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Review

Dispersive Liquid–Liquid Micro Extraction: An Analytical Technique Undergoing Continuous Evolution and Development—A Review of the Last 5 Years

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Abstract: Over the years, monitoring the quality of the environment, food, and human health has emerged as a fundamental objective of scientific investigation. Various analytical techniques have been devised and continually refined to ensure a high standard of living. Among these methods, dispersive liquid–liquid microextraction (DLLME) stands out as a widely used approach to conduct analytical evaluations and pre-concentrations of chemical compounds. This review provides an account of the evolution of DLLME over the past five years (2018–2023). The Scopus search engine was used to search for scientific articles. The selection of relevant articles was carried out according to the criteria described below. Emphasis was placed on the evolution that DLLME has undergone over the years by integrating it with other pre-concentration methods in order to amplify the concentration factor and improve analytical precision. Factors such as solvent dispersion and extraction, dispersion formation, and the recovery of the solvent containing the extracted analytes were examined. Additionally, derivatization systems were evaluated to refine both qualitative and quantitative analysis. These efforts aim to introduce methods that are safe for operators, environmentally friendly, and economical. This review evaluates the advantages and disadvantages displayed by the evolution of this technique in the phases before, during, and after its application.

Keywords: DLLME; microextraction; green chemistry; preconcentration; environmental; foods; biological samples

Citation: Notardonato, I.; Avino, P. Dispersive Liquid–Liquid Micro Extraction: An Analytical Technique Undergoing Continuous Evolution and Development—A Review of the Last 5 Years. *Separations* **2024**, *11*, 203. https://doi.org/10.3390/separations11070203

Academic Editor: Antonio Canals

Received: 22 May 2024
Revised: 25 June 2024
Accepted: 26 June 2024
Published: 28 June 2024

1. Introduction

The extraction and analysis of compounds which are potentially dangerous to human health or the environment have become two of the main objectives of scientific research in recent years. An ever-increasing number of articles dedicated to the quality of food products and the quality of the air, water, and soil, as well as the analysis of biological samples, are constantly published in international scientific journals. In most cases, the main problem relating to a qualitative–quantitative analysis of compounds present in more or less complex matrices is that of obtaining a sample that is as clean as possible and that can be injected into current analysis instruments. Furthermore, in most cases, a further problem is linked to the very low concentrations in which these analytes are present. We often talk about ppm, ppb, or even ppt concentrations that cannot be detected even by current precise and accurate instruments. The need therefore arises to develop techniques for the pre-concentration or pre-treatment of samples in order to make them injectable into a measuring instrument. There are numerous techniques used to extract various types of analytes from different matrices. Examples include simple liquid–liquid extraction (LL), solid-phase extraction (SPE), solid phase microextraction (SPME), and supercritical fluid extraction (SFE). All techniques have their own advantages and disadvantages. Currently, these extraction methods tend to be used less frequently due to the high consumption of organic solvents and the excessive amount of time required. Therefore, scientific research is continually proposing new high-performance sample preparation techniques that produce minimal environmental pollution or that tend to eliminate or reduce the disadvantages of these mentioned techniques. A technique that has recently become the subject of study and continuous improvement, used in environmental, food, and biological matrices, is dispersive liquid–liquid micro extraction (DLLME). DLLME is an easy-to-implement approach, and the fields of its application are becoming increasingly broad. The use of a small quantity of solvent guarantees greater protection for the operator. The speed of analysis and other parameters, which will be discussed in this work, make this technique suitable for the extraction of many compounds from different matrices. However, DLLME remains an extraction technique based on the use of solvents, and therefore the effectiveness and efficiency of the extraction depend on the partition coefficient (K_D) of the analytes between the solution and the extraction solvent. This technique is based on the quick insertion of the extraction solvent into the solution, which gives rise to a cloudy solution. This is formed because the extraction solvent, immiscible with the solution, is dispersed in the solution in the form of microdroplets. Factors that influence the extraction performance of the typical DLLME include the extraction solvent, the dispersant solvent, and their volumes. In fact, this technique uses the immediate dispersion of a minimum quantity of extraction solvent immiscible with the starting solution. In the literature, there are works that use a quantity of solvent that varies from 30 μL to 300 μL [1]. The combinations that can be used are usually a polar initial solution and an apolar extraction solvent or anapolar initial solution and a polar extraction solvent. The extraction technique works with the contribution of a dispersing solvent which favors the dispersion of the extraction solvent in the initial solution. The dispersing solvent must be soluble with both the initial solution and the extraction solvent. Furthermore, in most cases, the extraction solvent is mixed with the dispersing solvent and rapidly injected into the solution containing the analytes with a micro syringe. Usually, the dispersing solvent has a volume/volume ratio of approximately 5:1 [2] with the extraction solvent, but this ratio has also been discussed several times in the literature. This rapid injection generates the dispersion of micro drops of the extraction solvent, which leads to the formation of an opalescent solution. The presence of these micro drops within this cloud increases the contact surface between the two phases. Consequently, the rate of distribution of the analyte increases and chemical equilibrium is reached in less time. Liquid–liquid microextraction was first presented by Rezaee and Asadi in 2006 to identify organic compounds in aqueous samples [3]. This technique ends with the separation of the two phases by means of centrifugation [4]. The advantages that DLLME presents compared to the aforementioned techniques are numerous [5]. First of all, very small quantities of solvent are used, and consequently greater safety is provided for the operator. Furthermore, DLLME is a technique that does not require specialized personnel, since its application is simple and of low cost. Finally, analysis times are also limited when compared to the techniques previously described. All of these reasons make DLLME a technique of absolute interest in the scientific world and make it applicable in all sectors of micropollutant analysis. DLLME has had continuous modifications and applications in different sectors over the years, and a 2018 review compared approximately 250 articles published from 2008 to 2018 regarding the optimization of the parameters that characterize DLLME [6]. The high number of articles present in this review suggests the interest shown by the scientific world with regard to this technique. The aim of this work is to report the evolution that this technique has undergone in the last 5 years, from 2018 to 2023, and evaluate the related advantages.

