Dispersive Liquid–Liquid Microextraction

Alaa Bedair and Fotouh R. Mansour

Abstract Dispersive liquid–liquid microextraction (DLLME) was initially described as an effective sample preparation technology in 2006. However, researchers are still interested in making it more efficient, and ecologically friendly. The dispersion of extraction solvent in aqueous samples is the critical stage in DLLME, which is commonly accomplished using dispersive solvents. Because hazardous dispersive solvents offer a significant environmental danger, attempts have been undertaken to produce greener dispersion procedures while maintaining high extraction efficiency. When it comes to ordinary DLLME, the number of fascinating approaches for changing disperser solvents has expanded. As a result, the goal of this chapter is to provide a overview of current developments in DLLME dispersion modes. Different strategies are covered, including the employment of environmentally-benign dispersers as well as other dispersion methodologies. The most noteworthy approaches that have been implemented to date are highlighted. The problems and prospects for the future of these techniques are discussed. The chapter offer new study avenues, reinforce existing hypotheses, and discover trends among existing DLLME research papers.

Keywords Dispersive liquid–liquid microextraction · Sample preparation · Green analytical chemistry · Air-assisted · Supramolecular

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Abbreviations

ACN	Acetonitrile
DES	Deep eutectic solvent
DLLME	Dispersive 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
THF	Tetrahydrofuran
EF	enrichment factor
DLLME-SFOD	solidified organic droplet
ST-DLLME	solvent terminated-DLLME
AA-DLLME	Air assisted-DLLME
VA-DLLME	vortex assisted-DLLME
USA-DLLME	Ultrasound assisted-DLLME
MSA-assisted DLLME	magnetic stirrer assisted DLLME
n-DLLME	normal DLLME
DES	deep eutectic solvent
NADES	Natural deep eutectic solvent
IL	ionic liquid
PIL	polymeric ionic liquid
CAC	critical aggregation concentration
CMC	critical micelle concentration
K	Partition coefficient
LDS	low density solvent
UV	ultraviolet spectrophotometry
MS	mass spectrometry
GC	gas chromatography
HPLC	high performance liquid chromatography
CE	capillary electrophoresis
FAAS	flame atomic absorption spectroscopy
FIA	flow injection analysis
SIA	sequential injection analysis
USAEME	USA emulsification microextraction
LWCC	liquid waveguide capillary cell
ISFME	in situ solvent formation microextraction
DeA	decanoic acid
PAN	2-pyridylazo-2-naphthol

1 Introduction

Liquid–liquid extraction (LLE) is the most commonly used technique of sample preparation. In LLE, a few milliliters of a water immiscible organic solvent is mixed and shaken with the aqueous to allow for analyte partitioning. After that, the extract is left to evaporate under a stream of nitrogen to evade sample oxidation. Then, the residue is dissolved is the least possible amount of a suitable organic solvent to keep the sample highly concentrated. These procedure are not only time consuming, but also health hazardous due to the large volume of organic solvents that either evaporate or disposed after extraction [1]. In addition, The automation of LLE steps is a real challenge [2]. For these reasons, LLE is considered ecologically unfriendly and laborious.

Miniaturization of extraction technologies has grown significantly in recent decades [3] to solve the problems of classical LLE while benefiting from its cost-effectiveness and high efficiency. A tiny amount of a water-immiscible organic solvent is employed in liquid–liquid microextraction (LLME) to extract target analytes from aqueous samples. This smaller variant of LLE offers a more environmentally friendly approach to improving extraction efficiency with fewer chemicals and quicker analytical times. Moreover, LLME was readily automated, which aided in the analytical process and safeguarded workers [4].

DLLME technique was developed in 2006 by Rezaee and colleagues as a modification of the LLME technique [5, 6]. The purpose was to improve the recovery rate of LLME. In DLLME, an immiscible organic solvent is combined with an organic disperser to create an emulsion. Manual shaking is then used to disperse the organic extractant into tiny droplets, resulting in a homogeneous solution. This dispersion process extends the contact surface area between the extractant and the sample, thereby increasing extraction kinetics. Following this, the sample is centrifuged to separate the extractant and break up the emulsion. In 2007, Zanjani et al. proposed a new variation of DLLME that uses low-density solvents of long-chain alcohol. These solvents solidify at low temperatures, allowing for easy phase separation. This method, called DLLME with solidified organic droplet (DLLME-SFOD), has been widely used in various applications [7]. A year later, ultrasound was utilized instead of manual or mechanical shaking to induce dispersion, eliminating the need for a dispersing solvent [8]. In 2010, Chen et al. introduced the solvent-terminated DLLME (ST-DLLME) technique, which avoids the centrifugation step by adding an auxiliary solvent to break the dispersion and induce phase separation [9]. This mode aided in the automation of the method. In 2011, Jafarvand and Shemirani used coacervates and reverse micelles to form supramolecular self-assemblies, resulting in higher extraction efficiency and selectivity for specific analytes [10, 11]. The following year, Farajzadeh and Mogaddam introduced air-assisted DLLME (AA-DLLME) using repeated aspiration/injection cycles to induce dispersion [12]. In 2014, magnetic ionic liquids were employed in DLLME to induce phase separation using a strong magnet, eliminating the need for centrifugation [13]. In 2020, water-immiscible natural deep eutectic solvents (NADES) were utilized in DLLME to extract various

analytes, including nine phthalic acid esters [14]. Figure 1 illustrates the milestones of DLLME development over the last years. DLLME is one of the most successful miniaturized sample preparation techniques, due to the high EF, high sensitivity, acceptable precision, accuracy and selectivity according to the acceptance criteria and guidelines of the Food and Drug Administration (FDA). In addition, DLLME is a fast mode of sample preparation in comparison with conventional techniques. The speed of DLLME could be even accelerated by using semiautomated-DLLME or fully automated DLLME [15].

2 Fundamentals

The efficiency of the DLLME technique is governed by the same experimental conditions as LLE. Both extraction and microextraction processes are equilibrium-based and are controlled by the partition coefficient (K), which can be calculated using the following equation:

$$K = \frac{C_{org,Eq}}{C_{aq,Eq}}$$

where, $C_{org,Eq}$ represents the concentration of the analyte in the extracting solvent, and $C_{aq,Eq}$ represents the concentration of the analyte in the aqueous sample, both measured at equilibrium. The main difference between microextraction and extraction lies in the use of tiny amounts of the extractant (microliters) in DLLME, compared to milliliters in conventional LLE. As a result, $C_{org,Eq}$ is substantially higher in DLLME when compared to LLE for two primary reasons. Firstly, the small volumes of organic solvents used in DLLME leads to the analyte being highly concentrated due to the inverse relationship between volumes and concentrations. Secondly, $C_{aq,Eq}$ at equilibrium is very high because only a small amount of the analyte migrates to the small layer of organic extractant. However, K must remain constant, which only occurs if $C_{org,Eq}$ is also very high to maintain the ($C_{org,Eq}/C_{aq,Eq}$) ratio.

In DLLME, the analyte partitioning takes place at the interface between the aqueous sample and the immiscible organic extracting solvent. Increasing this interface enhances the efficacy of partitioning and in turn, the efficiency of microextraction. In DLLME, the organic extract is dispersed in the aqueous sample with the aid of a disperser, mechanical force, or both. This dispersion step increases the contact surface area between the two layers, leading to better extraction and higher efficiency. The efficacy of the process can be assessed by calculating the enrichment factor (EF) using the following formula:

$$EF = \frac{C_{org,Eq}}{C_{aq,int}}$$

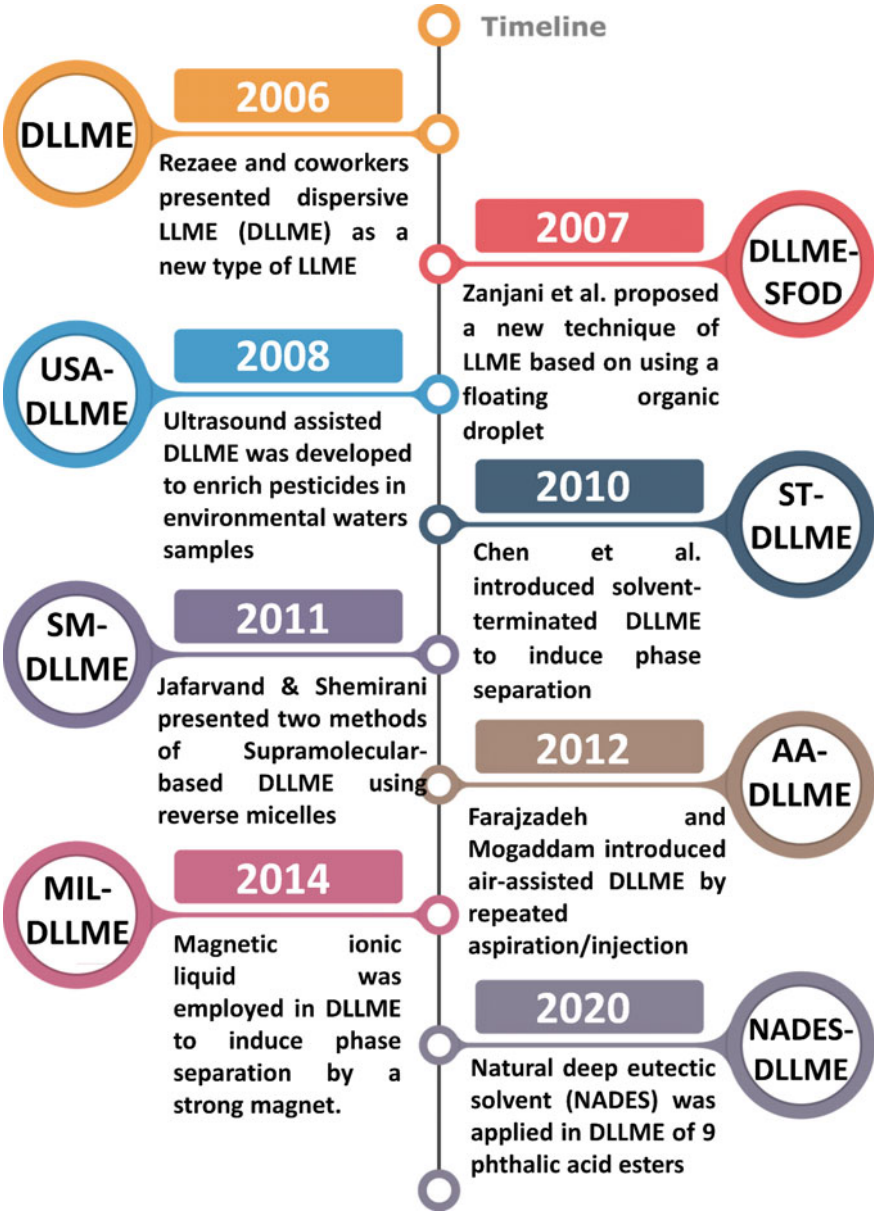

Fig. 1 Timeline of the development in dispersive liquid–liquid microextraction (DLLME)

where, $C_{aq,int}$ denotes the starting concentration of the analyte in the aqueous sample. The EF can be enhanced by selecting appropriate organic solvents and optimizing the experimental settings that influence the DLLME process. These optimization techniques will be discussed in the following sections.

2.1 Requirements of Organic Solvents Used in DLLME

The DLLME technique relies on the utilization of water immiscible solvents as extractants, while a disperser is used to increase their miscibility in the aqueous sample. A diverse range of organic solvents can serve as organic extractants, and their properties are determined by the specific DLLME mode employed. However, there are certain fundamental characteristics that must be satisfied before utilizing organic solvents as extractants in DLLME. Firstly, the extractant must exhibit low miscibility with the aqueous medium to achieve proper phase separation; this is especially critical as the use of a disperser increases the extractant's miscibility in the aqueous medium. Secondly, the extractant should possess the capacity to dissolve the target analyte, with high partition coefficients being desirable. Unfortunately, partition coefficient data for all analytes across various solvents is not widely reported, so the documented Kow value for the octanol/water system is often utilized to estimate the lipophilicity of the target analyte. Thirdly, after manual or instrumental shaking, the organic solvent should be dispersible either using an organic disperser or not. Fourthly, the extractant used must be compatible with the subsequent procedure, or else it must be evaporated first. This additional phase may negatively affect the accuracy of the sample preparation procedure, besides the effort and time involved. Finally, the cost of the extractant should also be taken into consideration, as it should be inexpensive to minimize the overall cost of the analytical procedure. Table 1 summarizes the properties of the most widely used solvents in DLLME.

2.2 Experimental Variables in DLLME

There are several experimental factors that can be optimized to increase extraction efficiency in DLLME including solvents types and volume used in extraction and dispersion, sample temperature and pH, salt addition, extraction duration and stirring rate. The most significant of these factors are proper choices of the kind and amount of disperser and extractant. In traditional DLLME, Halogenated hydrocarbons, including chloroform, are frequently employed as extractants, however, in cases where low density solvents are utilized in DLLME modes, 1-undecanol has emerged as the most prevalent extractant. Typically, maximum extraction efficiency is found at lower extractant quantities (20–100 μL). The type and volume of disperser come next in significance. Acetonitrile (ACN) [17] and methanol [18, 19] are the most often utilized dispersants. A few hundreds of microliters (200–800 μL) are

Table 1 Physicochemical properties of common organic solvents in DLLME [16]

Solventé	Chemical formula	Molecular weight (g/mol)	Boiling point (°C)	Melting point (°C)	Density (g/mL)	Solubility in water (g/L)
Amyl alcohol	$C_5H_{12}O$	88.15	131–132	−78.2	0.809	Slightly soluble
Benzene	C_6H_6	78.11	80.1	5.5	0.88	1.79
Butyl acetate	$C_6H_{12}O_2$	116.16	126.1	−78.8	0.882	1.11
Carbon tetrachloride	CCl_4	153.82	76.7	−22.9	1.586	0.8
Chloroform	$CHCl_3$	119.38	61.2	−63.5	1.49	8.98
Cyclohexane	C_6H_{12}	84.16	80.7	6.5	0.779	2.9
Decanol	$C_{10}H_{22}O$	158.3	232	10-Sep	0.824	Insoluble
Dichloroethane	$C_2H_4Cl_2$	98.96	83.5	−35.7	1.256	Slightly soluble
Diethyl ether	$C_4H_{10}O$	74.12	34.6	−116.3	0.713	6.9
Dichloromethane	CH_2Cl_2	84.93	39.6	−95	1.33	1.33
Diisopropyl ether	$(CH_3)_2CHOCH(CH_3)_2$	102.18	68.2	−111.4	0.725	Insoluble
Ethyl acetate	$C_4H_8O_2$	88.11	77.1	−83.6	0.902	77.68
Hexane	C_6H_{14}	86.18	68.7	−95	0.659	0.0053
Isoamyl alcohol	$C_5H_{12}O$	88.15	131–133	−117.3	0.815	Slightly soluble
Isopropyl ether	$(CH_3)_2CHOCH_2$	102.18	68.2	−117.5	0.725	12.5
Methyl tert-butyl ether (MTBE)	$C_5H_{12}O$	88.15	55	−109.8	0.74	3.9
n-Butyl alcohol	$C_4H_{10}O$	74.12	117.7	−89	0.81	Slightly soluble

(continued)

Table 1 (continued)

Solventé	Chemical formula	Molecular weight (g/mol)	Boiling point (°C)	Melting point (°C)	Density (g/mL)	Solubility in water (g/L)
Propyl acetate	$C_5H_{10}O_2$	102.13	101.3	−95	0.889	0.63
Toluene	C_7H_8	92.14	110.6	−93	0.866	0.52

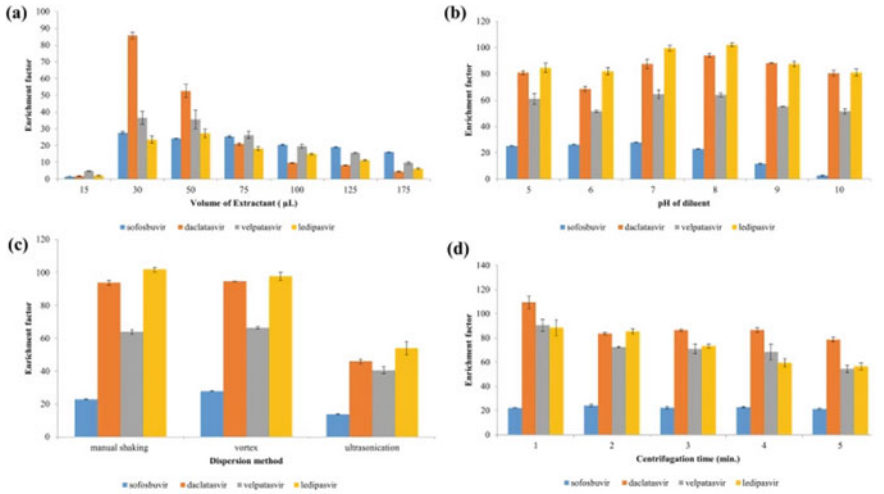

Fig. 2 Optimization of **a** extractant volume, **b** pH of diluent, **c** dispersion technique and **d** centrifugation time ($n = 3$). Reprinted from [21] with permission from Elsevier

frequently sufficient to spread the extracting solvent in the sample. Greater quantities of dispersants are mot recommended due to the unwanted co-solvency, which reduces the efficiency of DLLME [20]. While optimizing the extraction conditions, it is essential to consider the potential interactions between variables. The extraction efficiency of ionizable solutes can be affected by sample pH. The use of acids or bases can potentially alter the ionization process towards the unionized form of the analyte, which is theoretically easier to extract. Similarly, the salting out effect can boost extraction efficiency. Investigating the effects of sample temperature, salt concentration, stirring rate, and extraction duration may aid in achieving the best extraction conditions. Figure 2 shows the effect of extractant volume, pH, dispersion method and centrifugation time on the EF of four different antivirals. As the figure indicated, the most crucial factor was the extractant volume, with markedly higher EFs at lower volumes of the extractant [21]. These factors may be modified at the same time utilizing chemometrics, which can predict the optimal conditions for DLLME with the fewest experimentation, while also predicting variables' interactions [22, 23].

2.3 Modes of DLLME

The conventional mode of DLLME (also known as normal DLLME or n-DLLME) employs high density organic solvents as extractants, and manual shaking to facilitate in dispersion [24]. The different modes of DLLME can be classified according to the extractant type or the dispersion technique. As for the extractant type, different

solvents have been utilized such as low density solvent (LDS), ionic liquids (ILs), deep eutectic solvent (DES), and supramolecular (SUPRAS). On the other hand, DLLME can be categorized according to the dispersion technique into vortex-assisted (VA), ultrasound-assisted (USA), AA and magnetic stirrer assisted (MSA)-DLLME. Phase separation after dispersion is usually induced by centrifugation [25], although solvent-terminated DLLME has been frequently reported [26]. When a dispersion is subjected to centrifugal force, the tiny droplets within the dispersion experience a radial outward force. This force causes these droplets to move away from the axis of rotation, towards the outer edges of the sample centrifuge tube. The centrifugal force in this case accelerates the phase separation. Denser solvents will settle faster than lighter ones, causing them to migrate towards the bottom of the sample, while lighter solvents float on the top [27]. Figure 3 depicts the categorization of the various DLLME modes.

2.3.1 n-DLLME

The most widely employed method for biological analysis is conventional dispersive liquid–liquid microextraction (n-DLLME), which involves combining a suitable disperser with an extractant that is heavier than water [28]. Upon injection of the combined extractant/disperser solvents into the sample, shaking the solution leads to the formation of an unstable emulsion which can be rapidly disrupted by centrifugation. The bottom layer is then collected using a syringe and supplied to the assay equipment. In this context, n-DLLME has been successfully utilized to determine different classes of drugs including antipsychotics [29], antidepressants [30, 31], antimicrobials [32, 33], immunosuppressants [34], antiarrhythmics [35], and drugs of addiction [36–38]. Chloroform [39–41] is the most commonly used extractant, while methylene chloride [35] and carbon tetrachloride [37] are other often used halogenated hydrocarbons. It should be noted that the disperser needs to possess miscibility with both the sample and the extracting solvent in order to serve as a dispersant. Commonly employed dispersers in n-DLLME include ACN [30], methanol [29], acetone [33], ethanol [37], and tetrahydrofuran (THF) [40]. In some instances, the organic solvent is evaporated before utilizing the analytical tool, and the sample residue is reconstituted in a compatible solvent [41]. n-DLLME has been employed in a range of analytical techniques, including ultraviolet spectrophotometry (UV) [30], mass spectrometry (MS) [34], gas chromatography (GC) [36], high performance liquid chromatography (HPLC) [32], and capillary electrophoresis (CE) [40, 41]. The n-DLLME technique has certain limitations, such as low manual shaking efficiency, high toxicity of organic extractants, and difficulties in automation. Researchers have addressed these challenges by modifying the default processes and developing new modes of DLLME [28].

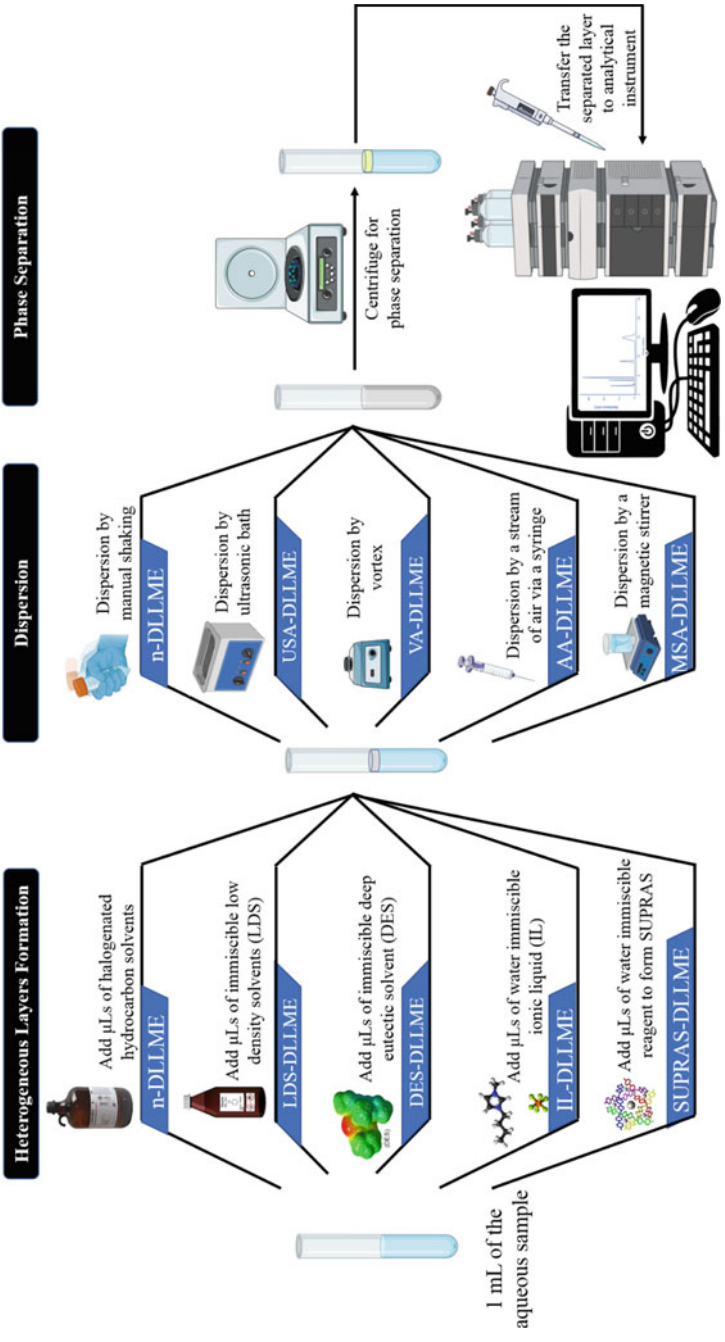

Fig. 3 Different modes of dispersive liquid–liquid microextraction

2.3.2 Ultrasound Assisted DLLME

The most critical step in DLLME is the dispersion. In USA-DLLME, ultrasonic waves are employed to induce better dispersion than manual shaking. This mode has also been termed USA emulsification microextraction (USAEME). The ultrasonic energy was preferentially employed to increase the turbidity of the solution and spread the extractant droplets into the aqueous phase. As a result, the analyte was trapped in these tiny droplets, which make it easily separated from the aqueous solution. Furthermore, the ultrasonic power hastens the transfer of analyte to the extractant phase. To monitor these effects, the ultrasonic settings (temperature, duration, and amplitude of sonication) could be optimized [42] to increase the frequency and rate of material molecular motion, enhance solvent penetration, and thus increase the dispersion degree of extraction solvents. This accelerates the speed of the analytes in the extraction phase, and promote extraction efficiency. Altunay et al. [42] developed USA-DLLME using NADES as extractants for extraction of trace metals from honey by using flame atomic absorption spectroscopy (FAAS). This application studied the effect of ultrasound time and temperature. The effect of sonication period on mass transfer and metal ion recovery was studied from 0 to 20 min at a maximum amplitude of 70%. The recovery values for metal ions were relatively low when ultrasound was not used. The recovery rate for all metal ions rose significantly as the ultrasound period increased up to 10 min, and there was no significant difference in recovery at longer ultrasound times. The influence of ultrasonic bath temperature on the production of NADES droplets with metal ion recovery was also investigated at temperatures ranging from 25 to 60 °C. The best phase separation was attained at 35 °C. No phase separation was accomplished, especially at temperatures over 45 °C. As a result, an ultrasound period of 10 min and a temperature of 35 °C were determined to be appropriate. Generally, ultrasonic bath [43–47] was widely used in USA-DLLME in addition to the ultrasound homogenizer probe, which could be more suitable for limited sample volumes or small extraction vessels [48].

Fernández et al. [49] examined n-DLLME and USA-DLLME for the detection of benzodiazepines in biological fluids; USA-DLLME had greater efficiencies due to the increased dispersion. Moreover, the ultrasonic waves in USA-DLLME obviated the need for a dispersant, reducing solvent usage [50]. Yet, most USA-DLLME applications employ both a disperser and an ultrasonic bath for enhancing the extraction. Fernández and coworkers [51] used USA-DLLME for determination of antidepressants in human plasma by adding 2.5 mL of ACN to samples to act as protein precipitant and dispersant. As an extractant, a volume of 200 μL of chloroform was used. The extracted drugs were tested using UPLC/UV, and the findings were compared to those obtained using traditional LLE connected to GC/MS, there were no substantial differences between the two techniques which indicated that DLLME could enable UV detection to give comparable results to the highly sensitive MS detection. USA-DLLME was also utilized in flow injection analysis (FIA) with inline derivatization through diazotized *p*-sulfanilic acid to determine tetracyclines in egg supplement samples [52].The reaction was carried out at 45 °C in a slightly

alkaline media, and the absorbance at 435 nm was measured using a liquid waveguide capillary cell (LWCC). GC–MS was also utilized to detect seven recreational drugs in human plasma, including meperidine, ketamine, methadone, amphetamine, and amphetamine derviatives. The impact of ultrasound application duration ranged from 0 to 5 min. After 2 min, the optimal sonication was reached. Because of the potential demulsification impact, prolonged duration in the ultrasounds application through a bath was undesired. USA-DLLME was used to extract different analytes from different matrices including aqueous samples [43, 48], food [42] and biological samples [53].

2.3.3 VA-DLLME

Instead of shaking or using ultrasonic waves, the sample can be vortexed with an extractant and a dispersant to induce dispersion. A principal role of vortex is to break down any extraction solvent into tiny droplets, increase the contact area between the droplets and water, and speed up extraction equilibrium, which is dependent on vortex speed and duration [54]. As a result, the vortex promotes the equilibration and dispersion of the target analytes in the extractant and aqueous solution, reducing the equilibrium period [55]. So, vortex time should be enough to achieve equilibration between the aqueous sample and the extractant [56]. Usually, the vortex step is performed with the aid of a vortex agitator [56–58]. The multi-tube vortexers were also employed to increase sample throughput. This allows for more applications within the same timeframe and facilitates automation.

Compared with other modes of DLLME, the vortex outperformed the other mechanical agitators in terms of extraction efficiency [59]. The sample/extractant combination is vortexed with or without an organic disperser to generate an emulsion in VA-DLLME. Herrera-Herrera et al. [60] created the VA-DLLME technique for extracting various sulfonamides and quinolones prior to HPLC–UV. As an extractant, chloroform was employed, while acetonitrile was used as a dispersant. Before centrifugation, the ternary mixture was vortexed for 3 min. Interestingly, vortexing had little effect on extraction efficiency, but it dramatically enhanced accuracy. This describes how vortices help to accelerate the equilibrium process. VA-DLLME was widely used for extraction various analytes from diverse sample types including beverages [61], biologicals [62, 63], food [64], and sewage [65]. However, VA-DLLME biological applications are still lower than expected [66].

2.3.4 AA-DLLME

To eliminate the need of equipment in DLLME, an AA-DLLME technique was introduced, in which dispersion was produced simply by aspirating and injecting the extraction mixture with a syringe repeatedly. This approach requires no extra instruments, facilitating the automation process [67]. The principle of AA-DLLME was similar to DLLME in many ways, but there was no requirement for an organic solvent

to disperse an extractant into the sample solution. A hydrophobic organic solvent at μL-concentration (extraction solvent) was dispersed into the sample solution using a syringe fitted with a needle and sucking/dispersing cycles numerous times. Despite the absence of a dispersant solvent, this approach considerably enhanced the contact area of the extraction solvent with the sample solution. The investigations revealed that the two primary factors in liquid phase micro extraction (LPME) procedures were extraction solvent viscosity and interfacial tension [68]. These parameters influence both the extractant droplet size and the analyte mass transfer rate. Aspirating-dispersing cycles transform the extraction solvent into extremely small droplets, increasing the contact area of the sample solution with the extraction solvent dramatically. During the aspirating/dispersing cycles in AA-DLLME, there is intense turbulence in the solution, and mass transfer of the analytes is mostly regulated by the convective process [67].

A syringe is used in AA-DLLME to repetitively withdarw and inject the extractant and sample until a hazy solution forms. Farajzadeh et al. [31] used AA-DLLME to preconcentrate NSAIDs in biological fluids. The hazy solution was back-extracted into 10 μL of ammonia buffer (0.1 M, pH 9) after four rounds of recurrent withdrawal and injection before being delivered to an HPLC equipment with UV detection. When the analytical figures of merit were compared to other methods of LPME, it was discovered that AA-DLLME had the highest EF, the maximum sensitivity, and a suitable extraction duration of 10 min. NSAIDs might potentially be chemically derivatized and extracted concurrently with AA-DLLME [69]. The derivatizing agent for GC-FID was butyl chloroformate, while the catalyst was picoline. A syringe was used to aspirate and disseminate the material, which was combined with the chloroform, in presence of the catalyst and the reagents. The number of extraction cycles was investigated; four rounds of repeated injection and withdrawal were found to be adequate to generate dispersion. With five or more extraction cycles, no further improvements in signal intensities were detected. The discovered method's sensitivity was higher than previously reported GC–MS approaches, and it was less expensive and time-saving. The AA-DLLME techniques' simplicity and ease of automation improve their potential in biological applications. Barfi et al. [70] compared the performance of ultrasound-enhanced AA-DLLME (USE-AA-DLLME) with previous DLLME techniques that extracted NSAIDs using an organic disperser. Higher EFs were reported with USE-AA-DLLME, which might be attributable to disperser-induced improved solubility in the aqueous sample. So, because of these advantages AA-DLLME including facilitating of the automation and absence of disperser, AA-DLLME was widely used for determination different analytes from different matrices including water [71–73], beverages [74], food [75–77], biological [78] and biodiesel samples [79].

Rahmani and coworkers [80] compared USA-DLLME, AA-DLLME and VA-DLLME to extract benzene, toluene, ethylbenzene and xylene isomers (BTEX) from water samples. There was no need for a dispersive solvent in any of these procedures, as the extractant is dispersed by air bubbles, vortex, and ultrasound for AA-DLLME, VA-DLLME, and USA-DLLME, respectively. The findings revealed that the three techniques used were highly effective, and the hazy solutions formed

were capable of extracting analytes in a relatively short time and with good recoveries (BTEX was used as a simple analyte in these tests). These three procedures were faster, simpler, more sensitive, less costly, and more environmentally friendly than the previous DLLME methods due to the absence of the dispersive solvent. AA-DLLME required a larger volume of extractant and, as a result, required less time to centrifuge. Consequently, AA-DLLME had the shortest analysis time (3 min). The linear dynamic range of AA-DLLME was greater (50–2600 μg /L), although VA-DLLME utilizes less solvent (only 25 μL) and had the best RSD. USA-DLLME has the highest enrichment factor, up to 245-fold.

3 New Developments in DLLME

Since the introduction of DLLME in 2006, tremendous efforts have been exerted to enhance the performance and widen its scope of application. These advances can be categorized into three main trends. The first involves exploring new extractants such as LDS, IL, or DES. The second direction focuses on facilitating the phase separation step such as in DLLME-SFOD. The third direction is geared towards method automation. The following sections discuss these new trends in more details.

3.1 New Extractants in DLLME

3.1.1 Using Low Density Solvents in DLLME

The main obstacles in n-DLLME is the restricted number of extraction solvents and the high toxicity of the halogenated hydrocarbons. These barriers were overcome by utilizing nontoxic organic solvents, with densities lower than water, such as hexane, toluene, xylene, octanol and others in a mode known as low density solvent DLLME (LDS-DLLME). Following dispersion and termination, the floating layer could be delivered to the analytical equipment using a syringe. The LDS-DLLME theory has been studied [81]; nonetheless, applicability in biological fluids are still quite beyond expectations. Ghambari et al. [82] used LDS-DLLME followed by HPLC/UV to extract and evaluate warfarin in plasma. The extraction was carried out in a separate cell. The extraction cell contains deproteinized plasma (pH 2.3 adjusted), an LDS (octanol, 150 μL), a disperser (methanol, 150 μL), and a magnetic stir bar. After the extraction procedure, the extractant collection was facilitated by the long and narrow neck of a special extraction cell. Warfarin extraction recovery was 91%. Applying ultrasonic waves during the dispersion stage boosted LDS-DLLME efficiency. Meng et al. [83] employed SA-LDS-DLLME to determine illicit drugs in plasma. The authors compared their approach to hollow fiber liquid-phase microextraction (HFLPME); USA-LDS-DLLME achieved greater efficiency in shorter extraction times. The fundamental benefit of LDS-DLLME is that the

LDS organic extractants are compatible with routinely used HPLC mobile phases. As a result, there is no need for solvent evaporation or reconstitution prior to sample injection. Unfortunately, LDS-DLLME has intrinsic limitations due to the incomplete phase separation following extraction and the challenging automation of the centrifugation step. Other DLLME modes, such as SFOD [84] and ST-DLLME [9, 85] could overcome these problems.

3.1.2 Using ILs in DLLME

ILs have inspired scientists in a variety of research and industrial fields over the last decade. This is demonstrated by the large number of articles in the area of analytical chemistry pertaining to ionic liquids. ILs can be effectively isolated and reused to greatly decrease application costs [86–89]. Another significant benefit of ionic liquids is the ability to select from a wide range of ions to create an IL with the desired physical and chemical characteristics such as melting point, viscosity, density, and miscibility with water and other solvents. As a result, ILs are frequently referred to as modelling solvents. Ionic liquids' distinctive characteristics piqued the curiosity of scientists and engineers in the field of extraction and separation [90]. For these reasons, ILs and polymeric ionic liquids (PILs) are used in a variety of applications in DLLME [91–93].

The physical and chemical characteristics of ILs are primarily determined by the size, placement, and type of the organic cation and the organic/inorganic anion. The potential of constructing IL structures by selecting the cation and anion that give the necessary physicochemical qualities opens up the possibility of widespread usage of these substances in academic research and industrial applications [94, 95]. ILs are commonly regarded as "green solvents" for their excellent solvation characteristics, low vapour pressure, and low toxicity [92].

Zhou et al. [96] and Baghdadi et al. [97] were the first to use ionic solutions in the DLLME method and to coin the term IL-DLLME [60]. Liu et al. [98] used this IL-DLLME mode for preconcentration and isolation of heterocyclic pesticides in water before HPLC/DAD determination. The IL employed was [C6MIm] [PF6], and the dispersive liquid was methanol [99]. This approach has recently been modified by changing the sample temperature, using ultrasound, microwaves, or more radical modifications such as the in situ IL formation during ME. This in situ IL-DLLME mode was initially suggested by Bahdadi and Shemirani in 2009 and is often referred to as in situ solvent formation microextraction (ISFME) [100]. This in situ IL-DLLME technique works by dissolving hydrophilic IL in an aqueous solution containing the analytes of interest, then adding an ion-exchange reagent to create an insoluble IL. An ion-exchange reagent supports a metathesis reaction, which transforms the hydrophilic IL into a hydrophobic one that settles and preconcentrates the analytes. Yao and Anderson [101] used a similar method for the measurement of aromatic hydrocarbons.

Although ILs have been shown to be good extractants in DLLME, phase separation still needs centrifugation, which is time-consuming and difficult to automate. So,

an innovative family of ionic liquids with magnetic properties, known as magnetic ionic liquids (MILs), has been synthesized, which frequently feature an imidazolium [102], choline [103], or phosphonium cation [104] and a paramagnetic metal (Fe, Co, Mn, or Gd) chloride anion. The higher the magnetic susceptibility, the easier the phase separation in the presence of an external magnet. For this reason, Abdelaziz et al. [105] used a hydrophobic gadolinium-based MILfor the first time as extraction solvent in DLLME. In this work, the produced Gd(III)-based MIL demonstrated hydrolysis resilience in aqueous samples as well as a minimal UV noise signal. Furthermore, the suggested MIL's acceptable viscosity promotes analyte partitioning, speeds phase separation, and simplifies extract handling and transfer into the analytical instrument. Furthermore, the introduced Gd-mased MIL showed significantly high magnetic susceptibility, enabling for quicker extraction solvent recovery with a powerful magnet.

3.1.3 Using Deep Eutectic Solvent in DLLME

One of the objectives of implementing the DLLME method is to utilize environmentally friendly green solvents [106]. The critical step in this aspect is to prepare a solvent that is not only green but also offers efficient extraction [107]. Typically, the solvents used in DLLME methods are toxic, which has spurred the development of remarkable and ecologically favorable green solvents [108]. DESs are typically made up of hydrogen bond acceptors (HBAs) and hydrogen bond donors (HBDs). HBAs are frequently quaternary ammonium compounds, whereas HBDs are amines, carboxylic acids, alcohols, polyols, or carbohydrates [109, 110]. Because of the creation of intramolecular hydrogen bonds, DESs have a much lower melting point than their separate components. DESs have low volatility, low vapour pressure, a reasonably broad liquid range, and high heat durability [111]. Furthermore, DESs are readily produced without the need for purification stages, and they are made from low-cost compounds with low or minimal toxicity. DES are also biodegradable and easily reusable. These characteristics make DESs superior to traditional solvents used in extraction processes [112], especially DLLME extraction and isolation of bioactive substances [113, 114]. One important benefit of DESs, for example, is their ability to be tuned to accomplish specific functionality due to the numerous possibilities of beginning components. The selectivity of DESs for extraction and separation can be adjusted by altering the structure and molar ratio of their hydrogen-bonding components [115]. DESs have been categorized into four kinds, as shown in Fig. 4: Type I (metal halide and quaternary salt), Type II (quaternary salt and hydrated metal halide), Type III (quaternary salt and hydrogen bond donor), Type IV (metal halide and HBDs), and Type V (HBD and HBA). This class is particularly important in the microextraction and sample preparation of ionic and highly polar analytes [116–118].

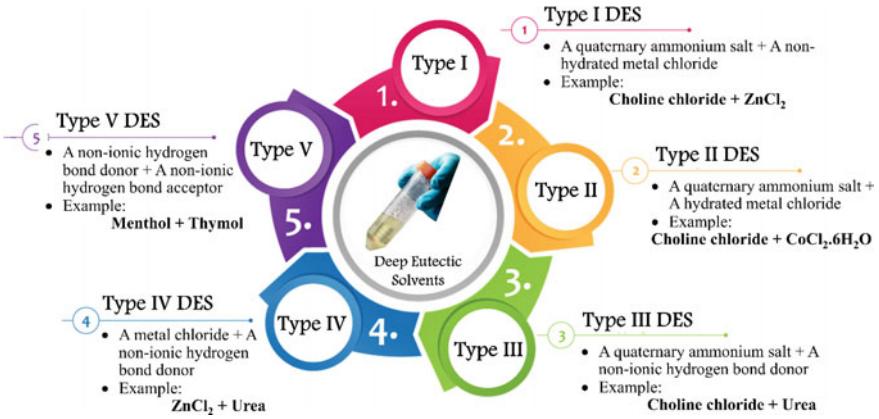

Fig. 4 Types of deep eutectic solvents (DES), with examples

3.1.4 Using SUPRAS in DLLME

SUPRASs are nano-structured liquids produced through self-assembly processes occurring at molecular and nanometer scales from amphiphiles [119]. These solvents have been used in extraction processes for many years under different names such as cloud point technique and coacervates [120, 121], and offer a set of appealing intrinsic properties, including the use of self-assembly based synthetic procedures, widespread availability of amphiphiles, tunability of solvent properties, and excellent solvation properties for various compounds [119]. SUPRASs are formed through consecutive self-assembly processes that occur at molecular and nanometer levels, where amphiphiles form three-dimensional aggregates that separate from the bulk solution as a new liquid phase via coacervation when the critical aggregation concentration is reached (Fig. 5) [122]. Two main types of SUPRAS, vesicle-based and reverse micelle-based, have been developed for analytical extractions, with driving forces for effective solubilization and high extraction efficiency being dispersion forces between hydrocarbon chains and analytes, cation interactions between aromatic rings of complexes and amphiphiles, and hydrogen bonding between nitrogen and oxygen atoms in complexes and carboxylic acids from [123, 124]. Reverse micelle-based SUPRAS using THF has shown greater potential for DLLME compared to vesicle-based SUPRAS [125, 126].

The initial self-assembly process in supramolecular solvent production is the accumulation of amphiphilic molecules in a variety of nanostructures. As a critical aggregation concentration (CAC) is reached, amphiphiles spontaneously aggregate to minimise adverse solvophobic interactions [128, 129]. It becomes energetically advantageous for amphiphiles to interact with one another at the CAC. Colloidal self-assembled structures result from the intricate interplay of solute–solvent and solute–solute interactions.

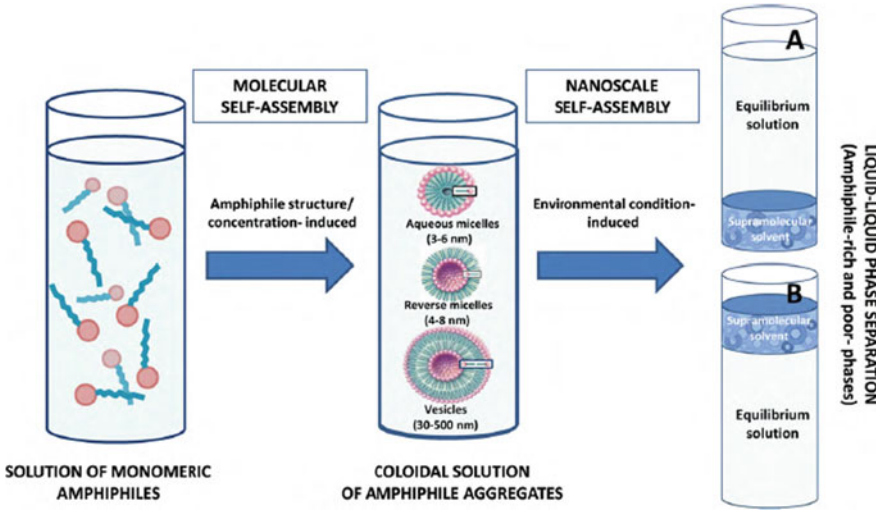

Fig. 5 Self-assembly processes in supramolecular solvent formation. Reprinted from [127] with permission from Elsevier

Seidi et al. [123] developed DLLME-SFOD based on a vesicular SUPRAS of decanoic acid and quaternary ammonium compound for extraction of cadmium, the extraction mechanism of cadmium depended on the SUPRAS structure contains polar and apolar groups, their various interactions with analytes can boost extraction efficiency. The interactions between the vesicular SUPRAS and the Cd(II)-(2-pyridylazo)-2-naphthol (PAN), PAN complex are shown in Fig. 6. The main extraction driving forces appear to be three types of interactions: (1) dispersion forces between the hydrocarbon chains of the amphiphile and the analyte; (2) -cation interactions between the aromatic rings of the Cd(II)-PAN complex and Bu4N+; and (3) hydrogen bonding between the nitrogen and oxygen atoms in the Cd(II)-PAN complex and hydrogen of carboxylic acid. These interactions allow for effective solubilization of Cd (II)-PAN in the SUPRAS as well as high extraction efficiency.

Bendito et al. [124] proposed a novel type of SUPRAS-based extraction constituted of reverse micelles of decanoic acid (DeA) distributed in a water/THF combination in 2007. They demonstrated that polar and non-polar molecules were extracted into SUPRAS using hydrogen bonding and Van der Waals interactions that reverse micelles may generate. A series self-assembly model predicts that the dissolved DeA in THF producing reverse micelles has at least three critical micelle concentration (CMC) points (4.8 $\pm$ 0.2, 7.6 $\pm$ 0.4, and 51 $\pm$ 2 M).When water is added to this combination, the aggregates partially dissolve, facilitating contact and encouraging the formation of larger reverse micelles as an immiscible liquid phase separate from the THF/water bulk solution [125, 126]. It is worth mentioning that using THF based SUPRAS is much more than vesicular SUPRAS in DLLME.

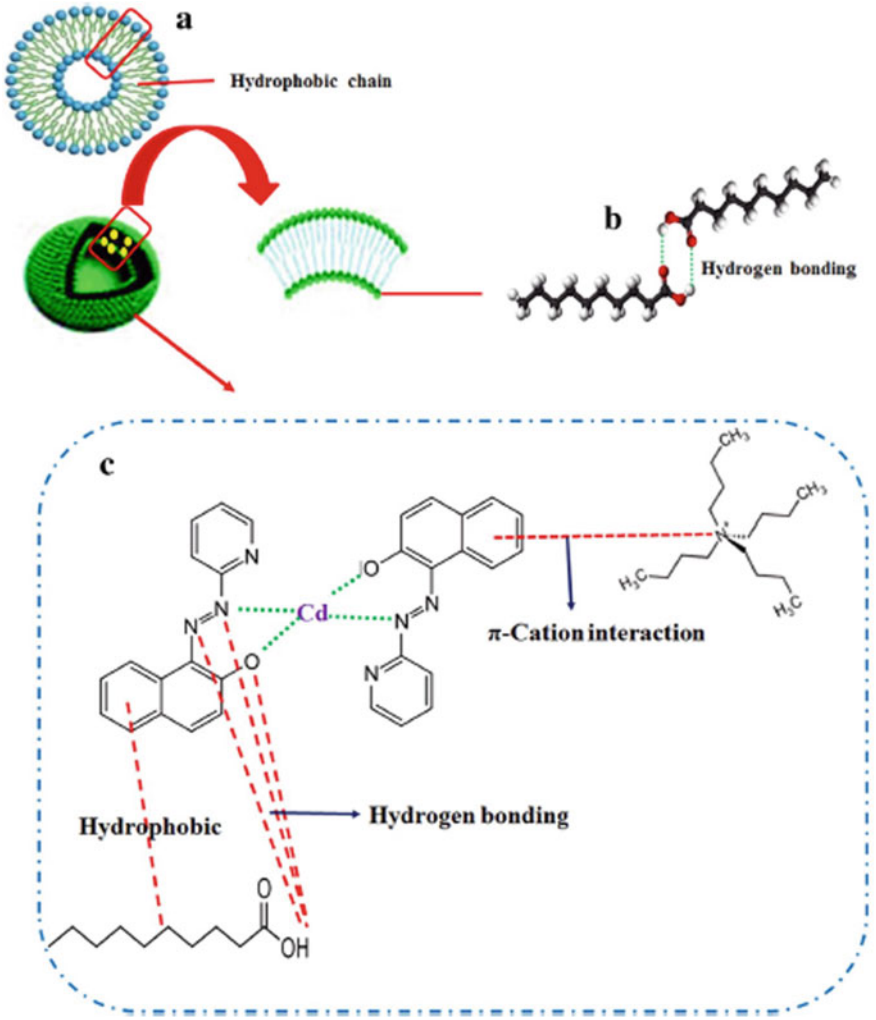

Fig. 6 **a** Chemical interaction can influence vesicle formation and its stability, **b** hydrogen bonding in vesicular formation, and **c** molecular mechanism of microextraction and different interactions between Cd (II)—PAN complex and the vesicle. Reprinted from [123] with permission from Springer Nature

3.2 Phase Separation by SFOD

DLLME-SFOD use low melting point solvents (10–25 °C), such as 1-undecanol and 1-dodecanol [84, 130]. The floating droplet is solidified using an icebox after dispersion and phase separation and then transferred using spatula or forceps. The key benefit of DLLME-SFOD is the ease with which the extracted phase may be separated. In pharmaceutical and biological analysis, DLLME-SFOD is the second most

often utilized mode of DLLME. DLLME-SFOD has been used to determine several pharmaceuticals [131–138] and drugs of abuse [139–142] in dosage forms as well as biological fluids such as urine [136], plasma [138, 140], milk [143] and tissues. While being extensively recognised in biomedical analysis, DLLME-SFOD has several drawbacks; to extract the analyte of interest, two organic solvents (the extractant and the disperser) are required. This issue can be avoided by using mechanically-induced dispersion, as in USA-DLLME-SFOD and AA-DLLME-SFOD [144]. The other issue stemmed from the centrifugation stage, which slowed the extraction process and hampered automation. ST-DLLME [145] can be used to solve this problem by adding a demulsifying solvent. To break the emulsion and produce phase separation, a demulsifying solvent is added to the sample/extractant/disperser combination in ST-DLLME. In this situation, the centrifugation stage can be skipped, allowing for process automation and a reduction in overall analytical time. The main barrier in DLLME-SFOD is the limited number of solvents that can solidify at relatively low temperature without causing the whole sample to freeze. Exploring other solvents especially those from botanical origin with relatively low melting point is highly recommended.

3.3 Automation of DLLME

Automation is one of the DLLME technique's ongoing problems. Several developments in DLLME have relied on flow analysis methods [146]. Initially, DLLME was automated using the sequential injection analysis (SIA) approach and used to determine metals by flame or electrothermal atomic absorption spectrometry [147–150]. A comparable method was developed utilizing the flow injection analysis methodology, which performed online DLLME using ionic liquids [151–153]. DLLME has also been automated utilizing a dual SIA system, which connects both syringe burettes by a conical tube that serves as the extraction container [154].

SIA rendered the automation of DLLME possible [155], through a multi-axis robotic arm with an integrated phase separator and temperature control. This setup allowed for the automatic solidification of the organic phase, followed by the collection of the organic extract for analyte measurement. The automated DLLME-SFOD of parabens was examined as a proof-of-concept, followed by analyte separation using liquid chromatography. Medina et al. [156] and coworkers developed an automated method in which everything was automated by combining a SIA technology with a custom-made robotic phase separator. Then, phase separation was performed in a 3D printed device incorporating a Peltier cell set and placed on a multi-axis robotic arm. A single software package controls the combined action of the flow system and the robotic arm, allowing for the solidification/melting and collection of the organic phase for subsequent analyte measurement as indicated in Fig. 7.

Another approach for DLLME automation is the completion of the extraction "in-syringe" [15]. In case, syringes are employed as DLLME containers, and the separated extractant droplets can be collected at the top of the syringe, ready to be

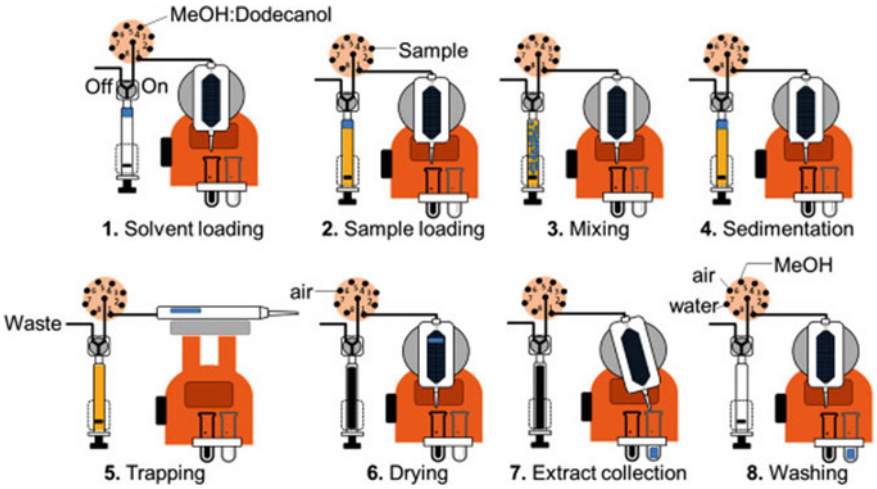

Fig. 7 Major steps of the automated DLLME-SFOD. Reprinted from [156] with permission from Elsevier

automatically injected into the detection system, which is interfaced by an injection valve, utilizing solvents lighter than water [81]. Shishov et al. [157] developed an automated in syringe DLLME for chromium detection in beverages. As indicated in Fig. 8, in the first phase, 0.6 mL of extraction mixture (port a, valve) was aspirated into the syringe via channel 1 by back movement of the syringe pump plunger at a speed of 1.5 mL/ min. The valve was then switched to port b, and 4 mL of sample was aspirated into the syringe at a rate of 10 mL /min. Furthermore, 0.4 mL of air (port c, valve) was sucked to eliminate any leftover sample in channel 1. For 60 s, the sample and extraction liquid were mixed together. The syringe pump and stirrer were turned off for 30 s to allow for extraction and phase separation. Finally, the upper phase was transported into the flow cell of the UV–Vis detector (channel 2), and absorbance was measured under stopped-flow conditions for 5 s at 540 nm before the solution was supplied to trash. After each measurement, the syringe and flow cell were rinsed with 1 mL of isopropyl alcohol (port d). The automation did not compromise the analytical figures of merits, including linearity, selectivity, sensitivity, accuracy and precision. Maya et al. developed a fully automated DLLME for the determination of rhodamine B with integrated spectrophotometric detection [15]. The results indicated that rhodamine B was measured in a working range of 0.023–2 mg/L with a limit of detection of 0.007 mg/L. The method also showed good repeatability for 10 successive extractions, with % RSD values of up to 3.2%. The EF for a 1 mg/L rhodamine B standard was found to be 23, and the method was capable of performing 51 extractions in 1 h.

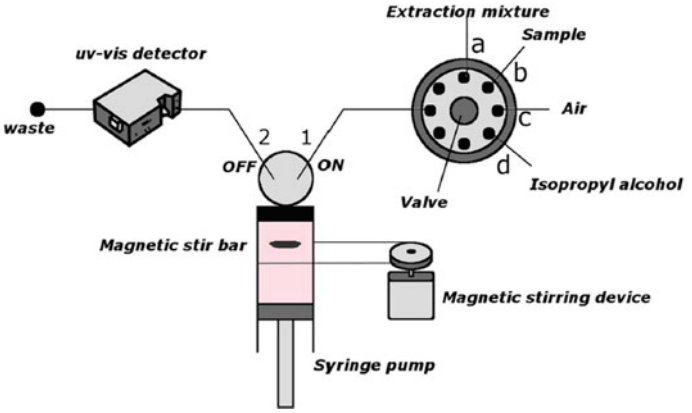

Fig. 8 The manifold of automated procedure for the determination of chromium (VI) in beverages. Reprinted from [157] with permission from Elsevier

4 Application of DLLME

The different modes of DLLME have been extensively used to pre-concentrate analytes of different nature from a variety of samples. Plasma, urine, hair, milk, fruits, vegetables, seafood and water samples were treated by DLLME before analysis. Drugs, toxins, pesticides, preservatives and heavy metals were all enriched with the aid of different modes of DLLME. According to the dispersion technique, n-DLLME and USA-DLLME are the most commonly used modes, followed by VA-DLLME and AA-DLLME. The average sample size is 5–10 mL, but amounts as small as 0.05 mL were also reported. In this case, a dilution step is required before sample preparation to facilitate dispersion. Large sample volumes were also prepared using DLLME, to allow for ultrasensitive determination of heavy metals. The type of extracting solvent depends on the selected DLLME mode, where chloroform is the widely used solvent in n-DLLME, while decanol is very common in DLLME-SFOD. Methanol, ACN and THF are the most popular dispersers due to availability, and high miscibility with both organic solvents and aqueous samples. The volume of disperser is usually less than 1000 μL, and it is highly dependent on the sample size and the extractant volume and type. DLLME has been extensively coupled to HPLC with different detectors including UV, FLD and MS. Application of DLLME before CE was also reported. Both HPLC and CE require minimal sample volumes to be injected into the instrument, which may explain the wide spread of DLLME with these particular analytical techniques. DLLME could also be used before UV/Vis spectrophotometric and spectrofluorometric determinations, if a microcuvette was available. An alternative approach in UV/Vis spectrophotometry was to measure the extracted small sample via a Nanodrop spectrophotometer. Table 2 shows some selected applications of the different modes of DLLME.

Table 2 Application of DLLME in various matrices

Analyte	Sample	Sample volume (mL)	Mode	Extractant	Extractant Volume (μL)	Disperser
Gliflozins	Human plasma	5	USA-DLLLME	1-dodecanol	100 μL	Methanol
Vincristine	Plasma of children	5	VA-DES-DLLME	DES: Methyl tri octyl ammonium chloride (MTOAC) and n-butanol in a molar ratio of 1: 3	80	N/A
Methotrexate	Plasma of children	5	MSA-DLLME	DES-SUPRAS 1-undecanol/ 1-dodecanol; 1:2 v/v)	45	N/A
Favipiravir	Human plasm	2	VA-IL-DLLME	Gadolinium based IL	50 mg	THF
Nateglinide	Human plasma	0.5	VA-DLLME	1-octanol	30	Methanol
Endocrine disrupting compounds	Water	5.0	AA-DES-DLLME-SFOD	DES: nonanoic (C9) acid, decanoic (C10): dodecanoic acid (C12) at ratio 1:1:1	200	N/A
NSAIDS	Milk and water samples	10	USA-DES-DLLLME	DES [TMGH]Cl: thymol at ratio 1:2 1,1,3,3-tetramethylguanidine (TMG)	200	N/A
Sartans	Water	1.2	IL-DLLME	Gadolinium based IL	30 mg	Methanol
Nitrophenol	Water samples	12	VA-DES-DLLME	DES Tetrabutylammonium bromide: thymol: octanoic acid with composition of 1:1:3	70	N/A

(continued)

Table 2 (continued)

Analyte	Sample	Sample volume (mL)	Mode	Extractant	Extractant Volume (μL)	Disperser
Sb(III) and Sb(V)	Water and plasma samples	9	AA-DLLME and narrow bore tube-DLLME	Octanol	100	Ethanol
Phthalic acid esters	Water and beverage samples	20	DES-DLLME	DES Menthol: acetic acid	100	N/A
Neonicotinoid Insecticide Residues	Water, Soil and Egg Yolk Samples	10	VA-DES-DLLME	DES Tetrabutylammonium bromide: decanoic acid	100	ACN
Enrofloxacin	Surface waters	8	USA-DLLME	Chloroform	500	ACN
Sulfonamides antibiotics	Water and Seafood Samples	NA	USA-DLLME	Tetrachloroethane	500	ACN
Chromium	Beverages and vegetables	125	USA-SUPRAS-DLLME	SUPRAS THF, tetrabutylammonium hydroxide and decanol	250	NA
Aucubin	Rat serum	0.05	VA-SUPRAS-DLLME	Pentanol	1000	THF
Carbaryl	Water, fruits and vegetables	15	VA-SUPRAS-DLLME	Heptanol	200	THF
Tricyclic antidepressants	Urine	10	VA-SUPRAS-DLLME	Decanol	50	THF
Traces of maneb	Food and water	10	USA-SUPRAS-DLLME	Decanol	200	THF
Copper	Water and hair	30	USA-SUPRAS-DLLME	Decanol	150	THF
Parabens	Environmental water samples	5	VA-MIL-SA-DLLME	MIL $Co(DMBG)_2NTf_2$	5 mg	ACN

(continued)

Table 2 (continued)

Analyte	Disperser volume (mL)	Instrument of analysis	Linearity (ng/mL)	%RSD	REF
Gliflozins	1	HPLC/DAD	1.1–2500	7.5–9.03	[158]
Vincristine	N/A	HPLC/UV	0.06–300	3.7	[62]
Methotrexate	N/A	HPLC /UV	0.1–150	2.6–4.8	[159]
Favipiravir	0.15	HPLC /UV	25–1.0 *10^5	4.07–11.84	[160]
Nateglinide	0.2	HPLC /UV	50–20,000	<6	[161]
Endocrine disrupting compounds	N/A	HPLC/PDA	3–300	<7	[71]
NSAIDS	N/A	HPLC /UV	5–2000	0.05–12.86	[162]
Sartans	70	UHPLC/UV–VIS	250–8000	2.48–4.07	[105]
Nitrophenol	N/A	HPLC /UV	1.0–500	<5.0	[163]
Sb(III) and Sb(V)	300	Spectrophotometric determination	0.03–20	3.5–4.7	[164]
Phthalic acid esters	N/A	HPLC/UV	4–425	<7.5	[14]
Neonicotinoid Insecticide Residues	400	HPLC/UV	3–1000	<5%	[165]
Enrofloxacin	500	HPLC/FLD	10–300	<2%	[166]
Sulfonamides antibiotics	900	HPLC/DAD	5–5000	0.1–8.1%	[167]

(continued)

Table 2 (continued)

Analyte	Disperser volume (mL)	Instrument of analysis	Linearity (ng/mL)	%RSD	REF
Chromium	NA	FAAS	0.1–350	2.1%	[168]
Aucubin	4000	UPLC/MS–MS	3–10,000	0.33–14.27	[169]
Carbaryl	800	UPLC-MS/MS	30–4000	7.1	[170]
Tricyclic antidepressants	200	HPLC/DAD	30–400	1.3–12.9	[171]
Traces of maneb	600	Spectrophotometric	67–1067	4.2	[172]
Copper	600	FAAS	N/A	2.2	[173]
Parabens	500	HPLC/UV	2.8–400	2.1–13.0	[174]

5 Conclusions and Future Trends

DLLME has attracted the interest of the analytical community since its introduction in 2006, owing to its simplicity and strong analytical capabilities. However, traditional DLLME has had one shortcoming from its emergence: the use of high-density halogenated solvents. Despite the high efficiency, these halogenated solvents are very hazardous, and a process utilising this type of solvent cannot be termed green even if the amount required was in microliter units. As a result, scientists have been seeking for solvents that are not only safe for the environment and operators, but also capable of improving the extraction efficiency of DLLME-based procedures. Many approaches have been presented in this regard. The development of the various types of solvents utilized in DLLME over the last 5 years has been examined in this chapter. SUPRAs and DESs offer exceptional qualities for microextraction and some advantages from being termed green solvents. Nonetheless, the field of chemistry is conservative in certain ways, and many DLLME experiments continue to employ traditional halogenated solvents in accordance with the guideline. The benefits of these traditional solvents, such as their ease of use and high density are obvious but we must not overlook the significant impact that these solvents have on health and the environment. As a result, the adoption of newer and greener solvents must be the goal of DLLME in the next years, with an emphasis on tailorable green solvents with high extraction capabilities and simple and safe synthesis.

The authors have declared no conflict of interest.

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