Homogeneous Liquid–Liquid Microextraction

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Abstract The development of liquid phase microextraction methods has led to significant progress in extraction processes by overcoming several challenges associated with conventional liquid–liquid extraction techniques. Liquid phase microextraction is a more cost-effective and eco-friendly alternative that is easier to implement compared to the traditional method. However, the use of water immiscible solvents as extractants in both liquid–liquid and dispersive liquid–liquid microextraction methods posed a challenge in extracting polar drugs. To address this limitation, homogeneous liquid–liquid microextraction emerged as the preferred mode for extracting polar analytes from complex matrices. HLLME uses hydrophilic, water-miscible solvents as extractants, leading to the formation of a homogeneous phase between the extractant and aqueous media. Because there is no interface between the sample and the extractant, HLLME provides superior extraction efficiency compared to other modes of liquid phase microextraction. Phase separation can be achieved by adding chemicals such as salt or sugar or manipulating the extractant's physicochemical properties, such as temperature or pH. In this chapter, we provide a detailed discussion of different homogeneous liquid–liquid microextraction modes, with emphasis on the fundamentals, the new developments and the applications.

Keywords Homogeneous liquid–liquid microextraction · Sample preparation · Green analytical chemistry · Salting-out · Sugaring-out

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Abbreviations

ACN	Acetonitrile
CHCl	Choline chloride
DES	Deep eutectic solvent
DLLME	Dispersive liquid–liquid microextraction
EHLLME	Emulsification induced homogeneous liquid–liquid microextraction
HBA	Hydrogen bond acceptor
HBD	Hydrogen bond donor
HLLME	Homogeneous liquid–liquid microextraction
LLE	Liquid–liquid extraction
LPME	Liquid phase microextraction
LLME	Liquid–liquid microextraction
PSA	Phase separating agent
SALLME	Salting-out induced liquid–liquid microextraction
SHS	Switchable hydrophilic solvent
SULLME	Sugaring-out induced liquid–liquid microextraction
THF	Tetrahydrofuran
DMSO	Dimethyl sulfoxide
IPA	Isopropyl alcohol
SIPTE	Solvent induced phase transition extraction
SULLE	Sugaring-out induced liquid–liquid extraction
EF	Enrichment factor
ISFME	In situ Solvent formation microextraction
HLLE	Homogeneous liquid–liquid extraction
IL	Ionic liquid
SA-HLLME	Surfactant-assisted HLLME
MA-IL-HLLME	Microwave assisted-IL-HLLME
NPs	Nanoparticles
APA	Analytical process automation
DEHPA	Bis(2-ethylhexyl) phosphoric acid
HSLLME	Hydrophobic substance induced HLLME

1 Introduction

Nowadays, there is a growing need for novel analytical techniques to monitor drugs, residues, and pollutants in complex matrices. To meet this demand, technological advancements have been made in the field of analytical chemistry. Analysing analytes at very low concentrations involves various processes, including sample preparation and data processing, each of which can impact analytical performance. Despite recent

developments in analytical chemistry instruments, a sample treatment step is necessary before instrumental analysis in most cases to process raw complex matrices. This step aims to remove matrix interferents, clean up the sample, and preconcentrate target compounds before injection into the instrument, which can improve analyte response [1, 2].

Sample preparation is typically considered the most error-prone and time-consuming phase in the analytical workflow. Traditional extraction procedures, such as liquid–liquid extraction (LLE), were invented decades ago and are still used in sample processing [3, 4]. LLE involves using large volumes of water immiscible organic solvents (e.g. chloroform, ether, or ethyl acetate) combined with the aqueous sample, which are then separated, evaporated, and reconstituted in the lowest amount of a suitable solvent.

However, these classic sample preparation procedures have significant limitations, including high solvent consumption, high production of waste, a tedious routine, a common source of sample contamination, and analytical mistakes arising from the operator's handling required to conduct these processes [3, 4]. Liquid–liquid microextraction (LLME) is a contemporary trend that aims to address these issues by saving solvents, preserving the environment, and enhancing sensitivity [5, 6]. In LLME, small volumes of a water immiscible organic solvent are used as extractants, which makes the analyte highly concentrated in the organic phase.

LLME can be categorised into homogeneous or heterogeneous modes, based on the miscibility of the extractant in the aqueous sample [7–9]. Heterogeneous LLME relies on using a water immiscible organic solvent similar to conventional LLE, but the volume used is much less (30–200 μL versus 3–10 mL). This kind of heterogeneous LLME is known as liquid phase microextraction (LPME) and results in a significant increase in analytical method sensitivity due to the tiny volume of the extractant, which makes the analyte extremely concentrated. Dispersive liquid–liquid microextraction (DLLME) is a kind of heterogeneous LLME that uses a dispersant (such as methanol or acetonitrile (ACN) with the water immiscible extractant to increase the contact surface with the aqueous phase and improve analyte accessibility [10–12]. However, both modes show low extraction efficiency for polar analytes due to their dependence on hydrophobic, water immiscible solvents as extractants.

Homogeneous liquid–liquid extraction (HLLE) depends on the creation of a homogeneous phase between the extractant and the aqueous sample, which enormously increases the accessibility of the extractant to the target analyte. The system can be composed of water-miscible organic solvents, water-immiscible solvents/cosolvents, surfactants, or smart polymer to create the homogeneous phase. When water-miscible solvents are used, homogeneous phases emerge spontaneously. In this case, the extraction solution is a binary combination of the water-miscible solvent and the aqueous sample at room temperature. Despite the expanded number of water miscible solvents available, only a handful were used in HLLE. This could be explained by the difficulties of initiating phase separation following homogeneous phase development in most common solvents. Phase separation is achieved by the addition of chemicals such as salt, sugar, buffer, hydrophobic substances, or by changing the environment of the system (pH, temperature).

The principle of HLLE was first introduced by Matkovich and Christian using salt as a phase separating agent (PSA) to extract polar analytes [13]. The first miniaturized form of HLLE was developed by Verma's group in 2009 to extract carbonyl compounds, before HPLC/UV analysis [14]. In the same year, Baghdadi and Shemirani developed in situ solvent formation microextraction (ISFME) as modified form of homogeneous liquid–liquid microextraction (HLLME) [15]. Since then, HLLME was employed to overcome the challenge of extracting polar analytes from aqueous samples by using a few microlitres of water-miscible organic solvents such as acetonitrile, ethanol, acetone, or tetrahydrofuran (THF). In 2010, solvent induced phase transition extraction (SIPTE) was tried for the first time to extract three structurally diverse drugs from human plasma [16]. Later on, new solvents were tested in HLLME such as ionic liquid (IL) [17] and deep eutectic solvents (DES) [18]. In 2021, sugaring-out assisted HLLME (SULLME) was employed in the extraction of 14 drugs from three theraputic classes, and was found more efficient than salting-out assisted homogenous liquid–liquid microextraction (SALLME) and DLLME [5]. Figure 10.1 shows the milestones of HLLME development over the last decades.

2 Fundamentals

HLLME is a technique of sample preparation that involves the formation of a homogeneous phase between an aqueous sample and a small amount of a water-miscible extractant, such as acetonitrile, acetone or tetrahydrofuran. The separation of phases is achieved using a PSA, which may be a salt, sugar, or hydrophobic substance. Depending on the type of PSA used, HLLME can be classified into three categories: SALLME, SULLME, and hydrophobic substance-assisted HLLME.

The contact surface between the aqueous phase and the extractant in HLLME is enormous, which enhances the accessibility of the target analyte to the extractant. Consequently, HLLME facilitates higher extraction efficiency than other microextraction techniques such as LPME [19] and DLLME [20, 21]. In addition, HLLME is a greener techniques of sample preparation because the water-miscible solvents used are typically safer and more environmentally friendly. It is worth mentioning that water-miscible solvents like THF, ACN, IPA are greener than water immiscible solvents such as chloroform (hepatotoxic) and ethers which are harmful to the lung and the other organs. HLLME is particularly suitable for extracting very hydrophilic drugs due to the high dielectric constants of the water-miscible extractants employed, as indicated in Table 10.1.

The various types of homogeneous liquid–liquid extraction (HLLE) are categorized based on the dmethod used to create a uniform phase and the process of separation. The creation of a uniform phase can be achieved through the use of a water-miscible organic solvent (in HLLME), an ionic liquid (in IL-HLLME), a deep eutectic solvent (in DES-HLLME) a surfactant (in SA-HLLME), or a smart polymer (in switchable hydrophilic solvent (SHS-HLLME). Additionally, the separation process can be initiated by adding certain chemicals or altering the physical

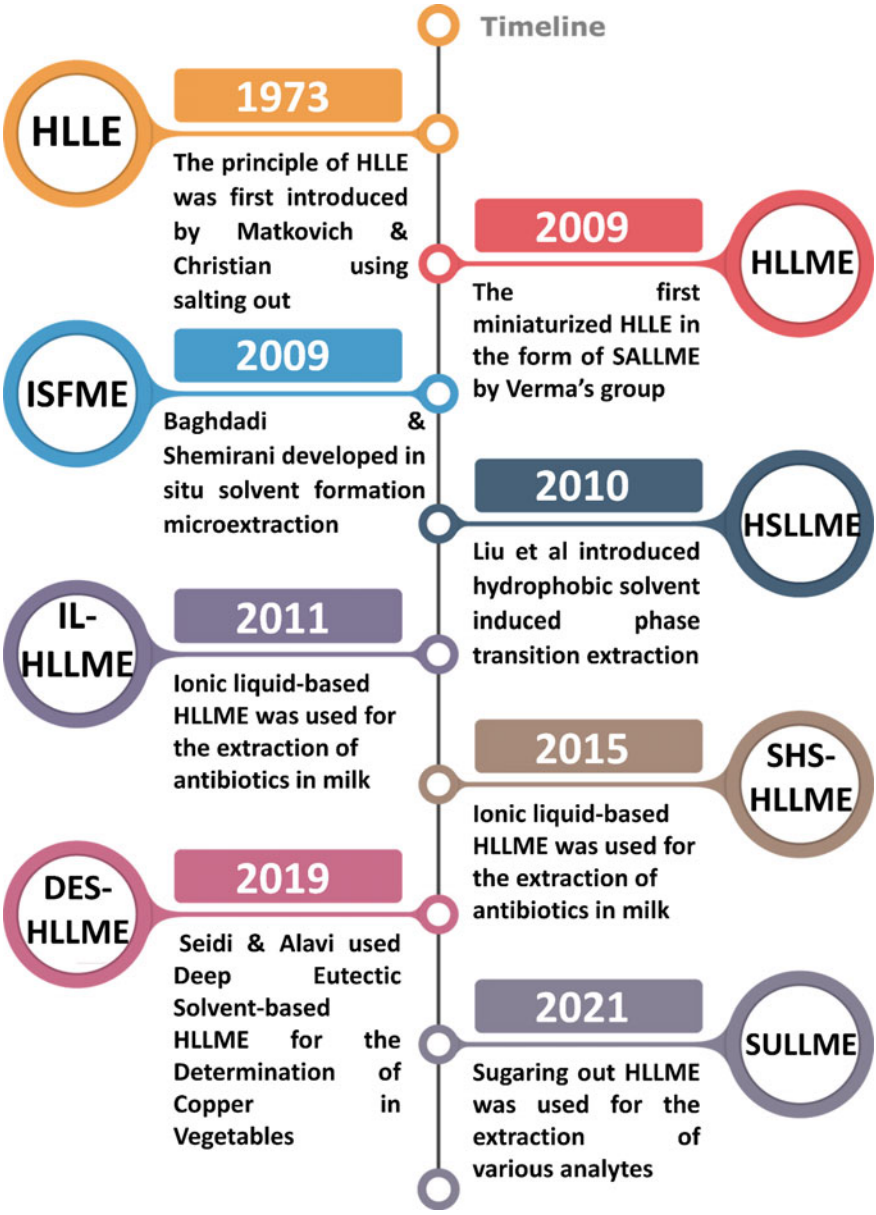

Fig. 10.1 Timeline of the development in Homogeneous liquid–liquid microextraction (HLLME)

Table 10.1 Properties of common organic solvents in HLLME [22]

Solvent	UV cut off (nm)[4]	Viscosity (mPa s)[4]	BP (°C)[4]	Polarity (P')[2]	Refractive Index[3] n^{D}_{20}	Dipole[2,5] π*	Acidity[2] α	Basicity[2] β	Density at 20 °C
Acetone	330	0.306	56.2	5.1	1.359	0.56	0.06	0.38	0.791
Acetonitrile	190	0.369	81.6	5.8	1.344	0.60	0.15	0.25	0.787
Chloroform	245	0.542	61.2	4.1	1.443	0.57	0.43	0.00	1.4832
Dimethysulfoxide (DMSO)	265	1.987	189	7.2	1.478	0.57	0.00	0.43	1.101
Dioxane	215	1.177	101.2	4.8	1.420	0.60	0.00	0.40	1.036
Ethanol	210	1.074	78.3	5.2	1.361	0.25	0.39	0.36	0.79
Hexane	210	0.300	68.7	0.1	1.357	–	–	–	0.659
Isopropyl alcohol (IPA)	210	2.04	82.4	3.9	1.377	0.24	0.36	0.40	0.785
Methanol	210	0.544	64.7	5.1	1.328	0.28	0.43	0.29	0.792
THF	220	0.456	66.0	4.0	1.407	0.51	0.00	0.49	0.888
Water	191	0.89	100	10.2	1.333	0.45	0.43	0.18	1.000

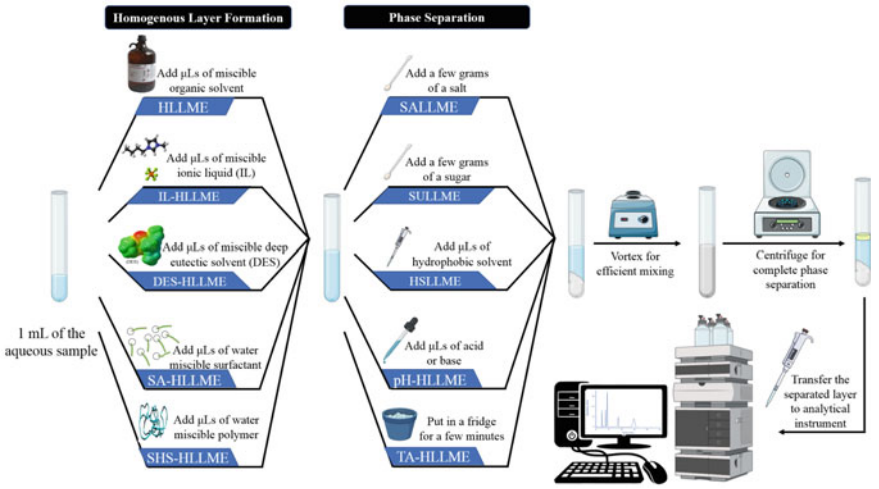

Fig. 10.2 Different modes of homogeneous liquid–liquid microextraction

conditions of the extraction media. Chemical-induced phase separations are the most common form of HLLE, where an extractant is removed from the extraction media by adding a more water-soluble substance such as salts (in SALLME), sugars (in SULLME), or a hydrophobic solvent (in HSLLME). Phase separation can also be induced by changing the pH in case of smart polymers or by changing the temperature. Figure 10.2 illustrates the different modes of HLLME.

HLLME is an efficient, cost-effective, and environmentally friendly approach for extracting biomolecules, such as enzymes, hormones, and proteins. HLLME is compatible with liquid chromatography-mass spectrometry (LC–MS) for metabolomics and proteome research. The effectiveness of HLLME depends on several factors, including the type and amount of extractant, the type of PSA, the volume of the aqueous sample and extractant, and the pH of the aqueous sample.

The Hydrophilicity of the extractants plays a significant role in the extraction process, as it follows the like-dissolves-like principle. Therefore, the polarity of the extractant should be matched with the target analyte's polarity. Similarly, the type of PSA used affects the efficacy of the extraction process. Not all sugars and salts can achieve phase separation, and not all water-miscible solvents can be separated.

Although SULLME has weaker phase-separation ability than SALLME, it has more preconcentration capacity in extraction because it achieves a lower retrieval volume. It is important to use an appropriate amount of PSA to achieve reproducible phase separation. However, excessive PSA can reduce preconcentration capacity by dilution effects. The hydration hypothesis may explain the salting out phenomenon [23]. It should be noted that PSA should have considerably higher solubility in aqueous samples than the extractant to induce phase separation.

Generally, sample volume directly correlates with preconcentration capacity, while extractant volume inversely correlates with extraction efficiency. Finally, pH

plays a major role in extraction efficiency, as it influences analyte solubility. The analyte should be in a non-ionized form for better extraction.

The preconcentration capacity of HLLME is assessed using the enrichment factor (EF) which can be calculated from the ratio between the analyte concentration in the extractant (C_{org}) and the concentration in the sample (C_{aq}):

$$EF = C_{org} / C_{aq} \tag{10.1}$$

The extraction recovery can also be calculated based on the ratio between the analyte amount in the extractant (n_{org}) and the initial amount in the aqueous sample (n_{aq}) as follows:

$$\%ER = \frac{n_{org}}{n_{aq}} \times 100 = \frac{C_{org} V_{org}}{C_{aq} V_{aq}} \times 100 = \%EF \times \frac{V_{org}}{V_{aq}} \times 100 \tag{10.2}$$

where V_{org} and V_{aq} are the volumes of the separated extractant and of the aqueous sample, respectively.

One of the most interesting aspects of HLLME is that it fits under the umbrella of green analytical chemistry (GAC). Historically, GAC is a branch of green chemistry that focuses on the role of analytical chemists in making laboratory operations more environmentally friendly, and it has attracted the interest of chemists [24–26]. The 12 principles of green chemistry were developed by Anastas and Warner in 1998 [27]. However, only a few of these principles can be directly applied to analytical chemistry because they were originally designed for synthetic chemistry. Gałuszka et al. [28] reported 12 principles of GAC that are better suited for analytical methods. From the perspective of environmentalists who also consider the economic aspects of analytical methodologies, special attention should be paid to the inherent risks of certain sample types and solvents used, the energy consumption associated with advanced instrumentation, and, of course, the resulting laboratory wastes and emissions from the numerous steps of analytical methodologies. In this regard, HLLME is a miniaturized sample preparation technique that reduces reagent consumption, minimizes waste production, and utilizes greener extractants such ILs and DESs. Moreover, HLLME is time-saving and cheaper compared to conventional sample preparation techniques, and it has a high potential for automation. The green characteristics of HLLEM and the high efficiency in extracting highly polar analytes may explain the increasing numbers of publications every year.

3 Novel Developments

HLLME modes are classified based on the approach utilized to produce a homogenous phase or the technique used in the separation of phases. Recent developments in HLLME research have led to three emerging trends being pursued by researchers. The first trend involves exploring novel materials that can form a homogeneous layer

with water. This approach is accomplished through the use of IL [17, 29], DES [30], surfactants [31] or switchable solvents [32] to facilitate the formation of a stable homogenous liquid phase, leading to a more efficient extraction process. The second trend focuses on developing advanced techniques for the separation of phases. In particular, the use of gas flotation [33], liquid nitrogen [34], magnetic fields [35], and ultrasound [36] has gained considerable attention due to their effectiveness in separating the two liquid phases. These techniques also enable better control over the extraction process, allowing for enhanced precision in the determination of target analytes.