2. DLLME Combined with Other Extraction Techniques

The problem of determining substances present in traces within environmental or food matrices is often linked to their low concentrations or to the analytical difficulty of having injectable samples in analysis instruments. In fact, in most applications, DLLME is associated with liquid or gas chromatographic analysis. Those who work with chromatographic techniques know that one of the main problems is the clean-up phase of the sample—in fact, the sample to be injected into the instrument must have a very high degree of purity. Therefore, DLLME is often combined with other analytical techniques that improve some technical aspects. In this review, the Scopus search engine was used as the main source of data collection. A systematic review of the literature was carried out. To optimize the selection process, the automatic filters present in the search engine were applied. The first selection concerned the year of publication, and therefore the filter was set from 2018 to 2023. However, some articles from 2024 were also considered significant. Subsequently, again using the automatic filters, the articles were filtered within the following subject areas: Chemistry, Biochemistry, Genetics and Molecular Biology, Agricultural and Biological Sciences, Environmental Science, and Chemical Engineering. The proposed articles were automatically sorted according to the number of citations from the highest to the lowest. Finally, manual selection was carried out among the articles, identifying the works most relevant to the purpose of this work. The scientific works chosen are only representative of the respective technique. Where possible, all of the research results were analyzed; alternatively, a selection of the results were analyzed. All searches were carried out using the keywords DLLME and the acronym of the combined technique taken into consideration.

Ultrasound-assisted extraction (UAE) increases the dispersion of the extraction solvent and consequently decreases the time taken to reach chemical equilibrium. This technique was used in 2018 on food samples to extract acrylamide from bread [7] and to extract alpha-toxin B1 from eggs [8]. In 2021, this technique was used on food samples of water, fresh foods, and tobacco to extract nickel with subsequent spectrophotometric analysis [9]. The advantage of UAE–DLLME is often linked to the simplicity of its application. One of the most important advantages of this technique is the contribution of ultrasound to the dispersion of the extraction solvent within the solution.

Quick, Easy, Cheap, Effective, Rugged and Safe (QuEChERS) has also been combined with DLLME. This analysis technique has been applied in the determination of organophosphorus and pyrethroid pesticides in fruit and vegetable samples [10], in the determination of neonicotinoid pesticides in cereals [11], and in the determination of polycyclic aromatic hydrocarbons (PAH) in baby food [12] and crustaceans gammarids that live in the depths of the sea [13]. One of the major advantages of this technique is the degree of cleaning that can be achieved with QuEChERS.

There are a few works in the literature that combine microwave-assisted extraction (MAE) with DLLME for new analytical determinations. In 2019, this technique was used to extract heterocyclic aromatic amines from fried chicken nuggets [14], while in 2021, this technique was used to extract organic additives from films [15]. MAE–DLLME presents greater difficulties than UAE–DLLME, since the regulation and optimization of the microwave conditions are often not immediate and take a long time to optimize. The microwave extraction process is currently obsolete.

