

Applications of Experimental Design to the Optimization of Microextraction Sample Preparation Parameters for the Analysis of Pesticide Residues in Fruits and Vegetables

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Sample preparation has been identified as the most important step in analytical chemistry and has been tagged as the bottleneck of analytical methodology. The current trend is aimed at developing cost-effective, miniaturized, simplified, and environmentally friendly sample preparation techniques. The fundamentals and applications of multivariate statistical techniques for the optimization of microextraction sample preparation and chromatographic analysis of pesticide residues are described in this review. The use of Plackett-Burman, Doehlert matrix, and Box-Behnken designs are discussed. As observed in this review, a number of analytical chemists have combined chemometrics and microextraction techniques, which has helped to streamline sample preparation and improve sample throughput.

The analysis of contaminants in environmental samples involves both qualitative and quantitative analyses, and there is the need to design efficient and effective analytical methods in order to produce accurate and reproducible analytical results. A well designed analytical procedure is a very powerful tool that can increase the efficiency of analysis with relatively low cost and can help to identify the sources of errors or irregularities (1).

Microextraction methods are based on the same basic concept, which is to extract, selectively isolate, and concentrate analytes from complex environmental matrixes containing other interfering high MW compounds prior to instrumental analysis using little or no solvents (2, 3). Conventional extraction techniques have been found to be tedious, time-consuming, costly, and multistep, which can lead to the introduction of contaminants and involve various cleanup methods. Chemical analysis involves several steps, such as sample collection, sample pretreatment (extraction, chromatographic

separation, concentration, and purification), determination of target compounds (identification, qualitative and quantitative analysis; 3–5), and data analysis and interpretation.

To achieve the best separation results, microextraction and chromatographic conditions must be optimized based on the analytical objectives. There are many factors that affect sample preparation and instrumental analysis of contaminants in environmental samples. They must be optimized in order to achieve effective and efficient analysis. This includes extraction time, extraction temperature, pH, ionic strength (salt addition), stirring rate, type of organic solvents, volume of acceptor and donor phase solutions, desorption time, and desorption temperature (3, 4, 6–8).

In optimizing these factors, several researchers have used one-factor-at-a-time (OFAT). It optimizes a single factor while holding the others constant. OFAT involves many experimental runs and does not take into consideration the possible interactions between factors. So, it is usually misleading, not reproducible (2, 9, 10), and sometimes misinterpretes the results (11). The aim of this review is to discuss the applications of chemometric tools to optimize the various factors affecting microextraction techniques in the analysis of pesticide residues in fruits and vegetable samples.

Importance of Pesticides

Human-made pesticides are unavoidable parts of agriculture and public health. They have been produced in large quantities since the end of World War II (12, 13). Their worth has been demonstrated through the huge increase in global agricultural production, eradication of insect borne and epidemic diseases and conservation of the ecosystem (14). The use of pesticides increased significantly in the late 1940s. Thus, the immediate benefit of their uses overshadowed their toxicities. The most widely used pesticides in agriculture are insecticides, herbicides, rodenticides, and fungicides (9). In many parts of the world, especially in the developing and underdeveloped countries, excessive loss of farm produce to insects and other pests has been reported to lead to starvation and famine (15). Postharvest losses of crops contributed to hunger and malnutrition, which has killed more than 15 million children (16).

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The use of pesticides seems to have allowed the production of inexpensive, affordable, and low cost food, especially fruits and vegetables, which are vital for protection against cancer and heart disease (17, 18). Although the most obvious use of pesticides in agriculture is in the improved yield of crops, there are some salient features that provide subtle or incremental benefits distributed over a large area. Cooper and Dobson (16) adopted the effect and benefits model for analyzing the numerous potential benefits of using pesticides. The other benefits include an increase in revenue for farmers due to reduced labor costs, reduced fossil fuel use for farm machines, reduced production of highly toxic alkaloids like mycotoxins, and increased shelf life of fruits and vegetables. Thus, higher yields of farm produce reduce pressure to cultivate uncropped land, which is beneficial for the environment, thereby conserving the natural ecosystem (19, 20).

Human-made pesticides are considered by some to be among the most dangerous contaminants in the environment because of their persistency, biotransformation in the food chain, bioaccumulation in animals, mobility in the environment, and possible risks to human health (21–23). Due to the nonselectivity of pesticides for the target species, they can sometimes cause an adverse effect on nontarget organisms (15). Pesticides affect normal and basic metabolic activities in the human system. Pesticides are meant to be poisonous and pose a hazard with their production, transport, and applications, while their normal use often leads to the contamination of the environment. Pesticides alter the electrophysiological properties of the nerve cell membrane and its associated enzymes, disrupting the kinetics of essential mineral ions flowing in the membrane. They interfere with the sodium channel in the axonal membrane and cause imbalance in the ratio of sodium and potassium surrounding the nerve fibers and also cause irreversible inhibition of acetylcholinesterase enzyme, which causes interference in the nerve endings of the central nervous system (15, 24, 25). This results in nerve motor unrest and increased frequency of continuous transmission in the nerves and abnormal susceptibility to external stimuli. However, these effects are dose-dependent. That is, workers who are exposed to kg quantities of human-made pesticides are much more susceptible to toxicity than people who consume μg quantities of them.

Analysis of Pesticide Residues in Fruits and Vegetables

Different classes of pesticides have been used effectively to control pests and diseases of fruits and vegetables, and after their application they penetrate into the tissue and remain as residues. The qualitative and quantitative analyses of fruit and vegetable samples for pesticide residues is an important QC procedure, put in place to ensure their quality and safety for human consumption. Hence, their concentration must always remain minimal and below the maximum residue limit (MRL) in fruit and vegetable samples (26).

To ensure that the residues on fruits and vegetables are below the MRL and not harmful to consumers, the joint Food and Agricultural Organization of the United Nations and World Health Organization Food Standard established the Codex Alimentarius Commission that set the MRLs for pesticides and other contaminants in fruits, vegetables, and other foods of

plant and animal origin (3, 27, 28). Several other countries also set default MRLs through various monitoring agencies such as the U.S. Environmental Protection Agency, U.S. Food and Drug Administration, or regional organizations such as the European Union Commission and Parliament (29), and the MRLs may vary by country (9).