The third trend is the automation of HLLME processes. Automation offers several advantages, including increased efficiency, reproducibility, and reduced risk of human error. The use of automated systems also facilitates the handling of large sample volumes, which is particularly useful in industrial settings. These emerging trends demonstrate the ongoing efforts to optimize HLLME techniques, improve their efficiency, and expand their applications. In the following sections, we will delve into each trend in greater detail to provide a more comprehensive understanding of their potential contributions to the advancement of HLLME.

3.1 New Solvents for HLLME

3.1.1 Using Ionic Liquids in HLLME

ILs have emerged as a promising class of solvents due to their unique combination of properties that offer advantages over common organic solvents. These solvents are a type of green solvents that are nonmolecular, ionic and have melting temperatures below 100 °C [37–39]. They possess unique physicochemical properties such as low vapor pressure, high solubility in both organic and inorganic compounds, and excellent thermal stability [40–42]. Due to the customizable structure of ionic liquids, they are often referred to as designer solvents [43, 44]. By altering the cation/anion combination or incorporating specific functional groups into their structure, the characteristics of ionic liquids can be easily modified [45]. As a result, ionic liquids exhibit specific solvation characteristics that provide selectivity and a range of separation mechanisms. Consequently, they have gained acceptance in various liquid-phase microextraction techniques, including HLLME [46]. Wang et al. [47] performed microwave-assisted IL-HLLME (MA-IL-HLLME) for the determination of anthraquinones in *Rheum palmatum L.* by HPLC–DAD. The extractant used was 1-octyl-3-methylimidazolium tetrafluoroborate ($[C_8MIM][BF_4]$), an ionic liquid dissociated into its ions in aqueous media and converted into a hydrophilic form, as illustrated in Fig. 10.3. Following the extraction, ammonium hexafluorophosphate (NH_4PF_6) was utilized as an ion pairing agent. This produced $[C_8MIM][PF_6]$, a hydrophobic compound that promoted phase separation. The MA-IL-HLLME approach demonstrated high sensitivity, with extraction recoveries for anthraquinones ranging from 81.13% to 93.07%, indicating its effectiveness

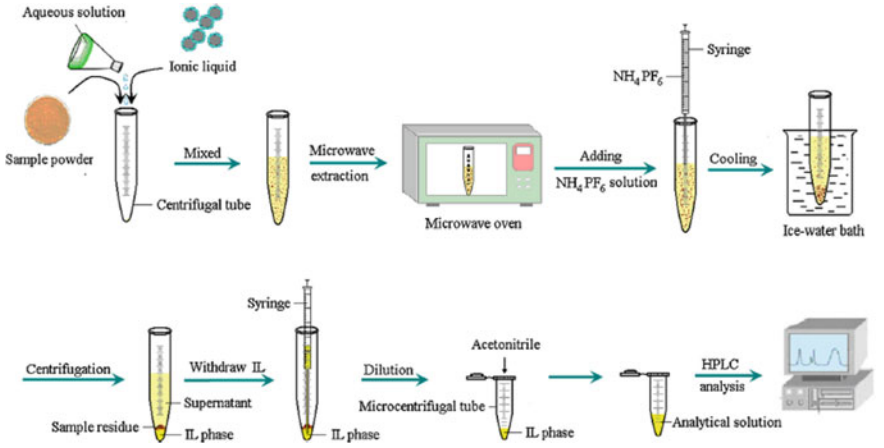

Fig. 10.3 Schematic procedure of MA-IL-HLLME. Reprinted from [47] with permission from Elsevier

in extracting these compounds from plant sources [47]. These applications and advantages collectively make ionic liquids attractive alternatives to traditional solvents in HLLME. The major challenge in using IL-HLLME is to develop a hydrophilic IL that can be miscible with water, and then to find the proper PSA to induce phase separation. This area of research is still overlooked, and there are a lot to expect in terms of future developments and progress.

3.1.2 Using DES in HLLME

The continuous effort to promote sustainable chemistry has resulted in the development of new materials that achieve the principles of green chemistry. In this context, DESs have risen as one of the most promising alternatives to the use of toxic organic solvents. Their unique properties have led to a massive development of these materials and a sharp increase in their applications in analytical chemistry in recent years [48]. DES is considered a natural extension of ILs due to their similar preparation and properties. However, DES offer several advantages over ILs, as they can be prepared from readily available and renewable starting materials, which makes DES cost-effective, environmentally friendly, and less toxic, than ILs. Many recent researches on the environmental effect of ILs have revealed that, despite their unique features and evident benefits in a growing number of applications and processes, ILs are not inherently green. DESs were created in the hunt for biodegradable and low toxicity ILs [49].

DESs have distinct and adjustable features including easy tunability by components variations. Furthermore, they may be made from a wide range of readily accessible components using simple and low-cost synthesis processes. In addition, DESs also have a low vapor pressure and remain liquids over a wide temperature range.

Furthermore, eutectic mixtures intended for use as solvents must meet basic requirements in order to be considered as such. In this regard, it should be noted that the many features changed depending on the components, although there are three main criteria in general: (i) the eutectic point must be significantly lower than the melting points of its individual components and far lower than the projected melting point of an ideal liquid combination; (ii) the eutectic point is dependent on the molar composition of the mixture; and (iii) DESs resemble liquids at ambient temperature. Towards the development greener analytical method, natural deep eutectic solvents (NADESs) were developed depending on natural components in synthesis of NADES including sugars, certain amino acids, choline salts, and organic acids such as malic acid, citric acid, lactic acid, and succinic acid [48].

In 1884, the term "eutectic" was coined by British chemist Frederick Guthrie to describe metal alloys with lower melting temperatures than their basic components [50]. The term "eutectic mixture" now refers to a combination of two or more compounds with a certain molar ratio indicating a minimum melting point on the relevant phase diagram. This position is known as the eutectic point in phase diagrams [51]. There are five types of DESs: type I, formed by combining a quaternary ammonium salt and a non-hydrated metal chloride; type II, formed by combining a quaternary ammonium salt and a hydrated metal chloride; type III, formed by combining a quaternary ammonium salt as a hydrogen bond acceptor compound (HBA) and a hydrogen bond donor compound (HBD); type IV, formed by combining metal chloride and HBD., while type V DES composed of non-ionic chemicals [52].

One of the enticing properties of DESs is the ease of their production methods, which include heating, freeze-drying, and grinding. The most common method for preparing DESs is heating, which involves stirring and heating the mixture until a homogenous and clear solution develops. The physicochemical properties of DESs may be altered by adjusting the synthesis temperature, the kind or molar ratio of the constituents, and the addition of a certain amount of water. Florindo et al. [49] offered adjusted densities, viscosities, and refractive indices for DESs made using choline chloride as the hydrogen bond acceptor and different carboxylic acids as the hydrogen bond donors (levulinic, glutaric, malonic, oxalic, and glycolic). The thermophysical characteristics of the produced DESs were evaluated using two separate synthetic techniques, heating and grinding. A range of eutectic combinations were synthesized in this work using a reasonably simple, cost-effective, and ecologically friendly approach. DESs were created by combining cholinium chloride with several carboxylic acids that served as hydrogen bond donors. Due to differences in the experimental thermophysical properties, particularly viscosity, two different synthetic methods were used, and the formation of an ester during the heating method led to the conclusion that when carboxylic acids are used as HBD in combination with cholinium chloride, the grinding method should be preferred to prepare DESs. The comparison of the thermophysical parameters of the created DESs with the comparable ILs revealed that DESs had identical densities but substantially lower viscosities, making mass transfer procedures easier. Furthermore, DESs may be made with varied molar ratios of HBA:HBD, providing further tunability.

DESs have recently attracted attention as an ecologically friendly alternative to hydrophilic organic solvents commonly used as extraction solvents, particularly in the conventional HLLME approach. Using DES in HLLME can be achieved by using an aprotic solvent as a phase separation agent, a mode known as emulsification-induced HLLME (EHLLME). The suggested approach was used to successfully extract several organic chemical components from water samples.

Switchable solvents are liquids that may be transformed reversibly between hydrophilic and hydrophobic forms by altering the pH or temperature of the system. DES can be used as switchable solvents by changing the pH or the temperature of the medium. Both pH-induced HLLME and temperature-induced HLLME were used to enrich the target analytes, with the latter having two types based on the mechanism of phase separation: (1) using DESs with a low melting point and inducing phase separation by cooling the homogeneous solution and freezing the DESs; and (2) using temperature switchable DESs and inducing phase separation by temperature adjustment. At different temperatures, the temperature-switchable DESs have varying water solubility. Table 10.2 summarizes the most recent applications of DES in HLLME.

3.2 New Techniques of Phase Separation

A crucial aspect of HLLME development is the phase separation technique. Proper phase separation is essential for achieving accurate and efficient extraction of analytes from complex matrices. Traditionally, centrifugation has been used to accomplish this task. However, centrifugation can be time-consuming and requires skilled technician. To overcome these limitations, novel techniques have been developed that eliminate the need for centrifugation.

