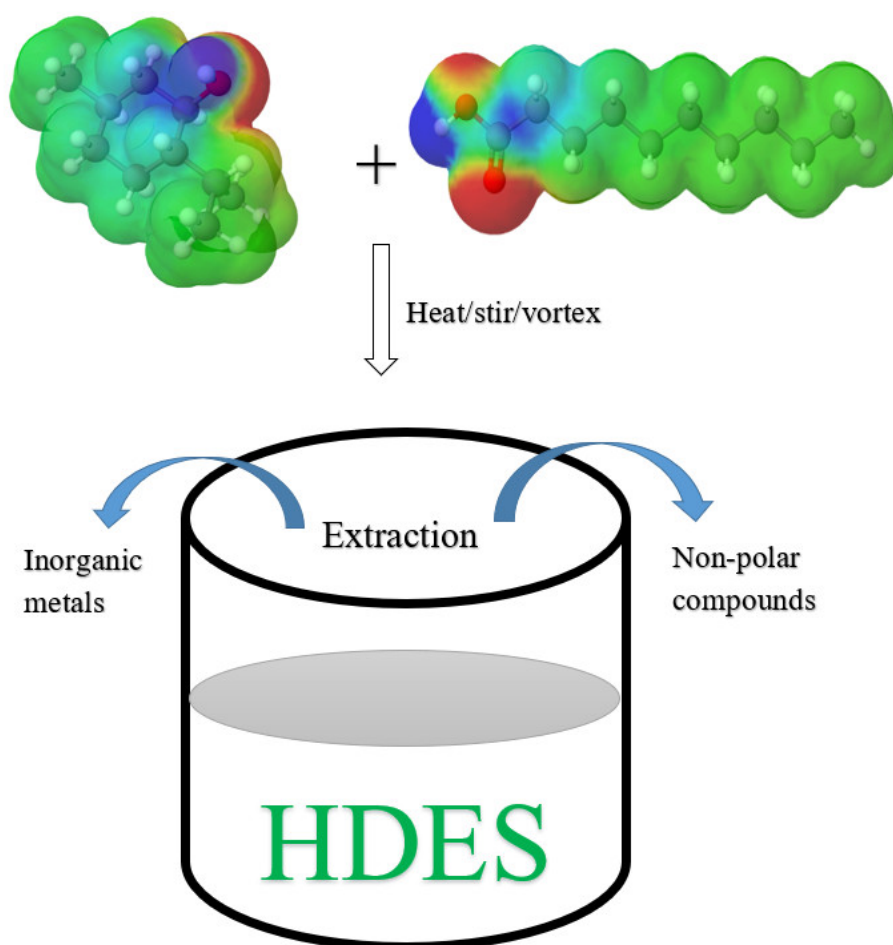

Figure 2. Synthesis of hydrophobic deep eutectic solvents (HDES) from DL-Menthol (HBA) and Decanoic acid (HBD) at 1:1 molar ratio. The synthesized HDES can be used to extract non-polar compounds and transition metals. Graphics by MolView version 2.4.

Among the HBAs, DL-menthol is gaining much popularity for its use in solvents for extraction whereas decanoic acid (DecA) is the most used HBD in HDES synthesis (Table 2). There is no single way for synthesizing HDES since this process depends on the starting raw materials. HDES can be synthesized by simply mixing the constituents at ambient temperature [50] or by heating as high as 80 °C with or without stirring [51,52]. Figure 3 and Figure 4 lists a number of hydrogen bond donors and hydrogen bond acceptors commonly used for HDES, respectively. The physicochemical properties of most HDES depend on the nature of the constituents combined. However, most HDES form clear and transparent liquids, and are viscous. Due to the hygroscopic nature of most quaternary ammonium salt, HDES synthesized are stored in a desiccator to prevent moisture absorption. The addition of water to HDES can lead to the formation of a ternary complex which could alter the physicochemical properties of the solvent.