A combination that is often examined in the literature is with solid-phase extraction (SPE–DLLME). In the literature, this technique was used in 2018 for the extraction of cadmium (Cd) from water [16], in 2020 to extract quinolones from water [17], in 2021 to extract herbicides from water [18], in 2022 to extract and quantify benzoic acid, ibuprofen and Mecoprop from groundwater [19], and finally in 2023 to determine glucocorticoids in water [20]. SPE–DLLME coupling is certainly a widely used and continuously studied technique, as demonstrated by the number of works examined in the literature in the last 5 years. The advantage of this combination is linked to the high enrichment factor that is obtained by combining these two techniques. The main limitation is that, in all of the works examined, this technique is applied exclusively to aqueous samples. The combination with solid-phase microextraction (SPME–DLLME) also finds applications and is continuously studied in the scientific world. The main limitation of this technique remains the need to carry out headspace sampling; therefore, this technique becomes very limited, as it can only be applied to analytes that pass into the vapor phase while maintaining their chemical–physical characteristics. Despite these limitations, there are several works in the literature that use this technique in different environmental, food, and biological matrices [21–23].

Furthermore, the coupling of DLLME with stirred absorption extraction (SBSE) is of particular scientific interest. In general, this remains a good technique for the determination of polycyclic aromatic hydrocarbons(PAHs) in aqueous solutions [24], but in the last 5 years, this combination has undergone continuous applications and evolutions, and has been widely discussed in the literature, with two dedicated reviews, one in which this technique was used to extract active ingredients of drugs [25] and the other in which it was used for PAH extractions [26] from biological, environmental, and food samples. In 2022. It has also been used to extract and simultaneously derivatize acidic pesticides from aqueous solutions [27]. The main advantages of this technique include its simplicity, environmentally friendly process, disposal costs, reduced solvent consumption, and short shelf life.

The coupling of DLLME with matrix solid-phase dispersion (MSPD) found application in 2018 in the analysis of pesticides in soils and river sediments [28].

When DLLME was coupled with packaged syringe microextraction (MEPS), it was possible to determine benzodiazepines in non-alcoholic and low-alcohol drinks [29]. This technique is also used in biological and forensic fields to analyze a wide variety of drugs with different chemical properties [30]. MEPS–DLLME has demonstrated rapid development in sample preparation techniques in diverse fields, such as the biological, environmental, food science, natural products, forensics, and toxicology fields.

Electro membrane extraction (EME) coupled with DLLME is mainly used on biological samples. In 2019, it was used to extract basic drugs from biological fluids [31], and in 2020, it was used to extract ionic compounds from complex biological fluids [32]. In 2023, it also found application in the extraction of biogenic amines from non-alcoholic beverages [33]. EME–DLLME enables space, cost, and material savings, as well as low sample and energy consumption.

Finally, DLLME has been coupled with the solidification of organic droplets (SFOD). Over the last 5 years, this technique has also been used and applied in various sectors of chemical analysis, as it is considered a green chemistry method [34]. Examples include the determination of steroids in water [35], the determination of endocrine disruptors from water [36], the determination of iodate in table salt [37], the analysis of pyrethroids in cereals [38], and other applications [39]. This technique also finds space in the determination of heavy metals, such as nickel (Ni) and cobalt (Co) [40].

DLLME has been combined over time with other analytical techniques, such as supercritical fluid extraction (SFE), widely described in a 2019 review [25]; supercritical water extraction (SWE) [41,42]; and accelerated solvent extraction (ASE) [43,44], systems which in recent years have tended to disappear as they have been replaced by the techniques previously described which are faster, more practical, and more applicable.

Table 1 summarizes the works examined. It reports the technique combined with DLLME, the analyte determined, the type of matrix, and where possible the enrichment factor (EF), the linear dynamic range (RDL), the LOD, expressed in $\mu g\ kg^{-1}$, the LOQ, expressed in $\mu g\ kg^{-1}$, the percentage of analyte recovered (Recovery, %), and the analytical technique used to carry out the determination. The column relating to the RDL shows the value found in the article. Some articles report only the correlation coefficient (R^2) of the calibration lines, while others report only the concentrations, and others report both values. This table shows the values found in the respective articles. Furthermore, some works analyze classes of compounds, separated with chromatographic techniques, which damage the RDL at different concentrations. This table shows the lowest concentration value and the highest value. The enrichment factor (EF), the limit of detection (LOD), and the limit of quantification (LOQ) are also reported in this table.

Table 1. Selected examples of combined DLLME-based methods and related method indicators.

Technique	Analyte	Matrix	EF	RDL [1] (μg kg^{-1})	LOD (μg kg^{-1})	LOQ (μg kg^{-1})	Recovery (%)	Analytical Technique	Ref.
QuEChERS	Organophosphorus and pyrethroid pesticides	Vegetables		5–500	0.3–1.5	0.9–4.7	61.6–119.4	GC–MS	[10]
	Neonicotinoid	Grains		0.04–40	0.009–0.02	0.003–0.08	62–118	HPLC–MS	[11]
	PAH	Baby food		1 –15	0.1–0.3	0.25–1.0	81–112	GC–MS	[12]
	PAH	Crustacean		2–200	1.5–2.1	4.7–6.3	72–104	GC–MS	[13]
MAE	Heterocyclic aromatic amines	Chicken nuggets	165–210	5–500	2.9–4.0		90–97	HPLC–MS	[14]
	Organic additives	Mulch films		0.025–50 μg g^{-1}	0.0008–0.0586 μg g^{-1}	0.003–0.195 μg g^{-1}	93.0–109.8	GC–MS	[15]
UAE	Acrylamide	Bread		10–500 $R^2 = 0.9982$	0.54	1.89	98	GC–MS	[7]
	AFB1	Egg		0.1–20.0	0.12	0.32	91–94	HPLC–UV	[8]
	Nichel	Environmental samples	60	1.0–300	0.3	1.0		UV-VIS	[9]
SWE	PAHs	Sediment samples			0.0139–0.2334		57.63–91.07	GC-MS	[42]
	Endocrine disrupting	Sediment		5–5000 $R^2 = 0.9920$	0.006–0.639	0.021–2.130	42.3–131.3	GC-MS	[43]
ASE	vitamin E	Cosmetic products		0.5–200 $R^2 > 0.9958$	3–15		87–105	HPLC-UV	[45]
SPE	Cadmio	Water	210	0.4–1000	0.1	0.4	91–107	Electrochemical workstation	[16]
	Quinolones	Water		0.05–10 μg L^{-1}	0.011–0.015 μg L^{-1}		89.67–100.5	HPLC–UV	[17]
	Herbicides	Water	1725–2065	0.02–10	0.003–0.006 μg L^{-1}			HPLC–UV	[18]
	Benzoic acid, ibuprofen, and mecoprop	Water		0.048–4.60 μg L^{-1}				GC-MS	[19]
	Glucocorticoids	Water	1971–2857	$R^2 > 0.9932$	0.21–1.39	0.69–4.17	68–100	HPLC–MS	[20]
SPME	Fragrance Allergens	Personal Care Products		0.00025–0.0128 $R^2 \geq 0.9950$	0.019–0.060			GC-MS	[21]
	Flavor Enhancers	Seafood		$R^2 \geq 0.996$	2.5–5.0	5.0–15.0	89.0–118.6	GC-MS	[23]
SBSE	PAH	Water	18–717	$R^2 \geq 0.9920$	0.5–8.7 ng L^{-1}	1.7–28.7 ng L^{-1}	84–115	GC–MS	[24]
	Acidic pesticides	Water	1232–1532	$R^2 \geq 0.9969$	4–29 ng L^{-1}	47–98 ng L^{-1}	74–92	GC–MS	[27]
MSPD	Chiral pesticides	Soils and river sediments		2–500	0.22–1.54	0.91–4.00	87.0–104.1	HPLC–MS	[28]
MEPS	Benzodiazepine	Low alcolic beveRage		2.50–250 ng μL^{-1}	0.86 and 1.91 ng μL^{-1}	2.18–5.83		HPLC-UV	[29]
EME	Basic drugs	Biological fluids	260–370	3.5–1000	1.0–3.0	3.5–10.0	52–74	GC–MS	[31]
	Ionic target	Biological fluids	21.5–35.5	0.25–500	0.1–0.5 μg L^{-1}	0.25–1.0 μg L^{-1}	43–70.8	GC–MS	[32]
	Biogenic Amines	Non–Alcoholic Beers	36–41	1–5000 $R^2 < 9760$	0.92–0.98	3.03–3.23	94–98	GC–MS	[33]
SFOD	Steroids	Water	44–112	0.01–20.0 μg mL^{-1} $R^2 \geq 0.998$	1.0–9.7 ng mL^{-1}	3.33–32.30 ng mL^{-1}	41.8–101.9	HPLC–DAD	[35]
	Endocrine disrupting	Water	38–134	3–300 $R^2 > 0.9996$	0.96–2.30	2.92–7.02	91.8–103.4	HPLC–PDA	[36]
	Iodate	Table salt	17.4–25.0	0.2–20 $R^2 > 0.9954$	0.2 μg g^{-1}	0.4 to 0.8 μg g^{-1}	89.3–109.3	UV–VIS	[37]
	Pyrethroids	Cereals		$R^2 > 0.997$		6.6–8.9	75.6–87.2	HPLC–UV	[38]

[1] In works with multiple analytes, the RDL varies, and the values represent the minimum and maximum. Furthermore, in some works, only the concentration interval is presented; in others, only the correlation coefficient is presented; and in others, both are presented.

DLLME proves to be a versatile and usable technique for the extraction and determination of numerous types of compounds. The works used to write this review represent a selection of works present in the literature. They were selected using the Scopus search engine and the focus was on the last 5 years. Despite its numerous applications in the environmental, food, and biological fields, DLLME remains a solvent extraction technique, as can be seen from the pie diagram in Figure 1, and the techniques most used to carry out analytical determinations following DLLME extraction are chromatographic techniques. In fact, these techniques represent 90.0% of all analysis techniques used on samples extracted via DLLME, among which 50.0% are characterized by the use of gas chromatography combined with mass spectrometry, 13.3% are characterized by liquid chromatography combined with mass spectrometry, and 26.7% are characterized by liquid chromatography combined with spectrophotometric detectors. The prevalent use of GC/MS is certainly linked to the purchasing and management costs of the instrumentation, which are considerably lower when compared to liquid mass chromatography systems. Only 6.7% of the analyses were carried out with spectrophotometric systems, while 3.3% of the determinations were carried out with electrochemical techniques.

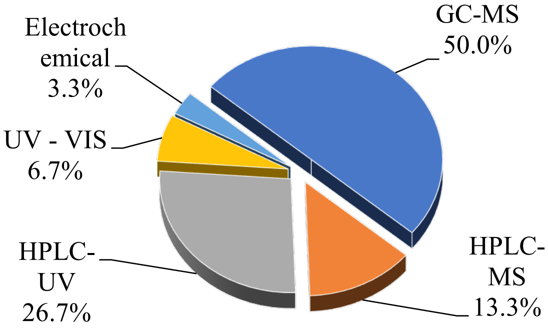

Figure 1. Analysis tools used following extraction in DLLME.

The fields of application concern different sectors and types of products. Although this technique is used to analyze environmental, food, and biological samples, DLLME continues to be a technique predominantly used on food samples (76.6%). Aqueous samples represent 30.0%, food samples represent 33.3%, and low-alcohol samples represent 6.7% of the determinations. The remaining 30.0% of determinations are divided between biological samples (10.0%), environmental samples (6.7%), personal care products (6.7%), and mulch films (3.3%). The percentages discussed are summarized in Figure 2. This analysis clearly provides an idea of the type of matrices most subject to extraction via DLLME. In fact, this technique is mainly used to extract low-polarity analytes from aqueous solutions, precisely because it is based on solvent extraction. Consequently, food matrices are more suitable, as they almost always have a higher percentage of water.

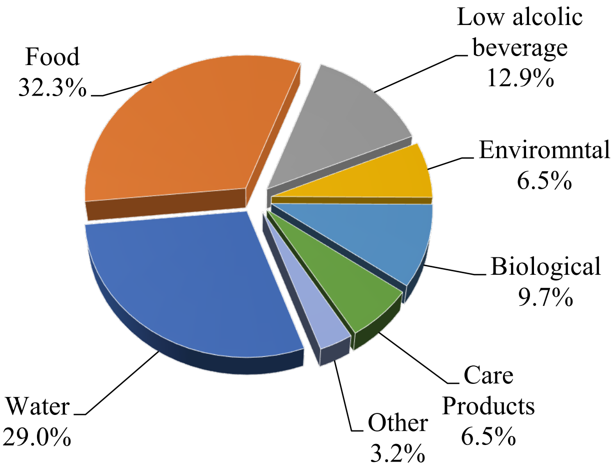

Figure 2. Most extracted matrices.

3. Extraction Solvents

In DLLME, numerous types of solvents are used to extract analytes. The extraction solvent must, in any case, respect some fundamental rules for the success of this technique. Usually, the choice of extraction solvent must respect the following criteria:

(a) Its density must be lower or higher than that of water so that it can be separated via centrifugation;
(b) It must be immiscible with the solution;
(c) It must form an opalescent solution when injected together with the dispersing solvent;
(d) It must have an affinity towards the target compounds.

Most solvents that meet these criteria are chlorinated, such as carbon tetrachloride, dichloromethane, and trichloromethane [45]. Furthermore, these criteria limit the choice to only a few solvents, which are not always suitable for all classes of compounds. Over the years, researchers have also tested brominated and iodinated solvents, but no improvements have been noted compared to the use of chlorinated ones [46]. These solvents tend to be used less and less, given their toxicity and danger to the operator. Currently, the choice of extraction solvent seems to be oriented towards the use of aliphatic solvents, which have a density lower than that of water. Examples include hexane, heptane, *iso*-octane, etc. These solvents certainly have a lower degree of toxicity when compared to chlorinated ones and tend to respect the principles of green chemistry [47,48]. The use of solvents lighter than water leads to the modification of the instrumentation used in DLLME. In fact, after centrifugation, the solvent stratifies in the upper part of the solution. This providesadvantages and disadvantages to the extraction technique. One of the main advantages is that the solvent can be withdrawn directly using a micro syringe; in the same way, this withdrawal can present difficulties linked to the imperfect cleaning of the apolar phase.

