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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 "there 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 population". 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

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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 "one variable at time" (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, "microextraction" 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 "Procedure" describes the basis of each microextraction, while the column "Option" 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 10–100 µL 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 µL) 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 "solvent-free" 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 "Natural Deed Eutectic Solvents" (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

unattended operation. Liu and Dasgupta [31] developed the first automated drop-based system in 1995, triggering the generation of numerous automation procedure reports. Several automation procedures based on microextraction with systems using continuous-flow (CFME) [32], syringe pump or chip device were reported. The wide variety of automation and devices can be consulted in the scientific literature [33, 34].

3. Response surface methodology

The well-known response surface methodology (RSM), based on the application of multivariate design of experiments (DOE) followed by optimization through mathematical modeling, plays an important role in sample pretreatment applications. Probably, it is due to the fact that the implementation requires fewer efforts and resources than those involved in univariate procedures, consuming less time to accomplish the same goal [10].

The application of RSM comprises the following consecutive steps: a) identification of the responses (for example, recovery percentage in the extraction of a substance), b) building the screening design to reduce the number of factors originally suspected of having influence in the response, c) building the response surface design and modeling to establish the relationship between one response (or several) and the factors, and d) application of multiple response optimization in those cases in which a large number of responses are involved in the study [35]. Hereafter, a brief description of each step will be presented.

3.1. Responses

In the field of sample pretreatment, and especially in extraction and preconcentration steps, the enhancement of the percent recovery of a substance is one of the main objectives. Since the expected situation is the complete migration of the analyte present in the sample to the final solution where the analysis will be carried out, this response should be maximized,

i.e. the combination of the factors which produces a maximum recovery must be found. On the other hand, the response related to the precision of the technique, evaluated by replicating the procedure and computing, for example, the coefficient of variation, should be minimized.

3.2. Screening designs

The screening step consists in the exploration of the factors (or variables) which could have an influence on the extraction process. In the beginning, a large number of factors are taken into account to perform experiments (following a screening design) and statistical analysis of the data (usually employing ANOVA) to finally decide which of them have a significant influence on the response (or responses).

Factors can be divided into quantitative (temperature, time, volume, etc.), qualitative (kind of agitation, material, etc.) and mixture-related (a mixture of solvents considering differences in the polarity of the analytes).

Mostly, screening designs involve factor variations in two levels (–1, +1), being the range the widest interval in which the factor can be varied in the system under study. This range is usually chosen based on the literature information or previous analyst knowledge. The most popular designs are full factorial, fractional factorial, Plackett–Burman (PBD) and Taguchi designs (TD). As mentioned, they consider two levels for each factor (k). The factorial fractional design is the most used and allows the evaluation of a large number of factors in a small number of experiments by fractioning a full factorial 2^k design in a 2^{k-p} design, being p the number chosen to fractionate the design. As an example, if eight factors should be studied, a fractional factorial design with $2^{8-3} = 32$ experiments is a better option against the 256 experiments required for a 2^8 full factorial design. On the other hand, PBD and TD are highly fractioned designs that permit studying a large number of factors through a reduced number of experiments, but with the drawback that the main effects are confounded

with double interactions, and, consequently, their application should be extremely careful [35].

3.3. Optimization designs

Several designs are available to model a second order response surface. Generally, the election of the design is related to different goals such as performing a reduced number of experiments, excluding zones from the experimental region, reaching high quality adjusted parameters, etc. The designs mostly reported in the literature are full factorial, central composite (CCD), Box-Behnken (BBD) and mixture simplex centroid designs, which will be briefly discussed below.

The full factorial design is an extension of the full factorial 2^k presented for screening designs. In this case, the number of experiments is equal to 3^k. In the case of three factors (k=3), 27 experiments are required, although replication of the central points is recommended to evaluate a lack of fit. Figure 3-A shows a 3^2 full factorial design with 9 experiments.

The central composite design is among the most popular options, built with two-level (−1 and +1) factorial design points, axial or star points and center points (with all factors set to 0). All factors in the star points are set to 0, except for one factor with the value $\pm \alpha$; a number that determines the location and usually varies from 1 to $\sqrt{k}$. Figure 3-B shows the experimental points of a CCD with two factors (x_1 and x_2). The number of experiments (equal to 9) results from the equation (2^k+2k+*central points*). For three factors (k=3) and one central point, at least fifteen experiments are required, plus several replicated points.

The number of experiments for a Box-Behnken design is computed as [2k(k–1)+*central points*]. For three factors (k=3) and one central point design, at least 13 experiments are required. As can be appreciated, this design requires less (or equal) amount

of experiments than the two designs previously presented (see Fig. 3-C). Another fact is that this design can only be implemented for 3 or more factors.

The mixture simplex centroid design is built in those cases in which the analyzed factors are the components of a mixture, i.e. their levels are not independent of one another, allowing the study of the effect of the ratio variations among the factors. The domain is a regular figure having as many vertices as components, in a space with dimensionality equal to the number of components minus one [10]. Figure 3-D displays the graphical representation of a mixture design with three components. As can be seen, the design is an equilateral triangle whose vertices correspond to combinations containing 100 percent of a single component, each of the three sides represents a binary mixture and the internal points correspond to ternary mixtures. These designs are usually augmented with additional points in the interior of the experimental region. It should be noted that the models (known as Scheffé polynomials) used in mixture designs differ from the polynomials used in response surface for independent variables.

3.4. Modeling

3.4.1. Least squares fitting (LS)

3.4.1.1. Modeling of screening design data

The general approach to conduct screening designs to perform factor selection consists in analyzing signs and magnitudes of factors by building a preliminary model for the response, performing statistical tests, refining the model (removing any non-significant factor from the initial model), and analyzing residuals to check model adequacy and assumptions. The effect of a factor on a response is calculated as the difference between the average response of the experiments with positive signs and the average response of the experiments with negative signs (in a codified design). The coefficients of the estimated model are related

to the later value. The response (y) in a screening experiment for two factors (x_1 and x_2) can be described by the following linear with interaction regression model:

$$y = b_0 + b_1\,x_1 + b_2\,x_2 + b_{1\text{-}2}\,x_1\,x_2 + e \tag{1}$$

where b_0 is the overall mean effect, b_1 and b_2 represent the effects of the factors x_1 and x_2, $b_{1\text{-}2}$ is the effect of the interaction between both factors, and e is a random error component, which represents other sources of variability not accounted for in the model.

Several graphical tools can be employed to assess the significance of the effects, in order to decide which of them should be included or excluded in the final model: a) normal and half-normal probability plots, in which it is considered that the negligible effects are normally distributed and tend to fall along a straight line on this plot, and b) the Pareto chart, where factor values are represented in descending order by bars, indicating if they are significant or not by a threshold established through a statistical test. However, the factors selected from the graph analysis should be examined by ANOVA, a statistical test used to assess the differences between group means and their associated procedures, such as variation among and between groups.

3.4.1.2. Data modeling of RSM designs by LS

For RSM modeling, a mathematical model can be built for each response fitting a second (or higher) order polynomial function, using the data collected during the optimization stage. The response (y) in an RSM experiment for two factors (x_1 and x_2) can be described by the following regression model:

$$y = b_0 + b_1\,x_1 + b_2\,x_2 + b_{1\text{-}2}\,x_1\,x_2 + b_{1\text{-}1}\,x_1^2 + b_{2\text{-}2}\,x_2^2 + e \tag{2}$$

where b_0, b_1, b_2, b_{1-2} and *e* are similar to Eq. 1, and b_{1-1} and b_{2-2} correspond to the quadratic terms. The significance of the coefficients is investigated through ANOVA, ascommented before for the screening step.

The fitted model must properly describe the data relationship to make accurate predictions inside the experimental region. For the optimization of two factors, the response can be represented as a solid surface in a three-dimensional space. For more than two factors, the graphical representation is made for two of them, maintaining the others at constant values. Another option is to use a contour plot representation, which consists of lines of constant response, corresponding to a specific height of the response surface.

As previously mentioned for the case of fitting linear models, an ANOVA test should be applied to determine the significance of the second order model. The latter can be considered satisfactory when the regression is significant, and a non-significant lack of fit is obtained for the selected confidence level (α=0.05). Nevertheless, a significant model does not necessarily mean that the variation in the data is correctly explained. Also, the analysis of the residual plots is mandatory, as well as both the coefficient of determination (R^2) and the adjusted coefficient of determination (R_{adj}^2) evaluations, which represent the percentage of variance explained by the model. The normal probability plot indicates that the residuals follow a normal distribution, one of the basic assumptions for the validity of ANOVA. The homogeneity of the variance (another ANOVA assumption) can be evaluated by the plot of residuals versus the ascending predicted response values.

In those cases in which lack of normality or heterocedasticity in residuals is detected, the use of non-parametric methods, as artificial neural networks (ANN), or the analysis of a transformed response is suggested [35].

3.4.1.3. Data modeling of RSM designs by artificial neural networks (ANNs)

ANNs allow modeling non-linear relationships among factors and responses, mimicking the human brain. The well-known multilayer feed-forward networks [36] or multi-layer perceptron (MLP) networks are commonly used for prediction, classification and optimization purposes. In these cases, the typical architecture consists of three layers of neurons or nodes (the basic computing units). The input layer has a number of active neurons equal to the number of factors being investigated. The hidden layer has a variable number of active neurons that should be optimized. The output layer has a unit for each response. These neurons are linked hierarchically: the outputs of one layer of neurons are used as inputs for the next layer and so on. The hidden layer commonly uses a sigmoid function in its nodes. On the other hand, linear functions are generally used both in the input and output layers. The number of hidden layers and the neurons in each of them must be optimized to achieve the satisfactory fitting ability of the network, associated with a satisfactory predictive ability.

It is important to stress that the main difference between modeling by LS regression or ANNs is that for the latter there is no need to know the exact form of the function on which the model should be built. Additionally, neither the functional type nor the number of model parameters needs to be given.

Another popular ANN is based on the use of radial basis functions (RBF) [37]. These networks have a single hidden layer of neurons incorporating Gaussian transfer functions, and a linearly activated output layer. In comparison with MLP networks, RBF offers some advantages such as robustness towards noisy data, as well as a faster training phase.

3.5. Multiple response optimization by means of the desirability function

Frequently, the optimization procedure involves several responses, i.e. the attainment of acceptable conditions for many analytes and good performance in terms of time or solvent

consumption [38]. In addition, the optimization criteria are often contradictory to each other. Thus, the overall solution must be included in an optimal region, leading to a compromise solution. Among the several approaches that have been presented for solving multiple response optimizations [39], the desirability function [40], which is the most popular tool, will be discussed.

After being presented by Derringer and Suich in 1980, the desirability function has been used extensively in several applications in a wide variety of disciplines [40]. It is based on the idea that the quality of a product (or process) having several outputs is unacceptable if one of them lies outside of a desirable limit. Under the later consideration, the function searches operating conditions to ensure agreement with the criteria of all the responses and, at the same time, to provide the best compromise value for all of them.

The first step is to compute an individual desirability function $d_i(\hat{y}_i)$ for each response $\hat{y}_i(x)$ using previously fitted models (by LS or ANN) [35]. The optimization criteria can be maximization, minimization, reaching a target value or a range of values. For that, different functions should be built, depending on the criteria adopted. The desirability figures vary within an acceptable range of response values established by [Ui (upper acceptable value)–Li (lower acceptable value)]. For maximization purposes, which is the case in which the recovery of a substance is studied, $d_i(\hat{y}_i)$ is described by the following equation:

$$d_i\left(\hat{y}_i(x)\right) = \begin{bmatrix} 0 & \text{if } \hat{y}_i(x) < L_i \\ \left(\dfrac{\hat{y}_i(x) - L_i}{U_i - L_i}\right)^{\text{s}} & \text{if } Li \leq \hat{y}_i(x) \leq Ui \\ 1 & \text{if } \hat{y}_i(x) > Ui \end{bmatrix} \qquad (3)$$

where s is a weight establishing the importance of the closeness of $\hat{y}_i$ to the maximum.

According to Eq. (3), the individual desirability takes values between 0 and 1. If

$d_i(\hat{y}_i)=0$, the response is undesirable. On the contrary, if $d_i(\hat{y}_i)=1$, the response is completely desirable (ideal value). Interestingly, intermediate values of $d_i(\hat{y}_i)$ indicate more or less desirable responses and can be accepted. It is important to remark that factor levels might also be included in the optimization procedure; for example, the use of a lower amount of certain solvent could be allowed.

Finally, once desirability functions are computed for each response (and factors if it is required), they are combined in a global desirability function (D), which allows to find out the best combined responses, through the following equation:

$$D = (d_1^{r_1} \, x \, d_2^{r_2} \, x .....x \, d_n^{r_n})^{\frac{1}{\sum r_i}} = \left(\prod_{i=1}^{n} d_i^{r_i} \right)^{\frac{1}{\sum r_i}} \qquad (4)$$

where r_i is the importance of each response (or factor) relative to the others, i.e. it allows to indicate if one or more responses should be more carefully taken into account than others.

The analysis of Eq. 4, which consists in a cumulative product, evidences that if D reaches a value different from zero, all the responses can be considered to have a desirable value. Whereas, if $d_i(\hat{y}_i) = 0$, D will be zero, thus, at least one of the responses is completely undesirable. It is important to consider that the goal of an optimization procedure is to find a good set of conditions to fulfill all the requirements, but not to get a D value equal to 1.

Let us consider the following example: a LPME procedure is being implemented for five analytes (A, B, C, D and E) whose experimental recoveries (%) obtained once the experiments (suggested by an experimental design) were carried out, vary inside the following ranges: (A), 50-90; (B), 30-60; (C), 80-100; (D), 50-80; and (E), 60-90. The goal is to obtain the best compromise values for the five analytes, but focalizing in analyte B, because it is expected maximize it recovery without affecting the others. Thus, the following

lower and upper values for the five analytes can be defined: (A), 80-90; (B), 55-60; (C), 90-100; (D), 70-80; and (E), 80-90. The question is: is it possible to obtain a combination of the factors that satisfies these conditions? The answer would be obtained after computing the individual desirabilities by applying Eq. 3, in the whole experimental space, using the models fitted for every response (the percent recovery for each analyte). The final step is to calculate the global desirability using Eq. 4. If the results show any region in which D is different from zero, any combination of the factors in that region satisfies the objective. Real examples showing the application of these concepts will be presented and discussed in Section 5.

3.6. Software

Several programs are available for implementation of DOE and optimization. All of them allow the utilization of different tools for screening assays and RSM. Among the most used, the following can be mentioned: Design Expert (http://www.statease.com/), Minitab (http://www.minitab.com/), SPSS (www.ibm.com/analytics/us/en/technology/spss/), JMP (https://www.jmp.com/), R: The R Project for Statistical Computing (https://www.r-project.org/), Six Sigma (https://www.isixsigma.com/six-sigma-software/), Unscrumbler (http://www.camo.com/), NCSS (http://www.ncss.com/), Cornerstone (www.camline.com/) and SAS (https://support.sas.com/rnd/app/qc/qc/qcdesign.html).

Very recently, an interesting graphical interface for the application of ANN in the domain of experimental design and optimization has been presented. It is a graphical user interface for multiple surface response optimization based on radial basis functions, a kind of ANN, which has been shown to furnish good results in optimization issues [41]. The codes, manual and examples are freely available at http://www.iquir-conicet.gov.ar/descargas/opt_rbf.rar.

4. Literature search

The works reported from 2009 to 2019 based on the implementation of microextraction supported by DOE and optimization are summarized in Table 2 (A and B). This table displays information about the different procedures and options carried out for microextraction, as well as the application of screening steps and optimization of factors for the determination of an analyte or a group of analytes in complex samples. Figure 4 shows the distribution of the microextraction techniques reported in the articles reviewed in this study. As can be appreciated, DLLME was the mostly applied procedure (72%), while SDME and LLME were almost implemented with the same frequency (13 and 15%, respectively).

5. Illustrative literature example

During the development of a microextraction process, several steps should be optimized preferentially using chemometric tools. In this section, an example will be described to illustrate the steps, the variables and the type of design that can be used during the development of a new analytical method requiring a preconcentration stage. It consists in the development of a microextraction method for the determination of six veterinary drugs in eggs by high performance liquid chromatography carried out in our laboratory [42].

Firstly, the extraction process should be defined. In this work, two pretreatment procedures were studied: (A) air assisted-dispersive liquid-liquid microextraction based on solidification of organic drop (AA-SFO-DLLME), and (B) dispersive liquid-liquid microextraction (DLLME).

Secondly, the factors and responses to be analyzed must be established. In this case, for the AA-SFO-DLLME procedure, the critical step was the obtainment of the analyte in solution, thus, the following factors were analyzed: volume of acetonitrile (A), methanol (B), isopropanol (C), acetone (D), water (E), and amount of salt (F). In order to figure out the

significance of the studied factors, and due to their high number, a fractional factorial (2^{6-2})

design was constructed for screening (see *Section 3.2*). The evaluated responses were: area of

chloramphenicol (CAP, R1), area of nicarbazin (DNC, R2), area of albendazole (ABZ, R3),

and purity of CAP (R4) (see details in Ref. 23). Table 3 shows the combination of factors and

the responses obtained after carrying out the experiments.

The following step includes the analysis of the significance of each factor and their

influence (negative or positive). This can be done using the Pareto chart, which allows

defining the significance by graphical inspection, and by application of the well-known

statistical Bonferroni limit test. Figure 5 shows the Pareto chart analyzed in this work

corresponding to the investigation of the factors affecting response number 3 (see above). As

can be seen, the factor F (amount of $ZnSO_4$) overcomes the boundary and can be labeled as a

highly significant factor in the system for R3. Moreover, the factor E (volume of water) and

the interaction AD (volumes of acetonitrile and acetone) have influence because they have an

effect value located between the *t* and the Bonferroni limit values, and should be considered

in the optimization step.

The analysis described above was repeated for each of the studied responses. Then,

with the gathered information, the factors that influence the system could be defined, i.e.

volumes of acetonitrile, methanol, acetone and water, and amount of salt.

The following step involves the optimization, which includes building a design

considering the selected factors and using the desirability function to obtain the combination

that satisfies the requirements for the four responses simultaneously. In this work, a quarter-

fractional central composite design with 24 experiments and five central points was

constructed to analyze the five factors defined in the previous study: volume of acetonitrile

(A), methanol (B), acetone (C), water (D), and amount of $ZnSO_4$ (E). Table 4 summarizes the

combination of the factors and the responses obtained after carrying out the experiments. In

this case, three responses (areas of CAP, ABZ and DNC) were analyzed, and the best fit of the model was quadratic, linear and linear with interaction for the CAP, ABZ and DNC areas, respectively. The criterion followed to simultaneously optimize the three responses was maximization, giving more importance to the one with the smallest recovery (ABZ). Finally, using the desirability function, the combination of the factors that allows the best extraction conditions was defined.

During the optimization step, the response surface plots become an important tool to analyze the results. Figure 6 shows the response surface plot for the global desirability function corresponding to the AA-DLLME-SFO procedure as a function of two factors: volume of acetonitrile (A) and water (D), while maintaining the other three factors at their optimum values. Under the optimization criterion, the experimental conditions corresponding to a maximum in the desirability function ($D = 1.00$) were: 1140 μL of water, 125 mg of ZnSO$_4$, 1175 μL of ACN, 1200 μL MeOH and 740 μL of ACE, using 1.00 g of homogenized egg and 50 μL of 1-dodecanol as extractive solvent. With this combination of factors, the prediction areas were: 5064 for CAP, 828 for ABZ and 4344 for DNC.

On the other hand, in the second studied procedure (DLLME), which includes a step of evaporation and re-suspension, the use of a mixture design allowed obtaining the best combination of solvents-aqueous solution for the extraction. In this work, a *lattice* mixture design was built to study the best proportion of the following factors: volume of methanol (A), acetonitrile (B) and buffer phosphate 10 mmol L^{-1} pH = 3.50 (C). Nine responses were simultaneously optimized (area of trimethoprim, oxitetracycline, enrofloxacin, CAP, ABZ and DNC, and peak width of oxitetracycline, CAP and trimethoprim), being the criterion for the optimization their individual maximization.

Table 5 shows the combination of the solvents and the responses obtained after the execution of the experiments. As in the case of the previous optimization, the use of the

response surface plot can help establish the system. Figure 7 shows the contour plot of the response surface for the global desirability function corresponding to the *lattice* mixture design for the optimization of the DLLME procedure.

Under the optimization criterion, the mixture corresponding to a maximum in the desirability function ($D = 0.683$) was ACN and sodium phosphate buffer 10 mmol L^{-1} pH = 3.50, whose proportion was 30 and 70 v/v, respectively. With this combination, the predicted areas were 570 for trimethoprim (TMP), 205 for oxitetracycline (OTC), 1299 for enrofloxacin (ENR), 562 for CAP, 449 for ABZ and 781 for DNC, and the predicted widths 0.300 for OTC, 0.128 for CAP and 0.278 for TMP.

As can be appreciated in Fig. 7, the blue parts correspond to $D = 0$, i.e. totally prohibited values because they do not satisfy the a priori established conditions (optimization criterion). Therefore, the experimenter should select any other combination, with a D value different from zero, located, in this case, in the green zone.

6. Conclusions

Liquid phase microextraction is a novel miniaturized sample pretreatment method to attain trace determination of target compounds in complex matrices. It can be considered as an environmentally-friendly, simple, easy to operate, and highly sensitive process for preconcentration, which has been introduced to simplify the extraction methods. Interestingly, the analysis of the reported applications shows that LPME positively impacts on selectivity, sample cleanup and efficiency, while allowing the extraction of a wide variety of analytes in complex samples.

A literature search reveals that numerous applications of LPME assisted by RSM for optimization have been reported during the last ten years. These reports evidenced that the coupling of the sample pretreatment with statistical tools allowed researchers to improve the

overall process by doing a reduced number of experiments while obtaining more reliable results.

Consequently, it could be expected that an increase in the use of the chemometric tools herein presented would become beneficial for the development of analytical procedures for the determination of analytes in complex samples.

In the present review, the LPME procedure and its different types of implementation reported during the years 2009 to 2019 were presented. The main focus was the application for the extraction of analytes in complex samples, considering those cases in which the performance of the technique was optimized by RSM.

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Author Contribution Statement

Maira Carabajal: Resources, Methodology, Investigation

Carla Teglia: Resources, Methodology, Investigation

Soledad Cerutti: Resources, Methodology, Investigation

María J. Culzoni: Methodology, Writing - Review and Editing

Héctor Goicoechea: Project administration, Visualization

Figure Captions
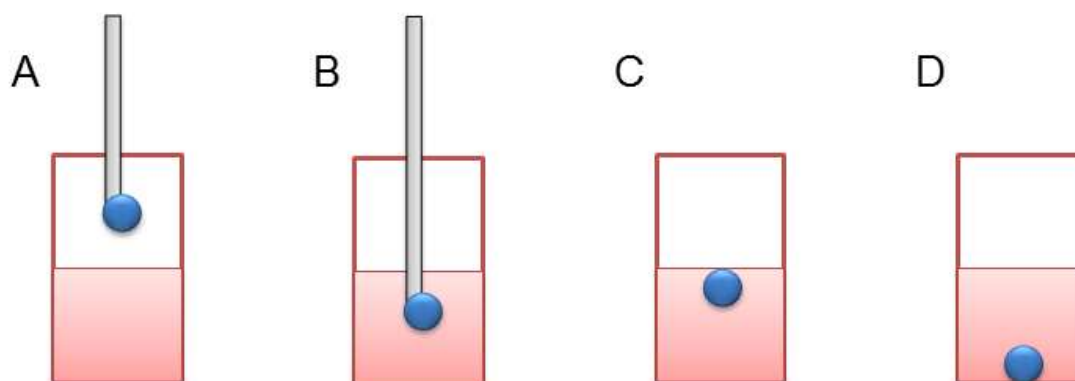
Figure 1. Schematic representation of the single-drop microextraction (SDME) variants: (A) headspace (HS-SDME), (B) directly-immersion (DI-SDME), (C) with low-density solvent and (D) with high-density solvent.
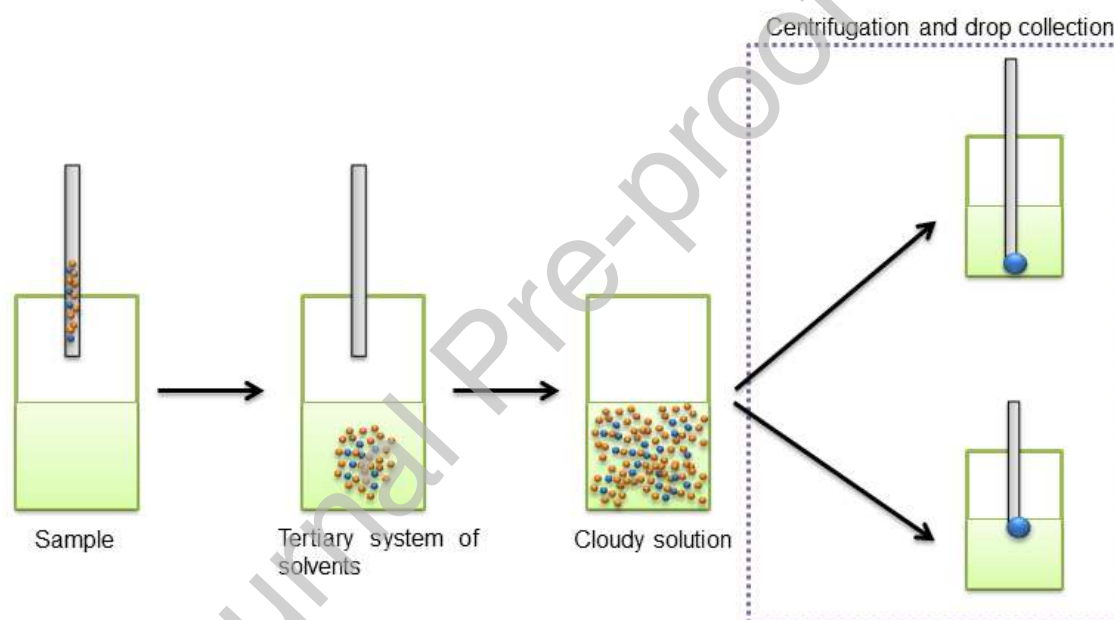
Figure 2. Schematic representation of dispersive liquid-liquid microextraction (DLLME) process. Orange: dispersant and blue: extractant.

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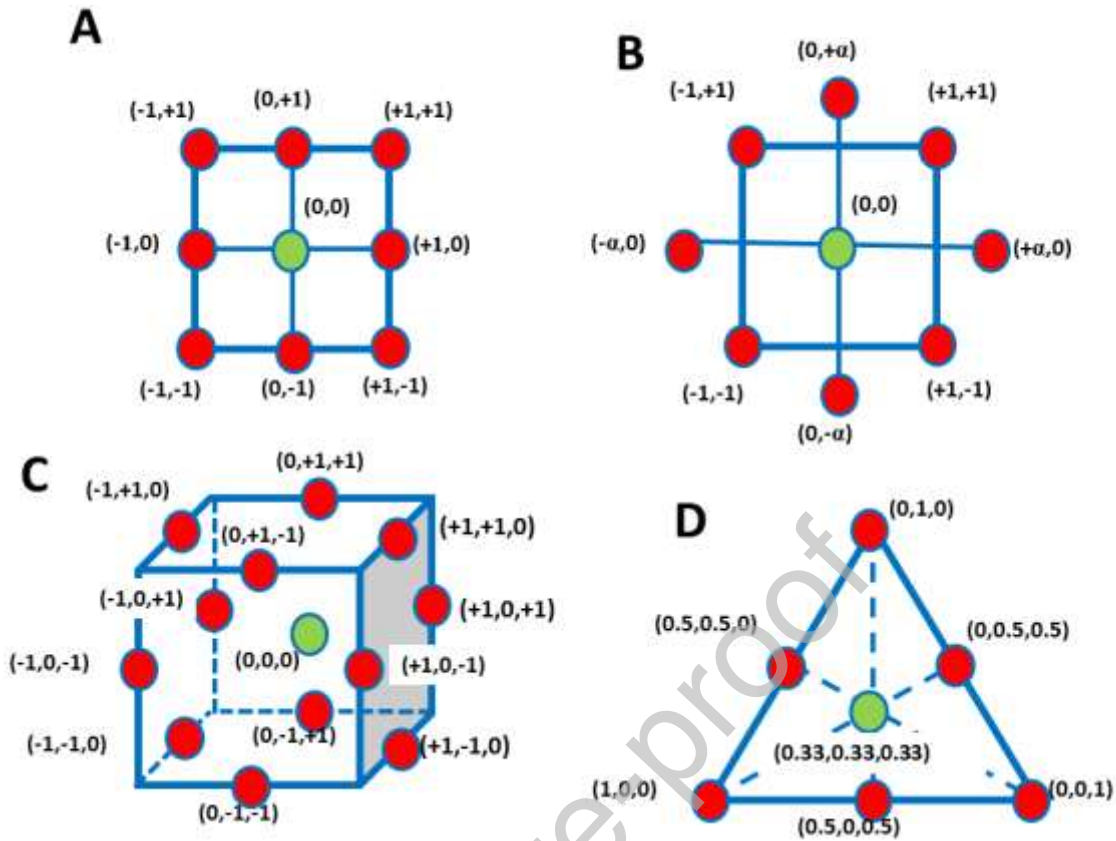
Figure 3. Schematic representation of: (A) a two factors full factorial design with ($2^3 = 9$) points, (B) a two factors central composite design with ($2^2 + 2 \times 2 + 1 = 9$) points, (C) a three factors Box-Behnken design with ($2 \times 3\ (3-1) + 1 = 13$) points, and (D) a three factors mixture simplex centroid design with 7 points.
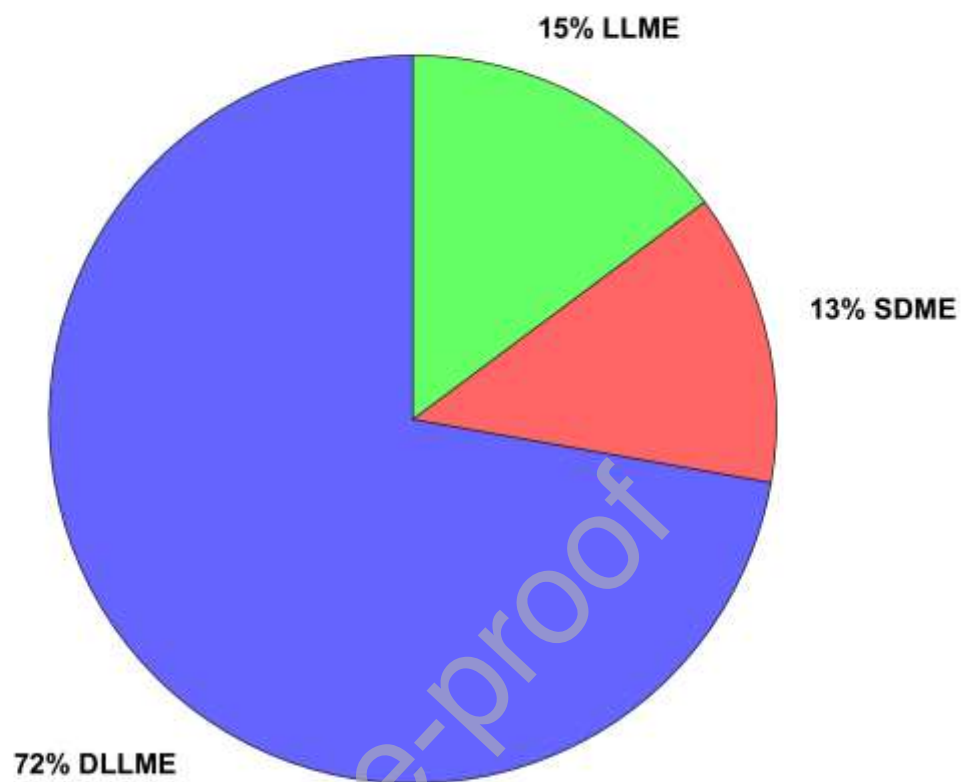
Figure 4. Percent distribution of microextraction applications of the articles cited in Table 2.
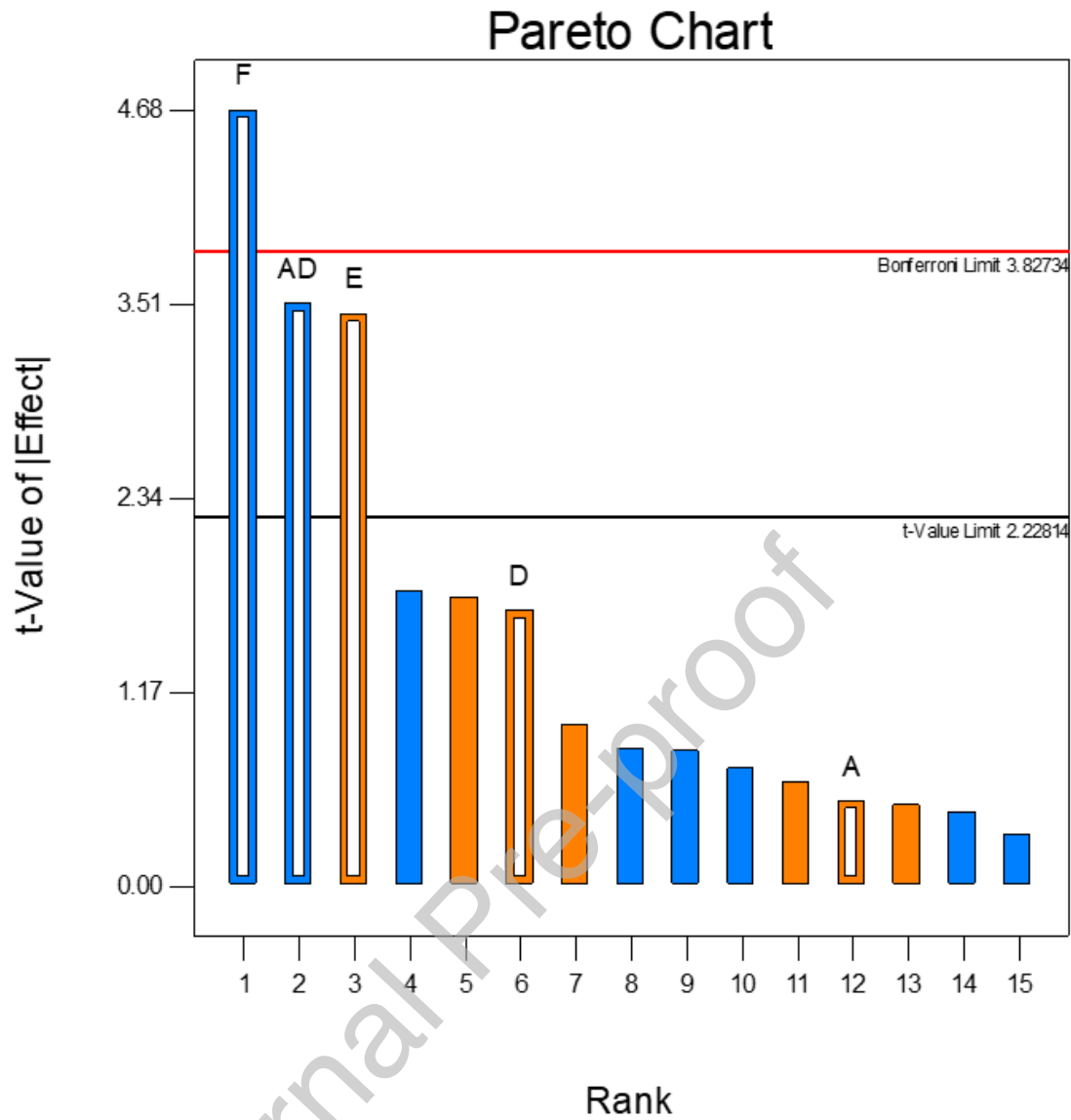
Figure 5. Pareto chart for analysis of factor effects when studying the response 3 by a fractional factorial 2^{6-2} design. For the model to be hierarchical, it is necessary to consider both factors A and D, since their interaction is significant [23].
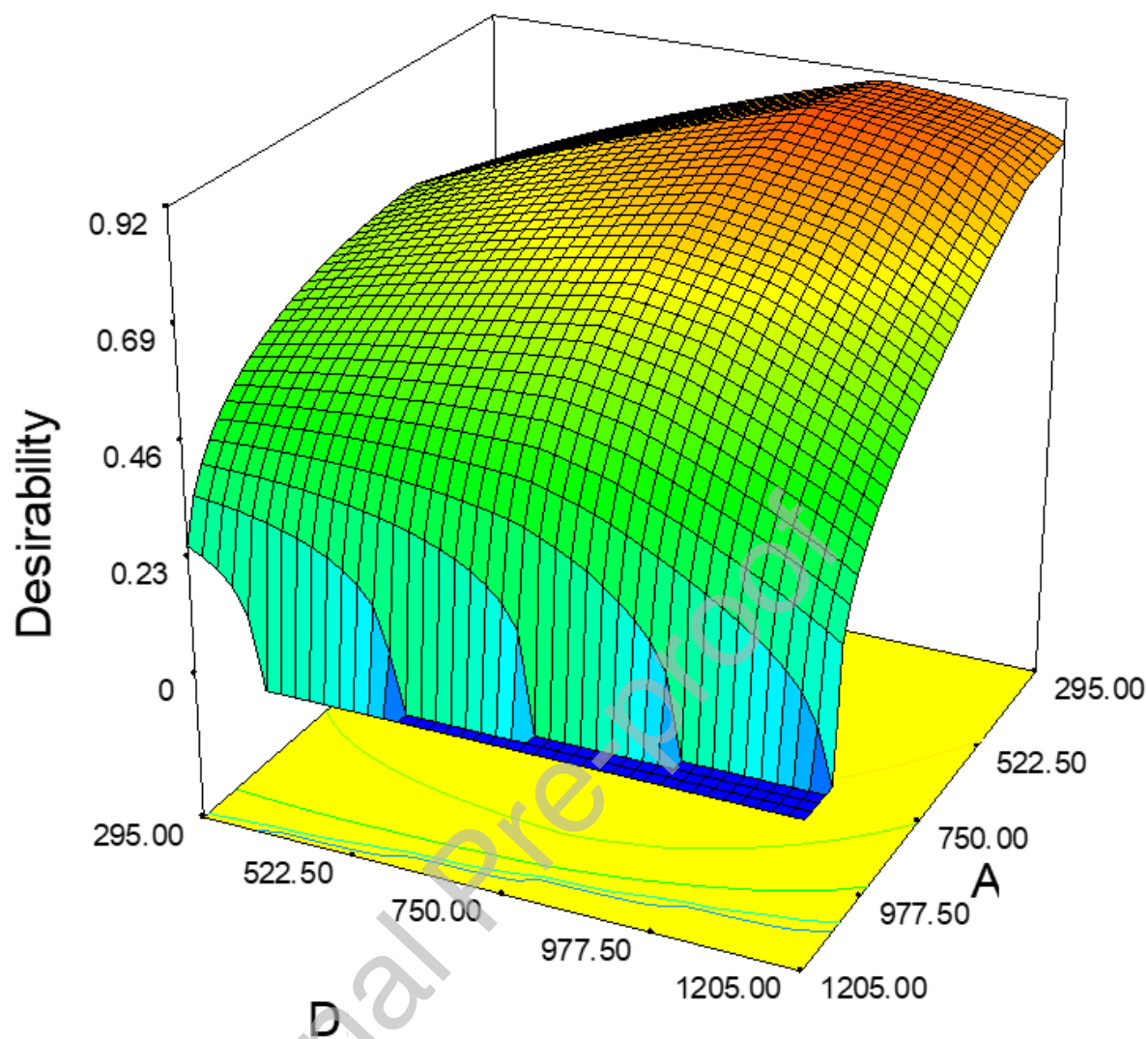
Figure 6. Response surface plot for the global desirability function corresponding to the AA-DLLME-SFO procedure as a function of two factors: volume of acetonitrile (A) and water (D). The other three factors are maintained at their optimum values.
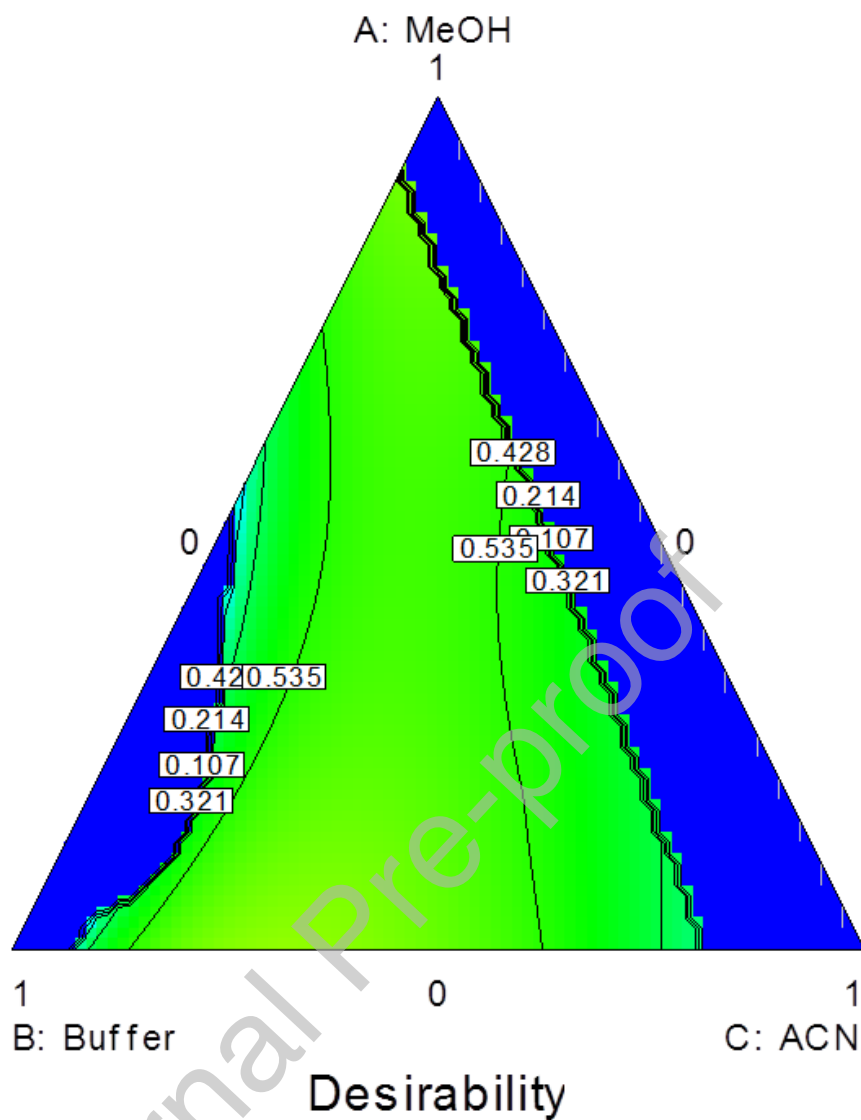
Figure 7. Contour plot of the response surface for the global desirability function corresponding to the *lattice* mixture design for the optimization of the DLLME procedure. (A) methanol, (B) buffer phosphate 10 mmol L^{-1} pH = 3.50, and (C) acetonitrile.

Table 1: Description of the different procedures and options, improvements and automation for microextraction. References correspond to the first time each procedure was presented.

Procedure	Option	Ref.
Liquid-liquid microextraction (LLME)		[43]
Single-drop microextraction (SDME)	Headspace (HS-SDME)	[44]
	Directly-immersion (DI-SDME)	[45]
	Drop to drop (DDME)	[13]
	Continuous-flow (CFME)	[32]
	Solidified floating organic (SFO-DLME)	[46]
Liquid-liquid-liquid microextraction (LLLME)		[47]
Dispersive liquid-liquid microextraction (DLLME)	Low-density solvent (LD-DLLME)	[48]
	High-density solvent (HD-DLLME)	[15]
	Solidified floating organic solvent (SFO-DLLME)	[46]
	Auxiliary solvent to adjust the density (AS-DLLME)	[49]
Hollow-fiber-protected microextraction (HFME)		[47]
Improvement		
UV-assisted (UV)		[50]
Vortex-assisted (VA)		[51]
Air-assisted (AA)		[52]

Ultrasound-assisted (UA)	[30]
Special extraction devices	[29, 53]
Magnetic stirring-assisted	[54]
Microwave-assisted	[55, 56]
Use of ionic liquids (IL)	[19]
Use of deep eutectic solvents (DES)	[57]
Automation	
Continuous-flow (CF)	[32]
Automated drop-based system	[31]
Sequential injection (SI-DLLME)	[58]
Automated dynamic in-syringe	[59]

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 – variables	Optimization step – variables	Analytes	Instrumental analysis	Sample	Ref.
2012	ISF-LLME	Full factorial design – reagent concentration, amount of IL, amount of ion-pairing agent and salt concentration.	CCD – reagent concentration and amount of IL.	Ni (II)	FAAS	Lettuce	[60]
	TIL-DLLME	PBD – IL volume, concentration of complexing agent, pH, incubation time and temperature.	CCD – IL amount, pH and temperature.	Pb(II)	FAAS	Blood	[61]
2015	UA-IL-DLLME	–	Full factorial design – 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 – $NaClO_4$ concentration, acetonitrile volume, agitation time, MIL volume and sample volume.	–	As (III)	ETAAS	Honey	[63]
	μS-SHS-LLME	DPB – volume of SHS, pH, volume of Na_2CO_3 and volume of H_2SO_4.	CCD – 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 – variables	Optimization step – variables	Analytes	Instrumental analysis	Sample	Ref.
2009	IL-DLLME	–	CCD – sample pH, NaCl percentage, IL amount and volume of disperser solvent.	Eight pesticides	HPLC-DAD	Banana	[65]
	DLLME	–	CCD – extraction temperature, sample weight, acetonitrile volume, extraction time, and CCl₄ volume.	Two antioxidants, (Irganox 1010 and Irgafos 168)	LC-DAD	Polymer	[66]
	HD-HS-SDME	–	CCD – 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 – sample volume, extracting agent volume, sample pH, ionic strength, cavitation time and centrifugation time.	CCD – 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 – extraction solvent volume, salt effect, extraction time and centrifugation time.	BBD – extraction solvent volume, salt effect and extraction time.	Six phthalate esters	HPLC-DAD	Shampoo, after shave gel and hair spray samples	[69]
	DLLME	–	CCD – 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	–	CCD – 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 – sample volume, solvent volume, extraction temperature, extraction time, centrifugation speed and time.	CCD – sample volume and solvent volume.	Geosmin and 2 – methylisoborneol	GC-MS	Water and wine (red, rose and white)	[71]
	RP-DLLME	–	CCD – disperser volume, extraction solvent volume, pH of the aqueous	Hydroxytyrosol and tyrosol	HPLC-UV	Virgin olive oil	[72]

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

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	DLLME	–	TD – 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	–	CCD –disperser solvent volume, extraction solvent volume, salt amount and sample pH.	Benzoate and sorbate salts	HPLC-UV	Yogurt	[81]
	EAE-IL-DLLME	–	CCD – pH, volume of extraction solvent, volume of disperser solvent and ionic strength.	Patulin	HPLC-UV	Apple juice	[82]
	UA-DLLME	–	CCD – temperature, sonication time, volume of preconcentration solvent and salt concentration.	Volatile components	GC-MS	Tea plants	[83]
	HS-SDME	–	CCD – weight salt, extraction time, extraction temperature and stirring rate.	Six furanic compounds	GC-MS	Coffee	[84]
	ILAM-HS-SDME	–	BBD – 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	–	CCD – volume and ratio of disperser and extracting solvents	Eighteen phenolic compounds	LC-DAD-MS	Virgin olive oil	[86]
	PLE-DLLME	–	TD – CCl_4 volume, aqueous phase volume, acetonitrile volume, NaCl concentration and centrifugation time.	Tocopherols, tocotrienols and tocopherol acetate	Capillary LC-DAD	Cosmetic products	[87]
2014	PLE-DLLME	–	TD – 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	–	BBD –surfactant and modifier volume, sonication and centrifugation time.	Acetoin	HPLC-UV	Butter	[89]
2015							

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	Method	Screening DOE	Optimization DOE	Analytes	Analytical technique	Matrix	Ref.
	DMAE-SDME	–	BBD – microwave power, extraction time and extraction solvent flow rate.	Seven organophosphorus pesticides	GC-MS	Tea samples	[90]
	MSA-SI-LLME	–	CCD – stirring time, pH, extraction solvent volume and centrifugation time.	Five fluoroquinolones	HPLC-FLD	Milk, eggs and honey	[91]
	UA-SI-LLME	–	CCD – solvent volume, pH, extraction time and weight of salt.	Five fluoroquinolones,	HPLC-FLD	Fish, chicken, pork and beef	[92]
	DLLME	–	CCD – extraction solvent, disperser solvent, pH of sample solution, centrifugation time and ionic strength.		UV Spectrophotometry	Cinnamon syrup and Cinnamon tea	[93]
	MA-DLLME	–	CCD – volume of extraction and disperser solvents, salt amount and ethanol ratio.	Sixteen PAHs	GC-MS	Grilled meat	[94]
	MSA-DLLME	Fractional factorial design – extraction solvent volume, disperser solvent volume, pH of sample, salt addition, temperature, stirring rate and time of extraction.	CCD – 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 design– 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	–	CCD – IL amount, volume of disperser solvent, pH, and KCl concentration.	Benznidazole and nifurtimox	HPLC-UV	Human breast milk	[97]
	QuEChERS-IL-DLLME	–	BBD – extractant volume, dispersant volume, and extraction time.	Six triazole fungicides	HPLC-PDA	Pear, apple, and grapefruit	[98]
2016	In-syringe DSIL-DLLME	DPB – amount of ionic liquid precursor, molar ratio of ionic liquid precursors, ionic strength, pH and sample volume.	CCD – ionic strength, pH and sample volume.	Triflumuron, hexaflumuron, lufenuron and chlorfluazuron	HPLC-UV	Honey	[99]

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DLLME	–	BBD – Derivatization: derivatization temperature, derivatization time and the molar ratio of BCEC–Cl 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	–	Full Factorial design – type of extraction solvent, type of dispersive solvent and protein precipitation. CCD – BGE concentration, pH, content of PDADMAC.	Nine fluoroquinolones	CE	Porcine blood	[7]
DLLME	Reduced factorial design – extracting solvent volume and, dispersing solvent volume.	CCD – dispersing solvent volume, and extracting solvent volume.	Gliclazide, glibenclamide and glimepiride	HPLC-DAD	Serum	[101]
AA-LLME	–	CCD – 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	–	BBD – volume of DES_1, the ultrasonic time and the temperature of ultrasonic bath.	Three phenolic acids	HPLC-UV	Vegetable oils	[103]
TAA-SFO-LLME	–	CCD – 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	–	Fractional factorial design– 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	–	Fractional factorial design (the factors were divided in different groups) – sample weight, extraction solution volume, sonication time,	Pesticides	GC-MS	Mango	[106]

2017

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

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		solution, volume of extraction and dispersive solvent.				
AA-SFO-DLLME	Fractional factorial design – acetonitrile volume, methanol volume, isopropyl alcohol volume, propanone volume, water volume and $ZnSO_4$ amount.	CCD – 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: ultrasound–assisted 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 liquid–liquid 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 liquid–liquid microextraction; UA-RM-DLLME: ultrasound-assisted reverse micelles dispersive liquid-liquid microextraction; MA-DLLME: microwave assisted – 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 liquid–liquid 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; μS-SHS-LLME: micropipette tip switchable hydrophilicity microextraction syringe system; in-syringe DSIL-DLLME: in-syringe dispersive liquid–liquid 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: Plackett–Burman 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 μL.
[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 μL.
[d]ZnSO$_4$ in mg.

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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^{-1} 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: