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Highlights

Applications of liquid phase microextraction for analytes in complex samples.
Focused on works optimized by the response surface methodology.
Literature search of the works reported from 2009 to 2019.
Illustrative example with information to carry out LPME.

Applications of liquid-phase microextraction procedures to complex samples assisted by response surface methodology for optimization

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Abstract

This review presents applications of liquid phase microextraction (LPME) for extracting analytes in complex samples. This process has been introduced to simplify the extraction methods, and enhance the selectivity, sample cleanup and efficiency, allowing the extraction of a wide variety of analytes. The revision was focused on those works in which the performance of the technique was optimized by the response surface methodology (RSM). Firstly, a description of the different LPME systems is presented. Then, a brief explanation of the most popular tools applied for optimization is displayed. After that, the results of a literature search of the works reported from 2009 to 2019 based on the implementation of microextraction supported by experimental design and optimization can be found summarized in a table. Finally, an illustrative example providing the necessary information to carry out this kind of work is presented. A list of the most popular software available to apply RSM is also presented.

Keywords: Liquid phase microextraction (LPME); Response surface methodology (RSM); Complex samples; Chemometrics

1. Introduction

Very recently, Miguel de la Guardia and co-workers have pointed out that there has been increasing concern in the experimental chemistry world related to environmental issues [1]. They stated that in different fields of analytical chemistry ñthere is a complete agreement about the need of taking care of the sustainability of analytical procedures and the need to extend the beneficial effects of the use of analytical data to the whole populationò. In this context, the use of miniaturized, simplified and automatized procedures for preconcentration and cleanup of complex samples plays an interesting role in the total analytical process [2].

It should be remarked that from an ideal point of view, a green analytical chemistry application should avoid preconcentration steps. However, the low thresholds established for several environmental contaminants lead analytical chemists to apply pretreatment steps to attain accurate measurements in samples containing small amounts of target analytes [3].

In this scenario, liquid-phase microextraction (LPME), a novel miniaturized sample pretreatment method, which allows trace determination of target compounds in complex matrices, can be considered as an environmentally-friendly, simple, easy to operate, and highly sensitive process for preconcentration. Complex samples can be defined as those that require a tedious cleanup effort to isolate the analyte(s) from the interfering substances present in the matrix. Therefore, their pretreatment step in analytical determinations could be considered as the procedure bottleneck. The sample pretreatment depends on several factors, such as class and concentration of the analyte, complexity of the sample matrix, detection mode, types of interferences, etc.

The aim of the sample pretreatment methods consists in converting a real matrix into a sample suitable for analysis, in terms of having the analyte in an adequate level of concentration, eliminating possible interferences, converting an analyte into a more adequate form (e.g. derivatization) and/or dissolving the analyte in a media compatible with the

instrumentation [4, 5]. The analysis of biological samples usually requires extra filtration and precipitation steps. For example, urine and plasma samples are generally centrifuged to separate a white solid phase, which can be attributed to co-sedimentation of matrix ingredients [6]. Moreover, protein precipitation with methanol or acetonitrile is a traditional technique for preparing blood samples [7]. On the other hand, food and environmental solid samples should be finely milled and homogenized in the first phase of the analytical process. This allows achieving representative sampling and suitable dissolution in a proper solvent [8, 9].

Interestingly, during the development of an LPME procedure, there is a need for carefully optimizing significant factors that affect the quality of the results. These factors could be types and volumes of extraction and dispersant solvents, extraction time, sample amount, pH, and salt addition, among others [2]. In this situation, the response surface methodology (RSM) plays an important role in finding the best combination of factors that produces the optimum response, e.g., sensitivity, percentage of recovery, peak area in a chromatographic method, etc. [10]. The latter is a collection of statistical techniques which represents an important tool for modeling and analyzing the effects of several parameters of the process under study. It should be noted that the underlying philosophy is to reach the optimum conditions carrying out the lesser number of experiments as possible and calculating interactions among the independent variables. Interestingly, this methodology is more practical compared to the conventional experimental work, which is called ñone variable at timeò (univariate approach), as it is carried out from experimental data which include interactive effects among the variables, obtained from a statistical experimental design built under certain requirements (multivariate approach) [10].

It should be stressed that, regrettably, RSM is not as known and applied as it should be desirable, and many reports show that the optimization of the procedures was performed

by the univariate approach. Thus, the goal of this review is to evidence the real advantages in terms of both the reduced experimental effort and the improved quality of information that can be obtained by following this approach in the implementation of a LPME procedure.

The review is focused on applications of LPME for extracting analytes in complex samples, considering those cases in which the performance of the technique was optimized by RSM. For this purpose, the works reported between the years 2009 to 2019 were taken into account.

2. Liquid phase microextraction

The term liquid phase microextraction was firstly introduced to describe two-phase systems in solvent microextraction [11]. By definition, ñmicroextractionò is an extraction technique in which a very small extractant solvent volume concerning the sample volume is utilized [12]. The extraction yield depends on the partition coefficient of the analyte(s) between the sample donor phase and the extractant solvent or acceptor phase.

Different LPME systems have been introduced to simplify the extraction methods, and enhance the selectivity, sample cleanup and efficiency, allowing the extraction of a wide variety of analytes. Currently, the classification of the LPME systems is carried out taking into account how the extractant solvent comes into contact with the analyte in the matrix. From the first method presented [13], several alternatives were developed with the object of improving the procedure. Until today, the researchers provide enhancements to generate the best analytical results. In this sense, Table 1 summarizes the advantages attained during the last years, describing the source of each liquid-liquid microextraction and the new improvements and automation in the procedure. In the latter table, the column ñProcedureò describes the basis of each microextraction, while the column ñOptionò shows the different alternatives. Besides, the improvements achieved in the last years due to technological

advances such as ultrasound or microwave were listed. These tools allowed enhancing the process through the development of automation systems.

In the following subsections, a brief description of the most important procedures applied for the implementation of liquid phase microextraction is presented, focusing on their differences, advantages/disadvantages, and essential characteristics.

2.1. Liquid-liquid microextraction or liquid-liquid-liquid microextraction (LLME or LLLME)

These procedures (LLME and LLLME) require two or three liquid phases, a magnetic stirrer, a vial and an immiscible solvent which should be less dense than water. Their implementation is very simple, also being feasible to the complete automation of the process of extracting analytes from water.

The traditional LLME technique employs 10ï100 εL of solvent, which is added to the center of a vortex originated in an aqueous sample during the stirring. The direct interface of solvent and water leads to rapid extraction and concentration of the analyte into the organic solvent, which is then removed with a capillary tube or syringe [14]. LLLME is similar to LLME, except for the fact that the analyte is firstly extracted into the organic solvent, and then back-extracted into an aqueous drop [14].

2.2. Single-drop microextraction (SDME)

This process is based on the use of a single drop of water-immiscible extractant solvent for the retention of the analyte(s) contained in an aqueous sample. SDME was the first developed LPME procedure and presents some advantages and disadvantages.

The first implementation was reported in 1996 and consisted in suspending a micro-drop of a water-immiscible solvent (ca. 1.3 εL) in a larger aqueous volume containing sodium docecyl sulphate (SDS) as ion-pair [13]. The external aqueous phase contains the analyte and

is continuously delivered and aspirated away throughout sampling. A negative aspect of this procedure in its different modes of implementation is that the extraction is rarely exhaustive. The major problem is that, in general, the distribution between the donor aqueous phase and the acceptor organic solvent drop is only favorable for one analyte or a group of them. Figure 1 shows the variants of the general procedure. In general, the variations are given by the immersion (direct-immersion) or not (headspace) of the drop, or the use of solvents more or less dense than water, commonly known as high-density or low-density solvents.

2.3. Dispersive liquid-liquid microextraction (DLLME)

In 2006, Rezaee et al. developed the dispersive liquid-liquid microextraction (DLLME) procedure for preconcentration of polycyclic aromatic hydrocarbons (PAHs) in water [15]. This method is based on a ternary system of solvents in which both the water-immiscible extractant solvent mixture and the dispersive solvent are injected rapidly into the aqueous solutions employing a syringe or micropipette. A cloudy solution or unstable microemulsion (water/dispersive solvent/extractant solvent) is formed in the mixture. Interestingly, high efficiency is attained in a relatively short time due to the large contact surface between the two immiscible phases. Figure 2 shows the variants of the overall procedure. Variations can be achieved using solvents with different densities than water.

2.4. Hollow-fiber-protected microextraction (HFME)

Although HFME is often mentioned in the literature as liquid-phase microextraction (LPME), this can be confusing since the same designation is also used for single-drop microextraction (SDME). HFME is based on the partition of analytes between an aqueous solution and a small quantity of organic solvent in a microporous tube (the rod configuration). Even though it is usually described as a liquid-liquid microextraction process,

this extraction should be considered as a hybrid process which does not follow the basis of the liquid-liquid microextraction, i.e. the use of two or more liquids to carry out the extraction, due the nature of the procedure, which involves the use of a solid phase (microporous tube).

2.5. New solvents used in extraction process

In line with the accomplishment of the principles of green chemistry, the development of alternative solvents has grown exponentially during the last decade [16]. Although the ideal situation is the achievement of ñsolvent-freeò extraction schemes [17], this concept is still rather utopic. Therefore, the search for substitute solvents is of utmost importance [18].

In this sense, ionic liquids (ILs) gained great attention as green media, because of their biodegradability, biocompatibility and sustainability. ILs are non-molecular compounds, with melting points below 100 °C, typically consisting of a big asymmetric organic cation, and a smaller organic or inorganic anion. Due to their proprieties, ILs have been applied in many analytical chemistry fields as an alternative to traditional organic solvents. Considering the specification of each extraction method, the utilization of ILs may be divided in solvent-based extraction and sorption-based extraction. Liu et al. described the first use of an IL in a LPME system for the extraction of PAHs in water [19].

Later, a new kind of solvents based on the eutectic behavior of their counterparts, emerged as an alternative to ILs. Deep eutectic solvents (DESs) were introduced by Abbott et al. [20], showing a wide liquid range and interesting properties. A DES consists in a mixture prepared by complexing an ammonium halide with a hydrogen-bound donor (HBD) such as carboxylic acids, alcohols, amides, among others, under simple laboratory conditions. The main physicochemical properties of DESs responsible for their use as green solvents at room temperature are: freezing points, density, viscosity, polarity, ionic conductivity and

acidity/alkalinity. Moreover, DESs have been successfully used as effective, reliable, inexpensive, non-toxic, biodegradable and biocompatible new solvents. Besides, in 2011 a new kind of DESs, the ñNatural Deed Eutectic Solventsò (NADES), formed by cellular constituents such as sugars, alcohols, amino acids, organic acids and choline derivatives were presented [21]. NADES are typically obtained by mixing a hydrogen-bond acceptor (HBA) with a hydrogen bond donor (HBD) molecule, leading to a significant depression of the melting point. The use of DESs and NADES is growing, and several reviews attaining their applications can be consulted in the literature [22-27].

2.6. Advances in LPME

Since the first applications of LPME reported in the mid-to-late 1990s, the researchers made the efforts to develop new devices, accelerate the extraction steps and automate the systems. In this context, the use of a polyethylene Pasteur pipette [28] or a special extraction vessel [29] for DLLME was reported.

Following the principles of green chemistry [16], the application of microwave, ultrasound and ultraviolet irradiation are genuine alternatives to conventional methods involving classical chemical reactions or to enhance the mass and/or heat transfer. In recent years, attempts have been made to introduce these clean energies in combination with microextraction techniques, thereby giving rise to the development of virtually reagentless and ecofriendly methods. Since the application of ultrasound to assist the extraction described by Huang et al. in 2006 [30], the use of clean energies and other strategies have been frequently reported (see Table 1).

Moreover, one of the goals of green chemistry is the automation of analytical methodologies to enhance the overall analysis. Automation of LPME procedures improves reproducibility compared to manual operation, and numerous samples can be analyzed in

Table 2A: Literature search (2009-2019) of the use of RSM for the optimization of microextraction procedures of inorganic analytes for complex matrices.

Year	Microextraction	Screening step ï variables	Optimization step ï variables	Analytes	Instrumental analysis	Sample	Ref.
2012	ISF-LLME	Full factorial design ï reagent concentration, amount of IL, amount of ion-pairing agent and salt concentration.	CCD ï reagent concentration and amount of IL.	Ni (II)	FAAS	Lettuce	[60]
	TIL-DLLME	PBD ï IL volume, concentration of complexing agent, pH, incubation time and temperature.	CCD ï IL amount, pH and temperature.	Pb(II)	FAAS	Blood	[61]
2015	UA-IL-DLLME	ï	Full factorial design ï pH, volume of IL, CCl_4 volume and sonication time.	Cu(II), Ni(II) and Pb(II)	FAAS	Vegetable and fruit	[62]
2019	MIL-DLLME	DPB ï $NaClO_4$ concentration, acetonitrile volume, agitation time, MIL volume and sample volume.	ï	As (III)	ETAAS	Honey	[63]
	εS-SHS-LLME	DPB ï volume of SHS, pH, volume of Na_2CO_3 and volume of H_2SO_4.	CCD ï pH, volume of the SHS and volume of Na_2CO_3.	Vanadium	ETAAS electrothermal atomic absorption spectroscopy	Tomato, spinach, potato and drinks	[64]

Table 2B: Literature search (2009-2019) of the use of RSM for the optimization of microextraction procedures of organic analytes for complex matrices.

Year	Microextraction	Screening step ï variables	Optimization step ï variables	Analytes	Instrumental analysis	Sample	Ref.
2009	IL-DLLME	ï	CCD ï sample pH, NaCl percentage, IL amount and volume of disperser solvent.	Eight pesticides	HPLC-DAD	Banana	[65]
	DLLME	ï	CCD ï extraction temperature, sample weight, acetonitrile volume, extraction time, and CCl_4 volume.	Two antioxidants, (Irganox 1010 and Irgafos 168)	LC-DAD	Polymer	[66]
	HD-HS-SDME	ï	CCD ï drop volume, extraction time, plant sample weight and cooling time after hydrodistillation.	Thymol and carvacrol	GC-FID	*Oleum thymi* essential oil	[67]
2010	UAE-DLLME	Fractional factorial design ï sample volume, extracting agent volume, sample pH, ionic strength, cavitation time and centrifugation time.	CCD ï extracting agent volume, sample pH, ionic strength, cavitation time and centrifugation time.	Seven sulfur compounds	GC-MS	White wine	[68]
2011	UAE-SFO-SDME	Full factorial design ï extraction solvent volume, salt effect, extraction time and centrifugation time.	BBD ï extraction solvent volume, salt effect and extraction time.	Six phthalate esters	HPLC-DAD	Shampoo, after shave gel and hair spray samples	[69]
	DLLME	ï	CCD ï volume of extraction solvent, NaCl percentage and water volume.	Aflatoxins B1, B2, G1 and G2	HPLC-FLD	Cereal products (maize, rice and wheat)	[8]
	DLLME	ï	CCD ï volume of dispersive solvent, extracting solvent, sample solution volume and pH.	Three organophosphorus pesticides	HPLC-UV	Water, fruit juice and fruits	[70]
	UA-DLLME	PBD ï sample volume, solvent volume, extraction temperature, extraction time, centrifugation speed and time.	CCD ï sample volume and solvent volume.	Geosmin and 2 ï methylisoborneol	GC-MS	Water and wine (red, rose and white)	[71]
	RP-DLLME	ï	CCD ï disperser volume, extraction solvent volume, pH of the aqueous	Hydroxytyrosol and tyrosol	HPLC-UV	Virgin olive oil	[72]

			phase and centrifugation time.				
	IL-DLLME	ï	CCD ï sample pH, IL amount, volume of dispersion solvent and NaCl percentage.	Eight pesticides	HPLC-FLD	Soil extracts	[73]
	SA-DLLME	ï	CCD ï pH, organic solvent volume, ionic strength and surfactant concentration.	Three cannabinoids	HPLC-UV	Urine	[6]
	SEV-DLLME	ï	CCD ï Silylation: NaOH concentration, HCl concentration, silylation agent solutions, NaOH, HCl and silylation agent contact times. CCD ï Microextraction: extraction time, $CHCl_3$ volume, methanol volume, centrifuge rate and time, and salting-out effect.	Six pesticides	GC-FID	Wastewater, well water, and fruit juice (apple and grape)	[74]
	DLLME	ï	Full Factorial design ï dispersive solvent and extraction solvent. CCD ï dispersive volume, extraction volume, pH, and NaCl concentration.	Sorbic and benzoic acids	GC-FID	Beverages (carbonated soft drinks)	[75]
2012	DLLME	Full factorial design ï volume of extracting solvent, disperser solvent, amount of salt and pH.	CCD ï volume of extracting solvent and amount of salt.	Five organochlorine pesticides	GC-MS	Honey	[76]
	HS-SDME	PBD ïwater volume used for honey dilution, NaCl content (w/v) in the donor solution, volume of the donor solution, and stirring rate.	CCD ïvolume of the donor solution and extraction temperature.	Six pesticide contaminants	GC-ECD	Honey	[77]
	DLLME	ï	CCD ï extraction solvent dichloromethane and dispersive solvent acetonitrile volumes.	Seven neonicotinoid insecticides	LC-MS/MS	Honey	[78]
2013	DLLME	ï	CCD ï extractor volume, disperser volume, ionic strength, and pH.	Chlordiazepoxide	HPLC-UV	Water, urine, plasma, and chlordiazepoxide tablet	[79]

	DLLME	ï	TD ï extractant organic volume, disperser volume, aqueous phase volume, aqueous phase pH, NaCl concentration and centrifugation time.	Vitamins D_2,D_3,K_1,K_2 and K_3	LC-DAD LC-APCI-MS	Spinach, cos lettuce, iceberg lettuce, lamb's lettuce and infant foods	[80]
	DLLME	ï	CCD ïdisperser solvent volume, extraction solvent volume, salt amount and sample pH.	Benzoate and sorbate salts	HPLC-UV	Yogurt	[81]
	EAE-IL-DLLME	ï	CCD ï pH, volume of extraction solvent, volume of disperser solvent and ionic strength.	Patulin	HPLC-UV	Apple juice	[82]
	UA-DLLME	ï	CCD ï temperature, sonication time, volume of preconcentration solvent and salt concentration.	Volatile components	GC-MS	Tea plants	[83]
	HS-SDME	ï	CCD ï weight salt, extraction time, extraction temperature and stirring rate.	Six furanic compounds	GC-MS	Coffee	[84]
	ILAM-HS-SDME	ï	BBD ï mass ratio of ILs, sample mass, extraction temperature and extraction time.	Monoterpene hydrocarbons and oxygenated monoterpenes from essential oil	GC-MS	*Forsythia suspense*	[85]
	RP-DLLME	ï	CCD ï volume and ratio of disperser and extracting solvents	Eighteen phenolic compounds	LC-DAD-MS	Virgin olive oil	[86]
2014	PLE-DLLME	ï	TD ï CCl_4 volume, aqueous phase volume, acetonitrile volume, NaCl concentration and centrifugation time.	Tocopherols, tocotrienols and tocopherol acetate	Capillary LC-DAD	Cosmetic products	[87]
	PLE-DLLME	ï	TD ï CCl_4 volume, methanol volume, aqueous sample volume, sample pH, NaCl concentration and centrifugation time.	Tocopherols and tocotrienols	LC-APCI-MS	Spinach, corn, cranberry, pomegranate and mango juice	[88]
	UA-RM-DLLME	ï	BBD ïsurfactant and modifier volume, sonication and centrifugation time.	Acetoin	HPLC-UV	Butter	[89]
2015							

	DMAE-SDME	ï	BBD ï microwave power, extraction time and extraction solvent flow rate.	Seven organophosphorus pesticides	GC-MS	Tea samples	[90]
	MSA-SI-LLME	ï	CCD ï stirring time, pH, extraction solvent volume and centrifugation time.	Five fluoroquinolones	HPLC-FLD	Milk, eggs and honey	[91]
	UA-SI-LLME	ï	CCD ï solvent volume, pH, extraction time and weight of salt.	Five fluoroquinolones,	HPLC-FLD	Fish, chicken, pork and beef	[92]
	DLLME	ï	CCD ï extraction solvent, disperser solvent, pH of sample solution, centrifugation time and ionic strength.		UV Spectrophotometry	Cinnamon syrup and Cinnamon tea	[93]
	MA-DLLME	ï	CCD ï volume of extraction and disperser solvents, salt amount and ethanol ratio.	Sixteen PAHs	GC-MS	Grilled meat	[94]
	MSA-DLLME	Fractional factorial design ï extraction solvent volume, disperser solvent volume, pH of sample, salt addition, temperature, stirring rate and time of extraction.	CCD ï extraction solvent volume, pH of sample, temperature and stirring rate.	Rhodamine B and rhodamine 6G	HPLC-Vis	Water samples, soft drinks and cosmetic products	[95]
	UA-SFO-DLLME	Fractional factorial designï extraction time, extraction temperature, volume of dispersant and salt addition.		Five phthalates	GC-FID	Food simulants, vinegars, wines, soft drinks and sangria	[96]
	IL-DLLME	ï	CCD ï IL amount, volume of disperser solvent, pH, and KCl concentration.	Benznidazole and nifurtimox	HPLC-UV	Human breast milk	[97]
	QuEChERS-IL-DLLME	ï	BBD ï extractant volume, dispersant volume, and extraction time.	Six triazole fungicides	HPLC-PDA	Pear, apple, and grapefruit	[98]
2016	In-syringe DSIL-DLLME	DPB ï amount of ionic liquid precursor, molar ratio of ionic liquid precursors, ionic strength, pH and sample volume.	CCD ï ionic strength, pH and sample volume.	Triflumuron, hexaflumuron, lufenuron and chlorfluazuron	HPLC-UV	Honey	[99]

DLLME	ï	BBD ï Derivatization: derivatization temperature, derivatization time and the molar ratio of BCECïCl to the EDCs. DLLME: extraction solvent volume, disperser solvent volume and ionic strength.	Six steroidal and phenolic endocrine disrupting chemicals	HPLC-FLD	Fish, chicken and pond water	[100]
DLLME	ï	Full Factorial design ï type of extraction solvent, type of dispersive solvent and protein precipitation. CCD ï BGE concentration, pH, content of PDADMAC.	Nine fluoroquinolones	CE	Porcine blood	[7]
DLLME	Reduced factorial design ï extracting solvent volume and, dispersing solvent volume.	CCD ï dispersing solvent volume, and extracting solvent volume.	Gliclazide, glibenclamide and glimepiride	HPLC-DAD	Serum	[101]
AA-LLME	ï	CCD ï pH value for the donor phase, volume of the organic solvent, pH value for the acceptor phase, and volume of the acceptor phase.	Three anti-inflammatory drugs (diclofenac, ibuprofen, and mefenamic acid)	HPLC-UV	Human plasma and wastewater	[102]
UA-DE-LLME	ï	BBD ï volume of DES_1, the ultrasonic time and the temperature of ultrasonic bath.	Three phenolic acids	HPLC-UV	Vegetable oils	[103]
TAA-SFO-LLME	ï	CCD ï pH value for the donor phase, volume of the organic solvent, pH value for the acceptor phase and volume of the acceptor phase.	Three cholesterol-lowering drugs (rosuvastatin, atorvastatin, and gemfibrozil)	HPLC-UV	Human plasma and wastewater	[104]
UA-DLLME	ï	Fractional factorial designï the dispersion solvent volume, the extraction solvent volume, the pH and the UA stirring time.	Six second-generation antidepressants	UPLC-PDA	Human plasma	[105]
DI-SDME 2017	ï	Fractional factorial design (the factors were divided in different groups) ï sample weight, extraction solution volume, sonication time,	Pesticides	GC-MS	Mango	[106]

			extractant solvent, drop volume, stirring rate, ionic strength, time, pH and temperature of extraction.				
	DLLME	Fractional factorial design ï ethylation time, addition of NaCl, volumes of methanol and tetrachloroethylene.	CCD ï volumes of the disperser and extraction solvents.	Three organotin compounds	GC-PFPD	Marine sediment	[107]
	IL-VA-LLME	DPB ï pH, ionic salt, extraction solvent volume, vortex time, vortex speed, centrifuge speed and centrifuge time.	CCD ï pH, vortex time, vortex speed and extraction solvent volume.	Bisphenol A and Bisphenol S	LC-MS/MS	Thermal paper receipts	[108]
	AA-SFO-LLME	ï	CCD ï volume of the organic solvent used, pH value for the sample solution, amount of salt solution (%w/v), and number of air-agitation cycles.	Amitriptyline and imipramine	GC-FID	Human plasma and wastewater	[109]
	AA-DLLME	ï	BBD ï volume of extractant, number of extraction, pH, and rate of centrifugation.	Deoxynivalenol	HPLC-DAD	Rice	[9]
2018	HFIP/Brij-35 SUPRAS-LLME	DPB ï concentration of Brij-35, concentration of HFIP, pH, vortex time, centrifugation time, centrifugation rate, standing time, ionic strength and sample volume.	CCD ï concentration of Brij-35 and concentration of HFIP.	Six parabens	HPLC-DAD	Environmental waters, pharmaceuticals and personal care products (sunscreen and lotion)	[110]
	IL-UA-LLME	DPB ï extraction solvent volume, dispersive solvent volume, cooling time, ultrasonic time and centrifugation time.	CCD ï extraction solvent volume, dispersive solvent volume and cooling time.	Bisphenol A, bisphenol B and bisphenol AF	HPLC-FLD	Milk and fruit juice	[111]
2019	DLLME	ï	CCD ï volumes of the disperser and extraction solvents. SLD ï combinations of acetonitrile, methanol and sodium phosphate buffer.	Albendazole, chloramphenicol, trimethoprim, enrofloxacin, oxitetracycline and nicarbazin	HPLC-DAD HPLC- FSFD	Egg	[42]
	UA-DLLME	ï	BBD ïamount of NaCl in honey	Chloramphenicol	UHPLC-MS/MS	Honey	[112]

		solution, volume of extraction and dispersive solvent.				
AA-SFO-DLLME	Fractional factorial design ï acetonitrile volume, methanol volume, isopropyl alcohol volume, propanone volume, water volume and $ZnSO_4$ amount.	CCD ï acetonitrile volume, methanol volume, propanone volume, water volume and $ZnSO_4$ amount.	Albendazole, chloramphenicol, trimethoprim, enrofloxacin, oxitetracycline and nicarbazin	HPLC-DAD HPLC- FSFD	Egg	[42]

