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## **Sustainable Separation of Bio-Carboxylic Acids using Deep Eutectic Solvents**

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**Key words:** Sustainable Separation, Bio-carboxylic Acid, Deep Eutectic Solvents, Extraction Efficiency, Parameters, Design

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## Sustainable Separation of Bio-Carboxylic Acids using Deep Eutectic Solvents

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### Abstract

Biocarboxylic acids are crucial platform chemicals derived from the biological conversion of renewable resources. Separating carboxylic acids from fermentation broth is significant and challenging. Biocarboxylic acids can be extracted from fermentation broths using reactive liquid-liquid extraction, which has been extensively researched. However, the commonly used petroleum-based solvents should be replaced with greener alternatives. Deep eutectic solvents (DES) have become a highly potential type of green solvent, with a wide array of well-documented applications. DESs, an ionic liquid, are created by mixing a hydrogen bond acceptor, like a quaternary ammonium salt, with a hydrogen bond donor, such as a metal halide. These solvents possess unique physicochemical properties such as non-toxicity, renewability, biodegradability, and ease of preparation, making them attractive green solvents. Rising concerns about environmental sustainability have driven many industries to replace synthetic organic solvents with greener alternatives in their manufacturing processes. Given the importance of DES as a solvent, the present paper focuses on an exhaustive literature study on the application for the separation of carboxylic acid. Further, various types of DES used for carboxylic acid separation and the effect of various parameters on performance efficiency have been discussed.

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## Introduction

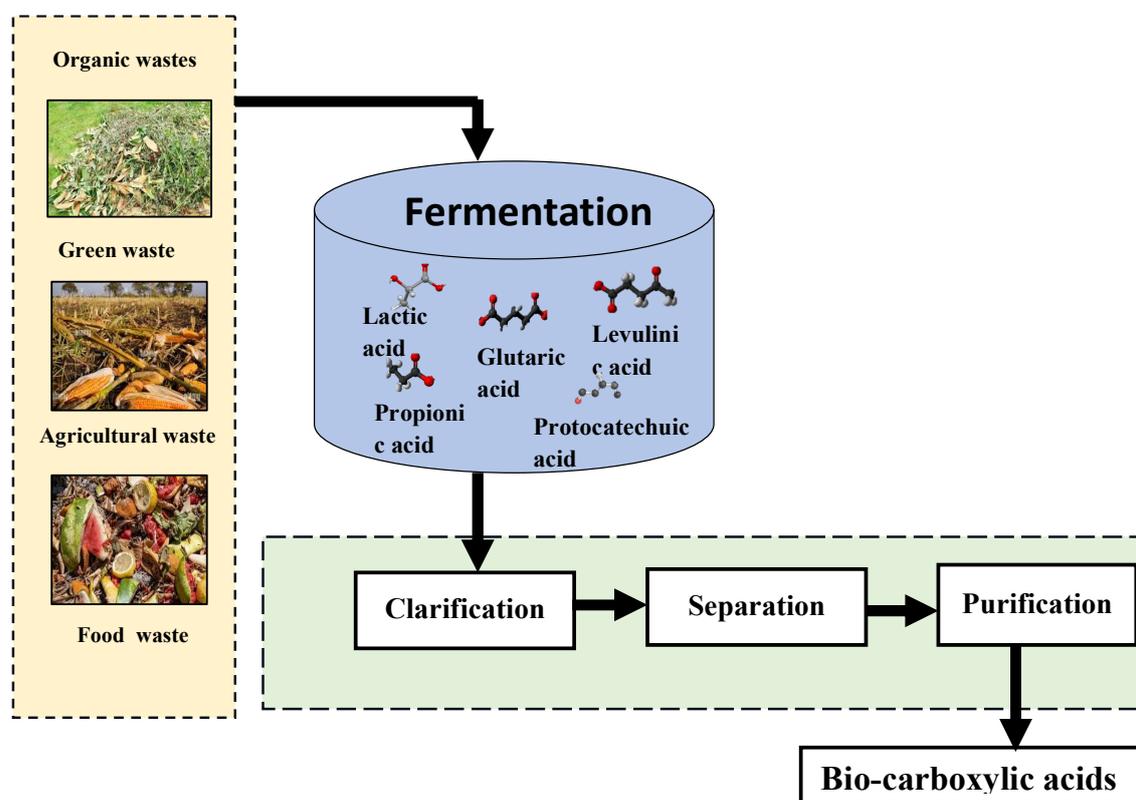
Environmental issues like climate change, rising greenhouse gas emissions, and excessive waste generation underscore the urgency of adopting renewable resources and enhancing the sustainability of industrial operations (Lan et al. 2017; Vea et al. 2018). An integrated biorefinery approach can facilitate the production of diverse products, including chemicals, fuels, and textiles, while utilizing renewable inputs and valorizing waste materials (Maity 2015). Promoting a circular economy is vital to combating climate change and preserving global resources (Yang et al., 2017). According to Djukić-Vuković et al. (2019), converting organic waste into valuable platform chemicals, such as carboxylic acids, offers a sustainable alternative to fossil-based chemical production and supports the synthesis of biodegradable polymers. Carboxylic acids serve as key intermediates in pharmaceuticals, polymers, food, and other chemical industries. While most industrial carboxylic acids are still derived through petrochemical routes, issues such as depleting fossil reserves and increasing environmental regulations have spurred interest in their bio-based production via fermentation. These biologically derived acids are valuable not only for bulk chemical production but also for high-end applications like drug delivery systems, biopolymer fabrication, and tissue engineering. The increasing demand for bio-based polymers has renewed attention on the effective separation of carboxylic acids from fermentation media. Liquid-liquid extraction (LLE) remains one of the most effective and widely used separation techniques due to its high selectivity and operational simplicity (Garzón and Straathof 2014). However, the recovery of these acids is challenging due to their low volatility, strong hydrophilicity, and the complex nature of the fermentation broth (Jantasee et al. 2017). Reactive liquid-liquid extraction is particularly attractive for industrial application due to its scalability, lower energy demands, and straightforward operation (Aimer et al. 2016). In this process, the solvent phase often includes a reactive agent such as phosphorus-based compounds (Wang et al. 2001) or amines (Demmelmayr and Kienberger 2022) combined with diluents like octanol, decanol, dodecane, or heptane. These diluents typically constitute 60–85 wt% of the solvent mixture, helping adjust its physical and chemical characteristics (Mungma et al. 2019).

Despite the advantages, traditional LLE techniques suffer from major drawbacks. The use of volatile, toxic, and non-renewable solvents poses severe health risks and contributes to environmental degradation (Costa et al. 2014). Exposure to solvents like dichloromethane, chloroform, and toluene has been linked to neurological effects and disruptions in biological function. Consequently, their usage has been restricted in several countries due to safety and environmental concerns (Domínguez de María 2017). To address these challenges, researchers have focused on neoteric or next-generation solvents and eco-friendly alternatives to conventional solvents. These include Deep eutectic solvents (DESs), ionic liquids (ILs), bio-based solvents, and switchable solvents. These modern solvents are typically non-volatile, biodegradable, and can be synthesized from naturally available components. They adhere to the principles of green chemistry by minimizing waste, reducing toxicity, and enhancing process sustainability (Canadas et al. 2020). Among these, DESs stand out for their simplicity of preparation and

versatility. Formed by combining components that result in a eutectic mixture with a significantly reduced melting point, DESs function as a sub-class of ionic liquids. Their growing popularity in separation science is attributed to their customizable properties, low cost, and compatibility with environmentally sustainable processing. This paper presents a detailed review of the role of DESs in the extraction and separation of biocarboxylic acids. It outlines the types of DESs employed, highlights their separation performance, and discusses the influence of key parameters on extraction efficiency.

### Biocarboxylic acid

Biocarboxylic acids are a class of organic compounds that contain one or more carboxyl (-COOH) groups and are commonly derived from renewable biomass sources as shown in Fig.1. Examples include glutaric, lactic, levulinic, aspartic, succinic, itaconic, and protocatechuic acids. These acids are extensively utilized in the pharmaceutical, polymer, rubber, cosmetic, energy, and food industries for the synthesis of value-added products.



**Fig.1** Production and Separation of Bio-carboxylic acids

Typically, they are produced through biological routes such as microbial fermentation, chemical synthesis, and other bioprocessing techniques, using feedstocks like sucrose, fructose, xylose, and cellulose (Chen et al. 2022). Owing to their high industrial demand and alignment with sustainable practices, fermentation has become the preferred method for their production. However, the downstream separation of carboxylic acids produced via fermentation is still considered a significant challenge due to

its cost, complexity, and environmental implications. Traditional solvents used for extraction, including octanol, toluene, benzene, methyl isobutyl ketone, hexane, and butanol, are often toxic and expensive. To address these limitations, there is a growing interest in adopting environmentally friendly extraction strategies. Green solvents such as deep eutectic solvents and natural oils, have been explored for their potential in separating these acids. While DES offers high extraction efficiency and tunable properties, natural oils, although sustainable, often exhibit lower efficiency and difficulties in recovery from the organic phase.