Ionic liquids (ILs) are increasingly used as extraction solvents in DLLME [49]. ILs are salt solutions mainly consisting of organic cations and organic or inorganic anions. They typically have a low melting point, usually below 100 °C, and are usually present in a liquid form over a wide temperature range. Their negligible vapor pressure, chemical stability, and particular affinity for ionic species are among their most important characteristics. Furthermore, they have significantly more environmentally friendly characteristics than chlorinated or aliphatic solvents. The chemical properties of IL solutions can be customized and optimized based on the target molecules. This method is based on dissolving the ILs within the solution by increasing the temperature. The aqueous solution and the IL become a single phase. The test tube is then immersed in an ice bath and the solution becomes cloudy. This allows the dispersion of the IL within the solution and consequently the movement of the analytes from the aqueous phase to the ionic solution. The separation of the two phases is achieved by means of centrifugation. The ionic liquid is taken and injected into HPLC. In the literature, there is a 2018 review dedicated to DLLME with ionic liquids [50]. These liquids can be easily dispersed within the solution and have the advantage that they can be recovered with the use of an external magnet, avoiding centrifugation. Also interesting is extraction with magnetic ionic liquids (MIL), whose application is found in a 2018 article on the determination of pyrethroids in aqueous solutions [51], in the extraction of estrogens from human urine samples [52], and in the extraction of doxycycline, a broad-spectrum antibiotic, from urine, blood, and milk samples [53].

The use of specific equipment, such as a centrifuge, remains a mandatory requirement for the separation of the extraction solvent from the solution. Researchers are moving to optimize this sector too, trying to develop demulsifiers to add to the opalescent solution in order to separate the two phases and eliminate the centrifugation phase [54], which in the complete DLLME process still remains one of the slowest steps, slowing down the entire procedure.

Typical DLLME is based on a ternary solvent system, which includes an extraction solvent, a dispersing solvent, and an aqueous solution. Researchers are also moving towards optimizing the extraction solvent dispersion process, trying to eliminate the dispersing solvent. The administration of external energy to the solution via ultrasound (US) is one of the most widely used methods. The energy supplied from the outside favors the dispersion of the extraction solvent without the use of a dispersing solvent. This allows the elimination of one of the solvents and consequently lowers the probability of introducing pollutants into the system. US–DLLME finds various applications in the literature, with examples including the determination of drugs in oral fluids [55] and organochlorine compounds in fish livers [56]. In some works, the use of ultrasound is preceded by the administration of kinetic energy to the system through the use of a vortex or a stirrer plate. Stirring causes the formation of an initial macroemulsion which favors the formation of a macrodispersion within the solution. The use of this technique has found applications in the food field for the determination of PAHs in honey [57] and in the determination of phthalates in hot drinks dispensed by vending machines [58]. A summary diagram of USVA–DLLME is shown in Figure 3.

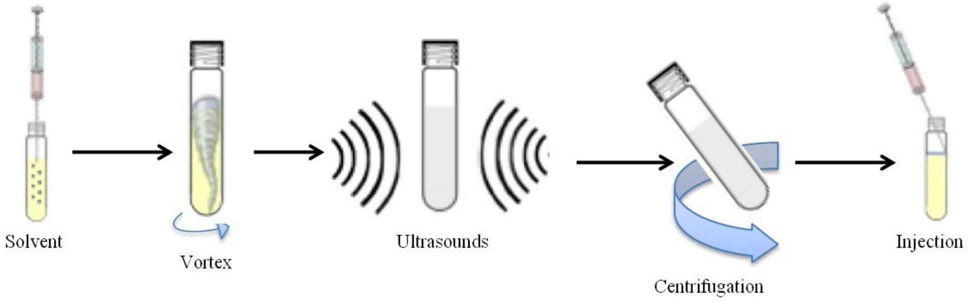

Figure 3. Operational scheme of USVA–DLLME carried out without the dispersing solvent.

Despite their high level, the recoveries and EFs for many classes of organic compounds are highly toxic and listed on the U.S. Environmental Protection Agency (USEPA) list of priority pollutants. Furthermore, they do not apply to the extraction of all classes of contaminants.

Deep eutectic solvents (DESs) have recently emerged as solvent alternatives for analytical extraction applications. DESs are obtained by mixing two or more compounds to obtain a mixture of substances whose melting point is lower than that of the individual substances that compose it. They are versatile and are more environmentally friendly than organic solvents. Among the main characteristics, we highlighttheir excellent thermal and chemical stability. They also have low volatility and flammability. They are easy to synthesize and do not require a purification step. Additionally, they are cost-effective and more environmentally friendly than other solvents commonly used in DLLME. The first articles on the use of DESs as extraction solvents in DLLME began to appear in 2016 [59], and since then, this technique has been continuously updated and studied by the scientific world. In fact, using the Scopus search engine, and carrying out a search using the keywords DLLME and DES, it is possible to notice that from 2018 to today, there have been 97 articles regarding this topic, of which 30 were published in the years 2023 and 2024. This demonstrates the importance that these solvents have in the scientific world. Most works have a relatively high number of citations based on the time of publication. Also, in this case, the field of application of this technique ranges from environmental matrices to biological matrices. In 2019, this technique was used to extract pyrethroids from tea and fruit juices [60]. Also, in the same year, an article was published that applied this technique to the determination of red dyes in food matrices [61], and a review dedicated to DES–DLLME [62] was also published. This technique has also been applied to particularly complex matrices; for instance, in 2020, an article was published on the determination of tetracyclines in milk [63]. It has also found applications in the biological sector, with the determination of some antidepressant drugs [64]. The use of DESs coupled with DLLME also includes the determination of metals, in particular mercury [65], arsenic and cadmium [66], and copper [67].

The use of switchable-hydrophilicity solvents (SHSs) is even more recent. These solvents represent another type of low-density solvent that has recently been studied and used in DLLME. SHSs are made up of secondary/tertiary amines or saturated fatty acids depending on whether the target molecules are basic or acidic, respectively. Their main characteristic is that they can change their hydrophilicity. As the nomenclature itself suggests, they can change from being completely soluble to being completely insoluble inwater. This action is mediated via theacid–base ratio. This technique was proposed in 2020 for the determination of higher main alcohols in the fermentation of alcoholic beverages [68]. It was then proposed again in 2023 for the determination of pyrethroids in wheat [69] and edible mushrooms [70]. This type of technique has not attracted much attention from researchers, since the three works cited are the only ones present on the Scopus database following our keyword search.

4. DLLME and Derivatization

Chromatography is the analytical technique mainly used for the determination of analytes extracted with DLLME. Used in both liquid and gaseous configurations, this technique is coupled with various detection systems. Mass spectrometry is certainly one of the most used due to its versatility, precision, and accuracy. Although this detection system presents a wide spectrum of determinations and detection limits that reach increasingly lower levels, unfortunately not all molecules are visible because they have structural properties incompatible with these detectors. In many cases, it is necessary to make the analyte detectable by the detector by adapting or modifying its molecular structure. A chemical process that helps us to achieve this is the derivatization process. This technique is particularly useful when analytes have low stability or low detectability in their native form. Derivatization transforms them into more stable and easily analyzable compounds. Furthermore, it increases the sensitivity of analysis tools and allows the identification of specific functional groups. Derivatization changes the chemical structure of analytes to form more stable or more easily detectable derivatives. In the analysis of organic compounds, derivatization can improve the sensitivity, specificity, and stability of the analytes. Volatility, reactivity, and polarity are also among the most affected properties. For example, derivatization can be used to convert functional groups such as amino acids into derivatives that are more easily analyzed through gas chromatography or mass spectrometry [71,72]. In other cases, when carried out with designated differentiating agents, the derivatization process improves the sensitivity and selectivity of the analytes to the available detection system.

In general, the derivatization process is a step that is not always welcome in analytical extractions. Derivatization usually takes a long time, the derivatizing reagents present a certain degree of toxicity for the operator, and their addition can lead to the insertion of contaminants. Additionally, some derivatizing agents, reagents, and derivatized compounds are sensitive to moisture and light and require a closed reaction system. However, for some analytes, derivatization has become a necessary and indispensable process. Coupling DLLME with derivatization is a very powerful analytical technique. Toxicity problems are reduced, since the consumption of derivatizing reagents is minimal. The most commonly used derivative processes and related improvements are listed below and are summarized in Table 2:

- Silylation: The addition of silyl groups to compounds containing active hydrogen (e.g., alcohols, amines, carboxylic acids). This improves the volatility and stability of the analytes.
- Methylation: The addition of methyl groups to compounds containing active hydrogen atoms. Useful for analyzing amines and phenols, it improves chromatographic separation and volatility.
- Acylation: The addition of acyl groups to compounds containing amino or hydroxyl groups. This improves detectability via chromatography.
- Etherification: The addition of ethyl or methyl groups to compounds containing hydroxyl groups. This improves stability and discoverability.

