

Review

Eco-Friendly Deep Eutectic Solvent-Based Extraction Technologies: A Comprehensive Review of Principles, Applications, and Comparative Insights

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Abstract

Sample preparation is frequently a time-consuming process and can be a major bottleneck in many analytical techniques that involve some form of modification to a sample so that it can be analyzed without interference or to increase its sensitivity. As part of the movement towards “green analytical chemistry”, the reduction in organic solvent usage and toxicity via alternative solvents compared to those traditionally used in analytical chemistry has gained increasing interest. Although ionic liquids were thought to have limitations, deep eutectic solvents (DESs) are being looked at as alternatives to traditional organic solvents in analytical chemistry because of their ability to produce a “tunable” set of physico-chemical properties that enable the selective and efficient extraction of a wide variety of analytes from a very diverse array of matrices. Although deep eutectic solvents have attracted increasing attention in analytical extraction applications, a systematic comparison of their performance across various extraction techniques is still lacking. This review fills this gap by offering a comprehensive and integrated evaluation of DES-based extraction approaches, emphasizing the interdependence between solvent characteristics, extraction efficiency, selectivity, and sustainability. The insights presented herein are intended to support the rational selection of appropriate DES-based extraction strategies for diverse analytical purposes. Moreover, these findings are expected to contribute to the advancement of greener, more efficient sample preparation methodologies within the field of green analytical chemistry. In this review article, we describe several analytical chemistry techniques that utilize DESs, such as dispersive liquid–liquid microextraction, solid-phase extraction, ultrasound-assisted extraction, etc., and explain the basic principles and mechanisms behind each technique. Additionally, comparative evaluations are provided to identify the relative advantages and disadvantages of the techniques mentioned above in terms of extraction efficiency and selectivity, and speculation regarding future trends and challenges in DES-based extraction systems will also be included. By integrating recent advances and comparative performance assessments, this review serves as a reference for researchers and industry practitioners, fostering innovation and promoting the wider adoption of sustainable extraction technologies.



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1. Introduction

Sample preparation represents a pivotal stage within the analytical process, encompassing a diverse array of operations crucial for sample modification. These procedures are

essential for preparing samples for chromatographic analysis and for improving important analytical characteristics such as accuracy and precision [1]. In addition, proper sample preparation helps minimize matrix interferences and enhances analytical sensitivity. In general, a sample contains two main parts: the target analytes that need to be measured and the sample matrix, which includes all other components that may interfere with the analysis. Therefore, sample preparation strategies may focus on isolating the analytes, modifying the matrix, or applying both approaches simultaneously. The main aim of these procedures is to achieve sample dissolution, purification, enrichment, or chemical modification in order to obtain reliable analytical results. In many untargeted analytical studies, particularly those involving trace-level compounds in complex matrices, sample preparation represents the most time-consuming and challenging stage and strongly influences both the accuracy and overall duration of the analytical workflow [2,3].

In recent years, considerable attention has been directed toward replacing traditional extraction techniques with more environmentally friendly alternatives. This movement is closely linked to the concepts of green analytical chemistry and the twelve principles proposed by Paul Anastas in 1998, which encourage the design of safer and more sustainable analytical methods [4], particularly in sample extraction. Green extraction approaches provide several benefits, including lower cost, faster processing, and reduced environmental impact in areas such as environmental monitoring, clinical testing, and food analysis.

Efforts to reduce the environmental impact of analytical procedures have mainly focused on three approaches: lowering solvent use during sample preparation, reducing the amount and toxicity of chemicals employed during analysis, and developing direct analytical methods that avoid the use of solvents and reagents whenever possible. As a result, the search for sustainable solvent systems has become an important research topic in many scientific and technological fields [5–9].

Among the proposed alternatives, ionic liquids attracted significant interest because they are organic salts with melting points below 100 °C and can replace volatile organic solvents. Nevertheless, their practical application has been limited by issues related to toxicity, biodegradability, stability, and the relatively high cost of preparation [10]. To overcome these drawbacks, deep eutectic solvents (DESs) were introduced in 2001 as a more sustainable substitute. DESs are generally easier and less expensive to prepare while exhibiting physicochemical properties similar to those of ionic liquids [11]. Consequently, the design of efficient and environmentally sustainable extraction methods has become a major focus in modern analytical chemistry.

The growing emphasis on green chemistry has encouraged researchers to investigate new solvent systems that comply with environmental sustainability requirements [12]. In this regard, deep eutectic solvents (DESs) have gained substantial attention as promising alternatives with the potential to reduce the environmental impact of extraction processes, depending on their chemical composition and intended application [13,14]. This review focuses on the characteristics and uses of DESs in microextraction techniques, highlighting their remarkable extraction efficiency and analytical performance, which have contributed to their increasing popularity in scientific research.

Although deep eutectic solvents have been widely explored in various individual extraction systems, the existing literature is still dispersed, as most reviews are limited to specific extraction techniques, targeted analyte groups, or select DES formulations. As a result, a holistic and updated comparison that systematically examines the application of DESs across different extraction platforms, while linking their physicochemical characteristics to extraction efficiency, selectivity, and environmental sustainability, remains insufficient. The present review addresses this limitation by presenting a unified comparative analysis of DES-based extraction approaches, covering both traditional and newly

developed methodologies. Particular attention is given to the interplay between solvent composition, extraction mechanisms, analytical performance, and green chemistry aspects. By integrating recent progress and critically evaluating the advantages and limitations of various DES-assisted systems, this work provides a consolidated perspective on their role in analytical science. The insights provided are expected to support researchers in the rational selection of DES-based extraction methods tailored to specific analytical problems and sample types. In addition, this review contributes to the advancement of more efficient and environmentally friendly extraction strategies, thereby promoting further development in sustainable analytical and green chemistry practices.

2. Deep Eutectic Solvents

Deep eutectic solvents (DESs) are a relatively new group of sustainable solvents formed by mixing two or more components, usually a hydrogen bond acceptor and a hydrogen bond donor, in a specific molar ratio. Strong hydrogen bond interactions between these components cause a significant decrease in the melting point, allowing the mixture to remain liquid at or close to room temperature [15]. DESs have attracted considerable attention because many formulations exhibit favorable physicochemical characteristics, such as negligible volatility, non-flammability, and tunable solvent properties [16]. This tunability provides DESs with excellent solubilizing ability for a broad range of organic, inorganic, and biological compounds [17]. However, their environmental sustainability, biodegradability, and toxicity are highly dependent on the nature of the hydrogen bond donor and acceptor, their molar ratio, and the final formulation.

2.1. Synthesis of Deep Eutectic Solvents

Deep eutectic solvents can be prepared using several simple and cost-effective methods (Figure 1), and the choice of method mainly depends on the physicochemical nature of the starting materials. The most commonly used approach is the heating method [18], in which the hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD) are mixed in a specific molar ratio and heated gently, usually between 50 and 80 °C, under continuous stirring until a clear and uniform liquid is formed. The formation of this transparent phase indicates strong hydrogen bond interactions between the components, which lower the melting point and produce a stable liquid system.

DESs may also be synthesized at room temperature by continuous magnetic stirring [19]. Although this method generally requires a longer preparation time, sometimes several hours, it is particularly suitable for thermally sensitive compounds because it avoids exposure to heat. Another common procedure is the evaporation method, where the HBA and HBD are first dissolved in a volatile solvent such as ethanol, followed by solvent removal through evaporation to obtain the eutectic mixture [20]. In addition, the freeze–thaw method has been reported as an effective preparation technique, where repeated freezing and thawing cycles improve component mixing and enhance hydrogen bond formation [21]. Regardless of the preparation route employed, these methods are generally simple and energy-efficient and may reduce solvent consumption compared with conventional preparation methods. Nevertheless, the overall sustainability of the resulting DES depends on its specific formulation.