One such technique is flotation-assisted HLLME (FA-HLLME), pioneered by Hosseini et al. [33, 74]. To perform this technique, a special microextraction cell (Fig. 10.4) was constructed, and organic solvent was transported to the conical section of the cell using N_2 or air flotation. This approach eliminated the need for centrifugation and made the procedure faster and more automated. The technique was successfully applied to extract polyaromatic hydrocarbons from soil and water samples followed by GC/FID. Rezaee et al. [75] developed a simple home-designed extraction cell for extracting malathion from water samples using GC/FID. Another technique involves ultrasound-assisted HLLME, as demonstrated by Xu et al. [76]. In this method, sonication was used to float a water-miscible organic phase such as ACN in a Pasteur pipette, with salt added to promote the separation of the phases. The technique was successfully applied to extract triazole pesticides from aqueous samples. Hosseini et al. [33] applied FA-HLLME for the extraction of polycyclic aromatic hydrocarbons (PAHs) from soil samples. The homemade extraction cell was created to allow for the collection of the low-density extraction solvent without the need of centrifugation. PAHs were extracted from soil samples into methanol and water (1:1, v/v) in two phases using ultrasound, followed by filtering as a clean-up

Table 10.2 Application of DES in HLLME

Analyte	Sample	Sample volume (mL)	DES composition	DES Volume (μL)	PSA	Type of HLLME	Technique of analysis	Linearity ng /mL	LOD ng/mL	%RSD	REF
Sulfonamides	Water	1.5	CHCl: glycol	100	THF	EHLLME	HPLC/UV	N/A	1.2–2.3	≤4.15	[53]
Malachite Green	Farmed and ornamental aquarium fish water samples	10	CHCl: Phenol	500	THF	EHLLME	UV–VIS spectrophotometry	45–900	3.6	2.7	[54]
Aluminum	Water	25	CHCl: Phenol	500	THF	EHLLME	ETAAS	0.05–20.0	0.032	3.3	[55]
Anti-depressants	Human plasma and pharmaceutical waste water sample	6	CHCl: Phenol	200	THF	EHLLME	HPLC/UV	10–8000	3.0–4.5	3.6–5.7	[56]
Vanadium	Food	25	CHCl: Phenol	1000	THF	EHLLME	ETAAS	0.5–5.0	0.025	3.4	[57]
Selenium species	Water and food samples	25	CHCl: Phenol	500	THF	EHLLME	ETAAS	0.2–8	0.00461	4.1	[58]
Curcumin	Food and Herbal Tea Samples	10	CHCl: Phenol	400	THF	EHLLME	UV–VIS spectrophotometry HPLC/DAD	9–920	2.9	1.8	[59]
Cadmium	Food and water sample	50	CHCl: Phenol	500	THF	EHLLME	ETAAS	0.005–0.15	0.000023	3.1	[60]
Lead	Food and water sample	30	CHCl: Phenol	600	THF	EHLLME	GFAAS	0.12–2.5	0.0006	2.9	[61]
Phthalates	Beverages	10	CHCl: Phenol	440	THF	EHLLME	HPLC/DAD	170–4490	5.3–17.8	<11	[62]
Thiophenols	Water samples	1.5	CHCl: p-cresol	50	Acetone	EHLLME	GC/FID	20–100,000	10–15	≤3.3	[63]
Arsenic and selenium	Rice samples	1.5	Proline: malic acid	500	THF	EHLLME	AAS	0.005–0.45	0.003	≤2.6	[64]
Methyl-mercury and total mercury	Fish and environmental waters	25	Betaine hydro chloride:sorbitol:water	600	ACN	EHLLME	UV–VIS spectrophotometry	0.7–340	0.25	≤3.2	[65]

(continued)

Table 10.2 (continued)

Analyte	Sample	Sample volume (mL)	DES composition	DES Volume (μL)	PSA	Type of HLLME	Technique of analysis	Linearity ng /mL	LOD ng/mL	%RSD	REF
Mercury	Water and biological samples	10	CHCl: Phenol	500	THF	EHLLME	ETAAS	0.1–10.0	0.073, 0.091	≤4.05	[66]
Pesticides	Traditional Chinese medicine	10	CHCl: Phenol	650	THF	EHLLME	HPLC/DAD	54–107,000	20–200	<4.7	[67]
Carbamazepine	Plasma	1	CHCl: Phenol	314	THF	EHLLME	HPLC/UV	10–1500	1.17	≤6.85	[68]
Curcumin	Tea and honey species	5	CHCl: maltose	762.5	THF	EHLLME	UV–VIS spectrophotometry	0.4–120	1.2×10^{-5}	≤4.3	[69]
Benzotriazole and benzothiazole derivatives	Surface water samples	5	CHCl: Phenol	1000	THF	EHLLME	UHPLC- MS	5–200	0.02–0.15	≤8	[70]
Copper	Vegetables	20	Benzyl triphenyl phosphonium bromide:ethylene glycol	80 mg	Room temperature	Temperature induced HLLME	FAAS	5.0–250	0.13	≤2.6	[18]
Pesticides	Fruit juice and vegetable samples	5	CHCl:*p*chlorophenol	142	Ice bath (0 °C	Temperature induced HLLME	GC/FID	0.45–5000	0.13–0.31	≤9	[71]
UV-filters	Surface and bathing waters	10	Tetrapropylammonium bromide:octanoic acid	200	Sulfuric acid	pH assisted HLLME	HPLC/DAD	0.139–500	0.021–0.336	≤6.3	[72]
Daclatasvir and sofosbuvir	Urine samples	5	Tetra butyl ammonium chloride:Pamino phenol	105	Ammonia	pH assisted HLLME	HPLC/DAD	1.6–250	1–1.3	≤9.3	[73]

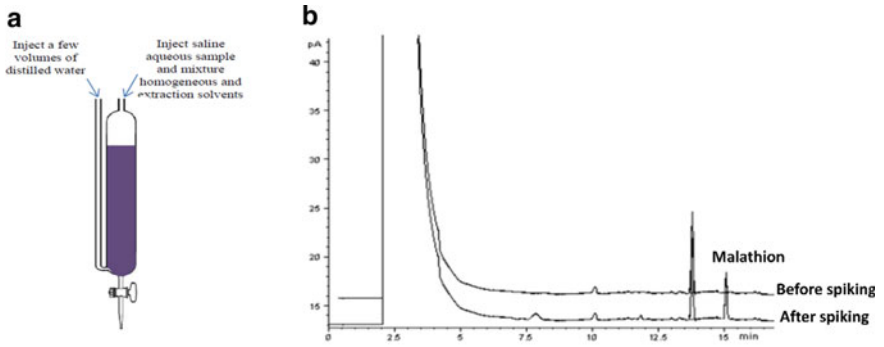

Fig. 10.4 **A** Schematic of the home-designed extraction cell, **B** GC-FID chromatograms of malathion in river water, before spiking (upper) and after spiking with 5.0 μg/L of Malathion (lower). Reprinted from [75] with permission from AJOL

step. The filtrate was mixed with 1.0 mL methanol (homogenous solvent) and 150.0 μL toluene (extraction solvent) in a home-made extraction cell. Using N_2 flotation, the dispersed extraction solvent was transported to the mixture's surface and collected with a micro-syringe. The recovered organic solvent was then fed into the GC-FID for further examination. Gas flotation can improve the HLLME process by enhancing the separation efficiency and reducing the extraction time. It also lowers solvent consumption and reduces emulsion formation during ME.

A novel approach to HLLME without the need for a centrifugation step is magnetic retrieval of SHS-HLLME, developed by Çabuk et al. [35]. In this approach, bis(2-ethylhexyl) phosphoric acid (DEHPA) was employed as SHS, and iron oxide nanoparticles (Fe_3O_4 NPs) were used for magnetic retrieval. After extraction, DEHPA containing the target analytes was separated and collected from the sample solution using Fe_3O_4 NPs, eliminating the need for centrifugation or special extraction devices. This approach was successful due to DEHPA's strong binding affinity for Fe_3O_4 NPs. These methods have been applied to extract various analytes from complex matrices, showing potential for future applications in analytical chemistry. Trying other nanoparticles with higher magnetic susceptibility will make phase separation easier and faster. Magnetic ILs is another area of development in this regard [77, 78].

Liquid nitrogen offers several advantages for enhancing the performance of HLLME. Liquid nitrogen creates a cryogenic environment that prevents thermal degradation or loss of thermally labile compounds during the extraction process, thereby improving their recovery. Additionally, the use of liquid nitrogen accelerates the phase separation process in HLLME, enabling faster formation of distinct phases between the extraction solvent and sample matrix. This accelerates the separation and collection of desired analytes. Lastly, liquid nitrogen cooling enhances precision and reproducibility by minimizing temperature fluctuations during extraction, ensuring consistent extraction conditions and yielding more reliable and repeatable results. However, all precautions must be taken when working with liquid nitrogen

due to its extremely low temperature (−196 °C), necessitating adherence to appropriate personal protective equipment and safe handling procedures. Okhravi et al. [34] developed liquid nitrogen HLLME for extraction of Co(II) and Ni(II) ions prior to measurement by FAAS. The proposed method presented a simple and fast sample preparation procedure. More progresses is expected to be made in the future regarding the application of liquid nitrogen-enhanced HLLME, with a multitude of potential advancements on the horizon.

Ultrasound has emerged as a promising green technique for enhancing the efficiency and effectiveness of ME [79]. This method utilizes ultrasound waves to accelerate mass transfer between immiscible liquid phases, thereby accelerating the extraction process. Additionally, ultrasound promotes increased contact area and contact time between the sample and the extraction solvent through its agitation effects. Consequently, ultrasound-assisted HLLME offers reduced extraction time, improved extraction efficiency, and lower solvent consumption, leading to enhanced overall performance and sustainability of the extraction process [36].

3.3 Automation of HLLME

Analytical Process Automation (APA) is a recent development in analytical chemistry, which involves the automation and downsizing of various analytical procedures. Flow-based technologies have been shown to be suitable for this purpose [80–82]. Pochivalov and colleagues [83] have designed and developed a fully automated microextraction technique using a SHS, DEHPA, contained within a syringe. The process involved the dissociation of the extractant in an alkaline sample solution leading to a homogenous solution, followed by the development of an organic phase by acidification and subsequent separation. This microextraction process was utilized in determining antimicrobial medications, sulfamethoxazole and sulfamethazine, in human urine samples using HPLC with UV detection. The automation process consisted of aspirating 0.175 mL of DEHPA (port b, 10 mL/min) and 1.5 mL of sample solution (containing 0.4 M NaOH, port a, 0.7 mL/min) into the syringe pump in the first stage (Fig. 10.5A). The sample solution was then transferred using 0.2 mL of air (port c, 15 mL/min) sucked into the syringe pump. The creation of water-soluble sodium bis (2-ethylhexyl) phosphate led to the achievement of a homogenous solution after 15 s of magnetic stirring. In the second stage, 0.210 mL of 3 M H_2SO_4 (port d, 2 mL/min) and 1.7 mL of air (port c, 15 mL/min) were fed into the syringe pump successively, and organic phase formation and analyte extraction were carried out with magnetic stirring. After the cessation of magnetic stirring, phase separation occurred in 15 s. The aqueous phase was removed to waste, while the organic phase was transferred to a 0.5 mL Eppendorf tube containing 0.2 mL of methanol. The process demonstrated good linearity, sensitivity, and a sampling rate of 12 samples per hour.

Vakh and colleagues [84] have devised an automated process of effervescence-assisted switchable solvent-based liquid phase microextraction for the determination

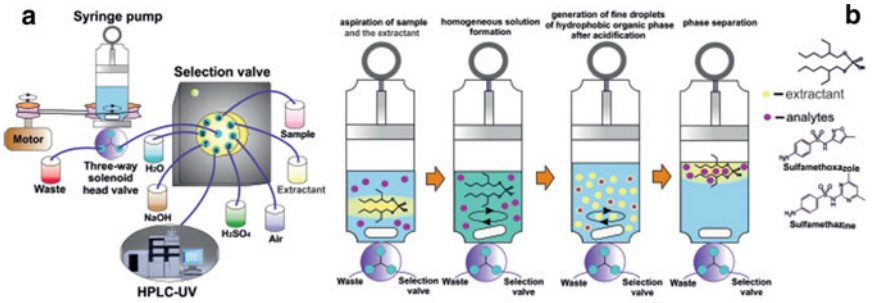

Fig. 10.5 Flow system set-up (**A**) and extraction mechanism (**B**) for in-syringe switchable hydrophilicity solvent-based microextraction method. Reprinted from [83] with permission from Elsevier

of ofloxacin in human urine utilizing a syringe pump-based system. In this extraction process, medium-chain saturated fatty acids were investigated as switchable hydrophilic solvents. In the presence of sodium carbonate, the fatty acids were transformed into a hydrophilic state. The introduction of sulfuric acid into the solution reduced the pH value, leading to the creation of microdroplets of the fatty acid. The in-situ production of carbon dioxide bubbles facilitated the extraction process and the eventual phase separation. The automation of the microextraction procedures was achieved as shown in Fig. 10.6. In the first step, the syringe pump consecutively aspirated 350 μL of 2 M Na_2CO_3 (port 1, valve 1), 1 mL of diluted urine sample (port 2, valve 1), and 50 μL of hexanoic acid (port 3, valve 1) into the mixing coil. A homogeneous solution of sodium hexanoate, ofloxacin, and excess carbonate ions was developed while the reagents were passing through the mixing coil. Subsequently, this mixture was then supplied (through port 4, valve 1) into the mixing chamber by the syringe pump. The mixing coil (MC) was rinsed twice with water (port 5, valve 1) to eliminate sodium carbonate residues. Then, 260 μL of 2.5 M H_2SO_4 was drawn into the MC and fed into the mixing chamber (port 6, valve 1). This led to the transformation of water-soluble hexanoate ions into hydrophobic hexanoic acid, subsequently accompanied by effervescence-assisted microextraction of ofloxacin and phase separation. The aqueous phase was discarded (port 7, valve 1), while the organic phase remained in the mixing chamber. The peristaltic pump then added a mixture of 450 μL of phosphate buffer (pH 6.4) and methanol (1:1, v/v) (port 11, valve 2) into the mixing chamber for dissolving hexanoic acid containing the extracted analyte for HPLC analysis. Air bubbles (port 12, valve 2) stirred the mixture for 20 s. Using a peristaltic pump, the resulting solution was aspirated (port 14, valve 2) into a chromatographic vial and analyzed by HPLC/FLD.

In their study, Cherkashina et al. [85] developed an automated SALLME method for the determination of tetracyclines in urine samples by HPLC/UV. In this approach, 1-octylamine was investigated as a new SALLME extractant. The process involved aspirating 1-octylamine and sample solution into a mixing chamber of a flow system, followed by air-bubble mixing to produce an isotropic solution. A solution of a

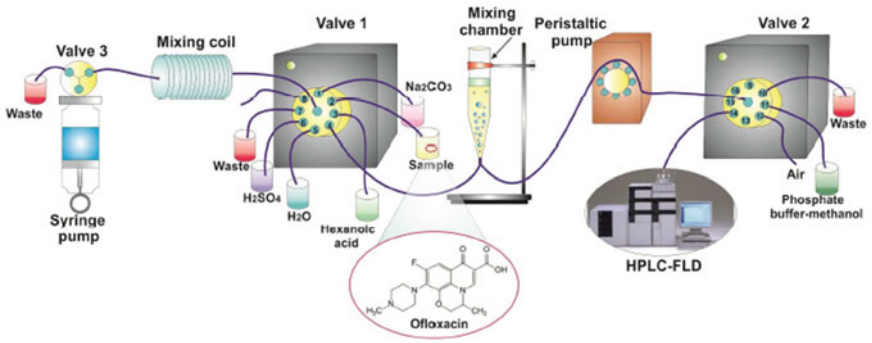

Fig. 10.6 The manifold for automated EA-SS-LPME system coupled with HPLC-FLD for the determination of ofloxacin in human urine samples. Reprinted from [84] with permission from Elsevier

salting-out agent was added to the mixing chamber to enable phase separation. The micellar 1-octylamine phase containing analyte was combined with methanol and delivered to an HPLC/UV system after phase separation.

During the first stage of the process, 50 μL of 1-octylamine (port 1, valve 1) and 1 mL of sample solution (port 2, valve 1) were aspirated using a syringe pump and supplied (port 4, valve 1) to the (MC). Next, the resultant mixture was injected with 300 μL of 20% NaCl (port 5, valve 1) into the MC. The contents of the MC were mixed with air bubbles generated by the peristaltic pump (port 12, valve 2), and phase separation occurred. The aqueous phase was then transferred to the trash (port 6, valve 1), while 50 μL of methanol (port 11, valve 2) was introduced into the MC and mixed for 60 s by air-bubbling. The resulting solution was transferred (through port 14, valve 2) to a chromatographic vial using a peristaltic pump and evaluated by HPLC/UV. The proposed method was found to be cost-effective, simple, and quick, making it a promising approach for the determination of tetracyclines in urine samples. The set-up of this study is presented in Fig. 10.7.

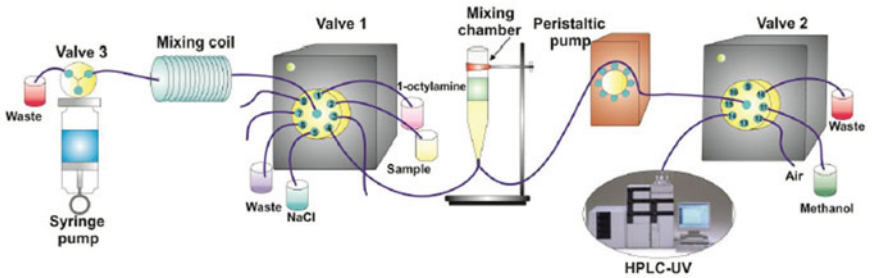

Fig. 10.7 The manifold of the automated salting-out assisted liquid–liquid microextraction procedure for the determination of tetracycline in urine. Reprinted from [85] with permission from Elsevier

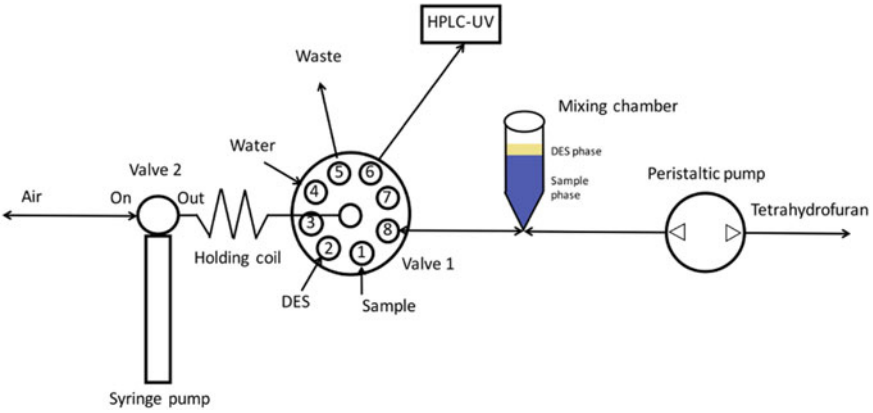

Fig. 10.8 The manifold of the Automated—HLLME procedure. Reprinted from [86] with permission from Elsevier

Shishov et al. [86] developed an automated HLLME method based on DES for the determination of caffeine followed by HPLC/UV. To automate this process, the researchers used a multiport valve, a syringe pump, and a peristaltic pump, as described in Fig. 10.8. The automated method began with the backward movement of the syringe pump plunger to aspirate 1 mL of sample (1) and 50 μL of DES (choline chloride with phenol at a 1:3 molar ratio) (2) into the holding coil via the multiport valve. The resultant mixture was then delivered into the mixing chamber by forward movement of the syringe pump from the holding coil. To dissolve the DES in the sample, the syringe pump was switched to the airport (On), and 10 mL of air was sucked into it before being delivered into the mixing chamber at a flow rate of 10 mL/min through port 8. The peristaltic pump then introduced 50 μL of THF into the mixing chamber leading to DES phase separation and analyte microextraction. The developed method was found to have the potential to be used as an alternative to traditional methods for obtaining organic analytes from aqueous samples. Additionally, it could be combined with other instrumental techniques, such as chromatography, and different detection systems, like UV–VIS spectrophotometry detectors" could be used.

4 New Phase Separation Agents in HLLME

HLLME is a preferred method for extracting hydrophilic analytes from aqueous matrices due to the special hydrophilic characteristics of extractants like ACN, acetone or THF. HLLME also achieves efficient extraction of more hydrophobic analytes by forming a ternary homogeneous system, where the addition of a few microliters of a water-immiscible solvent such as chloroform or toluene to the binary system modifies the hydrophilic nature of the extractant. Phase separation is induced

by adding salt (SALLME) or sugar (SULLME). The PSA should be more soluble in aqueous media than the extractant to expel it from the extraction media. The following section provides detailed information on different modes of HLLME, according to the phase separating agent or condition.

4.1 Salting-Out Homogeneous Liquid–Liquid Micro Extraction (SALLME)

SALLME utilizes salt as a PSA to induce phase separation between the aqueous sample and a few microliters of a water-miscible organic extractant. It is important to note that phase separation is achieved through a salting-out phenomenon. When salt is introduced into homogeneous water/organic solutions, the solubility of the water-miscible solvents diminishes, thereby resulting in the formation of a discernible phase either at the top or at the bottom of the aqueous sample. The positioning of this phase is contingent upon the density of the organic solvent. Typically, most water-miscible organic solvents are lighter than water, resulting in their flotation on top of the sample alongside other organic solutes and analytes. In contrast, salting-in [87] refers to increasing the solubility of a nonelectrolyte in water by raising the salt concentration. It has been observed in proteins and hydrophobic solutes due to the counterion impact of salts, which raises the charge on the solute's surface and promotes solubility. However, salting-out is more prevalent and is the focus of this section.

Salting-out is a phenomenon that can be controlled by various factors, such as the type of salt used. The selected salt should have high water solubility, low extractant solvent miscibility, and robust salting-out ability. In general, the anion effect is more significant than the cation effect [88]. Water is a strong electron acceptor solvent and therefore has a stronger ability to solvate anions more than cations. Moreover, anions have a significantly larger ionic radius than cations, resulting in weaker hydration. Anions also have larger and more polarisable electron clouds, making them more prone to selective interactions with nearby cations, which may polarise the anions in their vicinity [89].

The hydration hypothesis may explain salting-out: as the process of dissolution occurs, the interaction between the solvent and ions becomes more pronounced compared to the interaction between ions themselves, resulting in an expansion of the distance between the ions. This interaction of solvation causes the immobilization of water molecules, effectively rendering them unable to function as a solvent. In the case of binary systems involving water, a water-miscible organic solvent, and salt as a precipitating salt agent (PSA), there is a competition between the water-miscible organic solvent and the salt ions for the water molecules. Once the concentration of ions surpasses a specified threshold due to the strong electrostatic contact between salts and water molecules, the interaction between water and organic solvents is significantly diminished. The hydration Gibbs free energy (Ghyd) of salts plays a

vital role in determining their ability to induce salting-out. Ions with lower values of Ghyd exhibit a more potent salting-out ability [90]. In addition to Ghyd, other factors that must be taken into consideration when selecting a salt include the charge density of both anions and cations, the chemical properties of the analytes, the type of solvent used for extraction, and the analytical equipment employed. Ammonium acetate is considered the ideal salt for mass spectrometry, whereas non-volatile salts like magnesium chloride cannot be employed [4].

Aside from the salt type, additional parameters that may influence SALLME efficiency include the the nature and quantity of the solvent, the amount of salt used, and the pH of the aqueous sample. The major challenge in selecting water-miscible solvents is determining how to remove them from the aqueous phase. The salting-out phenomenon cannot separate all water-miscible solvents [88]. This explains why acetonitrile was the most commonly used extractant in SALLME applications due to its ease of separation compared to other water-miscible organic solvents, as indicated in Table 10.2. The quantity of salt is also crucial in SALLE optimisation since higher salt concentrations have been linked to better phase separation [91].

Finally, pH plays a critical role in SALLME if the analytes are weak acids or bases. pH adjustment in SALLME is crucial because the optimal extraction conditions are obtained when the drug is in the non-ionised form. The pH of the aqueous media should be two pH units higher than the pKa of the analyte and on the same side (i.e., acidic for acidic drugs and basic for basic compounds). One of the advantages of SALLME is that the chromatograms of plasma samples obtained after SALLME are superior to traditional protein precipitation due to its intense deproteinization by acetonitrile and salting-out. As indicated in Table 10.3. SALLME was employed to extract a diverse array of polarities of analytes from various matrices, encompassing food, water, and biological fluids.

4.2 Sugaring-Out Homogeneous Liquid–liquid Microextraction (SULLME)

SULLME is a miniaturised version of sugaring-out assisted liquid–liquid extraction (SULLE), which relies on using sugars as a PSA. SULLE is an extraction mode that can serve as an alternative to SALLE in bioanalysis, given its eco-friendliness, compatibility with MS detection and inertness, and less likelihood of modifying the pH of the medium compared to SALLE [106]. SULLE can enrich analytes with varying polarities by utilising the optimal sugar-to-aqueous phase ratio. It is worth mentioning that both SULLME and SALLME are compatible with RP-LC, the most prevalent mode in HPLC [107].

In SULLME, the separation of the phases is achieved by breaking the hydrogen bond between water and extractant, with the type of sugar used being a critical factor in extraction efficiency in both modes. Glucose is the most commonly used sugar in SULLE due to its low cost and availability [107–113]. However, glucose

Table 10.3 Application of SALLME

Sample	Analyte	Sample volume (mL)	Extractant	Extractant volume (mL)	Salt type	Salt amount (g)	Technique of analysis	Linearity (ng/mL)	LOD ng/mL	%RSD	REF
Waste water	Beta-naphthol, naphthalene and anthracene	10	ACN	0.8	Sodium carbonate	2.5	HPLC/UV	1–1000	0.22–8.34	<7.2%	[92]
Water samples	Triazole pesticides	3	ACN	0.65	Sodium chloride	1.3	GC/MS	10–1000	0.4–14.4	0.4–8.1	[76]
Human plasma	Alogliptin benzoate	1	ACN	0.5	Sodium chloride	0.250	HPLC/UV	100–5000	19	≤4.92	[93]
Fruit juice	Pesticides	5	IPA	0.2	Sodium sulfate	2	GC/FID	0.73–5000	0.22–0.48	**≤7**	[94]
Waste water	Azole compounds	5	IL	0.075	Sodium chloride	0.56	HPLC/DAD	25–2000	1.25–5	≤11.1	[95]
Human urine samples	Tetracycline	5	1-octylamine	0.05	Sodium chloride	1	HPLC/UV	500–20,000	170	≤8	[85]
Human serum and plasma	Tricyclic antidepressant	5	ACN	0.5	Ammonium sulfate	0.5	HPLC/UV	2–20,000	0.46–0.58	≤7.9	[96]
Water, food and bioligical fluids	Sulfonamides	0.5	ACN	0.15	Sodium chloride	N/A	HPLC/UV	10–10,000	1.4–4.5	≤8.7	[97]

(continued)

Table 10.3 (continued)

Sample	Analyte	Sample volume (mL)	Extractant	Extractant volume (mL)	Salt type	Salt amount (g)	Technique of analysis	Linearity (ng/mL)	LOD ng/mL	%RSD	REF
Cosmetics and personal care product	Triclosan	5	IPA	0.18	Ammonium sulfate	4	HPLC/UV	0.4–100	0.09	≤5.3	[98]
Water samples	Lead	5	IL	20 mg	Sodium sulfate	N/A	FAAS	5.0–500.0	0.1	1.3	[99]
Aqueous humor	Dorzolomide and timolol	0.15	ACN	0.09	Sodium sulfate	0.11	HPLC/UV	9–500	2.89–7.76	≤1.2	[100]
Human plasma	Daclatasvir	1	ACN	0.5	Ammonium acetate	0.2	Spectrophotometry	500–5000	130	≤8.323	[101]
Water, food and biological samples	Sulfanilamide	0.5	ACN	0.25	Sodium chloride	0.25	HPLC/UV	1–10,000	0.3	1.55	[102]
Water, food and biological samples	Fluoroquinolones	5	ACN	1	Magnesium sulfate	2	HPLC/FLD	2–100	0.07–5.58	≤6.8	[103]
Water samples	Carbonyl compounds	3	ACN	0.5	Ammonium sulfate	0.5	HPLC/UV	7–15,000	0.58–3.2	≤6	[14]
Table salt	Iodine	5	Ethanol	0.8	Ammonium sulfate	3–3.5	HPLC/DAD	10–10,000	3.7	≤12.4	[104]
Food grade salt	Iodate	4.0	2 propanol	1	Ammonium sulfate	2.6–3.5	Spectrophotometry	80–10,000	16	≤12.6	[105]

cannot achieve phase separation in SULLME due to its inability to separate a few microlitres of water-miscible solvent. Sucrose was found to be the most efficient PSA in SULLE for honokiol and magnolol extraction [114], while polyols like glycerol, sorbitol, xylitol, maltitol, and erythritol have also been studied for their ability to induce phase separation [23]. THF and fructose were successfully used in SULLE for diuron pesticide trace detection in water [115].

A previous study investigated different modes of LLME on various drug classes [5]. The results indicated that ternary SALLME had less preconcentration capacity in sample enrichment due to the high volume of separated phase caused by the large amount of acetonitrile required for homogeneous phase formation. NaCl used in SALLME not only separated the extractant (decanol), but it also separated some of the co-solvent (ACN) from the aqueous sample, which diluted the analyte in the extract and compromised the enrichment. In contrast, SULLME was found to be the most efficient mode for extraction of antivirals, antidiabetics, and β-blockers as shown in Fig. 10.9. Although SALLME and SULLME are both homogeneous modes, SULLME had more preconcentration capacity due to the smaller layer of acetonitrile separated on the top of the aqueous sample, making the sample more concentrated. This could be attributed to the electrostatic force of the salt, which makes salting-out more efficient in phase separation but reduces the analyte concentration in the extractant.

Chromatographic separation of the extracted analytes showed higher peak areas and a more stable baseline in SULLME compared to SALLME, improving the signal-to-noise ratio and method sensitivity. Additionally, SULLME uses only acetonitrile as an organic extractant, minimizing the use of other solvents and reducing potential risks associated with lipophilic solvents such as chloroform or long chain alcohols. Acetonitrile is also more compatible with conventional mobile phases because of its low UV cutoff point.

There are challenges associated with the use of SULLME, including the limited ability of some sugars to achieve phase separation, a limited number of extractants that can be separated, and the limited volume of aqueous samples that can be used. Nonetheless, SULLME is suitable for bioanalysis applications, including analysing plasma, urine, and aqueous humour samples [116]. For example, SULLME was successfully used to determine favipiravir in human plasma with comparable or superior sensitivity than the LC–MS/MS approach [116]. The inert nature of sugars makes them less likely to impact the pH of the sample or stability of the analyte. Combining SULLME with sensitive methods like LC–MS/MS shows promise for polar pharmaceuticals that are inefficiently extracted using standard solvents [117–119]. Additionally, self-assembly was formed using THF and fructose, resulting in enhanced extraction efficiency in the self-assembly core [116].

Recently, matrix-induced SULLME has been developed as a novel extraction method that relies on using the sample itself as a PSA source [120]. Alkan et al. developed matrix-induced SULLME for determination of pesticides in jams. The procedures involved weighing 1 g of pre-homogenised jam sample into 2 ml safe-lock Eppendorf microtubes and adding 600 μL of ACN/water combination (50/50%, v/v). The mixture was then shaken at 2500 rpm for 0.5 min before being centrifuged

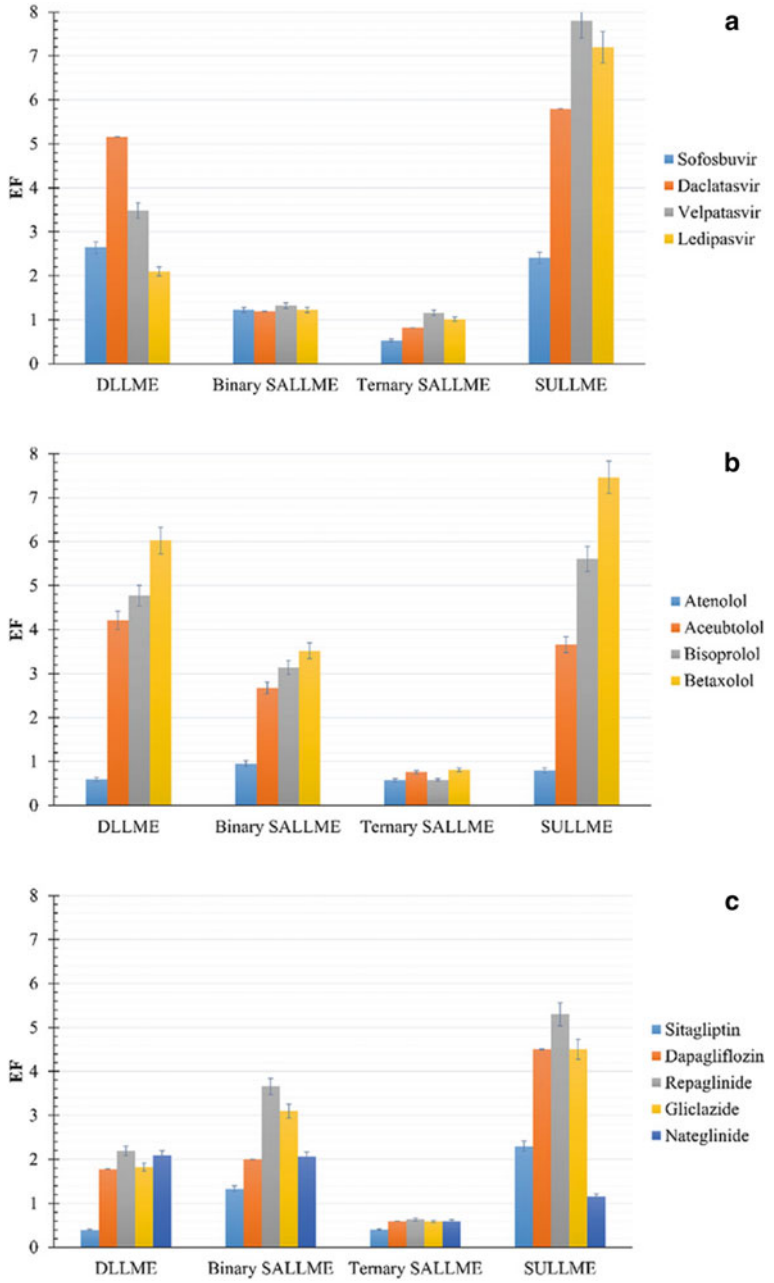

Fig. 10.9 Extraction efficiency of different microextraction modes for the antivirals (**A**), the β-blockers (**B**), and the antidiabetics (**C**). Reprinted from [5] with permission from with Wiley

at 6000 rpm for 4 min, with no external PSA being added. In this study, a quick and simple sample pretreatment procedure combining SULLME with HPLC/UV has been developed. The method is inexpensive and environmentally friendly since ACN is the only chemical required, and phase separation from homogeneous solution occurs through induction of the sample matrix's high sugar content. Satisfactory recoveries from manipulated jam samples indicated good reproducibility.

The matrix-induced SULLME method offers several advantages, such as requiring fewer steps, eliminating the need for an external PSA, and minimising the use of solvents. Furthermore, it is environmentally friendly and cost-effective, making it highly suitable for routine analysis of complex matrices. The method has also shown good reproducibility, which is essential for accurate quantification of analytes in real samples.

4.3 Hydrophobic Substance Induced Homogenous Liquid–Liquid Microextraction

In hydrophobic substance induced HLLME (HSLLME), the homogenous layer is formed as usual, while the phase separation is induced by adding a small amount of water immiscible hydrophobic solvent. This mode was also known as SIPTE and it was developed by Liu et al. [16] in 2010 to extract andrographolide, sildenafil, and finasteride. In this study, the authors examined the efficiency of SIPTE using different modifiers, including six commonly used non-oxygenated organic solvents, i.e. dichloromethane, chloroform, 1,2-didichloroethane, 1,2-dibromoethane, toluene, fluorobenzene and four oxygenated organic solvents i.e. ethyl acetate, ethyl ether, n-hexanol and n-octanol.

The results showed that non-oxygenated solvents were effective as modifiers, whereas oxygenated solvents were less efficient. Specifically, high recoveries of all test substances were obtained using non-oxygenated modifiers, while much lower extraction recoveries were observed with oxygenated solvents. Furthermore, at least 0.3 mL of an oxygenated modifier was required to separate 2 mL of the plasma-acetonitrile mixture, whereas only 0.05 mL of a non-oxygenated modifier was sufficient. The mechanism underlying this phenomenon could be considered a reversed process to the salting-out method. Instead of dissolving a salt in the aqueous sample to expel the extractant, a lipophilic solvent is dissolved in the organic to decrease its polarity, resulting in phase separation. Other solvents have also been used as PSA in HSLLME, such as dichloromethane [106], or toluene [121].

This technique of HSLLME avoid using salts to induced phase separation, which may interfere with mass detection. However, HSLLME employs highly toxic solvents. To overcome this problem, Abdallah et al. [122] developed a menthol-assisted HSLLE method to determine favipiravir in human plasma samples via HPLC/UV detection. This approach is less expensive, simpler, and more environmentally friendly than traditional sample preparation and other HSLLME methods.

Menthol has surfactant-like characteristics and can form micelles, which could be used to extract hydrophilic analytes like favipiravir. The menthol-assisted HSLLME method demonstrated equivalent or even better sensitivity than the LC–MS/MS method and performed well in extracting favipiravir from actual human plasma samples collected during a bioequivalence study examining favipiravir as a potential COVID-19 antiviral medication. This method does not require the use of expensive or complicated instruments, making it a promising sample preparation approach for polar drugs [122].

4.4 pH Induced Homogeneous Liquid–liquid Microextraction

SHSs are a type of environmentally friendly solvents that are increasingly replacing traditional organic solvents in microextraction [123]. These solvents can be categorised into various types based on different criteria, such as miscibility, ionic strength, polarity, surface activity, and properties like fluorescence, solubility, aggregation, hydrophilicity, and charge (CO_2-responsive polymers). It is important to note that the term "switchable solvents" typically refers to tertiary or secondary amines that undergo structural changes in solutions with varying pH values, resulting in altered hydrophilicity and solubility.

$$B + nH^+ \leftrightarrow BHn^{n+} \qquad \text{Equilibrium (1)}$$

In an acidic environment, the equilibrium (1) favours the formation of ionic forms which have high water solubility and can easily form homogeneous mixtures in aqueous solutions. As the pH increases, the equilibrium shifts to the left indicating that molecular compounds are predominant, exhibiting limited solubility in aqueous fluids, and resulting in biphasic systems. It is noteworthy that CO_2 can be used to facilitate such conversions, as has been reported in previous studies [124, 125].

$$B + nH_2O + nCO_2 \leftrightarrow BHn^{n+} + nHCO_3^- \qquad \text{Equilibrium (2)}$$

In the presence of CO_2, acidic conditions lead to a shift in equilibrium (2) towards the prevalence of quaternary ammonium cations that are water-soluble [125]. To obtain ionic forms from amines, small amounts of dry ice are typically added to a water-amine mixture [126]. The process for obtaining SHS is achieved by maintaining constant stirring until a homogeneous solution is obtained [64]. Prior to adding CO_2 to the aqueous phase, appropriate conditions such as reagent concentration, pH, and ionic strength must be established [125].

There are alternative methods for altering solvent polarity, such as sparging with carbon dioxide, and using carbonate salts, sulfuric acid or perchloric acid, but these are less common [125]. It should be noted that to establish a two-phase system and

concentrate analytes, CO_2 must be removed or the amine deprotonated. This can be achieved by adding concentrated alkali solutions or by other methods such as sparging with nitrogen, argon, or air, which can be carried out by heating a homogenous mixture [126].

Although different amines are commonly used for the formation of SHS, not all amines and their derivatives have the ability to transform homogeneous aqueous-organic phases to heterogeneous biphasic ones depending on pH [125]. Some amines, such as diethylamine, diisopropylamine, butylethylamine, and triethanolamine, have high water solubility and cannot form two-phase extraction systems. Conversely, some amines, such as dihexylamine, butylisopropylamine, and trioctylamine, have poor solubility even in acidic conditions, resulting in an inability to produce homogeneous water-organic combinations [125].

When selecting an appropriate SHS, stability, volatility, toxicity, and bioaccumulation are all key considerations. Stability is particularly critical for solvent reuse. From an environmental standpoint, the recommended amines should be as non-toxic and non-volatile as possible. Therefore, high molecular weight amines, which can be synthesized using functional groups such as alcohols, esters, ketones, acetals, and aromatic rings, are preferred [125]. Functional amines are often preferred due to their low toxicity, volatility, flammability, and potential for eutrophication. In addition to amines, other solvents such as saturated fatty acids can also be used as SHS. For instance, Vakh et al. and coworkers [84] used hexanoic acid as a switchable solvent to detect ofloxacin in urine. By interacting with Na_2CO_3 and H_2SO_4, the SHS's hydrophilicity was altered.

The use of SHSs in HLLME depends on solubilizing the solvent into the aqueous phase prior to extraction. This results in a stable homogeneous SHS/water combination that can then be used as the extractant phase. It is common to first dissolve the solvent in the aqueous phase with the aid of dry ice. This produces a stable and uniform mixture of SHS and water, which can then be utilized as the extractant phase. By manipulating the pH level through the addition of an acid or base, it is possible to alter the solubility of the SHS and induce a separation of the phases. The method described here employs a water-soluble extractant phase and utilizes a pH shift as a trigger for phase separation [127]. As indicated in Table 10.4, pH induced HLLME using SHS was widely used for extraction different analytes including antidepressants [128], antioxidants [129], metals [130] fungicide [131], herbicides [127, 132], benzophenone-type UV filters [35], anxiolytics [133] and toxicants [134] from different matrices including water [35], beverages [135], biological [136] and food samples [134].

The pH induced HLLME method offers an appealing advantage over other modes of HLLME, such as SALLME and SULLME. Specifically, this method allows for the use of a large volume of aqueous sample in combination with a very small amount of extractant. This is made possible by taking advantage of the pH shift-induced phase separation, which enables efficient extraction of the target compounds from the sample using a minimal amount of extractant. The most common SHSs used in pH induced HLLME are triethylamine [137], *N, N*-dimethyl cyclohexylamine

Table 10.4 Application of pH induced HLLME

Analyte	Sample	Sample volume (mL)	SHS composition	Extractant volume μL	Phase trigger	Technique of analysis	Linearity (ng/mL)	LOD ng/mL	% RSD	REF
Antidepressants	Waste water, human serum and breast milk	7.0	Dipropyl amine	50	NaOH	GC/FID	5.0–1000	1.0	≤8.7	[128]
Permethrin and deltamethrin	Water samples	10	Triethylamine	500	NaOH	GC/FID	0.5–2500	0.03–0.16	<5%	[137]
Chlorophenols	Water samples	5	bis(2-ethylhexyl) phosphate	60	HCl	HPLC/UV	5–500	1.4–2.7	≤4.7	[140]
Synthetic Antioxidants	Vinegar samples	5	Di-(2-ethylhexyl) phosphoric acid	10	Vinegar	HPLC/UV	10–500	3.2–5.5	<7.8	[129]
Copper	Oil samples	30	Triethyl amine	500	Nitric acid	FAAS	23.0–1000	6.9	≤9.4	[130]
Quercetin	Food samples	30	N, N-dimethyl cyclohexylamine	1000	NaOH	Spectrophotometry	29.9–500	9.0–11.9	≤8.9	[139]
Triazole fungicide	Water samples	10	N, N-dimethyl cyclohexylamine	400	NaOH	GC/MS	5–500	0.46–0.99	≤13.9	[131]
Herbicides	Water samples	10	N, N-dimethyl cyclohexylamine	125	NaOH	GC/MS	N/A	0.1–0.37	≤12.5	[127]
Paraquat	Biological and environmental samples	10	Triethyl amine	500	NaOH	HPLC/UV–VIS	0.5–500	0.2	<5	[132]
Benzophenone-type UV filters	Water samples	8	Di-(2-ethylhexyl) phosphoric acid	40	HCl	HPLC/UV	2.5–1000	0.7–0.8	<6	[35]

(continued)

Table 10.4 (continued)

Analyte	Sample	Sample volume (mL)	SHS composition	Extractant volume μL	Phase trigger	Technique of analysis	Linearity (ng/mL)	LOD ng/mL	% RSD	REF
NSAID	Biological fluids	9.5	N, N-dimethyl cyclohexylamine	500	NaOH	HPLC/DAD	130–100,000	40–180	≤7.7	[136]
Pyrethroid insecticides	Fresh fruits and fruit juices	10	Pivalic acid	260	HCl	GC/MS	0.023–500	0.006–0.038	<9	[135]
Nickel	Food and cigarette samples	10	1-ethyl piperidine	800	NaOH	FAAS	17–500	5.2	6.0	[138]
Nitrazepam	Urine samples	4	N, N-dipropyl amine	100	NaOH	DPV	0.03–20 and 20–450	0.009	7.4	[133]
Methamphetamine	Urine samples	4	Dipropyl amine	100	NaOH	GC/MS	5–1500	1.5	≤7.8	[141]
Bisphenols	Foods and Drinks	5	N, N Dimethyl cyclohexylamine	782	NaOH	HPLC/UV	0.27–0.67	0.17–0.67	≤5.7	[134]

[136], dipropyl amine [128], pivalic acid [135], 1-ethyl piperidine [138] and di-(2-ethylhexyl) phosphoric acid [35]. It is worth mentioning that the most common phase trigger agent was sodium hydroxide [136], hydrochloric acid [135], vinegar [129] and nitric acid [130]. This mode is compatible with wide range of analytical instruments including spectrophotometers [139], HPLC [129], GC [128, 131], FAAS [130] and DPV [133].

5 Conclusions and Future Trends

HLLME is very attractive among other ME modes owing to a lot of merits, including a huge surface area between the aqueous sample and miscible extractants like ACN, acetone, THF, and hydrophilic DESs. Phase separation could be achieved by the addition of chemicals such as salt (SALLME), sugar (SULLME), or by buffer. Additionally, manipulation of the properties of the system may also result in phase separation, such as pH and temperature. One of the important advantages of HLLME is its suitability for automation. HLLME has been successfully applied to extract different analytes from various matrices, including biological fluids and aqueous samples. The various applications and reports have proven that HLLME is a sensitive and effective technique for enriching desired analytes from various matrices. However, it has certain limitations, such as the use of hydrophilic solvents to extract analytes from complex matrices. Conventional HLLME procedures still employ organic solvents as extractants, which pose significant environmental risks due to their toxicity. To address this issue, new green solvents such as supercritical fluids, ILs, and DESs have been developed.

Among these, ILs have gained popularity due to their unique physicochemical properties that make them effective extraction solvents for a wide range of analytes during the HLLME mode. However, some methods of synthesizing ILs involve hazardous halogenated hydrocarbons and extended reaction periods, leading to potential environmental contamination. To overcome these limitations, DESs were developed as a greener alternative to ILs. DESs share similar physicochemical properties with ILs but have additional advantages such as low vapor pressure, nonflammability, low density, and low melting points. By using DESs instead of ILs, researchers can reduce the risk of environmental poisoning and secondary contamination from toxic byproducts produced during high-temperature processes.

Innovative approaches could also include the use of green solvents like propylene glycol and glycerol as extractants in HLLME. These solvents are considered safer alternatives to conventional solvents, and further research should be conducted to determine their efficacy in this application. The development of green solvents such as NADESs and the exploration of new green solvents hold promise for improving the sustainability and safety of HLLME procedures.

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