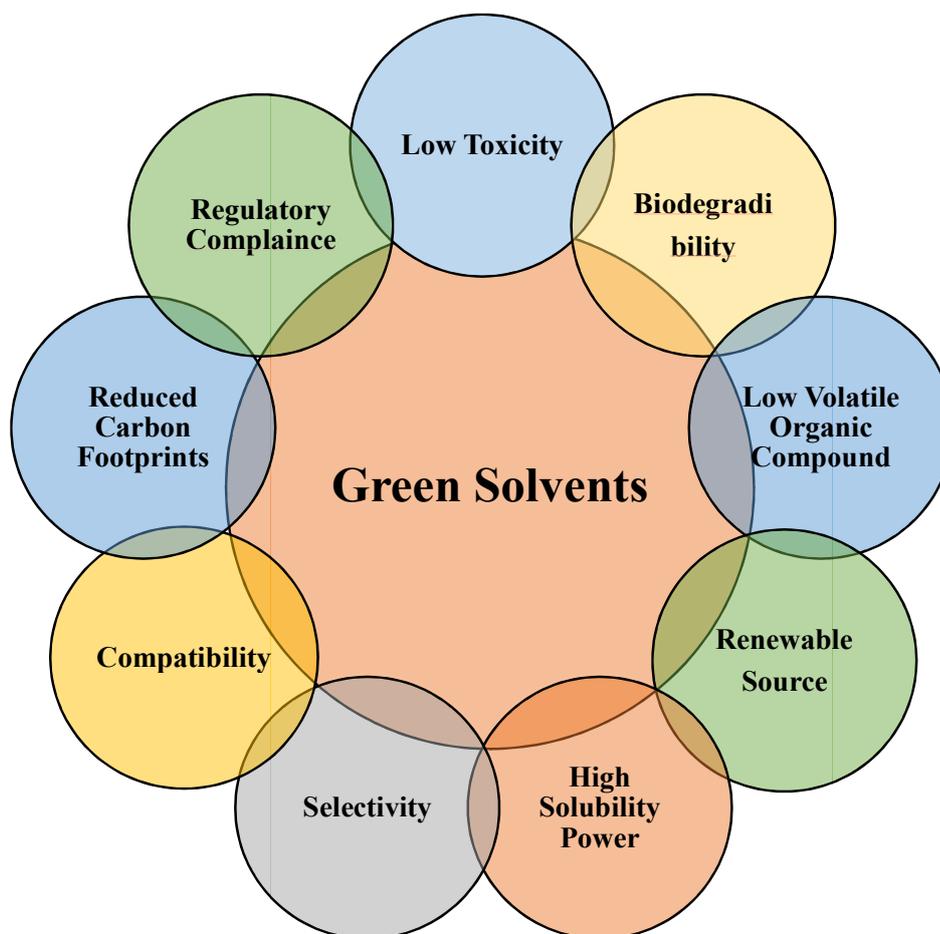
### **Conventional Solvents and Their Environmental Impact**

A wide variety of solvents are traditionally used in extraction processes, including aromatic hydrocarbons (e.g., benzene, toluene, xylene), aliphatic hydrocarbons (e.g., hexane, heptane, petroleum ether), chlorinated solvents (e.g., chloroform, dichloromethane, carbon tetrachloride), alcohols (e.g., methanol, ethanol, octanol, 1-decanol, isopropanol, butanol), ketones (e.g., acetone, methyl ethyl ketone, methyl isobutyl ketone, cyclohexanone), esters (e.g., ethyl acetate, butyl acetate, methyl acetate), ethers (e.g., diethyl ether, tetrahydrofuran, 1,4-dioxane), amides (e.g., DMF, NMP, DMA), nitriles (e.g., acetonitrile, propionitrile), organophosphorus solvents (e.g., Trioctylphosphine Oxide (TOPO), Tris(2-ethylhexyl) phosphine Oxide (TEHP), Tributylphosphate (TBP), Diphenylphosphinic Acid (DPPA), and amine-based solvents (e.g., Tri-n-octylamine (TOA), Tributylamine (TBA) (Sparkle et al. 2019). Most of these solvents are derived from petrochemical feedstocks, particularly from olefins like ethylene and propylene. Their widespread use in the chemical industry is largely due to their strong solvency, quick evaporation rates, availability, and low cost. Hydrocarbons, in particular, are commonly used in extractions for their excellent performance (Cravotto et al. 2022). However, the environmental implications of conventional solvents are considerable. Hydrocarbons, when released without combustion, can cause severe soil and water pollution. Exhaust emissions also contribute to air contamination, releasing substances that are toxic and potentially carcinogenic. Moreover, heavier hydrocarbon residues may lead to groundwater contamination (Straathof 2014). While esters are widely used for their favorable solvency, they are known to be harmful to aquatic ecosystems (Tamada and King 1990).

### **Green Solvents: A Sustainable Alternative**

The extensive use of organic solvents has raised serious concerns about environmental degradation and health risks. As a result, significant efforts have been made to develop green solvents environmentally benign alternatives that align with the goals of green chemistry. These solvents aim to prevent pollution at its source by minimizing the formation of toxic substances during chemical operations (Clarke et al. 2018). Derived from renewable resources such as agricultural feedstocks, green solvents are engineered to be safer and less hazardous. Key environmentally beneficial properties of green

solvents are summarized in Fig.2. They are increasingly favored for their reduced ecological impact, renewability, and economic viability (Varón et al. 2016). The adoption of green solvents represents a strategic shift in chemical industries toward more sustainable and health-conscious practices. Engine exhaust emissions release carcinogenic and toxic substances, while heavier hydrocarbons can contaminate groundwater and soil (Straathof 2014). Although esters are valuable solvents for extractions and other chemical processes, they pose a hazard to aquatic life (Tamada and King 1990).



**Fig. 2** Few properties of Green Solvents

When selecting the most appropriate solvent for a specific industrial application, it is essential to consider several factors carefully. These factors include solubility, polarity, volatility, flammability, boiling point, and cost. Organic solvents, widely used in industry and research, are highly volatile, lipophilic, highly volatile, and toxic, posing significant risks to the environment and human health. In recent years, scientists have developed various neoteric solvents, such as Ionic liquids, Deep Eutectic Solvents, bio-based solvents, and switchable solvents (Flores et al. 2018) a few examples are shown in Table 1. These neoteric solvents are considered safer alternatives to the hazardous organic solvents traditionally used. Researchers are increasingly interested in these unconventional solvents due to their

diverse potential applications, leading to a growing body of research in this field (Armenta et al. 2022)

**Table 1.** Types and Applications of a few Green solvents

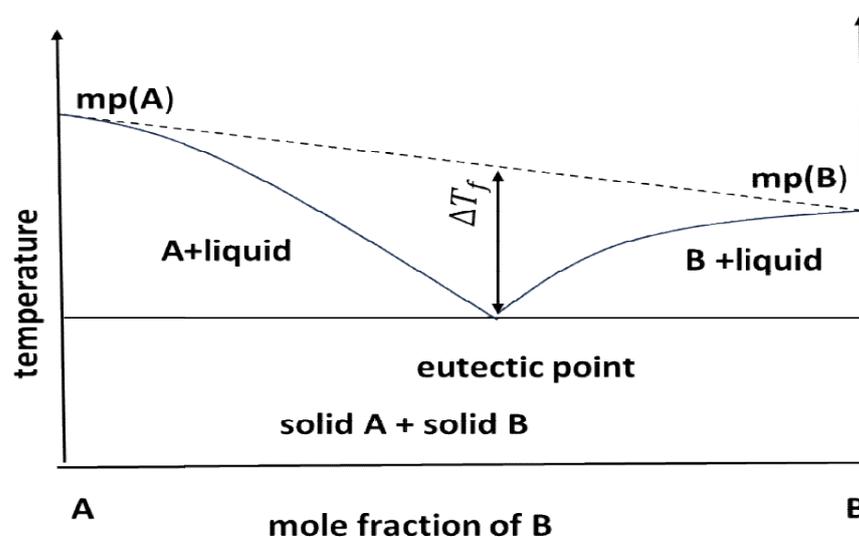
Type of Green Solvent	Examples	Applications	References
<b>Ionic Liquids (ILs)</b>	1-Butyl-3-methylimidazolium chloride ([BMIM]Cl), Choline acetate, 1-Ethyl-3-methylimidazolium tetrafluoroborate ([EMIM]BF <sub>4</sub> ), 1-Octyl-3-methylimidazolium hexafluorophosphate ([OMIM]PF <sub>6</sub> )	Extraction of bioactive compounds, biocatalysis, CO <sub>2</sub> capture, biomass processing, electrochemical applications	Rogers et al. (2003)
<b>Deep Eutectic Solvents (DES)</b>	Choline chloride + Urea, Betaine + Glycerol, Choline chloride + Ethylene glycol, Lactic acid + Glycerol	Nucleic acid genomics, drug delivery, metal extraction, biomass pretreatment, enzyme stabilization	Smith et al. (2014a)
<b>Switchable Solvents</b>	CO <sub>2</sub> -triggered solvents, Reversible ionic liquids, Piperidine-based solvents, Amidines	CO <sub>2</sub> capture, chemical separations, green synthesis, catalytic processes, recycling of solvents	Jessop et al. (2010)
<b>Bio-based Solvents</b>	Ethyl lactate, Limonene, 2- Methyl tetrahydrofuran, $\gamma$ - valerolactone (GVL), Bio- butanol, Dimethyl carbonate (DMC)	Pharmaceutical manufacturing, extraction of natural products, paints and coatings, renewable fuel production	Clark et al. (2015)

### Deep Eutectic Solvents

Carboxylic acids are integral to the food, pharmaceutical, and polymer industries, necessitating their recovery from dilute aqueous systems for further use. Conventional extraction methods have long relied on volatile organic compounds (VOCs); however, these are associated with severe environmental and health concerns. As a result, Deep Eutectic Solvents have emerged as an innovative and eco-conscious alternative. DES are a relatively new category of green solvents, gaining recognition for their biodegradability, low toxicity, and simple preparation methods (Ji et al. 2021). Their applications span a wide range of fields, including liquid-liquid extraction, electrochemistry, heterogeneous catalysis, organic reactions, and nanotechnology (Aşçı et al. 2021; van den Bruinhorst et al. 2018). In comparison, Ionic liquids have been acknowledged as cutting-edge solvents in separation science. These are typically composed of organic cations like 1-ethyl-3-methylimidazolium, tetraethylammonium, or dialkyl imidazolium, paired with either organic or inorganic anions (e.g., chlorate, nitrate, perchlorate, thiocyanate). Their melting points below 100°C and liquid state at room temperature offer advantages for separation processes (Haider et al. 2018). Despite their performance, ILs pose economic, environmental, and disposal challenges due to their high cost, potential toxicity, and non-biodegradable nature. To counter these limitations, Wasyłka et al. (2020) recommend replacing ILs with DES. These alternatives replicate many of the desirable features of ILs while avoiding issues like synthetic complexity and hazardous residues. DES are often described as ionic liquid analogs due to their comparable thermal stability, low vapor pressure, customizable viscosity, non-flammability, and adjustable melting points

(Liu et al. 2020a; Zhang et al. 2017). Nevertheless, their chemical behaviors diverge significantly from ILs, enabling distinct applications in green chemistry (Martins et al. 2017). While ILs consist of a discrete combination of a cation and anion, DES are eutectic blends formed through hydrogen bonding interactions between Lewis or Brønsted acid-base pairs. These can involve both ionic and non-ionic constituents, typically classified into binary or ternary systems depending on their composition. When mixed in precise molar ratios, the resulting systems exhibit melting points significantly lower than those of the individual components (Zhang et al. 2012).

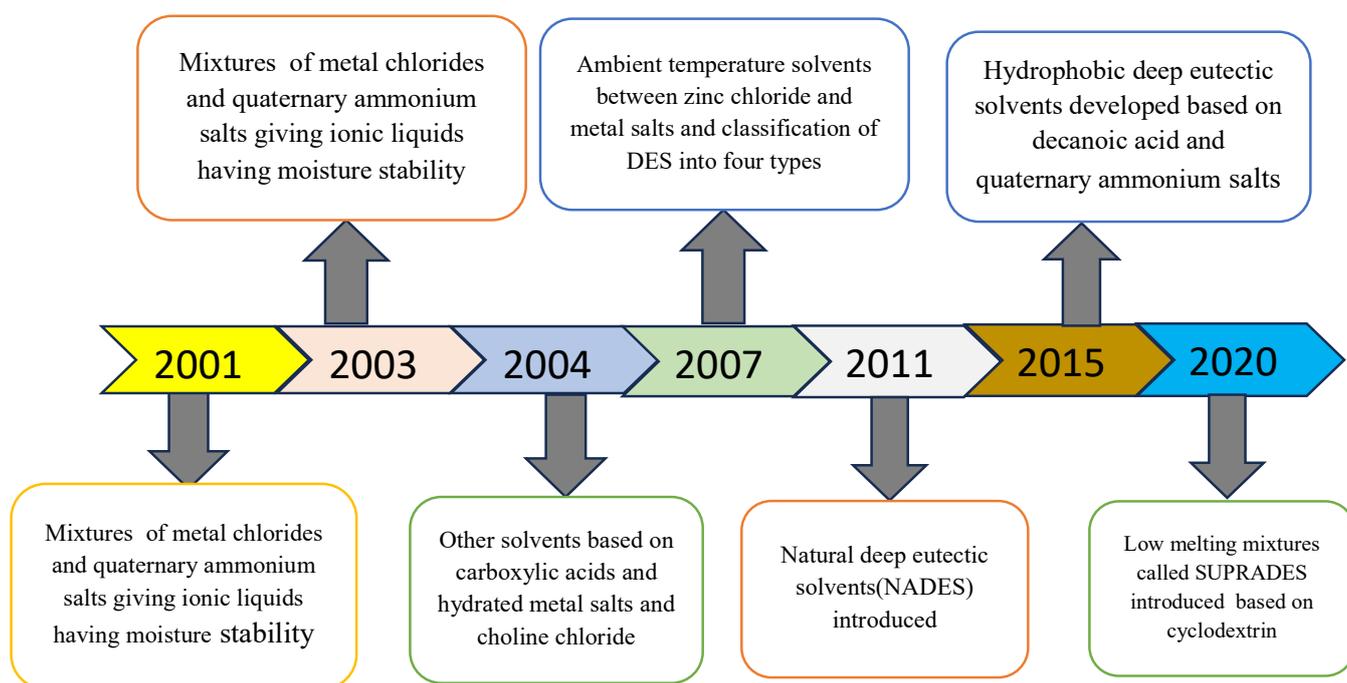
The term “eutectic” is rooted in the Greek word *εὐτέκτος*, meaning easily melted, referencing the unique melting behavior at the eutectic point. This is the specific composition and temperature at which the solid components transition to a liquid at the lowest temperature possible. However, defining a DES is still a topic of debate, as many immiscible solid mixtures can form eutectics, and numerous compounds can engage in hydrogen bonding when combined. In 2019, Martins et al. proposed a more specific definition of DES as "mixtures of two or more pure substances exhibiting a eutectic point temperature lower than that of an ideal solution, with considerable deviation from ideal mixing behavior." The adaptability in designing DESs lies in their tunable composition. Abbott et al. (2003) were among the first to coin the term "Deep Eutectic Solvents", when studying eutectic mixtures made from quaternary ammonium salts and hydrogen bond donors (HBDs). For example, combining choline chloride (melting point 302°C) and urea (melting point 133°C) in a 1:2 molar ratio resulted in a deep eutectic system with a melting point of 12°C, a drastic reduction due to hydrogen bonding between chloride ions and urea molecules. This behavior was verified via nuclear magnetic resonance (NMR) spectroscopy. These systems not only remain liquid at ambient temperature but also exhibit excellent solubilizing capabilities for various solutes. Other DESs formulated from choline chloride and carboxylic acids have demonstrated strong performance in dissolving metal oxides (Abbott et al. 2004).



mp – melting point,  $\Delta T_f$  – freezing point

**Fig. 3** Eutectic composition on a binary phase diagram

Smith et al. (2014) further explained that in a binary DES composed of components A and B, the freezing point depression ( $\Delta T_f$ ) from the ideal mixture is indicative of the interaction strength between the components—the greater the interaction, the more pronounced the  $\Delta T_f$ . This concept is represented visually in Fig 3. In Type I eutectics, involving halometallates, similar species are formed due to the interaction of metal halides with halide anions from quaternary ammonium salts. These eutectics often display melting point depressions ranging between 200–300°C. For practical DES systems near room temperature, the metal halide used should have a melting point around or below 300°C. Figure 4 highlights the key milestones in the evolution of deep eutectic solvents (DESs), as documented in various studies (Abbott et al. 2001, 2003; Capper et al. 2004; Osch et al. 2015).



**Fig. 4** Milestones in the Evolution of Deep Eutectic Solvents

### Advantages of Deep Eutectic Solvents (DESs)

Deep Eutectic Solvents (DESs) have become increasingly prominent in green chemistry due to their many environmentally and industrially beneficial characteristics. Table 2 shows the key advantages that make DESs favorable as green alternatives to traditional solvents

### Preparation Methods for DES

Multiple techniques are employed to synthesize high-purity DESs in a cost-effective manner. Abbott et al. (2004) identified three main methods for DES formation.

**Heating Method:** The most commonly used approach involves mixing and heating the DES components until a clear and uniform solution is obtained. The temperature generally ranges from 50°C to 100°C, depending on the thermal properties and melting points of the starting materials (Domańska et al.

2016; VandenElzen and Hopkins 2019).

**Table 2.** Advantages of Deep Eutectic Solvents

<b>Advantage</b>	<b>Description</b>	<b>References</b>
<b>Renewable and Biodegradable Sources</b>	Synthesized from bio-based materials like sugars and organic acids; non-toxic, biodegradable, and environmentally friendly.	Cvjetko Bubalo et al. (2015); Płotka-Wasyłka et al. (2017)
<b>Reduced Toxicity</b>	Pose minimal health and environmental risks across their lifecycle, making them safer for industrial and lab use.	Alshammari et al. (2021); Carpentieri et al. (2021)
<b>High Versatility</b>	Capable of dissolving a wide range of polar and non-polar compounds; tunable properties by adjusting HBDs and HBAs.	McReynolds et al. (2022)
<b>Enhanced Energy Efficiency</b>	Low vapor pressure results in slow evaporation, reducing energy consumption in recovery and lowering operational costs.	Ma et al. (2018)
<b>Minimal VOC Emissions</b>	Extremely low volatility minimizes release of harmful Volatile Organic Compounds (VOCs), ensuring cleaner processing environments.	Li et al. (2023)
<b>Reusability and Ease of Recovery</b>	Easily separated using simple methods like cooling or adding anti-solvents, supporting low-energy recycling and reducing solvent waste.	Isci and Kaltschmitt (2022)
<b>Green Synthesis Applications</b>	Serve as efficient media for biomass processing, catalysis, and metal recovery, promoting sustainable and clean chemical synthesis.	Jha et al. (2023); Nam et al. (2023)

**Freeze Drying Method:** This technique starts by dissolving the components in water with ultrasonication, vortexing, or mild heating. The water is then removed using freeze-drying, leaving behind a dry eutectic mixture (Gutiérrez et al. 2022). Alternatively, centrifugal vacuum evaporation or rotary evaporation can be employed to eliminate water content (Dai et al. 2013; Wikene et al. 2017; Pisano et al. 2018).

**Grinding Method:** In this solvent-free method, the solid constituents are manually ground in a mortar at room temperature until a homogeneous mixture is formed. This technique is particularly appealing for its simplicity and low energy demand (Cui, Li, and Bao 2019; Florindo et al. 2014, 2019). The physicochemical characteristics of the resulting DESs such as viscosity, solubility, density, and melting point depend heavily on several factors: molar ratio of components, preparation temperature, presence of water, and the nature of the HBD and HBA used (Li et al. 2023). DES consist of a quaternary ammonium salt as a Hydrogen bond acceptor and a Hydrogen bond donor, as shown in Fig. 5. Most research has focused on quaternary ammonium and imidazolium cations, particularly using choline chloride  $[\text{ChCl}, \text{HOC}_{22}\text{H}_{44}\text{N}^+(\text{CH}_3)_3\text{Cl}^-]$ . Examples of eutectics include the well-known chloroaluminate/imidazolium salt melts and ionic liquids formed with imidazolium salts and various metal halides, including  $\text{FeCl}_2$ . Scheffler and Thomson's study highlights DESs with EMIC and metal halides like  $\text{CuCl}$ ,  $\text{AgCl}$ ,  $\text{LiCl}$ ,  $\text{CuCl}_2$ ,  $\text{SnCl}_2$ ,  $\text{CdCl}_2$ ,  $\text{ZnCl}_2$ ,  $\text{YCl}_3$ .

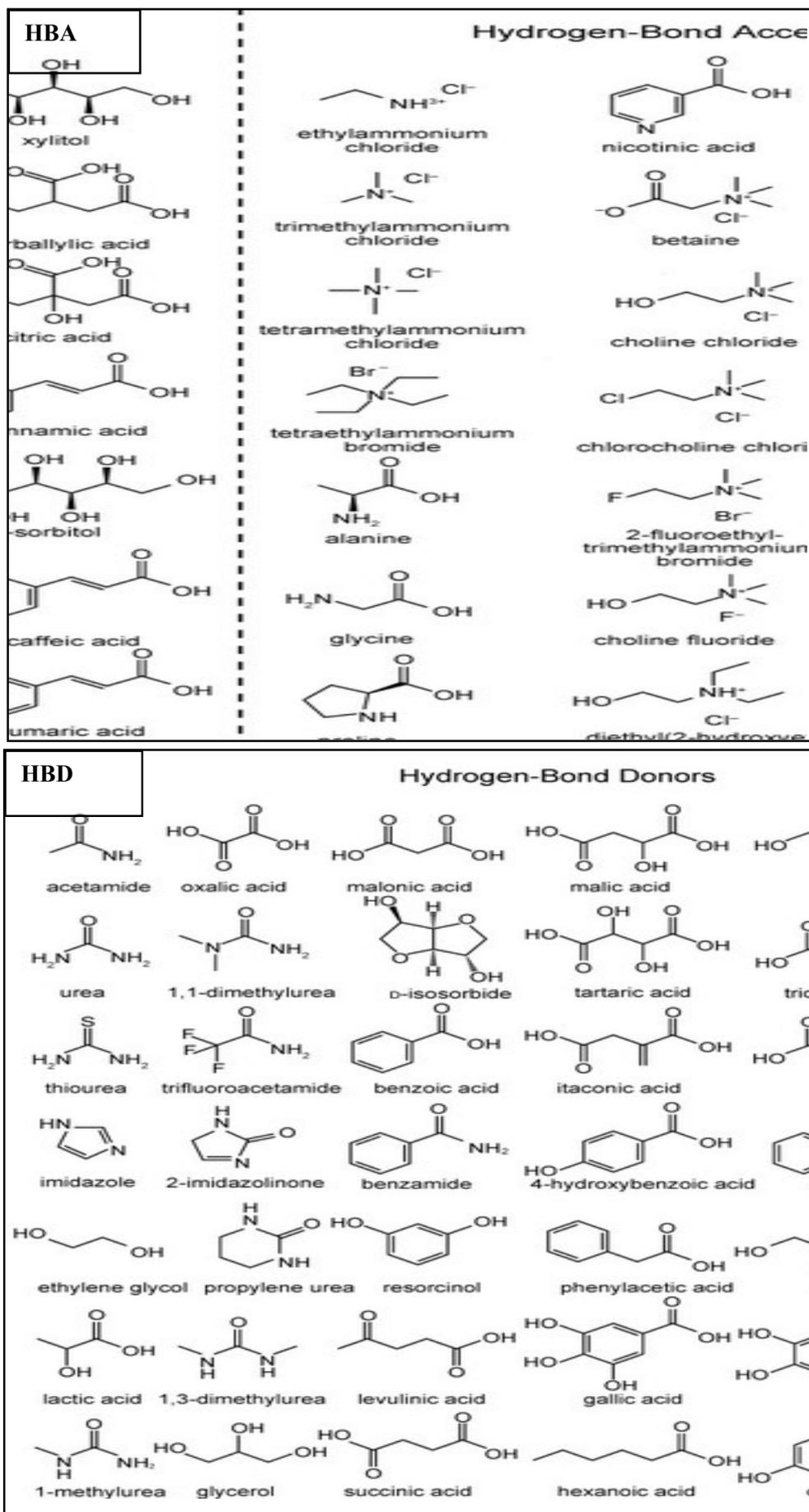


Fig. 5 Common Hydrogen bond acceptors (HBAs) and Hydrogen bond donors (HBDs)

### Applications of Deep Eutectic Solvents

Deep Eutectic Solvents have garnered significant attention due to their broad application potential across various scientific and industrial fields. Fig 6 illustrates some of the key domains currently under investigation. One emerging area of interest is carbon dioxide (CO<sub>2</sub>) capture, where DES demonstrate considerable potential as substitutes for ionic liquids. In the realm of energy storage, DES are being studied as electrolytes in lithium-ion batteries (LIBs). Their advantages include high ionic conductivity, low flammability, and a wide liquidus range, which contribute to safer and more efficient battery systems (Hansen et al. 2021). In biotechnology and molecular biology, DES are finding roles in genomic research. Specific mixtures, such as a 1:1 blend of acetic acid and choline chloride, have been shown to accelerate the fibrillation of lysozyme, illustrating the solvents' unique behavior in aqueous systems (Smith et al. 2014). Moreover, DESs have also been investigated for their use in cryopreservation and protein refolding, particularly in plant studies (Paiva 2014). DESs are gaining attention in biocatalysis, supporting various enzymatic reactions (Jiang et al. 2019). Their compatibility with bioactive solutes highlights their versatility in biochemical applications (Zhao et al. 2013). In the pharmaceutical sector, DES have shown promise in drug solubility enhancement (Shekaari et al. 2018). Additionally, DES have demonstrated effectiveness in biomass pretreatment and extraction, contributing to more sustainable and efficient bioresource utilization.

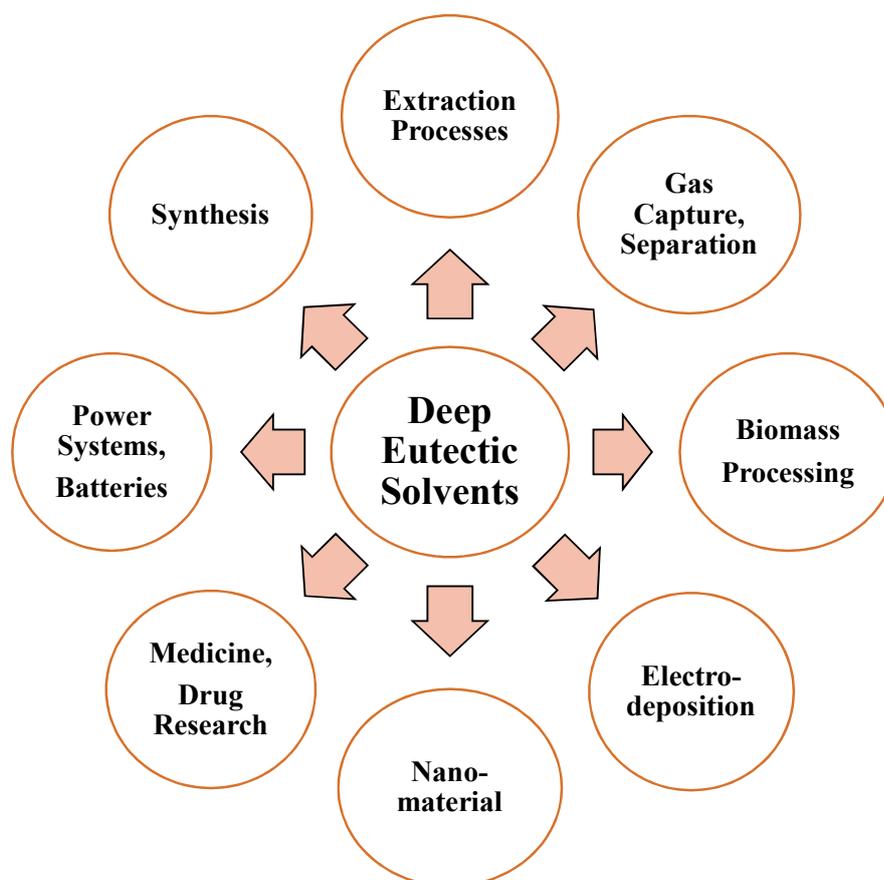
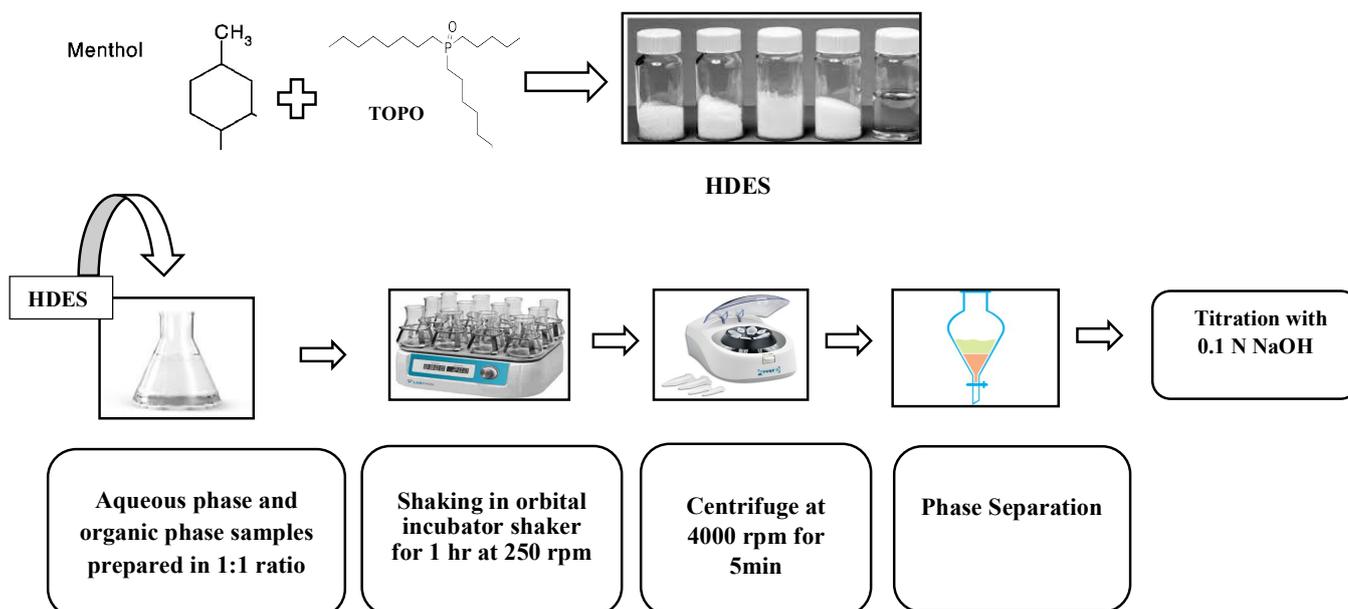


Fig. 6 Deep Eutectic solvent applications

## DES for Carboxylic Acid Separation

Carboxylic acids, widely utilized across the chemical, food, and pharmaceutical industries, are often generated through fermentation processes, resulting in dilute aqueous solutions typically around 10% by weight. Environmental regulations and economic considerations have intensified the need to recover these acids from wastewater streams and industrial effluents. Among the various methods studied, reactive extraction has emerged as a highly efficient strategy for isolating carboxylic acids from such media (Datta et al. 2015). This technique combines physical extraction, where undissociated acid molecules partition between the organic and aqueous phases, with chemical extraction, which involves acid-extractant interactions leading to complex formation (Wasewar 2012). This dual-mode extraction mechanism significantly enhances the overall efficiency of the process. Therefore, the selection of both diluents and extractants is pivotal in determining extraction effectiveness. Research has shown that hydrocarbons, alcohols, esters, and ketones are commonly employed as diluents, while amines such as Alamine 336, Aliquat 336, Trioctylamine, and Amberlite LA-2 and organophosphorus compounds like Trioctyl Phosphine Oxide (TOPO) and Tributyl Phosphate (TBP) serve as extractants. Studies suggest that among the two, amine-based extractants generally exhibit superior extraction performance compared to organophosphorus alternatives (Inyang et al. 2021; Pandey et al. 2020).



**Fig. 7** Experimental procedure for the separation of glutaric acid with Menthol-TOPO DES

Weighed amounts of glutaric acid was dissolved in double-distilled water to produce aqueous solutions with the desired initial concentration. Menthol was taken as HBD and TOPO (trioctylphosphine oxide) was taken as HBA in the molar ratio of 1:1 as shown in Fig 7. The prepared mixture was kept in a water bath shaker at 353 K for 60 min until a homogenous liquid was obtained. The HDES

solution(extractant) and glutaric acid aqueous solutions were mixed in a 1:1 ratio with (an aqueous solution of 10ml mixed with a 10 ml pure solvent(extractant)). The flasks were placed in an orbital shaking incubator (Model: S-24BL, REMI India) set at  $298.15 \pm 1$  K and 220 rpm for 1 hrs which was sufficient time to reach equilibrium based on preliminary experimental studies. Subsequently, the samples were centrifuged at 4280 rpm for 5 minutes (REMI CENTRIFUGE-4C, India) for phase separation. The aqueous phase was carefully collected using a syringe needle and its concentration was determined by titration with 0.1 N NaOH using 2-3 drops of phenolphthalein as an indicator

DES have emerged as highly adaptable systems that can be fine-tuned for the selective separation of carboxylic acids, particularly from complex solutions like fermentation broths. Once the extraction is complete, carboxylic acids can be efficiently recovered through changes in pH, temperature, or by adding water to disrupt the DES structure. The tunable characteristics of DESs enable them to optimize extraction efficiency, selectivity, and environmental sustainability in separation processes (Smith et al. 2014). Table 3 provides a comparison of various DESs used for the extraction of short-chain carboxylic acids, including acetic, propionic, and butyric acids, based on recent literature.

**Table 3.** Extraction efficiencies (E%) reported in the literature for various DES

DES	Acetic Acid (E%)	Propionic Acid (E%)	Butyric Acid (E%)	References
Thymol: Octanoic acid	35.5 %	73.1 %	82.1 %	Rodríguez et al. (2019)
Menthol: Octanoic acid	15.7 %	60.4 %	82 %	Rodríguez et al. (2019)
Decanoic acid: methyl-tri-octyl-ammonium Chloride	38 %	70.5 %	89.8 %	Osch et al. (2015)
Decanoic acid: tetra-heptyl-ammonium Chloride	32 %	76.5 %	91.5 %	Osch et al. (2015)
Decanoic acid: tetra-octyl-ammonium bromide	25 %	52.7%	81.3 %	Osch et al. (2015)
Decanoic acid: Methyl-tri-octyl-ammonium bromide	29.7 %	63.4 %	83.1 %	Osch et al. (2015)

The table illustrates the differing extraction performances depending on DES composition. Among the systems studied, DES made using decanoic acid combined with quaternary ammonium salts showed the highest extraction potential, especially for butyric and propionic acids. Notably, a formulation of decanoic acid and tetraheptylammonium chloride demonstrated excellent efficiency, achieving 91.5% recovery for butyric acid and 76.5% for propionic acid. Similarly, the combination of decanoic acid with methyltrioctylammonium chloride exhibited strong results, recovering 89.8% of butyric acid and 70.5%

of propionic acid. In contrast, DESs using menthol or thymol paired with octanoic acid were less effective, particularly for acetic acid. For instance, the menthol–octanoic acid mixture resulted in only 15.7% extraction efficiency for acetic acid. These outcomes highlight the significance of selecting appropriate hydrogen bond donors and hydrogen bond acceptors to enhance DES performance in extraction tasks. The results also indicate that more hydrophobic and longer-chain acids, such as butyric acid, are extracted more efficiently using DES. This suggests that acid molecular structure, particularly chain length and hydrophobicity, plays a key role in determining extraction success.

#### ***HDES for Monocarboxylic Acid Extraction***

In a study conducted by Lalikoglu (2022), hydrophobic deep eutectic solvents (HDESs) were formulated using menthol and a series of fatty acids (nonanoic, decanoic, and dodecanoic) to evaluate their capacity to extract formic acid from aqueous solutions. The experiments incorporated tri-n-octylamine (TOA) and Amberlite LA-2 as extractants. While physical extraction using HDESs alone provided a modest yield of 10–13%, incorporating TOA increased extraction to 90–93%, and Amb.LA-2 to 85–88%. The best performance was achieved using TOA with menthol-dodecanoic acid, reinforcing the established notion that tertiary amines (TOA) are generally more effective than secondary amines (Amb.LA-2), as also observed in Kumar et al. (2021).

In related work, Aşçı and Lalikoglu (2021) developed DES systems based on menthol and trioctylphosphine oxide (TOPO) in varying ratios to examine their efficiency in extracting acids of different structural complexities. Monocarboxylic acids like propionic acid achieved the highest extraction yield (79%,  $K_D = 3.76$ ), followed by formic acid (42.13%,  $K_D = 0.73$ ) and acetic acid (46.54%,  $K_D = 0.37$ ). Polyfunctional acids such as citric and glycolic acid showed lower extraction efficiencies, attributed to their higher hydrophilicity and stronger interactions with the aqueous phase. The study further utilized Response Surface Methodology (RSM) to optimize the conditions for efficient separation, confirming the potential of menthol–TOPO DESs in selective and reactive extraction applications.

#### ***Extraction Performance of TOPO- and Glycerol-Based DESs for Carboxylic Acids***

Gautam et al. (2022) prepared DESs by blending TOPO and menthol at molar ratios of 1:1 and 2:1 for extracting nicotinic acid. The 2:1 mixture remained liquid at room temperature and demonstrated an extraction efficiency of 88.33% ( $K_D = 7.8$ ). This DES system maintained stability over five extraction cycles and was efficiently regenerated using 1 N NaOH. In another study, Sahin et al. (2022) introduced glycerol-based DESs, pairing glycerol with quaternary ammonium salts and amine-based HBAs in a 1:2 ratio. When diluted with diethyl malonate, these systems enhanced acetic acid extraction to 16.98%, outperforming traditional solvents and ionic liquids. Brouwer et al. (2021) explored two DES systems: one composed of thymol and L-menthol (1:1) and the other using TOPO with L-menthol (1:3). Their results highlighted a positive relationship between extraction efficiency and acid hydrophobicity. The TOPO-L-menthol DES outperformed the thymol-based system, achieving distribution coefficients of 6.7

for propionic acid and 6.2 for butyric acid, confirming its effectiveness for selectively extracting more hydrophobic acids.

#### ***Thymol-Based DESs as Bio-Compatible Substitutes***

The biocompatibility of thymol-based DESs (tmDES) was investigated by Demmelmayer et al. (2022) for recovering acids from sweet sorghum silage press juice (SPJ). These DESs were synthesized by varying thymol content (20–70 mol%) and heating to form clear, stable solutions. As thymol concentration increased, extraction of acetic acid improved from 59.9% to 69.2%, while oxalic and lactic acid extraction decreased slightly. The results were linked to rising equilibrium pH levels, which affected acid solubility. The primary mechanism involved hydrogen bonding and proton exchange with TOA, particularly favoring strong acids with lower pKa values. In real biomass samples (pSPJ), acetic acid extraction efficiency rose to 86.5%, with lactic acid extraction also improving over model systems. DES formulations such as tmDES1 (33.3:66.7 thymol) and tmDES2 (60:40 thymol) outperformed 1-octanol, especially in recovering lactic acid (51.1%) and acetic acid (82.2%).

#### ***HDES Optimization for Maximum Efficiency***

Yıldız et al. (2023) further optimized the performance of a menthol–decanoic acid HDES using central composite design (CCD) and RSM. At a molar ratio of 0.5 HDES and 1.9 mol/L TOA, the extraction efficiencies for formic, propionic, and acetic acids were 88.71%, 92.52%, and 95.90%, respectively. The study emphasized the importance of acid concentration, solvent composition, and extractant dosage.

#### ***Structural Stability and Reusability of HDES***

To assess long-term performance, Vidal et al. (2024) synthesized HDESs by combining TOPO with thymol or menthol, confirmed by  $^{31}\text{P}$ -NMR spectroscopy. These solvents exhibited strong extraction performance for long-chain acids ( $\text{C}_5$  and above), with efficiencies up to 92%. They retained functionality over three regeneration cycles using 0.1 M NaOH, achieving 81% recovery for hexanoic acid and 65% for valeric acid, indicating suitability for industrial-scale separation.

#### ***Storage Stability of Ionic vs. Non-Ionic HDES***

Darwish et al. (2021) investigated the storage stability of six HDESs three and three non-ionic (menthol-based) used for extracting volatile fatty acids (VFAs) from fermented wastewater. The ionic HDESs showed instability, forming solids or precipitates due to poor hydrogen bonding and melting near room temperature. In contrast, menthol-based HDESs remained stable, with menthol–lauric acid (1.5:1) selected for further testing. This solvent achieved 91.35% extraction efficiency for acetic acid and showed increasing performance with acid chain length: valeric (96.5%) > butyric (89.9%) > propionic (72.3%) > acetic (40.5%). Regeneration through vacuum evaporation at 303.2 K and 20 bar effectively reduced water content from 2.1% to 0.08%, demonstrating the solvent's recyclability.

Table 4 provides insights into recent publications on carboxylic acid extraction with hydrophobic DES.

**Table 4.** Recent publications on carboxylic acids extraction with hydrophobic DES (HDES)

Acid	DES	Conditions	Extraction Efficiency (E%)	References
<b>Acetic Acid</b>	DBA: Geraniol, DBB: Geraniol	Temp: 28°C Phase ratio: 1:1 Conc.: 0.1 mol/L	DBA: 61.6%, DBB: 51.69%	Liu et al. (2023a)
	L-menthol: TOPO, L-menthol: thymol	Temp: 25°C Phase ratio: 1:1	Thymol: 39% TOPO: 66.66%	Brouwer et al. (2021)
<b>Adipic Acid</b>	TOPO: dodecanoic acid	Temp: 25°C Conc.: 10 g/L Phase ratio: 50% (v/v)	TOPO: 97.67%	Riveiro et al. (2020)
<b>Butyric Acid</b>	L-menthol: nonanoic acid, decanoic acid, dodecanoic acid	Temp: 250°C Conc.: 10% (w/w) Extraction time: 90 min Phase ratio: 2:1	menthol: nonanoic acid: 83.38%, menthol: dodecanoic acid: 84.73%, menthol: decanoic acid: 82.74%	Lalikoglu (2022)
	L-menthol: TOPO, L-menthol: thymol	Temp: 25°C Phase ratio: 1:1	TOPO: 87%, Thymol: 78.26%	Brouwer et al. (2021)
<b>Furfural</b>	Camphor: octanoic acid	Temp: 40°C Extraction time: 50 min Phase ratio: 1:1 pH: 7	Camphor: 86.71%	Chelstowska et al. (2022)
<b>Levulinic Acid</b>	DBA: Geraniol, DBB: Geraniol	Temp: 28°C Phase ratio: 1:1 Conc.: 0.1 mol/L	DBA: 42.52%, DBB: 27.53%	Liu et al. (2023)
	Camphor: octanoic acid	Temp: 40°C Extraction time: 50 min Phase ratio: 1:1 pH: 7	Camphor: 70.64%	Chelstowska et al. (2022)
	TOPO: dodecanoic acid	Temp: 25°C Conc.: 10 g/L Phase ratio: 50% (v/v)	TOPO: 80.37%	Riveiro et al. (2020)
<b>Propionic Acid</b>	L-menthol: TOPO, L-menthol: thymol	Temp: 25°C Phase ratio: 1:1	TOPO: 86.11%, Thymol: 69.69%	Brouwer et al. (2021)
<b>Succinic Acid</b>	DBA: Geraniol, DBB: Geraniol	Temp: 28°C Phase ratio: 1:1 Conc.: 0.1 mol/L	DBA: 74.1 %, DBB: 58.5 %	Liu et al. (2023)
	TOPO: dodecanoic acid	Temp: 25°C Conc.: 10 g/L Phase ratio: 50% (v/v)	TOPO: 88.07%	Riveiro et al. (2020)

### Factors Influencing Extraction Efficiency

Deep eutectic solvents (DESs), formed by combining hydrogen bond acceptors (HBAs) and hydrogen bond donors (HBDs), represent a flexible solvent system capable of selectively separating

carboxylic acids from aqueous environments. The extraction mechanism relies on the reversible interaction between the acid molecules and the DES components, resulting in the formation of acid DES complexes that enhance the efficiency of the process. Particularly, hydrophobic DESs (HDESs) offer an environmentally friendly alternative to traditional organic solvents and hold significant potential for use in biocarboxylic acid purification. The efficiency of reactive extraction using DESs depends on a variety of interconnected parameters. These include the initial concentration of the acid, operating temperature, molar ratio of the HDES components, aqueous phase pH, volume phase ratio, and type of DES used. These factors work synergistically, and optimizing their values is crucial to achieving maximum extraction performance.

### ***Effect of Stirring Time***

Stirring duration plays a vital role in facilitating the mass transfer of carboxylic acids from the aqueous layer to the organic DES phase. Adequate stirring allows the system to move toward equilibrium, thereby improving the overall efficiency of the extraction process (Inyang et al. 2020). If the contact time is too short, the system may not reach equilibrium, leading to partial extraction and reduced performance. In a study by Darwish et al. (2021), a menthol: lauric acid (1.5:1) HDES was employed for the extraction of 3% (w/w) acetic acid at 298 K. The results demonstrated a clear correlation between stirring time and extraction efficiency. Even with just 2 minutes of mixing, a notable 35.2% extraction was observed, likely due to the low viscosity and high affinity of the HDES toward acetic acid. As stirring time increased from 5 to 30 minutes, a gradual improvement in efficiency was recorded, reaching 40.5%. Beyond this point, up to 120 minutes, no significant changes were observed, indicating that 30 minutes of stirring was sufficient to attain equilibrium (Gano et al., 2017). Table 5 presents data from various literature sources detailing how stirring time affects the extraction efficiency of carboxylic acids using DES.

**Table 5.** Effect of Stirring Time on Extraction Efficiency of carboxylic acids using various HDES

<b>Acid</b>	<b>HDES</b>	<b>Stirring time</b>	<b>%E</b>	<b>References</b>
<b>Acetic acid</b>	Thymol: TOPO	30 min	44.1%	Vidal et al. (2024)
	Thymol: Menthol	30 min	58.7%	Vidal et al. (2024)
	Menthol: Lauric acid	30 min	40.5%	Darwish et al. (2021)
<b>Adipic Acid</b>	TOPO: Dodecanoic acid	60 min	80.4%	Riveiro et al. (2020)
	TOPO: Decanoic acid	60 min	61.2 %	Riveiro et al. (2020)
<b>Butyric Acid</b>	Thymol: Menthol	30 min	49.3%	Vidal et al. (2024)
<b>Propionic acid</b>	Thymol: Menthol	30 min	58.7%	Vidal et al. (2024)

It highlights the extraction efficiencies of various biocarboxylic acids using different hydrophobic deep eutectic solvents (HDESs). For acetic acid, Thymol: Menthol exhibited the highest efficiency (58.7%), while Menthol: Lauric acid showed the lowest (40.5%). Adipic acid was more effectively extracted using TOPO: Dodecanoic acid (80.4%) compared to TOPO: Decanoic acid (61.2%). Butyric and propionic acids also showed moderate efficiencies with Thymol: Menthol, at 49.3% and 58.7%, respectively. These results indicate that both acid type and HDES composition significantly influence extraction performance.

### ***Effect of phase ratio***

According to Keshav et al. (2014), when the volume of the organic phase is low relative to the aqueous phase, the extraction remains incomplete due to insufficient solvent to accommodate the acid load. In a study by Liu et al. (2023), the effect of varying the organic-to-aqueous ratio on the extraction of acetic acid (AA), lactic acid (LA), and succinic acid (SA) was investigated using di-n-butylacetamide-Geraniol (DBA-Ger) DESs at 303 K. The results showed that increasing the phase ratio from 1:1 to 5:1 led to an improvement in extraction efficiency by 20–35%, depending on the acid. Achieving higher extraction yields in fewer stages is critical in industrial applications, although the extractant did not reach its saturation point. Therefore, maintaining an extraction range of 50% to 70% is considered cost-effective in large-scale systems (Moreira et al. 2022). For specific fermentation broths, the recommended phase ratios are 2:1 for lactic acid, less than 1 for succinic acid, and 1:1 for acetic acid.

Further studies by Liu et al. (2023) evaluated menthol–lauric acid HDESs for the reactive extraction of 3 wt% acetic acid. By altering the phase ratio from 1:4 (20 wt% HDES) to 4:1 (80 wt% HDES), extraction efficiency increased from 13.5% to 56.6%. This highlights the significant sensitivity of acetic acid extraction to phase ratio, with higher HDES content in the presence of water resulting in improved performance. Despite the improvement, the distribution coefficient ( $K_D$ ) remained relatively low, as also observed by Almustafa et al. (2021).

### ***Effect of Temperature***

Temperature significantly affects both mass transfer kinetics and the thermodynamic properties of the system. It influences how well the acid-extractant complex forms and remains stable, with an optimal temperature required to balance efficiency and solvent integrity. Using a 1:1 phase ratio, Liu et al. (2023) tested a temperature range of 298 K to 338 K with DBA-Ger DESs. As shown in Table 6, extraction efficiency varied with temperature for different acids. To understand the underlying thermodynamics, changes in Gibbs free energy ( $\Delta G$ ), entropy ( $\Delta S$ ), and enthalpy ( $\Delta H$ ) were calculated based on the methods outlined by Liu et al. (2020). These parameters are essential for translating lab-scale data into industrial-scale processes. The extraction was found to be exothermic, as indicated by negative enthalpy values. The calculated enthalpies were 4.53 kJ/mol for acetic acid, 2.35 kJ/mol for lactic acid, and 16.72 kJ/mol for succinic acid. The magnitude of the enthalpy change followed the order:  $\Delta H(\text{SA}) > \Delta H(\text{AA}) > \Delta H(\text{LA})$ . This indicates that succinic acid is more responsive to temperature changes than lactic acid. Once extracted, succinic acid becomes harder to strip back into the aqueous phase when heat is applied, suggesting a stronger interaction with the HDES (López et al. 2023). Higher temperatures can also disrupt hydrogen bonding between carboxylic acids and DES components, which may reduce extraction efficiency (Athankar et al. 2016). Therefore, identifying a suitable temperature range is crucial to maintaining both complex stability and solvent performance.

Table 6 presents the extraction efficiency of various carboxylic acids using different hydrophobic deep eutectic solvents (HDESs) across a range of temperatures. For citric acid, a TOA + Menthol-TBP

system showed a decreasing trend in efficiency from 65.60% at 298.15 K to 57.50% at 338.15 K, indicating temperature sensitivity. Adipic acid demonstrated consistently high extraction with TOPO–Decanoic acid, maintaining over 84% efficiency at both 298.15 K and 313.15 K. Levulinic acid also performed well with the same solvent, although its efficiency dropped from 82.32% to 64.85% with increasing temperature. Succinic acid showed moderate efficiency with TOPO–Decanoic acid and a slight decline with rising temperature. DBA–Geraniol emerged as an effective solvent system for levulinic, acetic, and lactic acids, although all three showed a gradual decrease in extraction efficiency as temperature increased. Overall, the results underline the critical influence of both solvent composition and operating temperature on the extraction behavior of different acids.

**Table 6.** Extraction Efficiencies of various acids with DES at different working temperatures.

Carboxylic Acid	HDES	Temperature (K)	Extraction Efficiency (E%)	Reference
Citric Acid	TOA + Menthol-TBP	298.15	65.60	Baş et al. (2024)
		318.15	62.08	
		338.15	57.50	
Adipic Acid	TOPO - Decanoic Acid	298.15	84.58	Riveiro et al. (2020)
		313.15	84.11	
Levulinic Acid	TOPO -Decanoic Acid	298.15	82.32	Riveiro et al. (2020)
		313.15	64.85	
Succinic Acid	TOPO -Decanoic Acid	298.15	57.05	Riveiro et al. (2020)
		313.15	55.94	
	DBA - Geraniol	298.15	76.85	Liu et al. (2023)
		308.17	71.10	
Acetic Acid	DBA - Geraniol	333.33	68.85	Liu et al. (2023)
		298.15	57.68	
		308.17	54.93	
Lactic Acid	DBA - Geraniol	333.33	52.39	Liu et al. (2023)
		298.15	42.52	
		308.17	40.87	
		333.33	39.65	

### ***Effect of Initial Acid Concentration***

The initial concentration of carboxylic acid is a crucial factor in reactive extraction, as it significantly influences the distribution coefficient ( $K_D$ ), extraction efficiency (E%), selectivity, and the overall design of the process (Wasewar 2012). If the acid concentration is too low, the driving force for mass transfer into the organic phase becomes inadequate. Conversely, when the acid concentration is too high, it may lead to saturation of the solvent, resulting in a decline in extraction performance. Therefore, identifying the optimal initial acid concentration is essential for achieving maximum efficiency, especially in industrial-scale operations. In a study by Lalikoglu (2022), the extraction of formic acid was investigated using initial acid concentrations ranging from 2% to 10% (w/w) and a tri-n-octylamine (TOA) concentration of 1.6 mol/L. The study focused on three hydrophobic deep eutectic solvents (HDESs): menthol–nonanoic acid (M-NA), menthol–decanoic acid (M-DA), and menthol–dodecanoic acid (M-DDA). For acid concentrations up to 6% (w/w), the distribution coefficient, extraction efficiency, and loading factor (Z)

were analyzed. In this range,  $Z$  remained below 1, indicating that the extractant was not saturated, and extraction performance improved as acid concentration increased. Specifically, extraction efficiency rose from 91.83% to 95.44% for M-NA, 92.73% to 95.72% for M-DA, and 93.66% to 96.07% for M-DDA, consistent with trends observed in earlier studies (Kar et al. 2017). However, at higher formic acid concentrations of 8% and 10% (w/w), the extraction performance began to decline. For instance, the efficiency for M-NA dropped from 94.89% to 90.87%, for M-DA from 95.44% to 91.68%, and for M-DDA from 95.61% to 93.26%. In these cases, the  $Z$  values exceeded 1, indicating that the DESs became overloaded and could no longer efficiently accommodate the acid load (Athankar et al. 2013). This behavior suggests a possible shift in the extraction mechanism at higher acid concentrations. As the amount of acid extracted per mole of amine increases, the system may no longer follow the same extraction pathway observed at lower concentrations, leading to changes in efficiency trends (Wasewar et al. 2010). Table 7 presents a comparative overview of how initial acid concentration affects the extraction efficiency for different carboxylic acids under varying conditions.

**Table 7.** Effect of initial acid concentration of various carboxylic acids on extraction efficiency

Carboxylic Acid	Initial Acid Concentration (w/w%)	HDES	Extraction Efficiency (E%)	Reference
Formic Acid	2	TOA + Menthol: Decanoic Acid	91.83%	Lalikoglu (2022)
	4		93.38%	
	6		95.44%	
	8		94.89%	
	10		90.87%	
Acrylic Acid	2	Menthol: TOPO	87.83%	Aşçı et al. 2021)
	9.73		83.86%	
	3	TOPO: Decanoic Acid	61.64%	
Levulinic Acid	10	TOPO: Decanoic Acid	82.32%	Riveiro et al. (2020)

Above table shows that extraction efficiency of carboxylic acids depends on both the acid concentration and the HDES used. Formic acid exhibited consistently high efficiency (over 90%) with TOA + Menthol: Decanoic Acid across all tested concentrations. Levulinic acid showed good results with both Menthol: TOPO and TOPO: Decanoic Acid, with higher efficiency at lower concentrations.

#### ***Effect of HDES type***

The choice of hydrophobic deep eutectic solvent (HDES) plays a pivotal role in determining the selectivity, efficiency, and effectiveness of reactive extraction processes. HDESs, being water-immiscible, are particularly suited for isolating moderately polar or hydrophobic compounds from aqueous media. These solvents are a specialized class of DESs formulated to enhance liquid-liquid

extraction by remaining phase-separated from water. In the recovery of formic acid, HDESs prepared by mixing menthol with long-chain carboxylic acids served as the diluents (Lalikoğlu 2022). At a fixed TOA concentration of 1.6 mol/L, the extraction efficiencies recorded were 90.87% for menthol–nonanoic acid (M-NA), 91.68% for menthol–decanoic acid (M-DA), and 93.26% for menthol–dodecanoic acid (M-DDA). When Amberlite LA-2 was used instead as the extractant at 1.55 mol/L, the corresponding efficiencies were slightly lower: 85.68% for M-NA, 87% for M-DA, and 88.53% for M-DDA. Among these, M-DDA proved the most effective, likely due to its higher hydrophobicity from the longer alkyl chain in dodecanoic acid, which improves its interaction with hydrophobic solutes and favors separation from the aqueous phase (Jakovljević et al. 2020).

#### ***Effect of DES Molar Ratio on Extraction***

The molar ratio of components in a DES formulation is another essential factor that affects its complexation ability with target acids. This ratio determines the strength and stability of the hydrogen-bonding network within the solvent, influencing how effectively it can interact with carboxylic acids. A balanced molar ratio ensures better complex formation, whereas an imbalance may weaken solvent performance. Brouwer et al. (2021b) investigated the extraction of levulinic acid and formic acid using two systems: an equimolar mixture of L-menthol and thymol, close to their eutectic composition, and a 1:3 molar ratio of TOPO to L-menthol to increase the TOPO content. For the thymol–menthol DES, the distribution coefficients ( $K_D$ ) were 0.09 for formic acid and 0.914 for levulinic acid. In contrast, the TOPO-L-menthol DES showed higher  $K_D$  values of 1.88 for formic acid and 0.914 for levulinic acid, suggesting improved extraction for formic acid in the presence of TOPO. The relatively low  $K_D$  for formic acid in the thymol-menthol system is attributed to dimer formation of the acid and its weaker interactions with the aromatic and aliphatic hydroxyl groups in thymol and menthol (Chen et al. 2019). Meanwhile, TOPO, with its phosphine oxide group, formed stronger bonds with formic acid dimers, enhancing extraction efficiency. For levulinic acid, both DES systems exhibited good performance, possibly due to the affinity of its carboxyl and ketone functional groups for both organic and aqueous environments and the presence of a C<sub>5</sub> hydrocarbon chain, which improves its compatibility with hydrophobic solvents (Kumar et al. 2019). The type of hydrophobic deep eutectic solvent (HDES) used in reactive extraction processes can significantly influence the efficiency, selectivity, and overall performance of the extraction. HDESs are a subclass of DES designed to be immiscible with water, making them particularly effective for extracting hydrophobic or moderately polar compounds from aqueous solutions. For formic acid recovery from aqueous solutions, HDES, consisting of a mixture of menthol and carboxylic acid (long-chain) were used as diluents (Lalikoğlu 2022). The extraction efficiencies (E%) for M-NA were 90.87 %, M-DA was 91.68 %, and M-DDA was 93.26% at a fixed concentration of TOA 1.6 mol/L. When Amberlite LA-2 was used as an extractant at a concentration of 1.55 mol/L E% values were found to be menthol-nonanoic acid (M-NA) (85.68%), menthol-decanoic acid (M-DA) (87%), and menthol- dodecanoic acid M- DDA (88.53%). menthol-dodecanoic acid (M-DDA)

was the most efficient solvent of the group, having the longest chain which makes it more hydrophobic than the other carboxylic acids used for HDES preparation, as it has the longest chain (more hydrophobic) (Jakovljević et al. 2020). Table 8 shows the effect of molar ratio of HDES on extraction efficiency of different carboxylic acids.

**Table 8.** Effect of molar ratio of HDES on extraction efficiency of different carboxylic acids

Carboxylic Acid	HDES	Molar ratio HDES	Extraction Efficiency (E%)	References
Citric Acid	Menthol-Tributyl phosphate (TBP)	0.2 :1	98.25%	Baş et al. (2024)
		0.4:1	96.8%	
		0.6:1	94.8%	
Acetic Acid	Thymol: TOPO	1:1	44.1 %	Vidal et al. (2024)
		1:2	12.6 %	
Propionic Acid	Thymol: TOPO	1:1	67.3%	Vidal et al. (2024)
		1:2	32.3%	
Butyric Acid	Thymol: TOPO	1:1	78.9%	Vidal et al. (2024)
		1:2	71.1 %	

### ***Effect of pH***

The pH of the aqueous phase plays a pivotal role in reactive extraction, as it affects the degree of ionization of carboxylic acids. Typically, non-ionized (undissociated) acid molecules are more efficiently transferred into the organic DES phase compared to their ionized counterparts. In the study conducted by Darwish et al. (2021), a menthol: lauric acid (1.5:1) HDES was employed for extracting 3 wt% acetic acid at 298 K. The researchers measured the pH of the aqueous phase before and after extraction. Post-extraction, the pH increased, indicating a shift in acid-base equilibrium. Simultaneously, there was a 40% reduction in the concentration of undissociated acetic acid [HA], while the concentration of acetate ions [A<sup>-</sup>] remained unchanged across all tested acid concentrations. This observation suggests that only the undissociated form of acetic acid [HA] was removed by the DES, while the ionized form remained in the aqueous phase. Therefore, the efficiency of extraction is closely linked to the amount of [HA] present. At higher pH levels, where the majority of the acid exists in its ionized form [A<sup>-</sup>], the extraction efficiency tends to decline due to reduced availability of [HA] for transfer. While these findings provide important insights, further studies across a wider pH spectrum and varied temperature conditions are needed to better understand the combined effect of pH and temperature on acid extraction performance.

### ***Comparison of DES with other Solvents***

Table 9 gives the comparison of Deep eutectic solvents with other solvents for the extraction of biocarboxylic acid. DESs show high extraction efficiency (often >80%) for dicarboxylic acids like adipic, succinic, and levulinic acid, particularly when combined with TOPO. For monocarboxylic acids (e.g.,

formic, acetic, propionic), DESs like Menthol-based and Thymol-based HDES show moderate efficiency (40–60%), but this can improve significantly when paired with reactive agents like TOA. Ionic liquids offer excellent extraction for many acids but are costlier and less green than DESs. Amines (e.g., TOA) combined with diluents provide very high efficiency, but come with toxicity and environmental concerns. Conventional alcohols/esters are less efficient and selective compared to DESs or ILs.

**Table 9.** Comparison of Extraction Efficiency (E%) of DESs vs Other Solvents for Biocarboxylic Acids

Carboxylic Acid	Extraction Efficiency, %E				References
	DESs	Ionic Liquids	Alcohols / Esters	Amines	
Formic Acid	TOA+ menthol: Decanoic acid - 91.8-95.4%	NA	29.5 %	TOA in benzyl alcohol 94%	Lalikoglu (2022); Mansour et al. (2019)
Acetic Acid	Menthol: Lauric acid -40.5% Thymol: TOPO 44.1% Thymol: Menthol 58.7%	[Bmim][NTf2] 80-90%	Octanol 40–55%	TOA in 1-decanol 85–88%	Darwish et al. (2021); Brouwer et al. (2021)
Propionic Acid	Thymol: Menthol 58.7%	IL (e.g., [ChCl][AcOH]) 75–82%	Hexanol: 50-60%	TOA 86.1%	Vidal et al. (2024); Lee et al. (2018)
Butyric Acid	Thymol: Menthol 49.3% TOPO: Menthol 87%	ILs - 82–89%	1-Octanol 60-65%	TOA 87-92%	Brouwer et al. (2021); Mokrani (2017)
Levulinic Acid	TOPO: Decanoic acid 61.6–82.3%	[Bmim][PF6] - 91%	Ethyl acetate : 45-55%	TOA :85-89%	Riveiro et al. (2020); Ramadoss (2019)
Succinic Acid	TOPO: Dodecanoic acid 88.1%	ILs (e.g., [Emim][HSO4]) 90–95%	Methyl isobutyl ketone 48–55%	TOA in benzyl alcohol 91%	Riveiro et al. (2020); Martak & Schlosser (2019)
Acrylic Acid	Menthol: TOPO 83.9–87.8%	ILs (e.g., [Emim][OTf]) 89%	Ethanol 50-55%	TOA in dodecane 91-93%	(Aşçı et al. 2021), (Keshav & Kamal 2014)
Adipic Acid	TOPO: Dodecanoic acid 97.7% TOPO: Decanoic acid 61.2%	ILs 95%	Alcohols 40–55%	TOA 96-98%	(Riveiro et al. 2020), (Keshav et al. 2018)

### Multi-stage Extraction

Liu et al. (2023) explored the reactive extraction of 3 wt% acetic acid using a menthol–lauric acid HDES. The study found that increasing the solvent-to-feed ratio from 1:4 to 4:1 improved extraction

performance. However, the use of large volumes of solvent raised economic concerns. To mitigate this, a multi-stage extraction approach was adopted. After the initial extraction, the HDES-rich organic phase was separated, and fresh HDES was added to the raffinate. This cycle was repeated four times with a consistent 2:1 solvent-to-feed ratio. The process achieved an overall extraction efficiency of 87.6%, reducing the aqueous acetic acid concentration from 3 wt% to 0.36 wt% within just four stages. The findings highlighted that a lower phase ratio combined with multiple stages offers a more economical and efficient extraction process (Antony et al. 2018).

### ***Continuous Extraction Column Simulation and Mini-Pilot Study***

Liu et al. (2023) modeled a countercurrent extraction column for lactic acid separation using DBA-Ger and DBB-Ger DESs. The simulation, based on the Kremser equation and equilibrium distribution coefficients, estimated extraction yields as a function of number of theoretical stages (NTS) (De et al., 2018). For DBA-Ger, nearly 100% lactic acid recovery was achieved in 9 stages, thanks to the favorable balance of hydrophobicity and polarity. In contrast, DBB-Ger required 16 stages to reach a 75% extraction yield, suggesting that amide-based DESs have superior performance over conventional systems.

### ***Mini-Pilot Scale Evaluation***

To validate the simulation outcomes, Liu et al. (2023) conducted a mini-pilot trial using phase equilibrium data for lactic acid with DBA-Ger DES. A small-scale countercurrent extraction setup was built to examine the feasibility of scaling up. In this system, lactic acid fermentation broth was continuously introduced at a flow rate of 60 mL/min, while HDES was added from the bottom at 130 mL/min. The operation was maintained at 303 K and atmospheric pressure, reaching steady-state after 3 hours. The aqueous raffinate exiting the system contained less than 0.003 mol/L lactic acid, and the HDES achieved 99% extraction efficiency. For further purification and product recovery, the process was complemented by scrubbing and multi-step back-extraction techniques.

### **Challenges and Prospects in DES-Based Carboxylic Acid Separation**

Despite their promise, DESs used in carboxylic acid separation present several operational and scalability challenges. Key issues include Achieving high selectivity and solubility for different carboxylic acids, managing high viscosity of certain DES formulations ensuring efficient recycling and regeneration of the solvent Maintaining thermal and chemical stability, assessing environmental safety and overall economic feasibility, ensuring compatibility with industrial equipment, delivering high-purity products to overcome these barriers, both experimental refinement and theoretical modeling are essential. Several key research areas are emerging as critical to the future of DES applications in industrial separations:

1. Tailored DES Design: Creating new DES formulations by selecting specific HBDs and HBAs that match the target acid's properties. Utilizing computational modeling to improve selectivity and solvation

efficiency.

2. **Hybrid Separation Technologies:** Combining DES extraction with membrane separation, adsorption, or distillation to improve throughput. Investigating in-situ extraction approaches during fermentation or reaction processes to increase efficiency.

3. **Sustainability and Process Optimization:** Performing life cycle assessments to evaluate environmental impact. Addressing scale-up limitations through robust engineering designs and optimizing conditions like temperature, pressure, and mixing.

4. **Advanced Materials Integration:** Exploring DES-based composites with metal-organic frameworks (MOFs), ionic liquids, or nanomaterials to enhance selectivity and performance in complex separation tasks.

Focusing on these directions will help transition DES-based systems from laboratory research to commercial-scale applications, promoting more sustainable and efficient separation technologies.

## **Conclusion**

The use of Deep eutectic solvents for carboxylic acid separation offers a compelling, eco-friendly alternative to conventional solvent systems. DESs are inherently biodegradable, non-toxic, and highly tunable, aligning well with the principles of green chemistry. This study has demonstrated the practical potential of DESs in extracting carboxylic acids efficiently and selectively, while minimizing environmental footprint. Although DESs show great promise, there are still key challenges that must be addressed, including issues with selectivity, solubility limitations, viscosity control, and solvent recovery. The economic viability and integration with current industrial infrastructure also require careful evaluation. With continued innovation in DES formulation, process integration, and fundamental mechanistic understanding, DES-based systems are well-positioned to revolutionize the separation of carboxylic acids. Their adoption can foster sustainable industrial practices and support the advancement of multiple sectors, including pharmaceuticals, bioprocessing, and green chemical production.

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## **Competing Interests**

The authors have no relevant financial or non-financial interests to disclose.

## **Authors Contributions**

All authors conceptualized the topic of the review and designed the structure. Ms. Ashwini S. Thakre drafted the complete manuscript. She conducted the literature review and synthesized the findings. Dr. Kanti Kumar, Dr. Diwakar Shende, and Dr. Kailas Wasewar contributed to the critical revision of the manuscript. All authors approved the final version for submission.

## Data Availability

Data will be made available on request.

## Declarations

### Conflicts of Interest

The authors declare no conflict of interest to report regarding the present study.

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