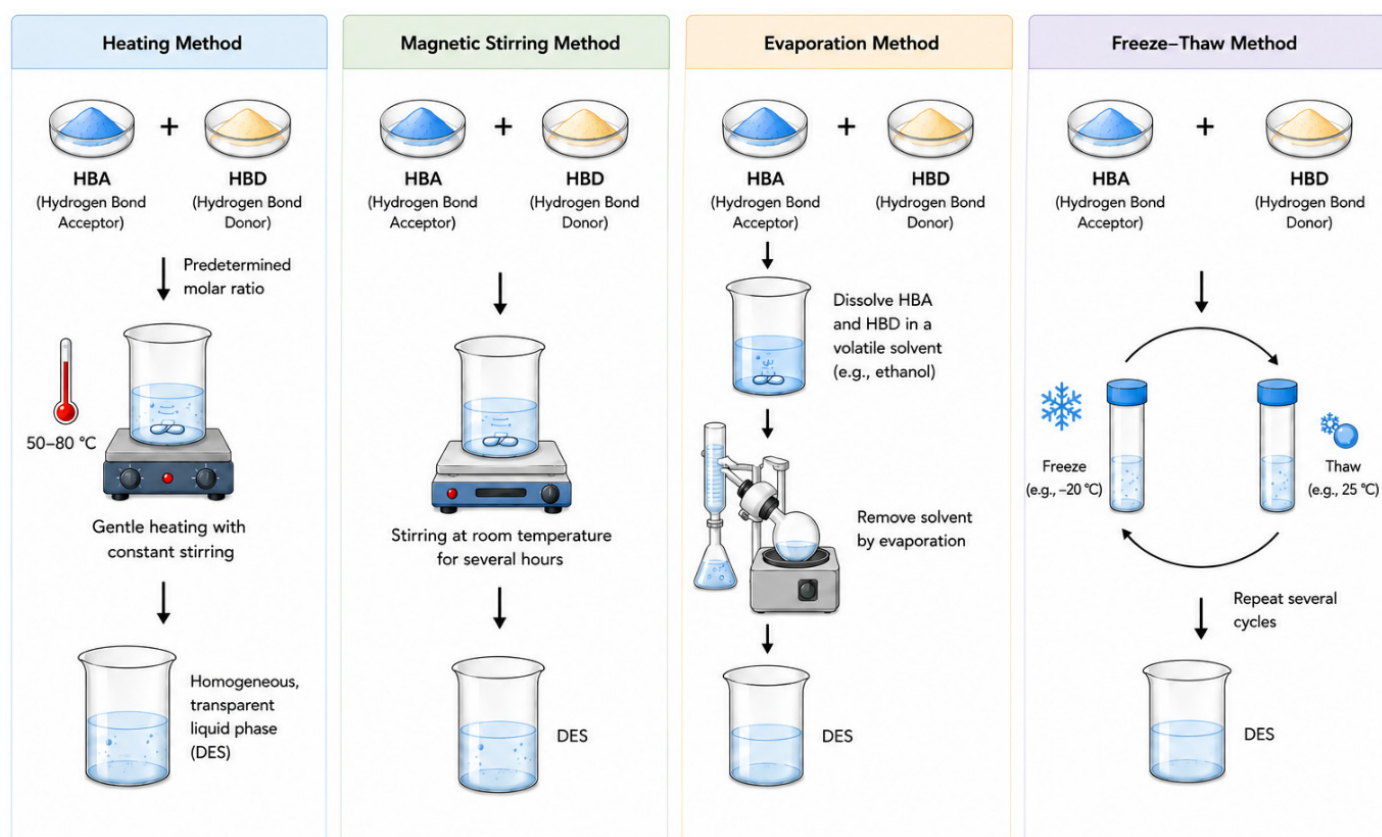


Figure 1. Synthetic methods of deep eutectic solvents.

2.2. Classification of Deep Eutectic Solvents

The classification of deep eutectic solvents is predicated based on the chemical composition of their constituent elements and the specific intermolecular interactions facilitating eutectic formation. The classification system proposed by Andrew Abbott and co-workers in 2004 remains one of the most widely used approaches for categorizing deep eutectic solvents (DESs) [22]. In this system, DESs are divided into four main types according to the nature of their components (Table 1), including metal salts, quaternary ammonium or phosphonium salts, and organic hydrogen bond donors. This classification helps explain how interactions between hydrogen bond acceptors (HBAs) and hydrogen bond donors (HBDs) lead to a substantial reduction in the melting point of the mixture.

Table 1. Types of DESs [22].

Type	Composition	Example	Description
Type I	Metal chloride + metal chloride hydrate	$\text{ZnCl}_2 + \text{SnCl}_2$	Metallic-type DESs; often used in electrodeposition.
Type II	Metal chloride + hydrogen bond donor	$\text{ZnCl}_2 + \text{urea}$	Contain an organic donor; lower toxicity than Type I.
Type III	Quaternary ammonium salt + hydrogen bond donor	Choline chloride + glycerol (1:2)	Most common; widely used in green chemistry and extraction.
Type IV	Metal chloride + organic compound (HBD)	$\text{AlCl}_3 + \text{malonic acid}$	Exhibit ionic–organic interactions; used in catalysis.

Type I DESs are composed mainly of metal salts and produce ionic liquid systems with metallic characteristics, making them useful in electrochemical applications. Type II DESs consist of a metal salt combined with an HBD, such as urea or another amide-based

compound, and are generally associated with lower toxicity and versatile solvent properties. Type III DESs are the most common category and typically contain an organic salt, such as choline chloride, acting as the HBA together with an organic HBD like glycerol, lactic acid, or ethylene glycol. Because many Type III DESs are prepared from inexpensive and naturally derived components, they are frequently explored in green chemistry applications, although their environmental profile varies depending on composition. Type IV DESs contain a metal chloride mixed with an organic compound, where strong ionic–organic interactions dominate, making these systems particularly useful in catalysis and advanced material synthesis.

Although the classical classification introduced by Andrew Abbott mainly categorizes deep eutectic solvents according to the general chemical nature of their constituents—such as metal salts, quaternary ammonium salts, or organic hydrogen bond donors—another classification approach based on hydrogen bond donors and hydrogen bond acceptors provides a more detailed understanding of their composition and functionality [23]. This alternative system focuses on the exact molecular role and origin of each component within the DES structure.

Abbott's classification primarily highlights the type of ionic interactions present and distinguishes metallic DESs from organic ones. In contrast, the HBD/HBA-based system classifies DESs according to the specific identity of the donor and acceptor species, leading to categories such as choline-based, ammonium-based, phosphonium-based, metal–salt-based, and natural DESs (Table 2). This approach demonstrates how the careful selection of HBD and HBA can strongly affect the physicochemical properties of the solvent, including viscosity, polarity, conductivity, and biocompatibility.

Table 2. Classification by HBD/HBA categories.

Category	Hydrogen Bond Acceptor (HBA)	Hydrogen Bond Donor (HBD)	Example	Application
Choline-based DESs	Choline chloride	Urea, glycerol, lactic acid, ethylene glycol	ChCl:urea (1:2), ChCl:glycerol (1:2)	Extraction of metals, phenolics, dyes
Ammonium-based DESs	Tetraethylammonium chloride, trimethylammonium chloride	Carboxylic acids, sugars, alcohols	TEAC:lactic acid	Catalysis, bioprocessing
Phosphonium-based DESs	Tetrabutylphosphonium bromide	Alcohols, polyols, fatty acids	TBPB:1,4-butanediol	Electrochemistry, phase separation
Metal–salt-based DESs	ZnCl ₂ , FeCl ₃ , AlCl ₃	Amides, urea, glycerol	FeCl ₃ :urea (1:3)	Electrodeposition, extraction of metals
Natural DESs (NADES)	Choline, betaine	Organic acids, sugars, amino acids	ChCl:glucose (1:1), betaine:lactic acid (1:1)	Food, pharmaceuticals, plant extraction

In addition, the HBD/HBA-based classification is particularly useful for describing biologically derived and sustainable systems, especially natural deep eutectic solvents (NADESs), which are not easily accommodated within Abbott's original four-type model. Therefore, this classification broadens the understanding of DESs by emphasizing their tunable nature, functional diversity, and growing importance in green chemistry rather than focusing only on the general chemical category of their components.

3. Applications of DESs in Extraction Techniques

Deep eutectic solvents (DESs) have become increasingly important in modern extraction science because of their strong solvating ability and tunable physicochemical properties.

Depending on their formulation, DESs may also offer environmental advantages over conventional organic solvents. As sustainable alternatives to volatile organic solvents, DESs can improve extraction performance through multiple interactions with analytes, including hydrogen bonding, ionic interactions, and π - π interactions. Their tunable polarity and viscosity also allow for selective extraction of a wide variety of substances, ranging from metal ions and dyes to natural bioactive compounds [24]. As a result, DESs are now widely applied in both conventional and advanced extraction techniques, where they contribute to improved selectivity, lower toxicity, and reduced solvent usage. In addition, their low vapor pressure, non-flammability, and biodegradability make them particularly attractive for environmentally sustainable extraction processes [25]. This section discusses the theoretical background and practical applications of DESs in different microextraction techniques, with particular emphasis on the physicochemical characteristics that make them more advantageous than conventional organic solvents and, in many cases, even ionic liquids. Figure 2 illustrates the applications of deep eutectic solvents (DESs) in various microextraction techniques. In addition, Table 3 summarizes the main extraction techniques that have been applied in the last two decades using deep eutectic solvents (DESs), natural DESs (NADES), and hydrophobic DESs (HDES). Each method is briefly described in terms of its principle, the role of DESs, and main applications.