In designing HDES for extraction, a critical consideration of the amount of the raw materials and their alkyl chain length should be noted. The physical and chemical properties of HDES were tailored for pyrethroids [53] and polycyclic aromatic hydrocarbons (PAH) [54] extraction by modifying the molar ratio of the constituents. The high extraction efficiency of pyrethroids by dispersive liquid–liquid extraction (DLLE) is due to the high-density hydrogen bond donor, hexafluoroisopropanol, which is able to form water immiscible HDES with betaine or L-carnitine. During dispersive LLE, the high-density HDES containing the analyte lie at the bottom of the flask making it easier for collecting and analysis [53]. High-density HDES make dispersive LLE of nonpolar analytes from aqueous environment easier compared to most DES. In the extraction of bisphenol A, Florindo et al. [55] showed that octanoic acid (C_8), nonanoic acid (C_9), decanoic acid (C_{10}), and dodecanoic acid (C_{12}) can act as either a hydrogen bond acceptor (due to the carbonyl group) or a hydrogen bond donor (due to the hydroxyl group) to form HDES. Fatty acid-based DES can be synthesized to form a binary or a ternary mixture depending on the nature of applications required. Moderately high extraction efficiencies of 76.04%, 88.32%, and 81.81% were obtained by using C_8–C_{12} (3:1), C_9–C_{12} (3:1), and C_{10}–C_{12} (2:1) HDES, respectively. Additionally, these phase change materials or long chain fatty acid eutectics can be modified to develop a new class of HDES to be used in water purification systems [55].

Low alkyl chain carboxylic acids like acetic acid, butyric acid, levulinic acid, hexanoic acid, and pyruvic acid have been used together with the DL-menthol or N_{4444}–Cl for HDES synthesis [56]. Varying the alkyl chain of either the HBA or the HBD is necessary to tune the polarity of the HDES for a defined application. Martins et al. [57] recently designed and synthesized HDES from terpenes (thymol and L (-) menthol) and monocarboxylic acids and characterized the solvent through density measurements, viscosity, solid-liquid equilibria, and Kamlet-Taft solvatochromic parameters. Thymol-based HDES were found to be less viscous (1.3−50.6 mPas) and denser than L (-) menthol-based eutectic mixtures [57]. As expected, despite the similarities between thymol and L (-) menthol, the physical and chemical properties of their resulting solvent differ with thymol having higher hydrogen bonding acidity character and menthol having higher basicity behavior [57].

Table 2. Synthesis of HDES by combining HBA and HBD.

HBA	HBD	Molar ratio	Synthesis	Ref.
DL-menthol	acetic acid	1:1	heating at 50 ℃ for 15 min	[58]
	lactic acid	1:2		
	lauric acid	2:1		
	pyruvic acid	1:2		
choline chloride	phenethyl alcohol	1:4	stirring at ambient temperature	[50]
DoDecA	octanoic acid	1:3	heating at 40 °C	[55]
	nonanoic acid	1:3		
	DecA	1:2		
betaine L-carnitine	HFI	1:2, 1:2.5, 1:3	heating at 80 °C in screw-cap pressure tube	[53]
N_{8881}−Br	DecA	1:2	stirring and heating at 35 °C	[59]
N_{4444}−Cl N_{8881}−Cl N_{8881}−Br N_{8888}−Cl N_{8888}−Br	DecA	1:2	vortex mixing at room temperature and heating at 308 K in oil bath	[60,61]
DL-menthol	lauric acid	0.5:1, 1:1, 1.5:1, 2:1, 2.5:1	reflux condensing for 1 h at 50 °C with stirring	[62]
DL-menthol N_{4444}−Cl	acetic acid, levulinic acid, butyric acid, hexanoic acid, octanoic acid, DecA (1:1), pyruvic acid (1:2), DoDecA (2:1) acetic acid (1:1), levulinic acid, hexanoic acid, octanoic acid, DecA (1:2)	1:1, 1:2, 2:1	mixing with mechanical stirring at 350 rpm at 353.15 K	[56]
$C_{32}H_{68}PCl$ N_{8888}−Br	DecA hexanoic acid DecA	1:2	heating at 80 °C for 30 min	[52]
N_{81}−Cl	ethylene glycol, 1-propanol, 1,3-propanediol, glycerol, 1-butanol, 1,2-butanediol, hexyl alcohol, capryl alcohol, decyl alcohol, dodecyl alcohol, 1-tetradecanol, cyclohexanol, DL-menthol	1:2	heating at 80 °C	[51]
thymol	(±)-camphor 10-undecylenic acid DecA	7:3, 3:2, 1:1 7:3, 3:2, 1:1, 1:2, 1:3, and 1:4 3:2, 1:1, 1:2, 1:3	heat and stirred magnetically at 60 °C	[54]

Abbreviations: N_{8881}−Cl = methyltrioctylammonium chloride ; N_{81}−Cl = methyl trioctyl ammonium chloride; N_{8888}−Br = tetraoctylammonium bromide; N_{4444}−Cl = tetrabutylammonium chloride; N_{8888}−Cl = tetraoctylammonium chloride; HFI = hexafluoroisopropanol; $C_{32}H_{68}PCl$ = trihexyltetradecylphosphonium chloride; DecA = decanoic acid; and DoDecA = dodecanoic acid.
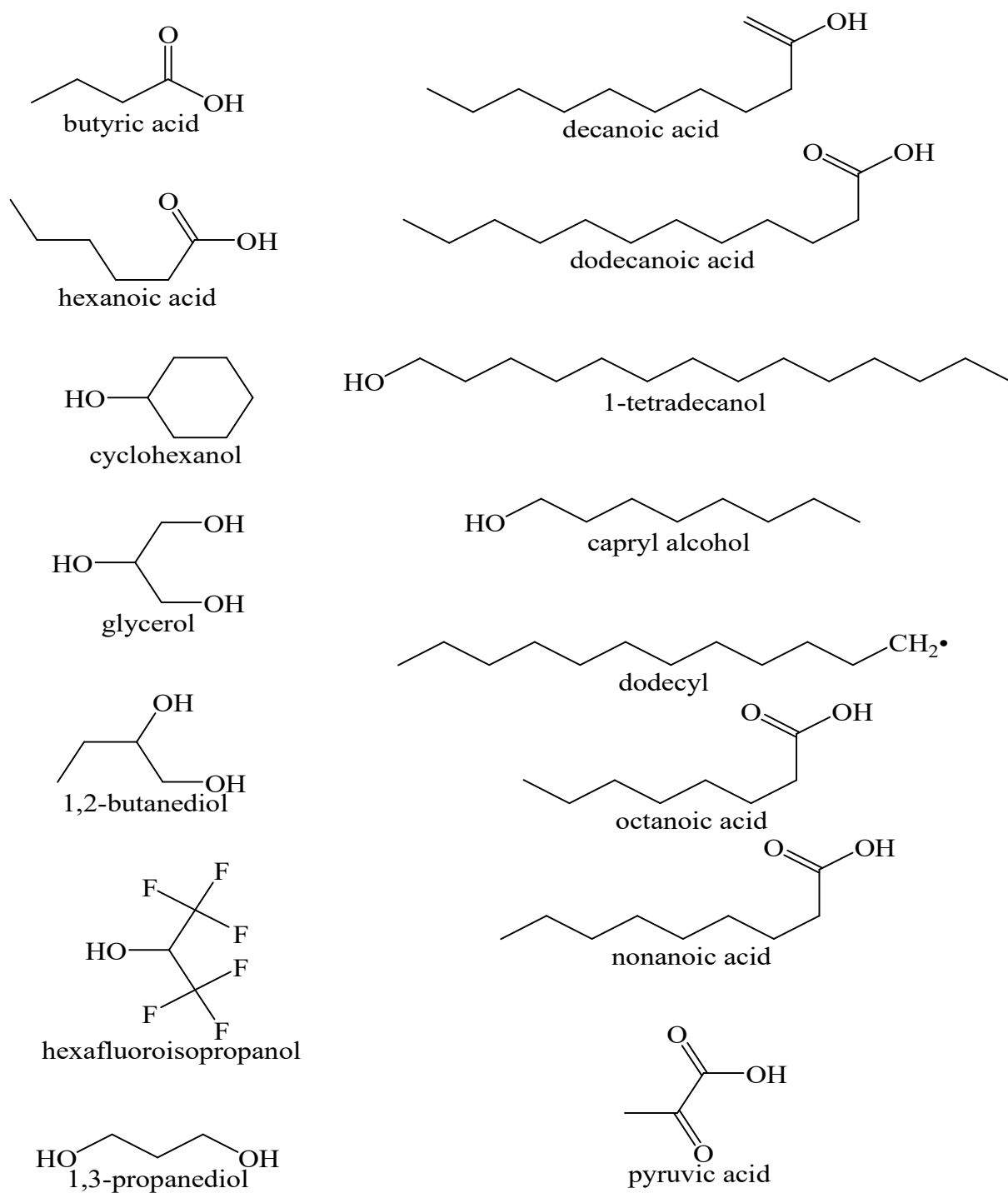
Figure 3. Common HBD used for HDES synthesis.

Menthol

Betaine

thymol

choline chloride

tetrabutylammonium chloride

methyltrioctylammonium bromide

trihexyltetradecylphosphonium chloride
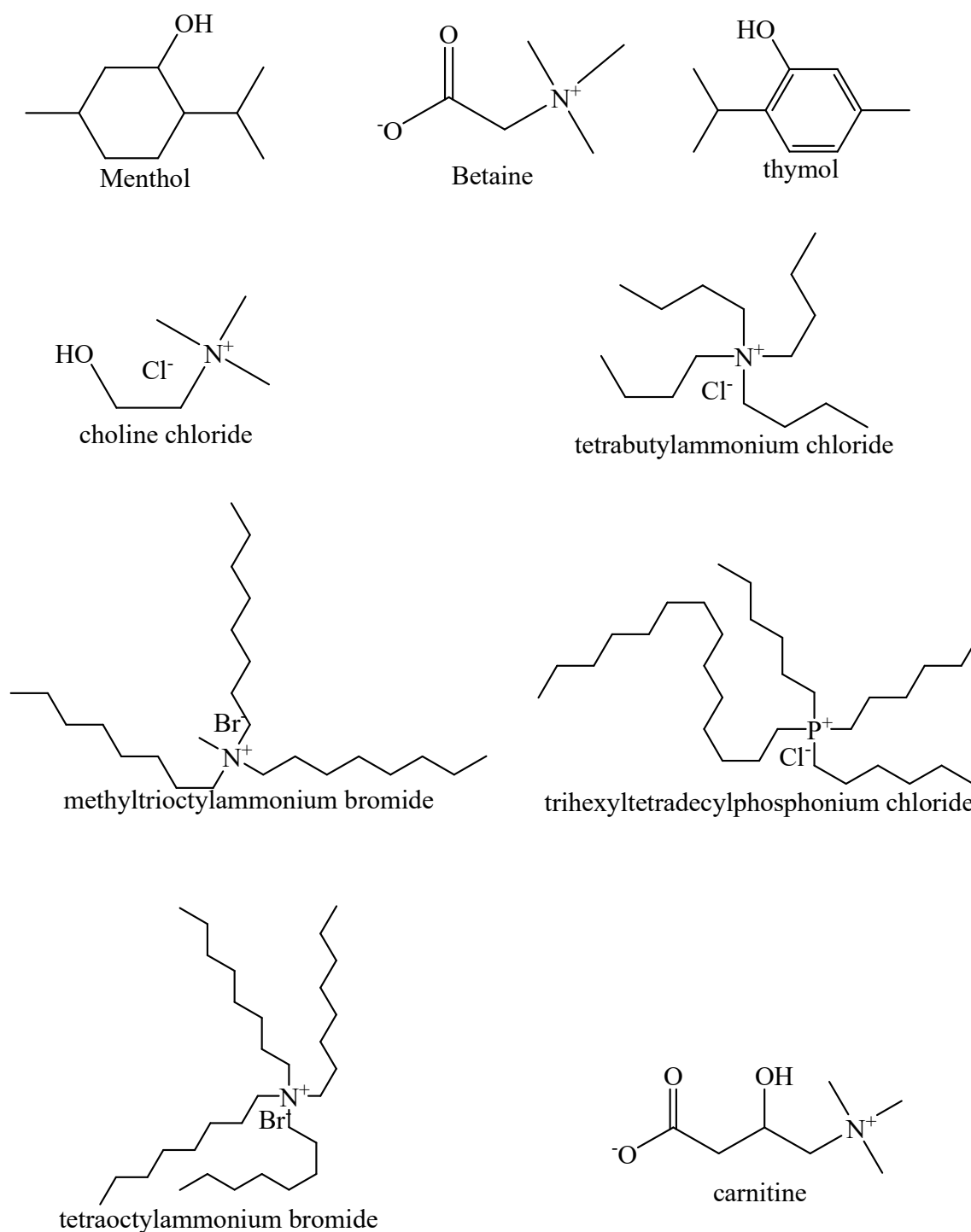
tetraoctylammonium bromide

carnitine

Figure 4. Common HBA used for HDES synthesis.

5. Applications of HDES in Extraction

DES hydrophobicity was introduced in 2015 by van Osch and co-workers, although the authors acknowledged earlier work involving hydrophobic menthol-based eutectic mixtures [21]. The first application of HDES involved liquid–liquid extraction of volatile fatty acids (VFAs) comprising of acetic, propionic, and butyric acid from the aqueous environment. The extraction efficiency of the VFAs was found to increase with increasing alkyl chain length. For example, N8881-Cl:DecA (1:2) efficiently extracted 38% acetic acid, 70.5% propionic acid, and 89.8% butyric acid [21]. The symmetric salt N8888-Cl and N7777-Cl, due to the steric hindrance of the alkyl chain makes the HDES much more hydrophobic and reduces its extraction capability to VFAs and accessibility to water. The high

extraction efficiency of HDES compared to amine-based extractant (TOA) for VFAs could be attributed to the hydrophobicity of HDES which increases the dispersive interaction between the acid and the solvent [21,63]. Furthermore, due to the hydrogen bonding potential of HDES, the solvent could interact and/or extract both the dissociated and the undissociated forms of acetic, propionic, and butyric acid [21].

Since this first report, active research is ongoing to investigate how HDES could be synthesized from different raw materials and their possible applications in diverse fields. Table 2 provides a comprehensive overview of some up-to-date HDES synthesized and their physical appearances. Four different HDES synthesized from trioctylmethylammonium chloride and DecA (1:2), trioctylmethylammonium chloride and octanoic acid, tetrabutylammonium chloride and DecA, and tetrabutylammonium chloride and octanoic acid found the latter as an effective solvent to efficiently extract eight synthetic pigments in beverages with recoveries between 74.5–102.5% and RSD less than 5.4% [64]. The high extraction efficiency exhibited by tetrabutylammonium chloride and octanoic acid HDES is due to the low viscosity of the solvent which enhances its diffusivity [64]. Since synthetic pigments are usually soluble in water, increasing the alkyl chain length of either the HBA or the HBD decreases the extraction efficiency. Additionally, selecting the appropriate pH, HDES type, and extraction time and type is important to enhance yield. Another liquid–liquid extraction of metal uranyl nitrate ($[UO2]^{2+}$) from aqueous acid using low viscous hydrophobic eutectic solvent from trioctylphosphine and phenol has been reported [65]. The presence of phenol in the mixture was crucial for generating the eutectic mixture composition rather than having a role in the uranyl complexation and extraction [65]. The thermal stability of the trioctylphosphine, phenol HDES mixture, which is defined by the loss of phenol from the liquid, is between 90–100 °C.

Recently, a low cost, highly porous, ultralight and hydrophobic HDES was synthesized (combined techniques of nanofibrillation, silylation, and freeze-drying) and the aerosol was capable of squeezing oil (superabsorbing agents) with an absorption capacity of 65–205 (g/g) [66]. The absorbed oil was recovered by mechanical squeezing and the aerosol could be used for about 30 cycles [66]. Since HDES uses low cost renewable raw materials, applying this economical solvent to mitigate environmental pollutants is a promising area for future research. A menthol-based HDES with acetic acid (1:1) showed efficient extraction of phytocannabinoids with yields ranging from 118.6% to 132.6%, which is higher than using terpenol, borneol, geraniol, and linalool as HBA [67]. This HDES has a higher extraction efficiency for phytocannabinoids than traditional liquids like methanol and ethanol [67]. Apart from acetic acid, other transparent liquid-based HDES formed by using volatile organic acids such as formic, propionic, butyric, hexanoic, octanoic, dodecanoic, lactic, phenylacetic, and mandelic acid as HBD with menthol as HBA (at 1:1 molar ratio) have been reported [67]. Menthol with oxalic, malonic, tartaric, phthalic, glycolic, malic, hippuric, pyruvic, and aspartic acid (1:1) form a solid–liquid mixture even after heat treatment at 80–95 °C [67]. A tailor-made HDES with methyl trioctyl ammonium chloride (N_{81}-Cl) and 18 different alcohols or aliphatic acids was able to extract between 13 mg/g to 23 mg/g of polyprenyl acetates from *Ginkgo biloba* leaves powder [68]. The initial screening method for polyprenyl acetates extraction involved vortexing, air-bath shaking, and centrifugation with an approximate extraction time of 20 min. Apart from air-bath shaking, the authors compared polyprenyl acetates extraction efficiency with methods including ultrasonic-assisted extraction, water-bath shaking, heating, and stirring. Irrespective of the extraction temperature used (25 °C or 60 °C), polyprenyl acetates extraction by stirring gave higher yield [68]. The extraction yield of this pharmaceutically bioactive compound regardless of the method used was also higher at 60 °C compared to the same process conditions at room temperature.

Lastly, few reports on using HDES for In^{3+} [69] and Co^{3+} [70] extraction from aqueous solutions have been established. A possible explanation for metal–HDES interaction involves an ion exchange mechanism. For instance, the positive charged Co^{2+} ion is able to exchange with the partially positive charged lidocaine ion during a LLE with a hydrophobic solvent comprising of DecA and lidocaine [70]. During metal ions extraction, it is important to note that pH, reaction time, and temperature optimization are significant factors affecting extraction yield. As reported, HDES synthesized from

lauric acid and the DL-menthol can only extract indium from aqueous environments when the pH is approximately 3 [69]. The ease of solvent regeneration, simple preparation of HDES, and low toxicity of HDES are among the numerous reasons why HDES are selected over hydrophobic ionic liquids or conventional organic solvents for transition metals extraction. For quantification purposes, HPLC coupled with UV/Vis is the most used separation and quantification technique. A low limit of detection (LOD) for amphetamine and methamphetamine is between 2 ng/mL to 5 ng/mL [50]. Other detecting techniques like HPLC-DAD, ^{1}H-NMR, GC-MS, and NaI(Tl) well counter detector are listed in Table 3.

Table 3. Applications of HDES in extraction.

Analyte	Separation/ Quantification	Ref.
caffeine, isophthalic acid, tryptophan, and vanillic acid	partitioning/UV-Vis	[58]
Amphetamine, Meth	HPLC/UV-Vis	[50]
bisphenol A	phase separation by equilibration/UV-Vis	[55]
pyrethroids	HPLC/DAD	[53]
derivatized MA and FA	HPLC/UV-Vis	[59]
CO_2 solubility	evacuation steps/magnetic suspension balance	[60,61]
ethanol, 1-propanol, 1-butanol	shaking and 24 h equilibration/ ^{1}H NMR	[62]
(neonicotinoids) imidacloprid, acetamiprid, nitenpyram and thiamethoxam	partitioning/gravimetric	[56]
pertechnetate ($^{99m}TcO_4^-$)	equilibration and TLC/NaI (Tl) well counter detector	[52]
artemisinin	HPLC/UV-Vis	[51]
polycyclic aromatic hydrocarbons	GC-MS	[54]

Abbreviations: MA = malondialdehyde; FA = formaldehyde; and Meth = methamphetamine.

6. Challenges, Opportunities, and Perspectives

Despite the numerous advantages of HDES in extraction, some of the notable limitations of these solvents are high viscosity, cloudiness, and difficulty in phase separation during liquid–liquid extraction [21]. Since the viscosity of DES depends on the hydrogen bond strength of the solvent, understanding the charge transfer and the molecular interaction between HBD and HBA occurring in HDES is an invaluable opportunity for future research. An investigation into HDES polarity by using solvatochromic molecular probes to measure hydrogen bonding acidity, hydrogen bonding

basicity, and dipolarity/polarizability should also be encouraged to curtail phase separation problems. Due to the ever-increasing applications of HDES, in silico models for predicting extraction efficiencies would be vital for future applications. For example, a PC-SAFT 'pseudo-pure' method was used for the modeling of CO_2 solubilities in HDES [71], a potential application in CO_2 capture. Developing such models to predict extraction efficiency and physicochemical and thermodynamic properties like viscosity, density, activity coefficient, and vapor pressure would cut-down cost and save time and labor. Additionally, for the first time, Dietz et al. [72] impregnated hydrophobic DES (DecA: N_{8888}-Br, DecA: Thymol, DecA: Menthol, and Thymol: Lidocaine) in a polyethylene support enhanced the separation of furfural and hydroxymethylfurfural from aqueous solutions. A significant transport of furfural and hydroxymethylfurfural through the polymeric membrane support was obtained by using HDES supported liquid membranes made from M3202B and thymol-lidocaine (2:1) [72]. Opportunities in tunneling HDES viscosity for enhanced transport and yield is requested [72].

Applications of HDES in biomass processing, drug solubilization and delivery, biofuels, and electrochemistry are underexplored, hence an opportunity for researchers to tailor HDES polarity for such applications. Ternary HDES systems involving water or polar solvent addition may be worthy of exploring to meet specific challenges. For example, in exploring the electrochemical behavior of ferrocenes, for the first time, Ruggeri et al. [73] demonstrated that addition of small water to tetrabutylammonium chloride and decanoic acid HDES (1:2) improved the electrical conductivity and viscosity of the solvent. Water content above 2% w/w in HDES enables effective mass transfer to and from the electrode surface [73]. Water disrupts the hydrogen bond between the donor and the acceptor to enhance the free flow of ions in the medium. In addition, the researchers showed that an aqueous solution containing a salt of metallic cation, Cr(VI), could be extracted by using a hydrophobic DES [73]. Furthermore, the electrochemical behavior of Cr(VI) species in HDES was studied for future applications in electroremediation.

Although HDES are considered as 'green' solvents, little has been done to monitor their toxicity, vapor pressure, or bioavailability. Moreover, since the hydrophobicity of HDES is relative, the distinction between hydrophilic and hydrophobic DES is sometimes confusing and hence a comprehensive guideline for calling DES hydrophobic should be established. Measuring the octanol-water partition coefficient (K_{ow}) of the synthesized HDES would be vital to predict the environmental fate as well as the degree of hydrophobicity of the solvent. Determining the K_{ow} values would also make it easier to select the best HDES for LLE of biomolecules or inorganic metals from an aqueous environment.

7. Concluding Remarks

This review summarizes the recent developments in HDES, a new subgroup of DES, mostly synthesized by using QAS or terpenes as HBA and fatty acids as HBD. Since most HDES are synthesized from natural raw materials, the solvent is considered as non-toxic, less volatile, environmentally benign and sustainable. The water immiscible or low water accessibility nature of HDES makes it promising in liquid–liquid extraction of non-polar analytes and transition metals from an aqueous environment. The development of HDES is a major breakthrough in analytical chemistry since DES and NADES are theoretically and practically limited to the extraction of only hydrophilic or polar compounds [48]. Despite only three years since its outset, the burgeoning interest in using HDES for extraction is growing rapidly. For now, almost all the applications of HDES are limited to extraction of biomolecules and transition metals, and, thus, there is an opportunity for scientists to explore their application in pharmaceutical, food, cosmetic, enzymatic, fuel, and biomass industries. Compared to DES and NADES, HDES offer a suitable medium for solubilization and delivery of non-polar drugs. A major drawback of HDES, like ILs, DES, and NADES, is that the high viscosity of the solvent affects analysis and separation of some extracts. Apart from using terpenes (thymol and menthol) and some fatty acids used as HBA, the most used long alkyl chain QAS, such as N_{4444}-Cl, N_{8881}-Cl, N_{8881}-Br, N_{8888}-Cl, and N_{8888}-Br, are expensive, making it difficult for industrial usage.

To fully understand the behavior of HDES, due to the infancy of this new generation of DES, extensive work is required to investigate the physicochemical and thermodynamic properties by both experimental and theoretical approaches. In the future, it is believed that more sustainable and tailored HDES would be developed to replace environmentally hostile organic solvents.

Conflicts of interest: The author has no conflicts of interest to declare.

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