The monitoring of pesticide residues in fruits and vegetables is undertaken to ensure their quality, due to the increasing awareness of the health effects of pesticide accumulation in the body. Therefore, fast, effective, and efficient analytical methods are needed to simultaneously determine multiclass and multiresidue pesticides with high selectivity and sensitivity, low cost, high sample throughput, less tedium, and ability to properly quantify the residues (30, 31). The analysis of fruit and vegetable samples for the presence of trace levels of different classes of pesticide residues with a broad range of physicochemical characteristics is not a simple task and poses a special problem for analytical and environmental chemists (32, 33).

The purpose of any analytical method is to obtain information about the nutritional value and quality of the product and to monitor its content of pesticide residues and other contaminants. Due to the complex nature of the fruit and vegetable samples, they cannot be handled directly by analytical instruments (32), and hence there is need for sample preparation prior to the instrumental analysis.

Microextraction Techniques

Analytical studies are undertaken in order to obtain information on the identity and quantity of contaminants present in the sample. Sample preparation is a very important step and, indeed, is the bottleneck of analytical methodologies. This also applies to the analysis of fruits and vegetables for the presence of pesticide residues (4). The preliminary steps in any instrumental analysis are sampling and sample preparation, with the latter involving various sample pretreatment methods (34, 35). This further involves the selective isolation of analytes from the sample matrix, which are present at trace concentration (usually $\mu\text{g}/\text{kg}$ or less), helps in the elimination of any interference, and reduces the volume of extracts (36). It involves the development, optimization, and application of analytical processes to provide reliable and effective answers to real world problems (37, 38).

The nature of the sample matrix and the physicochemical properties of the analytes determine the choice of separation and detection methods to be used (39, 40). The current trend of microextraction techniques is aimed at a reliable and accurate analysis of contaminants from complex samples, and is focused on reducing the sampling time, cost, and solvent volume with the online coupling of the sampling step to the analytical instruments (32, 41). The traditional sample preparation methods are liquid–liquid extraction (LLE), SPE, accelerated solvent extraction, and matrix solid phase dispersion (34, 42–49). They require tedious and time-consuming matrix pretreatment steps and use large volumes of sample and toxic solvents, which causes environmental pollution and health hazards with high operation cost (32).

Therefore, in order to reduce the sources of error, the number of matrix pretreatment steps needs to be reduced. Microextraction techniques are recently developed sample preparation methods that are effective and efficient ways to save time, reduce solvent

use, and increase sample throughput (50). The current trend of sample preparation techniques is focused on the simplification, miniaturization, and combination of different steps, such as extraction, concentration, isolation of analytes, cleanup, and instrumental analysis, into a single step (3).

Over the years, different researchers have developed microextraction techniques to complement the recent advances in the development of highly sensitive and efficient analytical instrumentation, such as GC, LC, and capillary electrophoresis (CE). They are compatible with the microextraction techniques and coupled to different detectors such as electron capture, flame ionization, nitrogen-phosphorous, MS, diode array, and UV (3, 51). These methods increased the information available from chromatographic instruments (1).

The low cost, easily understood operating procedure, and ease of addition of the microextraction techniques to analytical instruments has drastically reduced errors. This is due to avoiding contamination and sample losses and takes advantage of features of the combination of extraction and instrumental analysis such as high speed of analysis and high efficiency (2). The introduction of solid phase microextraction (SPME) by Pawliszyn and his co-workers in 1990 (52–59) opened the floodgate of interest in the development of microextraction techniques, such as liquid phase microextraction (LPME; 3, 6, 60–64), stir bar sorptive extraction (65–68), and microextraction in packed sorbents (69–72).

SPME

SPME is a solvent-free sample preparation technique that was developed by Pawliszyn and Arthur in 1990 (54). The technique was developed to eliminate the use of toxic solvents and to address the need to develop a rapid, effective, efficient, and field compatible sample preparation method (56, 59, 73). It helps to save sample preparation time, reduces overall cost of analysis, and offers the benefit of short sample preparation steps, small sample volume, and enrichment of analytes from solid, liquid, or gaseous samples. Its application for the analysis of pesticide residues in fruit and vegetable samples has been examined (23, 74, 75), optimized, automated (52, 76), and reviewed (4, 32, 41, 77–79).

SPME is a simple and effective sorption (adsorption/absorption) and desorption technique that can easily be automated. It combines sampling, isolation, concentration (enrichment), and sample introduction into analytical instruments in a single and uninterrupted sampling step, which results in high throughput analysis (58, 73, 80, 81). It was developed to overcome the problems associated with the solvent based, time-consuming conventional techniques, which are multistep and usually require large amounts of samples and solvents that can cause environmental pollution and be hazardous to human health.

SPME is a very attractive alternative technique in sample preparation that results in high throughput analysis, and remarkable analytical characteristics, including high linearity, reproducibility, repeatability, selectivity, sensitivity (low LOD and LOQ), and versatility with minimum matrix interferences (58, 73, 82, 83). It is widely used for the analysis of volatile or semivolatile organic compounds (84) when coupled to GC with variety of detection methods, and for analysis of thermally labile, polar, and nonvolatile compounds (78) when coupled to LC or CE.

The SPME process involves two basic steps: the partitioning of analytes between the coating and the sample matrix, and the desorption of the extracted analytes into the analytical instruments, thermally for GC or with organic mobile phase for LC (59, 73), without any need for cleanup (54). The extraction and sorption of analytes from the matrix begins with the exposure of the coated fiber to the vapor phase above the sample matrix or by inserting the fiber into the sample matrix. The analytes are transferred to the fiber based on the mass transfer process that follows the second law of thermodynamics (36); when exposed for a period of time, extraction is considered to be completed when equilibrium is attained.

The SPME fiber assembly is made of chemically inert fused-silica optical fiber, stable flex, or metal alloys (85), coated on the outside with a thin-film of sorbent (52) as the extraction phase containing a polymeric organic compound or a mixture of polymers (32, 59) that are permanently attached to a stainless steel rod. The SPME fiber, mounted on a fiber holder, consists of a spring loaded plunger, a stainless steel barrel, and an adjustable depth gauge with a hollow septum-piercing needle housed in a modified syringe (86).

SPME is based on the partitioning of analytes and establishment of an equilibrium between the analytes in the sample matrix and the stationary phase of the coated fused silica, which can either be liquid or solid particles suspended in liquid polymer or a combination of both (52, 78, 85). The attainment of an equilibrium depends on the partition coefficient (77), which reflects the chemical composition of the extraction phase and hence its selectivity towards a given analyte.