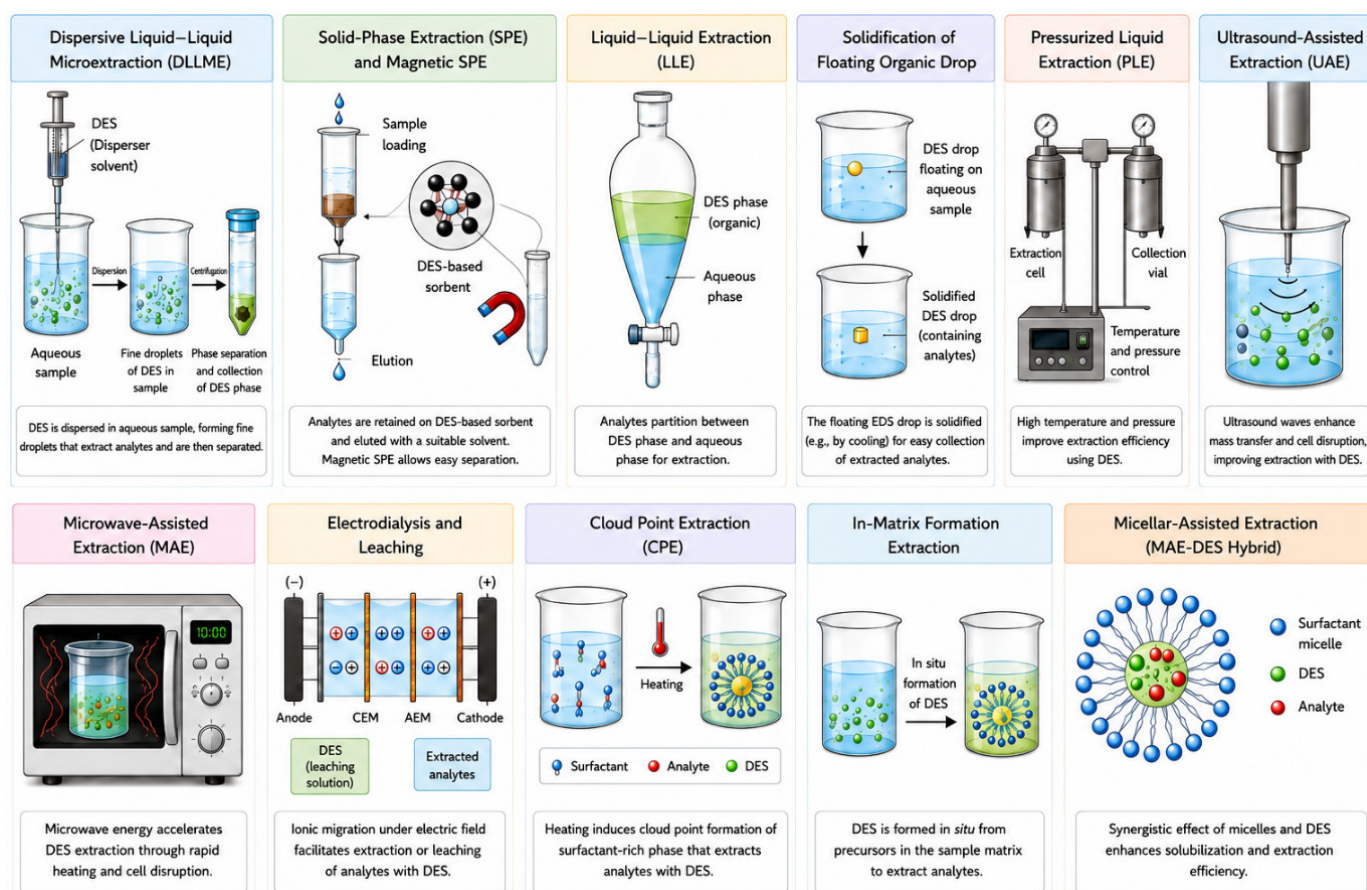


Figure 2. Applications of DESs in extraction techniques.

Table 3. Summarization of the main extraction techniques using deep eutectic solvents.

Extraction Method	Principle	Role of DESs	Main Applications
Dispersive liquid–liquid microextraction (DLLME)	A small amount of DES mixture is injected into the aqueous sample to form a fine dispersion, enhancing contact between solvent and analyte.	DES replaces toxic organic solvents, offering tunable polarity and potentially a more sustainable alternative to conventional organic solvents.	Extraction of pesticides, phthalates, PAHs, and phenols from water and food matrices.
Solid-phase extraction and magnetic solid-phase extraction (SPE/MSPE)	Analytes are retained on a solid sorbent (magnetic or non-magnetic) coated or modified with DES, then eluted by mild solvent.	DES acts as a coating or modifier, enhancing selectivity and magnetic separation efficiency.	Heavy metals (Pb, Cd, Hg) and pesticides from water, soil, and food.
Liquid–liquid extraction (LLE)	Partition of analytes between two immiscible liquids; DES serves as the extraction phase.	DES functions as a hydrophilic/hydrophobic medium, improving solubility and phase separation.	Recovery of metals (Cu, Ni, Co) from e-waste, batteries, and wastewaters.
Solidification of floating organic drop (SFOD)	A small amount of low-density hydrophobic solvent is dispersed in the aqueous sample and solidifies upon cooling, allowing for easy collection. When combined with DES, it becomes greener and more selective.	Hydrophobic DES (hDES) composed of menthol and fatty acids replaces organic solvents, enhancing extraction through hydrogen bonding and hydrophobic interactions while reducing toxicity.	Used for extracting heavy metals (Pb, Cd, Hg), organic pollutants, and pesticides analyzed by FAAS, ICP-OES, or ICP-MS.
Pressurized liquid extraction	Sample is heated with DES under controlled pressure to improve diffusion and solubility.	DES provides high thermal stability and environmental safety under elevated temperature.	Organophosphorus pesticides in animal products and egg powders.
Ultrasound-assisted extraction (UAE)	Ultrasound waves cause cavitation, disrupting matrices and enhancing mass transfer.	DES improves extraction efficiency by stabilizing target compounds and dissolving polar analytes.	Extraction of dyes, phenolics, and pesticides from plants and water.
Microwave-assisted extraction	Microwave heating increases molecular movement, accelerating analyte transfer to the DES phase.	DES efficiently absorbs microwave radiation due to its high polarity.	Extraction of organic pollutants and volatiles from food and soil samples.
Electrodialysis/leaching	An electric potential drives ion migration through membranes; DES serves as an electrolyte or leaching medium.	DES stabilizes ions and enhances leaching selectivity for metal recovery.	As, W, Ni, Co, Pb extraction from mining and industrial residues.
Cloud point extraction	Heating causes DES-surfactant mixture to separate into two phases, one enriched with analyte.	DES tunes the cloud point and acts as a more sustainable substitute for surfactant modifiers.	Concentration of rare earths and organics from water samples.
In-matrix formation extraction	DES forms directly within the matrix (e.g., milk or honey) when components are mixed in situ.	No additional solvent or pre-treatment required; DES extracts analytes directly in the matrix.	Extraction of pesticides, phenols, and bioactives in complex food systems.
Micellar-assisted extraction	Combination of DES with surfactants to form micellar systems enhancing solubilization of nonpolar analytes.	DES stabilizes micelles and expands the solubility range of the extraction system.	Extraction of dyes, fragrances, and aromatic pollutants from industrial effluents.

3.1. Dispersive Liquid–Liquid Microextraction (DLLME)

Dispersive liquid–liquid microextraction (DLLME) is based on the rapid injection of a small amount of extraction solvent into an aqueous sample, producing a fine cloudy emulsion that greatly increases the contact area between the solvent and the target analytes. As a result, the analytes are efficiently transferred and concentrated into the deep eutectic solvent phase, which can later be separated by centrifugation [26]. In this technique, DESs serve as safer alternatives to conventional organic solvents and offer adjustable polarity that enables the extraction of both polar and nonpolar compounds. For efficient DLLME performance, the selected DESs should generally possess relatively low viscosity and moderate polarity. This method has been successfully applied for the extraction of different contaminants and compounds, including pesticides, phthalates, and polycyclic aromatic hydrocarbons, from water and food samples.

3.2. Solid-Phase Extraction (SPE) and Magnetic SPE

Solid-phase extraction (SPE) and magnetic solid-phase extraction (MSPE) rely on solid sorbent materials that are coated or modified with deep eutectic solvents to selectively retain target analytes. In MSPE, combining DESs with magnetic nanoparticles allows for easy separation of the extraction phase using an external magnetic field and also improves the reusability of the sorbent material [27]. In addition, the DES coating enhances extraction selectivity and efficiency through specific interactions with the analytes. For these extraction techniques to perform effectively, the DESs used should generally exhibit moderate viscosity and hydrophilic properties to ensure fast and efficient mass transfer. These methods are effectively applied in the preconcentration of trace metals and the extraction of organic pollutants from diverse complex matrices.

3.3. Liquid–Liquid Extraction (LLE)

Liquid–liquid extraction operates based on the differential partitioning of analytes between two immiscible liquid phases. Deep eutectic solvents are increasingly used as alternative extraction media because of their high thermal stability and adjustable hydrophobic properties, which allow for selective extraction without relying on volatile organic solvents [28]. DESs have shown excellent performance in processes such as metal recovery and the removal of hydrophobic pollutants. Owing to these advantages, they are considered highly suitable for large-scale industrial and environmental extraction applications.

3.4. Solidification of Floating Organic Drop (SFOD)

The solidification of floating organic drop (SFOD) extraction technique is considered an efficient and potentially more sustainable alternative to traditional organic solvent-based methods [29]. In this approach, a small amount of hydrophobic deep eutectic solvent, commonly prepared from natural components such as menthol and fatty acids, is dispersed into an aqueous sample. The target analytes are then extracted into the DES phase through hydrophobic interactions and hydrogen bonding. After extraction, cooling the system causes the DES phase to solidify and float on the sample surface, making it easy to collect for further analysis by different analytical techniques. The use of DESs in SFOD improves extraction efficiency and selectivity while also reducing environmental and health concerns associated with hazardous organic solvents [30]. Another important advantage of this method is that it eliminates the need for centrifugation. In addition, DES-based SFOD systems are simple to operate, economical, reusable, and capable of providing high analyte enrichment and good extraction stability.