IL-DLLME: ionic liquid-dispersive liquid-liquid microextraction; MIL-DLLME: magnetic ionic liquid-dispersive liquid-liquid microextraction; DLLME: dispersive lliquid-liquid microextraction; HD-HS-SDME: hydrodistillation-headspace solvent microextraction; UAE-DLLME: ultrasound assisted-emulsification-dispersive liquid-liquid microextraction; UAE-SFO-SDME: ultrasoundïassisted emulsification microextraction with solidification of floating organic droplet; UA-DLLME: ultrasound assisted-dispersive liquid-liquid microextraction; RP-DLLME: reversed-phase dispersive liquid-liquid microextraction; SA-DLLME: surfactant-assisted dispersive liquid-liquid microextraction; SEV-DLLME: silylated extraction vessel -dispersive liquidïliquid microextraction; TIL-DLLME: temperature controlled ionic liquid- dispersive liquid-liquid microextraction; UA-IL-DLLME: ionic liquid based ultrasound assisted- dispersive liquid-liquid microextraction ;HS-SDME: headspace single-drop microextraction; UA-SFO-DLLME: ultrasound assisted -dispersive liquid-liquid microextraction based on solidification of organic drop ; IL-UA-LLME: ionic liquid based ultrasonic assisted liquid-liquid microextraction ; EAE-IL-DLLME: enzyme-assisted extraction and ionic liquid- based dispersive liquid-liquid Microextraction; ILAM-HS-SDME: ionic liquids assisted microwave distillation coupled with headspace single-drop microextraction; PLE-DLLME: pressurized liquid extraction and dispersive liquidïliquid microextraction; UA-RM-DLLME: ultrasound-assisted reverse micelles dispersive liquid-liquid microextraction; MA-DLLME: microwave assisted ï dispersive liquid-liquid microextraction; DMAE-SDME: dynamic microwave assisted extraction; MSA-SI-LLME: magnetic-stirring salt-induced liquid-liquid microextraction; UA-SI-LLME: ultrasound -assisted, salt-induced, liquid-liquid microextraction; MSA-DLLME: magnetic stirring assisted dispersive liquidïliquid microextraction; QuEChERS-IL-DLLME: QuEChERS-ionic liquid-dispersive liquid-liquid microextraction; AA-LLME: air assisted-liquid-liquid microextraction; UA-DE-LLME: ultrasonic assisted liquid-liquid microextraction method based on deep eutectic solvent; TAA-SFO-LLME: tandem air agitated liquid-liquid microextraction based on solidification of floating organic droplets; DI-SDME: directly-immersion - single-drop microextraction; IL-VA-LLME: ionic liquid based vortex assisted liquid-liquid microextraction; AA-SFO-LLME: air-agitated liquid-liquid microextraction with solidification of floating organic droplet; AA-DLLME: air assisted-dispersive liquid-liquid microextraction; εS-SHS-LLME: micropipette tip switchable hydrophilicity microextraction syringe system; in-syringe DSIL-DLLME: in-syringe dispersive liquidïliquid microextraction based on the direct solidification of ionic liquids; HFIP/Brij-35 SUPRAS-LLME: supramolecular solvent based on hexafluoroisopropanol-mediated Brij-35 for liquid microextraction; ISF-LLME: in situ solvent formation microextraction; IL: ionic liquid; PBD: PlackettïBurman design; CCD: central composite design; BBD: Box-Behnken design

Table 3. Fractional factorial 2^{6-2} design used in the illustrative example.

Std.[a]	Run[b]	Factors (*k*)						Responses			
		A: ACN volume[c]	B: MeOH volume[c]	C: IPA volume[c]	D: ACE volume[c]	E: water volume[c]	F: $ZnSO_4$ [d]	Area 1	Area 2	Area 3	Purity of response 1
1	6	500	500	500	500	500	100	13679.5	1572.9	4132.1	0.994
2	9	1000	500	500	500	1000	100	15076.2	3209.2	7338.8	0.946
3	7	500	1000	500	500	1000	500	6517.3	809.8	3213.9	0.907
4	1	1000	1000	500	500	500	500	2790.3	641.5	2893.5	0.860
5	5	500	500	1000	500	1000	500	9196.6	1705.5	3366.6	0.977
6	8	1000	500	1000	500	500	500	7970.3	1556	4566.4	0.965
7	12	500	1000	1000	500	500	100	3004.4	762.2	3277.0	0.922
8	4	1000	1000	1000	500	1000	100	12569.7	2712.8	5809.1	0.937
9	11	500	500	500	1000	500	500	8072.1	1078.3	2493.0	0.839
10	16	1000	500	500	1000	1000	500	12757.2	1428.3	4268.8	0.830
11	3	500	1000	500	1000	1000	100	10503.2	2117.8	7624	0.953
12	2	1000	1000	500	1000	500	100	7028.6	907.9	4327.3	0.999
13	15	500	500	1000	1000	1000	100	10753.1	2197.7	7456.8	0.789
14	10	1000	500	1000	1000	500	100	12159.3	1531.0	5053.1	0.816
15	13	500	1000	1000	1000	500	500	11012.2	1649.2	4920.1	0.840
16	14	1000	1000	1000	1000	1000	500	7774.0	902.9	3921.6	0.731

[a]Std. refers to the standard order in the design.
[b]Run refers to the experiment order.
[c]ACN: acetonitrile, MeOH: methanol, IPA: isopropanol, ACE: acetone and water in εL.
[d]$ZnSO_4$ in mg.