LPME

LPME, also called solvent microextraction or liquid–liquid microextraction (LLME), is a miniaturized LLE (87) that has helped to drastically reduce the amount of solvent used in extraction (63). It was developed in order to overcome some problems inherent in SPME, such as low recommended operating temperature of the coated fiber, swelling of the fiber in organic solvents, fiber breakage due to its fragility, stripping off of the coating, and possible bending of the needle (36, 88).

LPME is a rapid and less expensive sample preparation technique performed between a μL volume of water-immiscible solvent called the acceptor phase and an aqueous sample called the donor phase containing the analytes (88). The acceptor phase can either be immersed directly into the sample matrix or suspended above the sample for headspace extraction (50). The technique can broadly be classified into three major categories (89); their difference is the way the extraction solvent is supported in contact with the sample matrix (3, 90): single drop microextraction (SDME), hollow fiber LLME (HF-LPME), and dispersive LLME (DLLME).

SDME is based on the suspension of a single microdrop of water-immiscible organic solvents (typically 0.5–3 μL) from the tip of a microsyringe GC injection needle in aqueous solution (6, 39, 50, 88, 90–92), thereby reducing drastically the volume of organic solvent used. The transfer of analytes from the sample matrix to the extraction solvent is limited by a slow diffusion rate, and the analytes are distributed between the microdrop of the solvent at the tip of the microsyringe and the sample solution (62, 93). The solvent droplet that extracts the analyte by passive diffusion is retracted back into the syringe

and injected directly into the analytical instruments (GC, LC, or CE) for analysis (3, 5).

HF-LPME, also called liquid–liquid–liquid microextraction (LLLME), is described as a multiphase microextraction system, it was developed due to the limitation of the stability of the organic solvent inherent in SDME. The extraction technique is based on the principle of a supported liquid membrane (SLM), involving the filling of both the wall pores and the lumen of a semipermeable polypropylene HF with organic solvent (64, 94–96). It makes use of a polymeric membrane that forms a barrier between the solvent and the sample and acts as a support for the small volume of extraction solvent (97). The solvent used must be compatible with the membrane, strongly immobilized into the pores of the HF, have low viscosity for better diffusion through the SLM, and have a high partition coefficients to ensure that the pores in the wall of the membrane are completely filled by the organic solvent for efficient extraction of the analytes (88, 94, 96, 98–100).

DLLME was developed for the analysis of polyaromatic hydrocarbon in water samples, using tetrachloroethylene and acetone as the extraction and the dispersive solvents, respectively (101), and for the analysis of organophosphorus pesticide residues in water sample using acetone and chlorobenzene as the dispersive and extraction solvents, respectively (102). It makes use of a small volume of a mixture of extraction and dispersive solvents with high miscibility, thereby preventing the dislodgement of the organic solvent drop inherent in SDME. A cloudy solution is formed when an appropriate mixture of high-density water-immiscible extraction and dispersive solvents are injected rapidly into an aqueous solution of the sample matrix (101, 103, 104) containing the analytes. Its limitation lies in it being a manual procedure that requires centrifugation, which is time-consuming. Automation based on a sequential injection system has been used to overcome the drawback (105).

The analytes are then enriched into the extraction solvents, which are dispersed into the bulk aqueous solution when the mixture is centrifuged, thus making DLLME a two-step microextraction technique. After centrifuging, a sedimented phase of the extraction solvent accumulates at the bottom of the extraction vessel and can be injected into analytical instruments (105, 106) with or without further treatment (cleanup). The selection of the type and volume of dispersive solvent is as important as that of the extraction solvent, because it helps the extraction solvent to form fine droplets in the sample matrices and ensures a high enrichment factor (107).

Although microextraction techniques share some characteristics in common, i.e., the reduced amount of the sorbent materials and partitioning of analytes between the sorbent and the sample matrix, they differ significantly in the principles used for instrumentation, and therefore it is difficult to make a generalized theoretical analysis of the techniques (108).

Chemometrics and Multivariate Approach to Microextraction Techniques

The use of mathematical and statistical methods in optimizing factors affecting microextraction techniques helps to process large amount of data collected in a chromatographic experiment and to find hidden trends and properties (109). The univariate optimization of microextraction techniques involves an OFAT optimization procedure in which factors are kept constant

except for the one being optimized, and it involves many experiments. This does not allow the estimation of possible interaction between the studied factors, although there may be acceptable response, but the probability of finding a global optimum is very low (11). The design of experiment is used as a chemometric approach, which helps in the identification of significant factors. The experiment is designed to minimize the effects of uncontrolled factors. It uses statistical analysis to separate and estimate the effect and interaction of the various factors involved (110, 111).

Experimental design helps to identify the significant factors that maximize the response of an experiment and evaluation of robustness or roughness of the optimum condition (11). It also helps to improve the yield of chromatographic separations by optimizing the significant factors using central composite design (CCD), Box-Berhken design (BBD), and Doehlert design (DD). It saves time, requires few experimental runs, and can be used for quantitative modeling of mathematical relationships between factors and response (112, 113). Its use is aimed to understand the effect of each factor and model the relationship between the factors and response, with a minimal number of experiments carried out in an orderly and efficient manner (114) and then converted into new latent variables (1).

The multivariate experimental design is carried out in two stages. First, the significance of each factor is estimated using the first-order experimental design such as full or fractional factorial design and Plackett-Burman (P-B) design, which are very important for preliminary studies and in identifying the possible interactions between the studied factors. The second stage involves approximating a response function or optimizing the significant factors identified in the first stage. It uses second-order models such as CCD, DD, and BBD (2, 11, 115, 116).

Several factors affect the microextraction of pesticide residues in fruits and vegetables, as mentioned earlier. However, the use of the univariate method requires a large number of experiments, which is time-consuming (9). A well planned experimental design that could simultaneously determine the effect and possible interaction of all factors and determine the optimal condition in a few experimental runs is a more convenient approach (117). The use of full/fraction factorial or P-B design for determining the significant factors helps to screen out factors that have little or no effect on the extraction efficiency as measured by the peak area of a chromatogram and helps to predict the behavior of other factors (2, 110). The second-order designs are used to determine the interaction effect and the optimal extraction conditions using a response surface methodology (RSM; 117). Experimental design starts with the identification of all necessary variables and responses followed by a clear definition of the objective. This allows for the choice of the most appropriate design (118).

Factorial Designs

Factorial designs allow the adjustment of two or more variables at fixed levels and permit the evaluation of combined effects of two or more experimental variables when used simultaneously (111, 119). They also allow for the investigation of all possible combinations of factor levels (120). They explore the corners of a cube where one variable is changed and the other variables are given different values and allow for the estimation of main effects and interaction effects (11, 121).

They are the simplest and most widely used experimental design for screening, in order to determine the influence of a number of factors on a response or when there are a large number of possible factors (112, 113). Factorial design can either be full factorial or fractional factorial. The full factorial design is mainly used for determination of significant factors, but when detailed predictions are not required (118); the information provided by factorial design is adequate for qualitative analysis (112). The number of experiments (N) in a factorial design is given by $N = l^k$, where l is the number of levels and k is the number of factors/variables under study (112, 113, 121). The results of the N experiments can then be used to estimate the coefficients a_n of appropriate polynomial model for each response variable y (119):

$$y = f(x_1, \dots, x_n) \quad (1)$$

Two-level factorial design is described as 2^k , where the 2 represents the number of factor levels and k is the number of variables, which also corresponds to the number of experiments (11, 118, 120, 121). It takes into account all linear and all possible k way interactions (112) and the experiment will be carried out using all possible combinations of k factor under study (114). For a two-factor, two-level design, the number of experiments will be 4, and the response surface is given by the following linear model (116, 119):

$$y = a_0 + a_1x_1 + a_2x_2 + a_{12}x_1x_2 \quad (2)$$

The 2^k design is useful in the early stage of an experiment and can be used for factor screening experiments when many factors are likely to be investigated (120). If more than one factor is involved, the coefficients are proportional to the main effect and the interaction effect. The mathematical model for a three-factor, two-level design will involve eight experimental runs and will be given by the equation (121):

$$y = a_0 + a_1x_1 + a_2x_2 + a_3x_3 + a_{12}x_1x_2 + a_{13}x_1x_3 + a_{23}x_2x_3 \quad (3)$$

Hence, a four-factor, two-level design involving 16 experiments will have a response described by an equation with a total of 16 terms. The terms are: one interaction term, four linear terms (x_1, x_2, x_3, x_4), six two-factor interaction terms ($x_1x_2, x_1x_3, x_1x_4, x_2x_3, x_2x_4, x_3x_4$), four three-factor interaction terms ($x_1x_2x_3, x_1x_2x_4, x_1x_3x_4, x_2x_3x_4$), and one four-factor interaction term ($x_1x_2x_3x_4$; 110, 119).

Despite the obvious advantages of full factorial design, its limitation is that the increase in the number of factors leads to an exponential increase in the number of experiments (11, 111, 112, 113), e.g., an eight-factor, two-level design will require a total of 256 experimental runs, which is impracticable and defeats the advantage of time saving. Microextraction techniques depend on a large number of factors. For example, development of an SPME method depends on about 14 factors (7, 8), while LPME depends on more than eight factors (6), all of which must be optimized for effective and efficient extraction. Another limitation is when the high and low level of a factor are too close for a continuous variable. The effect of the factor may not be significant, and if the factor levels are too far apart the response may fall on either side of a maximum value, which causes an insignificant difference (110).

In order to minimize the number of experiments when there are a large number of factors, fractional factorial design can be applied, where one-half, one-quarter, or one-eighth of the total number of experiments will be required (110, 113, 114). The fractional factorial design is described by 2^{k-m} , where m is an integer defining the fraction of the corresponding full factorial design (11, 112). It is desirable because higher order effects are usually much smaller than main effects and two-factor interaction effects. Also, they are confounded by lower-order factors and the low-order effects. The low-order two-factor interaction is more likely to be present than the higher-order interactions, with the assumption that three-way and higher-order interactions are negligible. There is a need to define the confounded terms in a fractional factorial design, and individual experiment must be carefully selected to ensure that they yield the maximum information (11, 110, 113, 120). Fractional factorial design is used mainly for screening purposes, where many factors are considered with the objective of identifying the most significant factors (120).

The resolution, R, of a design expressed in Roman numerals (III, IV, V) is used to determine the extent of the confounding problem in a fractional factorial design (110), and it corresponds to the minimum number of characters in the fractional factorial design relations (11). This implies that for a resolution III design, the main effects are aliased with each other but can also be aliased with two-factor interactions, while two-factor interactions can be aliased with each other. A resolution IV has two-factor interaction confounded with each other and main effects and two-factor interactions are not aliased, while for a resolution V design, two-factor interactions are aliased with three-factors interactions, i.e., main effects and two-factor interactions are confounded with higher term interactions (11, 114, 120). A factorial design matrix generated using Minitab® (122) statistical software (Minitab Inc., State College, PA) to determine the main and interaction effects of three factors studied at two levels is illustrated in Table 1 (123). The design was executed in two blocks in order to eliminate sources of daily variability (124).

P-B Design

These are two-level fraction factorial and orthogonal designs introduced by Plackett and Burman (125) to study the $k = N - 1$ variables in N runs, where N is a multiple of 4 (120). It provides information on the main effects of the factors while all interactions that are present are ignored (11, 110), using two-level for each factor, with the higher level represented with "+" and the lower with "-" (126). They are selected based on previous experiments and taking into consideration the limitations of the experimental system (2, 127). It is a first order design that is used to identify the significance factors, although it does not yield the exact quantity but provides valuable information on each factor with relatively few experiments (2, 127, 128). The number of experiments is a multiple of 4, and the factors are one less than the number of experiments (113). This avoids the limitations of full factorial and fractional factorial designs. It can be used for the study of up to $4N - 1$ factors (110) and reduces the number of experiments (113).

The experiments are designed using a predefined pattern of high and low levels for each number of experiments. Also, a dummy factor (completely unrelated with the experiment, but used to estimate experimental error used in statistical

Table 1. Factors, levels of the variables, and factorial design matrix^a

Variables	Low	High
Extraction temperature, °C	30	60
Extraction time, min	30	60
Salt concentration, % (w/v)	5	10

Run order	Standard order	Block	Time, min	Temperature, °C	Salt, %
1	3	1	30	60	5
2	2	1	60	30	5
3	1	1	30	30	5
4	8	1	60	60	10
5	7	1	30	60	10
6	5	1	30	30	10
7	4	1	60	60	5
8	6	1	60	30	10
9	10	2	60	30	5
10	12	2	60	60	5
11	14	2	60	30	10
12	13	2	30	30	10
13	16	2	60	60	10
14	15	2	30	60	10
15	9	2	30	30	5
16	11	2	30	60	5

^a Generated using Minitab statistical software and reprinted with permission from (123).

interpretation) is added if the number of factors is smaller than the number of standard experiments (2, 11, 110, 112, 113). The main effect of each factor can then be estimated using the least squares regression model, which indicates the significance in relation to the experimental yield/response (127). The significant factors can also be estimated using analysis of variance (ANOVA), with a *t*-test at 95% probability level (2). The significant factors will be those that show effects that are higher than those of the dummy, while the factors that show effects lower than those of the dummy are not significant at any given probability (11, 110).

Response Surface Designs

Response surface designs are used for modeling and analyzing problems where the model of interest is influenced by several variables and the objective is to optimize the response (120). They are second order quadratic models (11, 115, 127) which originated from the graphical perspectives that are generated after fitness of the mathematical model (129). Response surface design consists of modeling and displacements that are repeated as many times as possible (118). An experimental design is first done to discover which experiment should be done in the experimental region under study before response surface design can be applied. These include the use of factorial and P-B designs (127, 129). The RSM is used for optimization, which gives maximum or minimum points depending on the objective and to produce a detailed quantitative model (112, 113).

There are six stages in the use of RSM for optimization of microextraction parameters including (130):

- (1) The independent factors that have major effects on the extraction efficiency should be selected through screening studies (127, 130). This is based on the limitations of the experimental region, the objective of the studies, and the experience of the researcher.
- (2) The experiments design is chosen and done according to the selected experimental matrix.
- (3) The obtained experimental yields are treated mathematically/statistically to fit to a polynomial function.
- (4) The model fitness is also evaluated.
- (5) The necessity and possibility of performing a displacement experiment is verified with respect to the optimal region.
- (6) The optimized values of each studied parameter are then obtained.

The response surface designs used for optimization of parameters include (2, 10, 11, 114–116, 127–135):

- (1) CCD.
- (2) BBD.
- (3) DD design.
- (4) Three-level full factorial design.

CCD

CCD is a second order design that consists of two-level full or fractional factorial designs with an additional star design (experimental point at a distance $\pm\alpha$ from its center) and at least one point at the center of the experimental region under study (2, 11, 113, 115, 116). CCD requires fewer experiments, thus providing a better alternative to full factorial design (116).

Also, it allows the constant, the linear terms, the interactions between variables, and the quadratic terms to be estimated (121).

Basically, the number of points in CCD contains a factorial run of 2^k , containing a total of n_{fact} points with coordinates $x_i = -1$ or $x_i = +1$, for $i=1 \dots k$; axial (or star) runs of $2k$, formed by $n_{ax} = 2k$ points with all the their coordinates null except for one that is set equal to a certain value $\pm\alpha$; and C_0 center point containing a total of n_c runs performed at the center points, where $x_1 = \dots x_k = 0$. Therefore, the total experimental runs (N) of CCD is given by: $N = 2^k + 2k + C_0$, where k and C_0 are the number of variables and the number of center points, respectively. Each of these three parts must be specified when building a CCD (2, 114, 116, 118, 129, 136), and all factors are studied in five levels ($-\alpha, -1, 0, +1, +\alpha$; 129). The value of α is chosen based on the desired characteristics for the design (11). The design rotatability (implies that the confidence in the prediction depends only on the distance from the center points; 116) and orthogonality (implies that all the terms of the model are independent of each other) are two criteria for choosing the value of α (11).

The rotatability and orthogonality (which depends on the number of replicates on the center points) can be obtained using Equations 4 and 5, respectively (11, 112, 116, 118):

$$\alpha = \sqrt[4]{N_f} \quad (4)$$

$$\alpha = \sqrt{\frac{\sqrt{N \times N_f - N_f}}{2}} \quad (5)$$

where N_f is the number of factorial points, and N is total number of experiments.

The complete quadratic model that contains the linear model and the polynomial term for k factors $(k+1)(k+2)/2$ parameter is given by Equation 6, and the total number of distinct levels is given by $n_{fact} + 2k + 1$ (2, 116, 118), which are used to determine the critical points (maximum, minimum, or saddle) (2):

$$Y = \beta_o + \sum \beta_i x_i + \sum \beta_{ii} x_i^2 + \sum \beta_{ij} x_i x_j + \varepsilon \quad (6)$$

where Y is the response, β_o is the constant term, β_i is the linear parameters, x_i and x_j represents the variables, β_{ij} is the coefficients of the interaction parameters (x_i and x_j), β_{ii} represents the coefficients of the quadratic parameters, and ε is the residual associated with the experiments. The experimental design should ensure that all variables are carried out in at least three-factor levels in order to estimate the parameters in Equation 6 (2).

BBD

Box-Behnken design (137) is a class of rotatable or nearly rotatable second order, three-factor quadratic incomplete factorial design that is evenly spaced. The experimental points are located on the midpoints of the edge of a cube and at the center (2, 115, 116). It suggests how a point can be selected from a three-level factorial arrangement, which allows the efficient estimation of the first- and second-order coefficients of the mathematical model (11, 129). It has a special arrangement of levels, which allows the number of design points to increase at the same rate as the number of polynomial coefficients. The number of experimental runs (N) is given by Equation 7,

and all factors levels are studied in three levels ($-1, 0, +1$) that are spaced at equal intervals (2, 11, 115, 116, 118, 129):

$$N = 2k(k-1) + C_0 \quad (7)$$

where k is the number of factors, and C_0 is the number of center points.

The advantages of BBD over CCD are that BBD does not contain any run for which all factors are simultaneously at the highest or lowest and that it also requires a lower number of experimental runs compared to the CCD (11, 116, 118). Therefore, it is slightly more efficient than CCD and much more efficient than a three-level factorial design (11).

DD

DDs (138) are second-order, polyhedral designs based on hypertriangles with a hexagonal structure (11). They describe the spherical experimental domain, which accents the uniformity of the studied variables in space filling with an equally spaced distribution of points lying on concentric spherical shells (11, 114, 115, 129). In DD, unlike CCD and BBD, the number of levels is not the same for all variables, i.e., a different number of levels can be studied at different levels. This allows for a free choice of factors (2, 11, 114–116, 129). It is neither orthogonal nor rotatable, and there is no significance divergence from the required quality for effective use (114, 116).

DD requires few experimental points, and the number of experiments required is given by Equation 8 (11, 129):

$$N = k^2 + k + C_0 \quad (8)$$

The advantages of DD over other second-order designs is the ability to introduce new factors during an experimental study without losing the runs already performed and the possibility of displacing experimental matrix to another experimental region using previous adjacent points (116, 129). It also allows for the estimation of the parameters of a quadratic model, permits building of sequential designs, and permits use of blocks and the detection of lack-of-fit of the model (115).

Three-Level Full Factorial Design

This is a design that provides information concerning interactions between variables at which main or linear and quadratic or curvature effects can be separated (2). The number of experimental runs is given by $N = 3^k$, where k is the number of factors. When the number of factors is higher than 2, it loses its efficiency in modeling a quadratic function because it requires higher number of experimental runs than can be accommodated (2, 129). Thus, it has limited application in response surface designs, but its efficiency is comparable to CCD when there are two factors (129).

Artificial Neural Network (ANN)

Other nonlinear modeling for response surfaces and optimization include ANN (129, 139–147). ANN was inspired by the organization of human brain in the arrangement of the cerebral network (129, 142) and is used to solve nonlinear or complicated calculations. It is composed of several neurons

and their connections that are composed of weights and biases with neurons. ANN operators are the transfer function and the summing junction (148). The neurons, arranged in a series of layers, are interconnected and comprise three nodes (an input, a hidden, and an output) that receive/or send number values to other nodes through the input node. One input layer has neurons representing independent variables and one output layer neuron representing dependent variables, with several hidden layers that associate the input layer with the output layer. The weighted sum of the input is calculated by the nodes and then subjected to nonlinear transformation (129, 141, 142, 149). The weights (w) and the biases (b) for the summing junction operator of a single neuron can be summarized into a net input (S) known as the argument to be processed (148, 149):

$$S = \sum_{i=1}^n x_i W_i + b$$

The argument S is received by the transfer function and is then used to produce scalar output for a single neuron (148). It provides the methodology for the modeling of a complex relationship, which can be investigated without the use of a complicated equation. It is also flexible in terms of the design and number of experimental data and has a better predictive power compared to the regression models (129). ANN has been used for pesticide residues analysis using electroanalysis (149) such as differential pulse voltammetry (141–144). To the best knowledge of the authors, ANN has not been used for the optimization of microextraction parameters for the analysis of pesticide residues in environmental samples, and this is an area that can be explored by analytical chemists especially in microextraction techniques

Derringer and Desirability Functions

The optimization of parameters is achieved by the application of multicriteria methodology such as Derringer

function or desirability function (150, 151), which is based on the construction of a desirability function for each response. The desirability scale ranges between 0, for a complete undesirable response, and 1, for a fully desirable response above which further improvement of the factors will have no significant effect. This will enable the combination of responses obtained for variables measured on different orders of magnitude (129). The desirability function can be determined using the available software for design of experiment. Figure 1 (127) shows the optimization of three parameters at desirability value $d = 1$, generated using Minitab 16 statistical software.

Software

Application of chemometrics has been made easy with the availability of a number of excellent software packages that can be used to design and analyze experiments. This includes Minitab® (Minitab Inc., State College, PA), JMP® (SAS Institute, Inc., Cary, NC), Design Expert® (Stat-Ease Inc., Minneapolis, MN), Statistica® (Statsoft, Tulsa, OK), StatGraphic® (Statistical Graphic, Rockville, MD), MATLAB® (MathWorks, Natick, MA), and MODDE (Umetrics, Umea, Sweden; 10, 11, 110, 123, 127, 131, 132, 152).

Applications in Microextraction of Pesticide Residues in Fruit and Vegetables Samples

A significant number of articles have been published on the applications of chemometrics to the optimization of parameters affecting the microextraction of pesticide residues in water samples (55, 129, 133, 135, 153–157). The use of design of experiment for the optimization of parameters in the development of microextraction techniques in the analysis of pesticide residues in fruits and vegetable samples, which is the scope of this review, is becoming increasingly important. This is due to the fact that it saves time and increases analytical

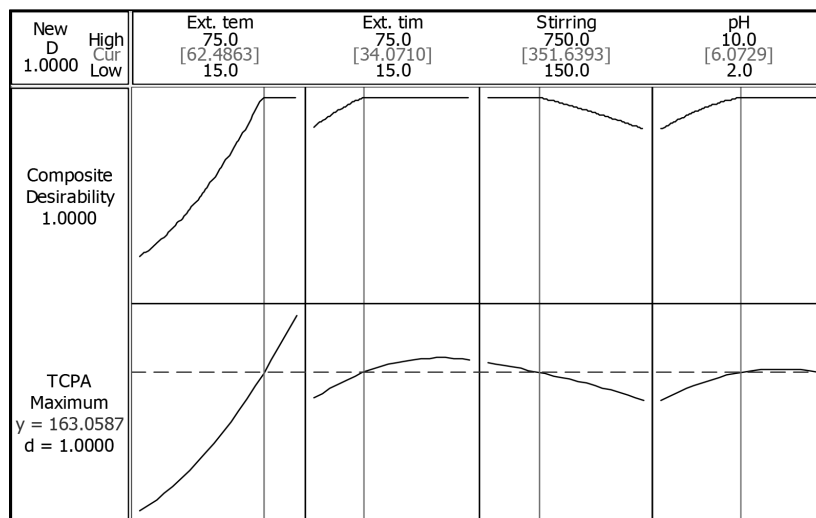


Figure 1. Desirability surface plot (127). TCPA = Total chromatographic peak area, ext. = extraction, d = desirability value, and y = maximum response.

throughput while providing an organized and efficient method for estimating and optimizing significant factors and the relationship that exists between various factors and their responses (158), depending on the sample matrix.

In a recently published article, the optimization of three factors affecting the magnetic solvent bar liquid-phase microextraction of organophosphorus pesticides in fruit juice samples was performed using Box-BBD. Three significant variables, viz., extraction time, number of magnetic stir bar, and extraction temperature, were chosen as the independent variable, while other factors were optimized using a univariate experiment. The experiments were randomized, and low, middle, and high levels of each factor were designated as -1 , 0 , and $+1$, respectively. The experimental runs consisted of 17 runs BBD matrix, performed in triplicate, designed using Design Expert software. The regression model was determined using ANOVA and was observed to be highly significant. The P value was found to be significant (<0.0001), and the lack-of-fit of the model was found to be insignificant (>0.0805). The nonsignificance of lack of fit (because it is greater than >0.05) shows that the quadratic model of the design is statistically significant for the response and that the model fitness is good (131). The response obtained was then illustrated using a three dimensional (3D) response surface design for TCPA.

In our recent paper, the significance of seven factors (extraction temperature, extraction time, salt addition, stirring rate, pH, desorption time, and desorption temperature) affecting the analysis of the residues of 14 pesticides in apple, tomato, cucumber, and cabbage samples using SPME coupled to GC/MS was determined using PB design, and the significant factors were then optimized with a CCD. The PB design and CCD matrixes were generated using Minitab 14 software. The PB design matrix with a 2^{7-4} (resolution III) reduced factorial design was generated for the screening of the most important factors affecting the SPME efficiency and recovery. The PB design consisted of 12 runs that were conducted in triplicate to annul the effects of extraneous variables. The significance of each factor was estimated using a least squares regression model. A Pareto chart and a normal plot was used to graphically represent the significance of each factor. The extraction temperature, extraction time, stirring rate, and pH were found to be significant. The significant factors were then optimized with a CCD that consisted of 31 runs as shown in Table 2 (containing 16 cube points, seven center points in cube, eight axial points, and 0 center point in axial with $\alpha = 2$ (selected to establish rotatability conditions). The surface and response optimizer plots were used to indicate the optimal conditions. The desirability surface plot is illustrated in the response optimizer plot in Figure 1 (127).

A multivariate strategy was also used to determine the significance of the factors affecting the SPME of the residues of four pesticides in apple samples using a randomized factorial design. The interactions and effects of temperature, time, and salt addition on the extraction efficiency were evaluated using a 2^3 factorial design. The factorial design matrix generated using Minitab software consisted of 16 runs of two blocks (eight in each block). The experimental design model was confirmed using ANOVA assumption for the response variable of each pesticide under study. The significance of each of the studied variables in the experimental design was graphically represented using a Pareto chart. The second- and third-order

interactions of the variables were found to have a positive effect on the chromatographic peaks that increases the efficiency of extraction (123).

A method for simultaneous LLME and polypropylene microporous membrane SPE of organochlorine pesticides in water, tomato, and strawberry samples were developed by Bedendo and Carasek (133). The parameters affecting extraction efficiency were optimized by multivariable designs with a BBD using three levels of each factor, followed by the estimation of analytical features. From the chromatographic response obtained, the combination of three factors (extraction temperature, extraction time, and salt addition) were plotted using response surfaces (Figure 2), and quadratic regression equations were obtained for each response surface and the optimum value for each factor was estimated. A triangular surface mixture design was used to define the best extracting organic solvent, and a CCD with two factors and five levels was used to verify the effects of the addition of methanol and the amount of sample on the extraction efficiency. In order to maximize the simultaneous pesticide extraction for the three optimization design, the geometric average of the peak areas for the pesticides was used as the response for optimization. The experimental data were processed using the Statsoft Statistica 6.0 computer program (133).

A method was developed for the multiresidue determination in industrial and fresh orange juice by HF-LLME of 18 pesticides of different classes by Bedendo et al. (134). The parameters affecting the extraction efficiency were optimized by multivariable design. A triangular surface mixture design was used to define the best organic solvent for the extraction step (hexane, toluene, or ethyl acetate) and desorption step (methanol, acetone, or acetonitrile). A CCD was applied to study the influence of sample pH, sample volume, extraction time, extraction temperature, and solvent volume on the extraction efficiency, while a univariate design was used to study the effect of mass and type of salt on the extraction efficiency. The experimental data were processed using the Statsoft Statistica 6.0 computer program to evaluate the agreement of the model with the experimental design (134).

A sensitive and reliable microextraction method was developed based on two-phase HF-LLME followed by GC/MS for determination of residues of three pyrethroid pesticides in fruit and vegetable juices. The parameters affecting extraction efficiency were studied via rotatable-centered cube CCD, which was generated using Design Expert 7.1.3 software. The design consisted of a factorial design ($2k$) augmented with ($2k$) star points, where k is the number of variables to be optimized, and with a central point that can be run n times. The star points are located at $+\alpha$ and $-\alpha$ from the center of the experimental domain. In order to establish the rotatability of the experimental design, α was set at $\sqrt[4]{2^k} = \pm 1.68$. The total number of experiments with three factors was 19, which were randomized to exclude bias. ANOVA was used to evaluate the model, and a module in the design expert software was used for optimization. This allows the software to search for a combination of factor levels that will simultaneously satisfy the requirements placed on the response and factors. A quadratic regression model, based on a multiple linear regression, was used to relate the response and the variables (132).

Table 2. Factors, levels, and CCD matrix^a

Variables		Level			Star points ($\alpha = 2$) ^b		
		Low (-)	Central (0)	High (+)	- α	+ α	
Extraction temperature, °C		30	45	60	15	75	
Extraction time, min		30	45	60	15	75	
pH		4	6	8	2	10	
Stirring rate, rpm		300	450	600	150	750	
Standard order	Run order	Point type	Blocks	A	B	C	D
10	1	1	1	60	30	300	8
6	2	1	1	60	30	600	4
8	3	1	1	60	60	600	4
13	4	1	1	30	30	600	8
18	5	-1	1	75	45	450	6
30	6	0	1	45	45	450	6
26	7	0	1	45	45	450	6
11	8	1	1	30	60	300	8
14	9	1	1	60	30	600	8
29	10	0	1	45	45	450	6
15	11	1	1	30	60	600	8
20	12	-1	1	45	75	450	6
24	13	-1	1	45	45	450	10
5	14	1	1	30	30	600	4
27	15	0	1	45	45	450	6
12	16	1	1	60	60	300	8
31	17	0	1	45	45	450	6
2	18	1	1	60	30	300	4
3	19	1	1	30	60	300	4
7	20	1	1	30	60	600	4
22	21	-1	1	45	45	750	6
9	22	1	1	30	30	300	8
25	23	0	1	45	45	450	6
4	24	1	1	60	60	300	4
16	25	1	1	60	60	600	8
17	26	-1	1	15	45	450	6
19	27	-1	1	45	15	450	6
23	28	-1	1	45	45	450	2
21	29	-1	1	45	45	150	6
28	30	0	1	45	45	450	6
1	31	1	1	30	30	300	4

^a Generated using Minitab® statistical software.^b Star points (selected to establish rotatability condition and estimate curvature).

Amvrazi and Tsiropoulos (130) developed a simple and rapid SDME method coupled to GC/MS for the analysis of 20 pesticides with different physicochemical properties in grape and apple samples, and factors were optimized by the use of multivariate strategy. Some factors such as type of organic solvent, drop volume, stirring rate, and extraction time were first optimized in a preliminary study using a univariate approach. The effect of other factors such as ionic strength, pH, and dissolved organic matter content were first screened using a two-level fractional factorial design containing 11 experimental runs. The three variables were found to have

significant effect on the extraction procedure. The factors were then optimized using a CCD with low central and high levels. The CCD consisted of the points of factorial design (2^2) augmented with $(2 \times 2 + 1)$. The star points were located at $+\alpha$ and $-\alpha$ from the center of the experimental domain with a total of 12 experimental runs. An axial distance α was selected with a value of 1.414 in order to establish the rotatability condition.

A sensitive procedure for the analysis of multiple pesticides in foods was developed by Hernandez-Borges, et al. (10). The method developed involved the comparison of the efficiency

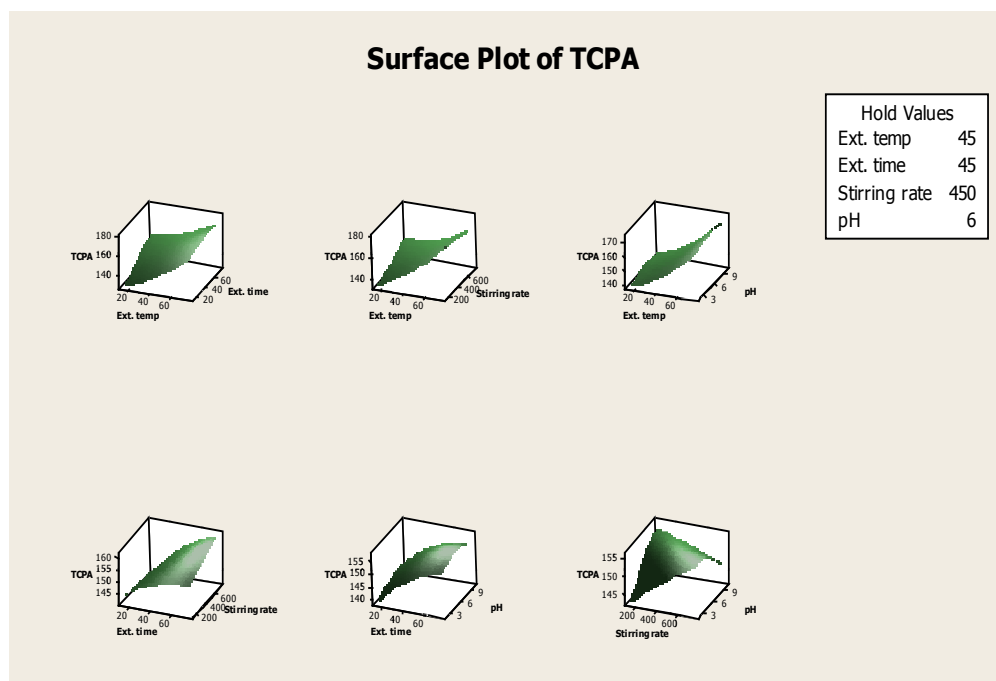


Figure 2. 3D Response Surface Plots (ext. time = extraction time and ext. temp. = extraction temperature).

of two detectors (UV and MS) coupled to a CE. A preliminary study was carried out to determine the best buffer solution suitable for the separation of the investigated pesticides, and optimization of ionic strength and pH was carried out using an OFAT approach. Optimization of SPME conditions (pH, salt addition, extraction time, and desorption time) was carried out using a CCD with an axial distance equal to 2, generated using a StatGraphic software. The optimized factors were determined using a response surface estimated for the CCD (10).

A green, simple, and efficient method was developed for preconcentrating and analyzing seven benzoylurea insecticides in fruit juice. The developed method involved the use of ionic liquid-assisted LLME based on the solidification of floating organic droplets. It was collected via a bell-shaped collection device and coupled to HPLC with variable-wavelength detection. Factors affecting the efficiency of the extraction technique were optimized using OFAT and an orthogonal array design. The experimental design and analysis was conducted using Minitab 16 software. The effect of the type and volume of the extraction solvent, effect of ionic liquid, effect of temperature, effect of rotation speed, effect of extraction and balancing time, and effect of ionic strength were optimized using a univariate approach. An orthogonal experiment [L25 (5^5)] containing 25 experimental runs performed at random was also used to evaluate the effect of five main factors (extraction speed, temperature, extraction time balancing, and salt addition) on the extraction efficiency. The results showed that the optimized values of each factor determined using the orthogonal array design were in good agreement with the OFAT experiment (152).

Conclusions

The main applications of chemometrics are factor screening, response surface examination, system optimization, and robustness. The following steps should be considered for effective and efficient applications (159):

- (1) The overall goals and objectives of the experiment must be known and determined.
- (2) The response/yield of the experiment should be clearly defined.
- (3) The variables with their levels should be carefully selected and defined.
- (4) A design that is compatible with the overall goals and objectives, number of variables considered, and level of precision should be chosen.

The need to frequently monitor pesticide residues and other contaminants in food commodities has led to the development of various sample preparation techniques. The microextraction techniques have been shown to be efficient, fast, and accurate for the qualitative and quantitative analyses of pesticide residues in fruits and vegetables, and they have continued to attract the attention of various stakeholders in the agricultural and food industries.

The use of microextraction techniques is emerging as a very reliable sample preparation method while using little or no solvent. The advantages of microextraction over the traditional methods include their simplicity of operation, rapidity, low cost, high recovery and enrichment factor, and environmental friendliness.

The use of a chemometric approach to screen and subsequently optimize extraction parameters has helped to reduce analysis time and to determine the optimized parameters. The application of chemometrics described in this paper shows its superiority over the univariate experiment. The combination of microextraction and chemometrics for the optimization

of parameters for the analysis of pesticide residues and other environmental contaminants is aimed towards developing green chemistry procedures. This is due to the fact that the number of experiment is reduced, thereby saving energy, money, time, and use of toxic solvents. The reduction in the number of experiments also fulfills the three facets of sustainability, economic viability, and social responsibility.

It was suggested that no single factor in microextraction techniques is independent, and therefore further studies and publications involving development of microextraction methods should be based on multivariate design of experiments. Leardi (121) has proposed that major journals should not accept any paper in which the developed method involves optimization of parameters using a univariate approach. There is also an urgent need for researchers to improve on the interpretations of various methods used in experimental designs

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