Table 2. Common derivatizations, target atoms or groups, and analytical improvements.

Type of Derivation	Target	Improvements
Silylation	Active hydrogen	Volatility, stability
Methylation	Active hydrogen	Volatility, separation
Acylation	Amine or hydroxyl groups	Detectability
Etherification	Hydroxyl groups	Stability, detectability

The first paper on DLLME and derivatization was reported in 2007 [73]. Since then, this technique has been continuously studied and improved. A review covering various aspects of the DLLME–derivatization combination was published in 2018 [74]. It should be kept in mind that the derivatization process can be carried out at various stages of DLLME. The most used forms of derivatization are pre-DLLME derivatization, post-DLLME derivatization, and in situ DLLME derivatization. The three techniques offer different advantages and disadvantages. The operator must evaluate the most suitable solution from time to time. Pre-DLLME derivatization provides partial cleanup before the extraction step, and can improve partition coefficients between the analyte and solvent, but involves many of the problems associated with the use of the derivatizer, such as loss of the analyte or the use of a larger amount of the differentiating agent. In this case, DLLME is used to extract the derivatized analyte. Post-DLLME derivatization partially solves this problem but still uses derivatizing agents that are potentially dangerous for the operator. Depending on the nature of the target compounds, the derivatization process needs to be experimentally studied and optimized. Therefore, the choice of the derivatizing agent, the calculation of the ratios of all volumes, and everything related to the derivatization process (energy source, temperature and reaction time) are part of the optimization of the method. There are also other derivatization systems that can occur simultaneously with the addition of the dispersing solvent and the extraction solvent and, in cases where chromatography is used as a preparation for the separation of the analytes, the derivatization is carried out after the chromatographic separation. Finally, we can carry out some derivatizations before injecting the sample. The differentiating agent is added inside the vaporization chamber of a chromatographic system. This process can be carried out with a single injection containing an analyte and differentiator or with two separate injections by injecting the first one and then the other before starting the chromatographic run. This technique exploits the reaction that occurs in the gaseous phase between the analyte and the derivatizing agent. In 2021, this technique was used to determine morphine in opium [75]. Each technique must be contextualized to the analyte considered and the available instrumentation. The combination of derivatization and DLLME has found application in various fields of analytical determination. In the food field, there are scientific works on the determination of fats [76], biogenic amines [77], and alpha toxins in vegetable oils [78]. In the environmental field, it has found applications in the determination of glyphosate and other herbicides [79] and in the determination of acidic pesticides [27]. It has also been applied in the biological sector, with the determination of stimulant and psychoactive substances in blood and urine samples [80] and in the determination of steroid hormones in urine [81]. DLLME is a liquid–liquid extraction technique that can be combined with derivatization to improve sensitivity and selectivity in chemical analysis. Both techniques are important tools for researchers in the field of food and environmental analysis and, despite the use of the differentiator, they continue to find significant applications.

5. Conclusions

From its first use to today, DLLME has become a consolidated technique used to separate and enrich organic and inorganic compounds. An analysis carried out on the articles selected for writing this article shows that DLLME continues to be a technique mainly used to carry out extractions from aqueous solutions, despite research having been carried out to develop methods for the extraction of molecules from different matrices. At the same time, the main analytical techniques used continue to be chromatographic techniques, in a liquid or gaseous configuration, in most cases combined with mass spectrometry. Significant progress has been made in the development of combined DLLME-based techniques, which are generally developed to handle more complex matrices. Many efforts have been made to overcome the initial disadvantages derived from the use of chlorinated solvents, which have been replaced by the use of aliphatic solvents which are more environment- and operator-friendly. Methodologies based on the administration of mechanical energy have been developed in order to eliminate the dispersing solvent and promote the dispersion of the extraction solvent. This technique's enrichment factors have also been expanded, leading to increased sensitivity of the analysis and facilitating analysis at the trace or ultra-trace level. The main characteristics of DLLME remain its simplicity, speed, effectiveness, low cost, and environment- and operator-friendliness. However, the application of DLLME is still linked to the use of laboratory equipment, such as the centrifuge, which involves limited use of the sample quantity and an extension of analysis time. Scientific research is also developing in this field, proposing demulsifying systems capable of reducing the technical times required for centrifugation. In the future, efforts should be devoted to researching automated coupled systems in order to make DLLME an increasingly used technique in the field of analytical determination.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

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