3.5. Pressurized Liquid Extraction

Pressurized liquid extraction utilizes high temperature and pressure conditions to improve the solubility and diffusion of analytes in the deep eutectic solvent medium. The applied pressure helps maintain the solvent in the liquid phase and minimizes solvent loss, while DESs generally remain stable under elevated temperatures [31]. For efficient application in pressurized liquid extraction, DESs should exhibit high thermal stability and low volatility. This technique has been successfully used for extracting organophosphorus pesticides, phenolic compounds, and a variety of bioactive compounds from complex solid samples.

3.6. Ultrasound-Assisted Extraction (UAE)

Ultrasound-assisted extraction (UAE) enhances the extraction process through cavitation phenomena, where the formation and collapse of microscopic bubbles help disrupt solid matrices and improve the mass transfer of analytes. Deep eutectic solvents further enhance this process by efficiently dissolving a broad range of compounds, including both hydrophilic and hydrophobic analytes, while also stabilizing sensitive or reactive species. In UAE applications, DESs with relatively low viscosity are generally preferred because they allow for more efficient transfer of ultrasonic energy.

This technique has been successfully applied for the extraction of dyes, polyphenols, pharmaceutical residues, and other compounds from environmental and food samples. In addition, the combined effect of ultrasonic energy and the unique solvent properties of DESs enables faster and more efficient extraction compared with conventional extraction methods [32,33]. This synergistic interaction not only shortens extraction time and improves recovery yields but also reduces solvent consumption, further supporting the role of DESs as environmentally friendly solvents in green extraction technologies, depending on the DES composition.

3.7. Microwave-Assisted Extraction

Microwave-assisted extraction uses microwave energy to heat both the sample and the extraction solvent simultaneously, which significantly accelerates the extraction process. Due to their ionic and polar nature, deep eutectic solvents can efficiently absorb microwave radiation, resulting in rapid heat generation and enhanced release of analytes from the sample matrix [34,35]. This technique is particularly suitable for the extraction of thermally stable compounds such as pigments, antioxidants, and hydrocarbons.

Compared with conventional heating methods, microwave-assisted extraction offers shorter extraction times and often provides higher recovery efficiencies. The strong dielectric heating behavior of DESs under microwave irradiation also improves extraction performance by promoting efficient and selective heating of the solvent-sample system while reducing unnecessary energy consumption.

3.8. Electrodialysis and Leaching

Electrodialysis and leaching techniques utilize an applied electric field to promote ion movement across membranes or to selectively dissolve metals in deep eutectic solvents [36]. The high ionic conductivity and suitable redox properties of DESs enhance the efficiency of metal extraction and recovery processes. In particular, acidic DESs have shown strong capability in the leaching of heavy metals and rare earth elements from solid waste materials [37]. These methods are widely applied for the recovery of valuable metals such as copper, nickel, cobalt, and rare earth elements from electronic waste and mining by-products.

3.9. Cloud Point Extraction

Cloud point extraction is based on surfactant–deep eutectic solvent systems that separate into two phases when heated above their cloud point temperature. In this process, DESs help adjust the cloud point temperature and enhance the selectivity of the extraction procedure [38]. Hydrophobic DESs are especially useful because they promote the transfer of target analytes into the surfactant-rich phase [28]. This technique has been successfully applied for the extraction of trace metals and hydrophobic organic contaminants from water samples.

3.10. In-Matrix Formation Extraction

This approach is based on the in situ formation of deep eutectic solvents directly within the sample matrix by mixing suitable precursors, such as choline chloride and organic acids, inside the analytical system [39]. Since the solvent is generated during the extraction process itself, there is no need to prepare DESs beforehand, which simplifies the procedure and reduces waste production. This technique has been applied for the extraction of compounds such as phenolic substances and pesticide residues from complex food samples such as milk and honey [40]. The direct formation of DESs within the matrix also enhances the interaction between the solvent components and the target analytes, creating a localized extraction environment that can improve extraction efficiency [41].

3.11. Micellar-Assisted Extraction DES Hybrid

Micellar-assisted extraction is a hybrid extraction approach in which deep eutectic solvents are combined with surfactants to form micellar structures that enhance the solubility of nonpolar analytes [42]. This technique benefits from both the solubilization ability of micelles and the adjustable properties of DESs. It has been successfully used for the extraction of compounds such as dyes, fragrances, and aromatic hydrocarbons from complex samples such as wastewater and textile materials. The integration of DESs with surfactants improves the extraction of compounds that normally exhibit poor solubility in aqueous media, providing a more environmentally friendly alternative to conventional organic solvents. In addition, the tunable characteristics of DESs make it possible to design micellar systems with specific solubilization properties suited for different analytical applications. The combined interaction between DESs and surfactants also promotes the formation of stable and selective micellar assemblies, which enhances the partitioning and extraction efficiency of target analytes [43].

Table 4 presents a selection of representative studies on the application of deep eutectic solvents (DESs) in analytical extraction and leaching processes reported in recent peer-reviewed literature. It encompasses a wide range of sample matrices, including environmental, industrial, biological, and food-related systems, and details the target analytes, DES compositions, and employed extraction or analytical methodologies. The table also covers both metallic and metalloid species as well as various organic contaminants, highlighting the broad applicability of DES-based extraction systems and their significance in the context of green analytical chemistry.

Table 4. Applications of DESs in analytical extraction for metallic and metalloid elements.

Matrix	Pollutant Group	DES Type	Technique/Instrument	
Food samples	Synthetic azo dyes (food dyes)	Hydrophobic DES (thymol:benzyltriethylammonium chloride)	DES-based vortex-assisted DLLME + HPLC	[44]
Rice (white/brown; flour)	Heavy metals (As speciation/total)	Hydrophilic DES (choline chloride-based; DES-vortex assisted-LPME)	DES-based vortex-assisted microextraction + hydride generation–AAS	[45]
Tea beverages; Fruit juices	Pesticides (pyrethroids)	Hydrophobic DES (hexafluoroisopropanol-based)	DES-DLLME + HPLC	[46]
Tea (infusions)	Herbicides	Hydrophilic DES (homogeneous LLE + in-syringe DLLME)	Homogeneous liquid–liquid extraction (DES) + In-syringe DLLME + HPLC	[47]
Aqueous samples	Pesticides (pyrethroids)	Hydrophobic DES	UA-DLLME (DES) + GC/HPLC	[48]
Real food and water	Heavy metals (Pb)	DES-based floating organic droplets (portable syringe)	DES-based floating organic droplet microextraction (portable syringe) + FAAS	[49]
Non-alcoholic beverages and food	Heavy metals (Pb, Cd, Cu, As)	Centrifuge-less DES-based magnetic nanofluid	Air-agitated liquid–liquid microextraction + electrothermal AAS	[50]
Water & tea beverages	Pesticides (pyrethroids)	Hydrophobic DES (membrane-assisted)	DES-based membrane microextraction + HPLC	[51]
Water; aqueous extracts	Heavy metals (Pb)	Hydrophilic DES	DES-based microextraction + FAAS	[52]
Beverages	Heavy metals (Cr(VI))	Hydrophilic DES as disperser (in-syringe flow)	In-syringe DES-DLLME + UV–Vis	[53]
Milk	Pesticides	In-matrix formed DES (hydrophobic)	Liquid-phase extraction +SFOD + DLLME (DES-based) + GC-FID	[54]
Milk samples	Heavy metals (Cd, Cu, Pb)	Synthesized ternary DES (ligand-less)	Ligand-less DES-DLLME + spectrometric detection	[55]
Food-contact plastics (migration)	Phthalates	Low-viscosity hydrophobic DES	Vortex-assisted liquid–liquid microextraction + HPLC	[56]
Cereals	Pesticides (pyrethroids)	Hydrophobic DES (SFOD mode)	DES-DLLME-SFOD + HPLC	[57]
Fruit juices; tea drinks	Fungicides	Hydrophobic DES (L-menthol:decanoic acid)	Ultrasound-assisted solidifying hydrophobic DES microextraction + HPLC	[58]
Tomato–chili sauces	Lipophilic dyes	Nonionic surfactant-based hydrophobic DES	Vortex-assisted DES-based liquid–liquid microextraction + HPLC	[59]
Tea infusions	Bisphenols + Polycyclic aromatic hydrocarbons	Hydrophobic DES (floating; solidifying)	Air-assisted LLME (solidifying floating DES) + HPLC	[60]

Table 4. Cont.

Matrix	Pollutant Group	DES Type	Technique/Instrument	
Wine	Heavy metals (Pb, Cd, Cu)	Hydrophobic DES (UA-DLLME)	UA-DES-DLLME + FAAS	[61]
Tea (brewed infusions)	Heavy metals (Pb, Cd, Cu, As, Hg)	Solidified deep eutectic solvent (ionic liquid-based DES)	Vortex-assisted liquid-phase microextraction with solidified DES + GFAAS	[62]
Soft drinks	Phthalates	Natural hydrophobic DES (NADES)	Vortex-assisted DLLME + HPLC	[63]
Hazelnut skin	Phenolic compounds	Hydrophilic DES (choline chloride-based)	DES-based ultrasound-assisted solid-liquid extraction + HPLC – UV	[64]
Soil (washing extract/leachate)	Heavy metals (Pb)	Acidic DES	DES soil washing + analysis of leachate (ICP-OES/ICP-MS)	[65]
Wine	Pesticides	Hydrophobic DES (L-menthol: butylated hydroxytoluene, 3:1)	DES-DLLME + HPLC-MS	[66]
Honey; fruit samples	Organophosphorus pesticides	DES as emulsifier (vortex-assisted LLME)	Vortex-assisted liquid-liquid microextraction + GC-MS	[67]
Water; juice; vinegar	Fungicides	Magnetic DES	MDES-DLLME + HPLC	[68]
Environmental water	Polycyclic aromatic hydrocarbons	Hydrophilic DES (as disperser in DLLME-SFOD)	DLLME-SFOD + GC-MS	[69]
Milk and milk-based products	Melamine	Air-assisted hydrophobic magnetic DES	Air-assisted-MDES-DLLME + UV-Vis	[70]
Capsicum spice	Mycotoxins (ochratoxin A/B)	Synthesized DES (hydrophobic)	DES-DLLME + LC-MS/MS	[71]
Water samples	Heavy metals (Hg speciation)	Natural DES (menthol:decanoic acid)	NADES-DLLME + LC-UV-Vis (speciation)	[72]
Water & food samples	Heavy metals (Pb)	Hydrophobic DES (electromembrane hollow fiber acceptor)	DES-based electromembrane hollow fiber extraction + GFAAS	[73]
Honeysuckle dew	Organophosphorus pesticides	Switchable DES (hydrophilic ↔ hydrophobic)	UA-DES extraction + GC-MS	[74]
Food and water samples	Heavy metals (Ni, Cu)	Magnetic hydrophobic DES-DLLME	Magnetic hydrophobic DES orbital-shaker DLLME + UV-Vis	[75]
Water & food samples	Heavy metals (As, Cd, Pb, Hg)	Natural hydrophobic DES (ligand-less)	Ligand-less NADES-DLLME + AAS/ICP	[76]
Water samples	Heavy metals (Cu, Ni)	Hydrophobic natural DES (dual-function)	DES-DLLME + spectrometric detection	[77]
Aqueous media (water)	Heavy metals (UO ₂ ²⁺)	Hydrophobic DES (HDES-based optode)	HDES-optode preconcentration + spectrophotometry	[78]

Table 4. Cont.

Matrix	Pollutant Group	DES Type	Technique/Instrument	
Water samples	Crystal violet; Congo red	DES-DLLME with nanoparticles (ultrasonic-assisted)	UA-DES-DLLME + UV-Vis	[79]
Water matrices	Heavy metals (Cd)	Natural DES (NADES); SFOD	NADES-DLLME-SFOD + AAS	[80]
Food	Pesticides, phthalates, and polycyclic aromatic hydrocarbons	Hydrophobic NADES	NADES-DLLME + LC-MS/MS	[81]
Beverages; foods	Benzoic acid (preservative)	Air-assisted hydrophobic DES-DLLME	Air-assisted HDES-DLLME + UV/LC	[82]
Food products	Dyes (polar & non-polar)	Quasi-hydrophobic DES	DES-DLLME + HPLC/UV	[83]
Drinking water; alcoholic beverages	Aliphatic aldehydes (off-flavor contaminants)	Terpene-based hydrophobic DES	DES-DLLME + GC method	[84]
Water	Polychlorinated biphenyls	Hydrophobic DES (solidifying) + hydrophilic DES (disperser)	DLLME (solidifying HDES) + GC-MS	[85]
Environmental water	Chlorobenzenes	pH-switchable hydrophobic DES	Switchable DES-based liquid-phase microextraction + GC-ECD	[86]
Environmental & food matrices	Neonicotinoid pesticides	Natural DES (NADES)	DES-DLLME + chromatography	[87]
Wastewater	Emerging contaminants (benzotria- zoles/benzothiazoles/ parabens/UV filters)	Hydrophobic NADES: thymol:menthol	NADES-DLLME + HPLC-QTOF-MS	[88]
Surface water	Multiclass emerging organic contaminants	Hydrophobic NADES: thymol + butyric acid	Vortex-assisted DLLME + LC-MS	[89]
Mineral water (plastic packaged)	Persistent organic pollutants	Hydrophobic DES: tetrabutylammonium chloride + p-cresol (acid dissociation with HCl)	Hydrophobic DES-based liquid-liquid microextraction + GC-MS	[90]
Orange pomace	Bioactive compounds (antioxidant phenolics)	NADES: choline chloride:lactic acid	UAE-NADES + HPLC-DAD-QTOF-MS	[91]
Honey	Biopesticide residues	NADES: urea-glycerol-water	NADES-SLE + LC-Q-Orbitrap-MS	[92]
Radish (roots/leaves)	Non-phthalate plastic additives	Hydrophobic NADES: choline chloride-2,3-butanediol	NADES-based solid-liquid extraction + UHPLC-Q-Orbitrap-MS	[93]

Table 4. Cont.

Matrix	Pollutant Group	DES Type	Technique/Instrument	
Milk	Antibiotic residues	DES-based nanofluid (graphene oxide aerogel)	Vortex-assisted liquid–liquid microextraction	[94]
Plant & food matrices (beverages/juices)	Heavy metals (As, Cd, Pb)	Natural DES (NADES)	UAE/microwave-assisted extraction with NADES + ICP-MS	[95]
Surface water	Synthetic musks (personal care product contaminants)	Hydrophobic DES-coated membrane: tetrabutylammonium bromide:hexanoic acid (1:3, molar ratio)	DES-coated cellulose acetate membrane microextraction + GC–MS	[96]
Mine wastes (solid samples)	Heavy metal (silver)	DES: choline chloride:urea (1:2, molar ratio) used as extraction solvent in SFOD microextraction	DES-based solidified floating organic drop microextraction + FAAS	[97]
Wild blueberry (Vaccinium angustifolium Aiton)	Bioactive compounds (flavonoids)	NADES: betaine:urea (1:3.3, molar ratio; 60% water content in optimized UAE per study)	Ultrasound-assisted NADES extraction; LC–MS/MS nontargeted metabolomics analysis	[98]
Water samples and drinks	Synthetic dye (eosin Y)	DES systems: tetrabutylammonium bromide + alcohol (hexanol/octanol/decanol) in various ratios	Vortex-assisted liquid-phase microextraction (DES-based) + fluorescence detection	[99]
Milk samples	Food adulterant/contaminant (melamine)	Hydrophobic DES (extractant): thymol:nonanoic acid + hydrophilic DES (disperser): choline chloride:ethylene glycol (β -cyclodextrin doped)	Supramolecular-DES-based DLLME + HPLC	[100]
Environmental water (tap/river/lake/sea water)	Herbicides (triazines)	Magnetic DES: heptanoic acid + methyltriocetylammmonium chloride + iron chloride	MDES-based single-drop microextraction + HPLC	[101]
Mineral water; river water; packaged drinking water (polycarbonate bottle migration study)	Bisphenols (endocrine disruptors)	NADES: decanoic acid: DL-menthol (1:2, molar ratio)	DLLME + LC-DAD	[102]
Orange; spinach; wheat	Pesticide residues (multi-class)	NADES: thymol: menthol (1:1, molar ratio)	Solid–liquid extraction + LC-MS/MS	[103]
Commercial cow milk; chicken eggs	Antibiotic residues (sulfonamides + fluoroquinolone)	NADES: anisaldehyde: octanoic acid (2:1, molar ratio)	NADES-DLLME + UHPLC-MS/MS	[104]

AAS: atomic absorption spectrometry; FAAS: flame atomic absorption spectrometry; spectrometry; GFAAS: graphite furnace atomic absorption spectrometry; spectrometry; ICP-MS = inductively coupled plasma mass spectrometry; ICP-OES: inductively coupled plasma optical emission spectrometry; UV-Vis: ultraviolet–visible spectrophotometry; HPLC: high-performance liquid chromatography; UHPLC: ultra-high-performance liquid chromatography; UV: ultraviolet detection; DAD: diode array detection; MS: mass spectrometry; MS/MS = tandem mass spectrometry; QTOF-MS: quadrupole time-of-flight mass spectrometry; LC: liquid chromatography; Q-Orbitrap: quadrupole Orbitrap mass spectrometry; GC: gas chromatography; FID: flame ionization detection; ECD: electron capture detection.

4. Comparative Overview of DES-Based Extraction Techniques

The comparison presented in this section is primarily qualitative because the analytical performance metrics reported in the literature are not fully standardized across different studies. Therefore, the discussion focuses on identifying general trends linking DES composition, extraction mechanisms, sample matrices, analyte classes, and overall analytical performance. No single DES-based extraction method can be regarded as universally optimal, since the analytical efficiency of each approach is highly dependent on the extraction mechanism, sample matrix characteristics, phase separation mode, operational conditions, and intended analytical goals. Within this qualitative comparative framework, however, noticeable differences can be identified among the various DES-assisted extraction strategies. Among these, DLLME-based methods are still widely adopted due to their fast extraction kinetics, reduced solvent usage, simple sample handling, and high preconcentration capability [46,47,57,63,66,67,71,81,83,85,87,89,90]. The rapid dispersion of fine DES droplets within the sample generates a large interfacial surface area, which enhances mass transfer of analytes and allows the system to reach extraction equilibrium in a short amount of time. Consequently, DLLME generally demonstrates excellent analytical performance for trace-level analytes in liquid matrices, particularly when rapid enrichment and high sensitivity are required. These features make DLLME especially suitable for routine applications and high-throughput analytical settings. Nevertheless, although the method is simple and fast, conventional DLLME typically requires effective phase separation and solvent recovery steps, which has led to the development of several modified variants.

Among these variations, vortex-assisted, ultrasound-assisted, and air-assisted DLLME methods have been introduced to improve solvent dispersion and enhance extraction performance through different operational mechanisms. In vortex-assisted DLLME, mechanical agitation is applied, offering a simple, economical, and instrumentally minimal approach [56,59,63,82,99]. Ultrasound-assisted DLLME is based on acoustic cavitation, which promotes mass transfer and reduces diffusion constraints, thereby typically achieving more rapid extraction and improved recovery efficiencies compared with conventional DLLME [48,58,61,74,79]. This improvement is particularly beneficial when relatively viscous DES formulations are employed, since ultrasound partially compensates for slower diffusion by enhancing solvent penetration and analyte transport. In contrast, air-assisted DLLME removes the requirement for disperser solvents by using repeated aspiration and injection cycles to form the extraction dispersion [50,70,82]. Accordingly, air-assisted approaches generally present a more environmentally benign profile while still providing acceptable extraction efficiency. These findings indicate that, although all DLLME variants are based on the same fundamental extraction principle, they differ significantly in their operational features. This diversity enables the selection of the most suitable DLLME variant according to the analytical requirements of a given application. In practice, the choice depends on the desired extraction efficiency, rapidity, operational simplicity, solvent consumption, physicochemical properties of the target analytes, viscosity and polarity of the selected DES formulation, and complexity of the sample matrix.

Solidification-based approaches, such as DLLME-SFOD and floating organic drop microextraction, overcome a key limitation of liquid-phase microextraction techniques, particularly the difficulty associated with post-extraction solvent recovery [49,57,60,62,69,80,85,97]. By using DESs that solidify upon cooling, these methods enable easier and more reproducible recovery of the extraction phase compared with conventional DLLME. The analytical performance of these systems is strongly influenced by the melting behavior, hydrophobicity, and viscosity of the selected DES formulation, since these properties determine both analyte partitioning and the ease of phase collection. This approach helps reduce solvent loss and simplifies phase separation and handling. In comparison to standard DLLME,

SFOD-based techniques typically provide higher extraction-phase recovery and improved reproducibility; however, they depend on DESs with specific melting characteristics and may require an additional cooling step during the procedure.

Magnetic DES-based extraction systems constitute another significant development in phase separation techniques [50,68,70,75,94,101]. In contrast to conventional DLLME and SFOD methods, which depend on centrifugation or temperature-controlled phase separation, magnetic extraction systems utilize magnetic nanoparticles or magnetic nanofluids to rapidly separate the extraction phase under an external magnetic field. This approach minimizes sample-handling procedures, decreases processing time, and facilitates integration with automated analytical platforms. In addition, DES-modified magnetic materials often provide extra active adsorption sites and enhanced intermolecular interactions, leading to improved extraction performance. These advantages are particularly evident in complex environmental, food, and biological matrices, where rapid phase separation and reduced matrix interference are essential for reliable analytical results. Nevertheless, the synthesis and characterization of magnetic materials can increase both the complexity and cost of the method compared with simpler liquid-phase extraction techniques.

Unlike liquid-phase microextraction techniques, solid-phase extraction (SPE), magnetic solid-phase extraction (MSPE), membrane-assisted extraction, and DES-modified sorbents are primarily designed to enhance selectivity and improve matrix purification [51,72,73,76,96]. DES-functionalized sorbents can interact with target analytes through multiple mechanisms, including hydrogen bonding, electrostatic attraction, π - π stacking, and donor-acceptor interactions, thereby producing cleaner extracts and reducing matrix-related interferences. Accordingly, these approaches are generally more suitable for complex matrices or analyte classes requiring higher selectivity rather than only rapid enrichment. As a result, these methods are particularly effective for the analysis of complex samples containing substantial amounts of interfering substances. In addition, many DES-based sorbents can be regenerated and reused, supporting the long-term sustainability of the extraction process. However, these techniques typically involve extra steps, such as sorbent preparation, conditioning, and regeneration, which may limit their applicability for rapid screening compared with DLLME-based methods.

For solid and semi-solid samples, DES-assisted ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), pressurized liquid extraction (PLE), and NADES-based solid-liquid extraction offer several advantages compared with traditional microextraction techniques [91,93,95,98,103]. Ultrasound-assisted extraction (UAE) promotes the release of analytes by inducing cavitation that disrupts plant and food matrices under relatively mild operating conditions, making this technique particularly suitable for thermally sensitive compounds. In DES-based UAE, cavitation also improves solvent penetration and mass transfer, which can partially overcome the high viscosity commonly associated with several DES formulations. Microwave-assisted extraction (MAE) employs microwave energy to rapidly heat both the sample and the extraction medium, thereby shortening extraction times and enhancing overall efficiency. Although MAE generally provides higher sample throughput than UAE, it may not be ideal for compounds that are highly susceptible to thermal degradation. Likewise, pressurized liquid extraction (PLE) uses elevated temperatures and pressures to accelerate analyte diffusion and dissolution, often yielding highly reproducible results within relatively short extraction periods. However, both MAE and PLE require specialized equipment and higher energy consumption compared with UAE. In addition, NADES-based solid-liquid extraction has emerged as a promising approach for the recovery of natural products because NADESs typically exhibit lower toxicity, improved biocompatibility, and greater suitability for food and pharmaceutical applications than many traditional extraction solvents [91,93,95,98,103]. However, these

advantages remain formulation-dependent and should not be generalized to all NADES systems. Overall, the selection among UAE, MAE, PLE, and NADES-assisted extraction depends on the thermal stability of the analytes, matrix rigidity, DES viscosity, polarity, hydrogen-bonding capacity, and required balance between extraction efficiency, selectivity, and operational practicality.

The development of emerging DES technologies highlights the progression of this field beyond the concept of merely replacing conventional solvents. In situ DES generation streamlines the extraction procedure by forming the solvent directly within the sample matrix, which reduces reagent usage, minimizes solvent preparation requirements, and enhances the overall sustainability of the process [54,100]. Switchable DES systems offer enhanced operational versatility because their hydrophilic and hydrophobic characteristics can be reversibly adjusted using external stimuli, thereby facilitating both the extraction process and subsequent phase separation. The ability to reversibly modify solvent properties allows these systems to accommodate analytes with different physicochemical characteristics while simplifying phase separation. Although these systems provide greater flexibility than conventional DESs, their successful application often depends on careful optimization of the extraction parameters. Consequently, their analytical performance is governed not only by the extraction mechanism but also by the composition of the DES formulation and the operational conditions used to induce solvent switching.

Recent investigations have extended the application of DESs to more advanced extraction platforms. Electromembrane extraction integrates DES-based systems with electrically driven analyte transport, providing improved selectivity and more effective pre-concentration of ionic species compared with many traditional liquid-phase extraction techniques [52,78]. This additional transport mechanism makes electromembrane extraction particularly advantageous for charged analytes, where electrokinetic migration complements conventional partition-based extraction. Similarly, membrane-based and chromatomembrane extraction techniques generate cleaner extracts and exhibit better compatibility with continuous-flow and automated analytical platforms, as analyte transfer takes place through a precisely controlled membrane interface [51,73,96]. Although these techniques may involve longer extraction periods than DLLME-based approaches, they generally offer enhanced selectivity and improved reproducibility, making them particularly suitable for applications requiring high analytical precision and minimal matrix interference.

Overall, the studies compiled in Table 4 demonstrate that DES-assisted extraction has progressed far beyond its initial role as a potentially more sustainable alternative to conventional organic solvents and has developed into a diverse and adaptable analytical platform. DLLME-based methods continue to be favored for their speed and high extraction efficiency, whereas SPE- and membrane-based strategies provide greater selectivity and improved sample purification. Magnetic extraction systems simplify phase separation procedures, SFOD techniques facilitate solvent recovery, and UAE, MAE, PLE, and NADES-assisted methods offer efficient alternatives for processing complex solid matrices. Furthermore, recent innovations, including in situ DES generation, switchable DESs, electromembrane extraction, and chromatomembrane technologies, have broadened the scope of DES applications by enhancing sustainability, analytical versatility, and suitability for automated systems. Taken together, the available studies indicate that no single DES-assisted extraction technique consistently outperforms all others. Instead, analytical performance depends on the interplay between DES composition, extraction mechanism, analyte chemistry, sample matrix complexity, and operational conditions. Consequently, the selection of an appropriate DES-assisted extraction strategy should be based on balancing extraction efficiency, selectivity, operational simplicity, solvent recovery, the physicochemi-

cal properties of the DES formulation, matrix characteristics, environmental considerations, and compatibility with the intended analytical instrumentation rather than relying on a single performance criterion.

5. Future Trends and Challenges in DES-Based Extraction Systems

The future trajectory of deep eutectic solvent-based extraction systems is characterized by the convergence of analytical miniaturization, automation, and intelligent solvent design. As laboratories increasingly prioritize green, high-throughput analytical workflows, DESs offer the requisite molecular versatility for developing tailored solvent systems within microfluidic and automated extraction platforms. Consequently, the ongoing advancement in DES applications underscores their prospective role as foundational elements within next-generation analytical chemistry platforms. Although DESs are frequently described as green solvents, their environmental and toxicological profiles are not universal. The biodegradability, ecotoxicity, bioaccumulation potential, and overall sustainability of DESs depend strongly on the chemical identity of the hydrogen bond donor and acceptor, their molar ratio, impurities, and the intended application. Therefore, each DES formulation should be evaluated individually using appropriate environmental and toxicological assessment methods rather than assuming that all DESs are inherently green or low toxicity.

5.1. Microfluidic and Miniaturized DES Systems

The integration of deep eutectic solvents into microfluidic systems has enabled extraction processes that require very small sample volumes, shorter analysis times, and high reproducibility [105]. These miniaturized platforms significantly reduce solvent consumption and support continuous-flow extraction, making them highly useful for real-time environmental and clinical monitoring [106]. In addition, the low volatility and adjustable polarity of DESs make them particularly well suited for use in narrow microfluidic channels, overcoming problems commonly associated with the evaporation of conventional solvents. The successful application of DESs in microfluidic devices often depends on optimizing parameters such as flow rate, channel design, and mixing conditions to achieve maximum extraction efficiency within the microscale environment. As a result, these systems frequently provide better performance than conventional batch extraction methods.

Several investigations have focused on incorporating deep eutectic solvents (DESs) into microfluidic and miniaturized extraction platforms to enhance analytical performance and process efficiency. Dowlatshah et al. [107] designed a microfluidic liquid-phase microextraction platform that employed natural deep eutectic solvents as supported liquid membranes, representing one of the earliest demonstrations of a fully green, biodegradable, and membrane-assisted microfluidic extraction system. More recently, Piryaee et al. [108] introduced a DES-hydrogel thin-film electromembrane microfluidic device for the extraction of bisphenol A from thermal paper, mineral water, and tap water samples, demonstrating the potential of DES-based membranes in the development of miniaturized, environmentally sustainable analytical platforms. In a subsequent study [109], a microfluidic extraction platform incorporating a hydrophobic DES was designed for the effective separation of cesium ions from acidic aqueous media, demonstrating the potential of DES-integrated microfluidic systems for metal ion recovery and environmental remediation applications. Furthermore, recently developed on-chip electromembrane extraction devices combined with thin-film solid-phase microextraction have illustrated the feasibility of miniaturized analytical platforms for detecting synthetic dyes in beverage and environmental samples [110]. Collectively, these findings demonstrate that DES-based microfluidic technologies can significantly reduce solvent consumption, enhance extraction performance, and promote the advancement of automated and environmentally sustainable analytical systems.

5.2. DES–Nanocomposite Hybrids

Recently, increasing attention has been directed toward hybrid systems that combine deep eutectic solvents (DESs) with nanostructured materials, including metal–organic frameworks, graphene, and magnetic nanoparticles. Such combinations have demonstrated notable improvements in surface area, selectivity, and adsorption efficiency. For instance, DES–graphene composites have shown effectiveness in recovering trace organic compounds from aqueous media [111], while DES-coated magnetite materials simplify phase separation during magnetic solid-phase extraction [112]. The combined properties of DESs and nanomaterials contribute to improved material stability and reusability, making them promising candidates for advanced extraction technologies [113]. Recent investigations have further emphasized the increasing importance of DES–nanocomposite hybrid materials in extraction and adsorption technologies. Deng et al. reviewed the application of DES-functionalized metal–organic frameworks and demonstrated their considerable potential for food and environmental sample preparation, which arises from the synergistic integration of the intrinsic porosity of metal–organic frameworks with the selective interactions provided by DES components [113]. Liu et al. synthesized DES/reduced graphene oxide composites and demonstrated their high efficiency in the adsorptive removal of dibenzothiophene from fuel oil, highlighting the potential of DES–graphene hybrid materials to improve adsorption capacity and overall separation performance [114]. In a recent study, Hang et al. fabricated DES-functionalized magnetic graphene oxide/metal–organic framework composites for magnetic dispersive solid-phase extraction, demonstrating enhanced extraction efficiency together with more convenient magnetic separation [115]. More recently, Chen et al. [112] developed poly-DES-functionalized magnetic graphene oxide nanomaterials and demonstrated their excellent performance in the solid-phase extraction of trypsin, highlighting the potential of polymeric DES coatings for efficient biomolecule enrichment. Likewise, DES-based ferrofluids constructed from Fe_3O_4 magnetic cores have been identified as effective magnetic extractants [116], further illustrating the advantages of integrating DESs with magnetic nanostructures to achieve rapid and environmentally friendly separation processes. Additionally, Chen et al. prepared a biomass-derived magnetic nanocomposite consisting of Fe_3O_4 , chitin, and a choline chloride/citric acid-based natural deep eutectic solvent for the magnetic solid-phase extraction of trypsin. The resulting material exhibited high extraction efficiency and excellent reusability, demonstrating the suitability of NADES-modified magnetic biopolymer nanocomposites for selective biomolecular separations [117]. Valipour et al. also synthesized DES-functionalized SiO_2 -coated magnetic nanoparticles using an arginine/choline chloride formulation. Their findings showed that anchoring DESs onto magnetic nanostructures can enhance material stability, facilitate recovery, and improve functional performance, thereby broadening their potential applications in sustainable catalytic systems [118]. In addition, incorporating DESs into solid nanostructured supports helps overcome viscosity-related limitations commonly associated with certain DES systems, leading to enhanced mass transfer during extraction processes [119]. Functional modification of nanomaterials can further promote selective interactions between DESs and specific target compounds, enabling more efficient and selective enrichment strategies [120].

5.3. Automation and Online Coupling

The integration of deep eutectic solvent (DES) extraction with chromatographic and spectrometric techniques through automated and online systems has significantly improved analytical performance [121]. By functioning in closed environments, automated DES-based systems reduce operator exposure while enhancing consistency and reproducibility. This approach supports high-throughput analysis and remains compatible with

regulatory requirements for monitoring trace-level contaminants. Several studies have demonstrated the feasibility of incorporating DESs into automated and online analytical platforms. For example, a Lab-in-Syringe automated DES-based direct immersion single-drop microextraction system coupled online with HPLC was developed for the determination of fluoroquinolones in environmental waters, showing reduced solvent consumption and improved reproducibility [122]. Similarly, a poly(deep eutectic solvent) monolithic column has been employed in an online in-tube solid-phase microextraction system coupled with HPLC for the analysis of non-steroidal anti-inflammatory drugs, demonstrating the effectiveness of DES-derived sorbents in integrated chromatographic workflows [123]. Automated liquid–liquid extraction using DESs has also been reported for acrylamide determination, emphasizing their applicability in streamlined sample preparation [124]. More recently, an automated DES-based chromatomembrane microextraction system was introduced for the preconcentration and separation of bisphenols from aqueous matrices, further illustrating the compatibility of DESs with environmentally friendly automated analytical platforms [125]. In addition, a semi-automated single-drop microextraction approach employing a natural deep eutectic solvent synthesized from oleic acid was developed for Zn(II) analysis, demonstrating that semi-automated DES-based methodologies can enhance analytical precision while reducing manual handling [126].

The direct connection between DES extraction and analytical instruments enables real-time sample processing, which helps shorten the time required for analyzing complex samples [127]. Advances in robotic systems tailored for DES extraction procedures are also expected to improve laboratory workflow by increasing operational accuracy and minimizing the possibility of human error.

5.4. Machine Learning and AI-Driven Solvent Design

The use of artificial intelligence (AI) and machine learning is increasingly contributing to the understanding of interactions between deep eutectic solvents (DESs) and target analytes, while also helping predict important solvent properties such as viscosity, polarity, and extraction performance [128]. In addition, multi-objective computational algorithms are being used to identify suitable combinations of hydrogen bond acceptors and hydrogen bond donors based on the structural characteristics of the analytes of interest [129]. These computational tools reduce reliance on extensive experimental testing, making the development of efficient and environmentally friendly solvents faster and more systematic. Recent work has highlighted the growing importance of machine learning techniques in the prediction and optimization of deep eutectic solvent (DES) properties. For instance, open-access predictive frameworks have been proposed to estimate key physicochemical parameters of DESs, enabling faster and more efficient solvent screening [130]. In addition, various machine learning models have been developed to predict eutectic temperature [131], viscosity [132], carbon dioxide solubility [133], and heat capacity [134]. Beyond property prediction, data-driven and hybrid approaches have been applied to elucidate hydrogen-bonding interactions within DES systems [135]. Combined experimental and machine learning strategies have also been used to design pharmaceutically relevant DES formulations, improving the solubility of drugs such as ibuprofen and ketoprofen [136]. Furthermore, physics-informed machine learning models have been utilized to estimate solvatochromic parameters of designer solvents, offering enhanced understanding of solvent polarity and solute–solvent interactions [137].

By applying predictive modeling, researchers can avoid time-consuming empirical screening and accelerate the rational design of DESs tailored for specific analytical purposes [138]. This predictive strength also supports the development of customized solvents

with improved selectivity and extraction efficiency, creating new opportunities for more targeted and application-specific analytical approaches [41].

5.5. Regulatory, Thermodynamic, and Scalability Challenges

Although significant advancements have been made, the widespread application of deep eutectic solvents (DESs) is still constrained by several challenges. A key limitation is their sensitivity to thermodynamic conditions, including temperature, composition, pressure, and water content, all of which can influence phase behavior, extraction efficiency, and operational stability, particularly in large-scale applications. This behavior is associated with the inherently non-ideal nature of DESs, where strong hydrogen bond interactions between hydrogen bond donors and acceptors result in melting-point depression and intricate phase equilibria [139–141]. Even minor changes in composition, precursor selection, or moisture level can noticeably affect viscosity, density, thermal and melting characteristics, and solvation behavior, thereby reducing reproducibility and complicating scale-up processes [141,142].

The development of predictive modeling approaches is strongly motivated by the vast number of possible deep eutectic solvent (DES) combinations, making the experimental determination of all relevant physicochemical properties impractical. Haghbakhsh et al. [143] introduced group-contribution and atomic-contribution models capable of estimating key DES properties such as density, refractive index, heat capacity, speed of sound, and surface tension based solely on structural descriptors. In addition, several other studies have reported predictive frameworks targeting individual properties, including viscosity, density, surface tension, heat capacity, and acoustic velocity [144–148]. Collectively, these developments emphasize the growing role of computational tools in the screening and rational design of DES systems. Such models are particularly useful in early-stage evaluation, solvent selection, and feasibility assessment, as they minimize reliance on extensive experimental trial-and-error and provide reliable property estimates prior to laboratory synthesis.

In addition, the relatively high viscosity characteristic of many DES formulations can significantly hinder diffusion and mass transfer during large-scale extraction processes, thereby limiting their suitability for industrial-scale and continuous-flow operations. Elevated viscosity reduces analyte mobility, decreases interfacial contact efficiency between phases, and increases the energy required for mixing and fluid handling. Experimental findings have shown that the physicochemical and rheological behavior of DESs is strongly influenced by temperature, water content, and the molecular structure of their constituents [142,149,150]. To address these limitations, several strategies have been proposed, including controlled addition of water, dilution with compatible co-solvents, temperature optimization, and the design of low-viscosity hydrophobic DES systems [141,151,152]. However, such modifications must be carefully controlled, as excessive dilution or compositional alteration may disrupt the hydrogen-bonding network, modify solvent polarity, reduce selectivity, or compromise overall stability.

Another critical challenge is the limited availability of comprehensive and consistent thermodynamic and thermophysical data describing DES–solute interactions, phase behavior, heat capacity, density, viscosity, surface tension, and thermal stability. This lack of reliable datasets complicates process modeling, scale-up design, and industrial implementation. Previous thermodynamic and transport-property studies have emphasized that accurate experimental data, together with validated predictive models, are essential for interpreting DES behavior and enabling reliable transfer from laboratory-scale studies to industrial applications [141,143,153]. Accordingly, establishing standardized reporting practices—covering DES composition, water content, and purity of precursors,

as well as temperature, pressure, and measurement conditions—is crucial for improving reproducibility and ensuring meaningful comparison across different studies.

5.6. Sustainability

Deep eutectic solvents (DESs) have emerged as sustainable alternatives in analytical extraction because of their renewable origins and reduced environmental impact. Their low toxicity, strong thermal and chemical stability, and ability to dissolve a wide range of compounds further support their role as environmentally friendly solvents in accordance with green chemistry principles. In parallel, the development of DESs is increasingly shifting from conventional trial-and-error experimentation toward reverse design strategies that combine computational modeling with advanced computing tools to tailor solvents for specific extraction purposes [154]. This transition improves control over the physicochemical properties of DESs while supporting green chemistry goals through the replacement of conventional volatile organic solvents with safer and more biodegradable alternatives [155]. Recent advances in supramolecular DES systems have also focused on overcoming persistent limitations, such as high viscosity and excessive hydrophilicity, through targeted modifications that improve analyte solubility and facilitate industrial-scale applications [156]. However, challenges remain, particularly regarding solvent viscosity and inefficient recycling in biomass-related processes. To improve large-scale sustainability, innovative recovery approaches, including anti-solvent precipitation and macroporous resin adsorption, are being explored [157,158].

One recent investigation has critically questioned the common perception that deep eutectic solvents (DESs) are inherently green and environmentally benign. The study emphasizes that the sustainability profile of DESs is more complex than generally assumed, since strong interactions between components can significantly modify their physicochemical behavior and toxicological impact, sometimes leading to biological effects that differ from those of the individual constituents. As a result, each DES system should be individually assessed for safety rather than assuming low toxicity or inherent biodegradability [16]. This viewpoint is further supported by several experimental studies employing different biological evaluation models. For instance, Radošević et al. [159] examined the toxicity and biodegradability of choline chloride-based DESs and demonstrated that their biological effects are strongly influenced by the nature of the hydrogen bond donor and the overall DES composition, rather than the properties of the individual components alone. Likewise, Wen et al. [160] investigated a range of DES formulations and reported that their environmental safety cannot be generalized, as certain systems may exhibit higher-than-expected toxicity depending on their specific composition.

At the cellular level, Hayyan et al. [161] examined the cytotoxic effects of natural deep eutectic solvents using mammalian cell-based models and showed that even NADESs composed of naturally derived components can exhibit concentration-dependent toxicity. Macário et al. [162] further assessed the cytotoxicity of DESs on human skin-associated cell lines, including keratinocytes, which is particularly relevant for applications in cosmetics, pharmaceuticals, and dermal exposure scenarios. Their results demonstrated that the observed toxicity is strongly dependent on both the composition and concentration of the DES, reinforcing the necessity of evaluating each system individually for safety purposes.

In addition to cytotoxicity assessments, several studies have also explored the antimicrobial and ecotoxicological behavior of DESs. Radošević et al. [163] investigated the antimicrobial, cytotoxic, and antioxidant activities of NADES formulations and reported that the biological responses vary significantly depending on both the solvent composition and the type of organism tested. Torregrosa-Crespo et al. [164] suggested that conventional toxicity evaluation methods may not be fully suitable for DES systems, as their high viscos-

ity, acidity or basicity, and extensive hydrogen-bonding interactions can potentially affect the reliability of standard bioassays. Accordingly, they emphasized the need to establish dedicated toxicity assessment protocols specifically tailored for DES-based materials.

More recent review articles have further emphasized the complex and sometimes inconsistent nature of reported DES toxicity data. Lomba et al. [165] analyzed both human and environmental toxicity studies and concluded that the toxicological behavior of DESs is governed by multiple parameters, including the structure of the hydrogen bond acceptor/donor, molar ratio, pH, organic acid content, and interactions between components. Martínez et al. [166] similarly argued that DESs should not be automatically regarded as non-toxic or inherently green, since the observed toxicity is highly dependent on the biological system employed and the experimental methodology applied. Furthermore, Nejrotti et al. [16] conducted a detailed assessment of six choline chloride-based DES formulations and demonstrated that evaluating sustainability requires an integrated approach that accounts not only for toxicity, but also for biodegradability, physicochemical properties, and environmental persistence.

Overall, the available evidence indicates that the safety and sustainability of deep eutectic solvents (DESs) cannot be universally assumed and must instead be assessed individually for each specific formulation, rather than inferred from the benign nature of their constituent compounds. A robust safety evaluation should therefore integrate a wide range of biological and environmental criteria, such as bacterial toxicity, mammalian and skin-cell cytotoxicity, biodegradability, bioaccumulation tendency, acute toxicity, and overall ecotoxicological impact. In addition, future work should aim to minimize current knowledge gaps by developing standardized assessment protocols and conducting systematic studies of key physicochemical and environmental parameters, including vapor pressure, surface tension, and long-term ecological effects, to enable safer and more reliable industrial application of DESs [156,157,167].

6. Conclusions

This comprehensive review highlights the significant role of deep eutectic solvents (DESs) in advancing analytical extraction methods. Owing to their tunable properties, these solvents can be tailored to meet the requirements of specific analytes, helping to overcome many of the limitations associated with conventional extraction systems. Their simple preparation, relatively low cost, and biodegradable nature make DESs attractive green alternatives to hazardous organic solvents, supporting the principles of sustainable chemistry. The review also demonstrates the broad applicability of DESs across different extraction techniques, ranging from microextraction methods to larger-scale processes, where they contribute to improved extraction efficiency, selectivity, and environmental sustainability. In particular, their application in liquid–liquid extraction and dispersive liquid–liquid microextraction has enhanced analyte recovery and enrichment while reducing the need for conventional organic solvents. Nevertheless, important challenges remain, especially regarding the limited understanding of the long-term environmental behavior, toxicity, and regulatory considerations associated with DESs, all of which must be addressed before large-scale commercial implementation becomes feasible. Future research should therefore focus on establishing standardized toxicity evaluation methods, developing clear regulatory frameworks for safe industrial application, and expanding thermodynamic databases supported by machine learning approaches to accelerate the rational design of task-specific DESs.

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