Table 4. Central composite design for AA-DLLME-SFO used in the illustrative example.

Std[a]	Run[b]	Factors (*k*)					Responses		
		A: ACN volume[c]	B: MeOH volume[c]	C: ACE volume[c]	D: water volume[c]	$ZnSO_4$[d]	Area 1	Area 2	Area 3
1	24	1000	1000	500	1000	150	3790.3	664.4	2730.8
2	6	1000	500	1000	1000	150	3938.8	667.0	1121.6
3	18	500	1000	1000	500	300	3932.8	412.9	2248.2
4	2	1000	1000	1000	500	150	5032.0	480.3	2042.7
5	7	1000	1000	500	500	300	4123.7	398.0	1419.6
6	9	1000	500	500	1000	300	3637.1	503.6	635.7
7	19	500	500	1000	1000	300	4253.0	511.6	1062.0
8	11	500	1000	500	1000	300	4414.2	506.1	861.3
9	15	1000	500	1000	500	300	4025.0	400.2	1856
10	23	500	1000	1000	1000	150	3451.6	570.0	1571.5
11	8	500	500	500	500	150	4881.9	450.0	1388.5
12	12	295	750	750	750	225	4101.8	430.1	1322.8
13	22	1205	750	750	750	225	4302.5	563.1	1333.4
14	13	750	295	750	750	225	4970.7	556.9	1633.3
15	16	750	1205	750	750	225	4134.6	485.5	1313.2
16	17	750	750	295	750	225	4134.6	485.5	1313.2
17	5	750	750	1205	750	225	4453.0	572.0	2144.6
18	20	750	750	750	295	225	4770.9	412.8	1752.1
19	1	750	750	750	1205	225	3461.5	583.2	1326.7
20	10	750	750	750	750	88	04738	755.1	1839.8
21	14	750	750	750	750	360	4529.9	402.9	987.4
22	21	750	750	750	750	225	4302.5	563.1	1333.4
23	4	750	750	750	750	225	4823.3	692.5	475.0
24	3	750	750	750	750	225	3552.9	485.9	1230.1

[a]Std refers to the standard order in the design.
[b]Run refers to the experiment order.
[c]ACN: acetonitrile, MeOH: methanol, ACE: acetone and water in εL.
[d]$ZnSO_4$ in mg.

Table 5. Lattice-mixture design for DLLME used in the illustrative example.

Std[a]	Run[b]	Factors (*k*)			Responses								
		A: % MeOH	B: % Buffer[c]	C: % ACN	Area 1	Area 2	Area 3	Area 4	Area 5	Area 6	Width response 2	Width response 3	Width response 1
1	11	1.00	0.000	0.000	512.3	186.6	1375.1	373.0	426.2	1485.0	0.271	0.230	0.302
2	2	0.500	0.500	0.000	918.7	309.6	1645.6	449.1	137.2	203.9	0.245	0.122	0.211
3	9	0.500	0.000	0.500	198.6	52.1	941.0	335.3	449.5	1563.4	0.340	0.217	0.377
4	12	0.000	1.000	0.000	989.1	269.0	1494.2	478.6	82.2	10.4	0.209	0.122	0.149
5	4	0.000	0.500	0.500	382.0	152.7	989.2	488.1	205.8	1108.1	0.332	0.242	0.293
6	7	0.000	0.000	1.000	165.4	4.0	305.9	195.6	59.9	1371.1	0.250	0.238	0.291
7	3	0.667	0.167	0.167	503.4	204.7	1192.9	467.1	338.7	1178.4	0.265	0.187	0.345
8	1	0.167	0.667	0.167	1090.2	311.3	2111.0	509.6	347.5	396.2	0.266	0.219	0.297
9	10	0.167	0.167	0.667	220.2	106.4	611.9	535.3	364.5	1127.0	0.304	0.234	0.258
10	13	0.333	0.333	0.333	408.2	231.2	1782.2	508.4	369.6	980.4	0.355	0.132	0.415
11	8	1.000	0.000	0.000	457.2	165.4	984.2	319.1	378.8	1409.9	0.308	0.234	0.301
12	6	0.000	1.000	0.000	849.3	228.6	1399.2	430.4	78.9	12.0	0.224	0.115	0.147
13	5	0.000	0.000	1.000	133.9	1.8	221.9	273.4	321.2	1245.6	0.241	0.251	0.289
14	14	0.500	0.500	0.000	818.1	225.1	1427.4	419.4	102.4	81.8	0.240	0.222	0.360

[a]Std refers to the standard order in the design.
[b]Run refers to the experiment order.
[c]Buffer phosphate 10 mmol L^{11} pH = 3.50

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: