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ORIGINAL PAPER

Development of an analytical procedure for the determination of emerging and priority organic pollutants in leafy vegetables by pressurized solvent extraction followed by GC–MS determination

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Abstract A new multiresidue method for the determination of 13 emerging and priority pollutants in lettuce, including pesticides, pharmaceuticals, personal care products, polycyclic aromatic hydrocarbons (PAHs), and phenolic estrogens, has been developed using matrix solid-phase dispersion combined to pressurized fluid extraction (PFE) followed by gas chromatography coupled to mass spectrometry determination. A sequential optimization strategy based on solvent optimization first, followed by experimental design, was performed in order to maximize target analyte extraction with the aid of response surface methodology. Firstly, a full factorial design was applied to choose the significant variables in PFE; extraction time and temperature were found to have the biggest overall effect on response for most of analytes. They were later optimized performing a central composite design and the variable response of these factors was modeled for all analytes. It was found that marked differences in physicochemical nature exerted a strong influence on extraction conditions and yield. Therefore, the effect of parameters on the response was rather different for some compounds. To overcome this conflicting behavior, a multiple response simultaneous optimization was applied using the desirability function to achieve global optimal operating conditions. The optimal conditions were attained at 13.5 min (two extraction cycles) and 104 °C in the PFE by using hexane acetone mixture (1:1). Limit of detection and limit of quantitation values were found to be between 6.6 and 58 and 7.6 and 61.7 μg kg^{-1}, respectively.

Keywords Matrix solid-phase dispersion · Pressurized solvent extraction · Multiresidue analysis · Multivariate optimization · Emerging pollutants · Vegetable

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Introduction

Four out of ten people in the world are affected by water scarcity, and, in many of the countries suffering from it, irrigated agriculture represents the bulk of water demand. Accordingly, it is usually the first sector impinged by water shortage. Therefore, in order to sustain food production, an efficient use of all water resources is needed [1]. In this regard, reclaimed wastewater is a good crop irrigation alternative already in use in some countries such EEUU, Israel, Australia, and Spain among others [2]. Nevertheless, there is a potential risk related to the contaminants not removed or partially removed in wastewater reclamation to be taken up by the irrigated crops and thus entering into the human food chain.

The classes of contaminants occurring in wastewater effluents include human and veterinary pharmaceuticals, personal care products (PCPs), pesticides, and phenolic estrogens [3]. While the potential health and environmental hazards derived from continued exposure to these chemicals are not well understood, estrogenic responses on aquatic organisms exerted by endocrine disruptors [4],

inhibition of multixenobiotic resistance in mussels caused by polycyclic musks [5], PCPs, the carcinogenicity and/or mutagenicity elicited by PAHs in humans, and the potential for development of antibiotic resistance as a result of low-concentration exposure to pharmaceuticals[6] are well documented. In addition, the uptake of veterinary medicines [7–9], PAHs[10], and pesticides[11] from soil into plants has also been documented, making a risk assessment of further importance.

The determination of these compounds, however, represents an analytical challenge due to the broad physicochemical properties and the complex nature of environmental matrixes. Consequently, most of the determinations of these contaminants are focused on water or sewage sludge matrixes through methods that group compounds with similar properties[12, 13] or activities[14]. However, due to the complexity of vegetation as a matrix, the analytical methods available are limited to pesticide residues and hydrophobic contaminants (i.e., polychlorinated biphenyls, dichloro-diphenyl-trichloroethanes, PAHs) but very few are related to pharmaceuticals and health products [15, 16].

To address the need for pollutant screening, a general analytical trend is the application of liquid chromatography/tandem mass spectrometry (MS/MS) and gas chromatography (GC)–MS/MS techniques due to high selectivity and sensitivity [3]. These techniques have already found application in the determination of pharmaceuticals, PCPs, endocrine disruptors, and pesticides [17–21]. Most of these techniques involve very little sample treatment but due to its high cost it is not very suitable for monitoring studies dealing with large number of samples.

On the other hand, GC–MS has been the technique of choice for the determination of semivolatile and volatile organic compounds due to its favorable combination of high selectivity and resolution, good accuracy and precision, and wide dynamic concentration range and high sensitivity [18]. When appropriate sample treatment is applied, one is able to effectively analyze these types of molecules even in complex matrices. Sample treatment remains an essential factor in order to obtain accurate and precise results. In addition to the classical extraction approach in vegetable matrixes such solvent extraction [22] and liquid–liquid extraction[23], there are other recent alternatives such QuEChERS [24], matrix solid-phase dispersion (MSPD) [25], solid-phase extraction [26], solid-phase microextraction [27, 28], stir-bar-sorptive extraction [29, 30], supercritical fluid extraction [31, 32], microwave-assisted extraction [33, 34], and pressurized fluid extraction (PFE) [35, 36] that have been successfully applied to this kind of matrixes, mostly, however, only in pesticide determination.

The aim of this study was to develop a sensitive and inexpensive multiresidue method for the determination of 13 pesticides, pharmaceuticals, personal care products, PAHs, and phenolic estrogens in vegetable matrixes. Analyte extraction has been carried out by MSPD in combination with PFE followed by GC–MS determination. In comparison to the single methodologies, coupling of MSPD and PFE showed an evident improvement in selectivity and extraction efficiency. This improvement can be attributed to the combination of temperature and pressure and the MSPD cleanup; also an important feature of this methodology is the minimization of solvent usage [37, 38]. Accordingly, extraction variables affecting analyte recovery have been optimized by a two-step experimental design approach in order to minimize the number of experiments and to take into account the possible variable interactions.

Experimental

Materials, reagents, and apparatus

All standards were of analytical grade with between 97% and 99% purity. Pharmaceuticals, fragrances, and phenolic estrogens (ibuprofen, carbamazepine, diclofenac, clofibric acid, triclosan, tonalide, bisphenol A, nonylphenol) were purchased from Sigma-Aldrich (Bornem, Belgium); polycyclic aromatic hydrocarbons and trimethyl sulfonium hydroxide (TMSH) were obtained from Fluka (Buchs, Switzerland) and pesticides (lindane, atrazine, chlorothalonil) were bought from Riedel de Haën (Seelze, Germany).

Stock solutions of each individual compound were prepared in methanol or ethyl acetate at a concentration of 5,000 mg L^{-1}. All prepared standards were stored in the darkness at −20 °C and used to prepare the single and mixed working standards solutions. Gas-chromatography-grade acetone, methanol, acetonitrile, and ethyl acetate were purchased from Merck (Darmstadt, Germany). Florisil was ordered from Merck. Magnesium sulfate anhydrous and sodium chloride were purchased from Fluka (Buchs, Switzerland). Disodium hydrogen citrate sesquihydrate was bought from Aldrich (Milwaukee, USA). Trisodium citrate dihydrate was from Sigma (St. Louis, USA). The $MgSO_4$ and NaCl were baked for 5 h at 450 °C in a muffle furnace. Reagent water was deionized in the laboratory using the ultrapure water system Arium 611 from Sartorius (Aubagne, France).

A PFE, PSE One (Allentown, USA), was used for the extraction of target analytes from the vegetable matrix.

MSPD procedure

The lettuce samples analyzed were obtained at a local market. About 500 g of lettuce were comminuted with the aid of liquid nitrogen. Then, a 0.5-g portion was transferred

to a porcelain mortar. One gram of florisil was vigorously blended with the sample for 8 min using a pestle, then 0.2 g Na_2SO_4, 0.05 g Na_3–citrate dihydrate, 0.05 g NaCl, 0.02 g Na_2H–citrate sesquihydrate, and 3 g of Hydromatrix were added and blended to obtain a thoroughly homogenous mixture [38, 39]. Samples were spiked after nitrogen comminution with 25 μl of a mixed standard solution at 120 mg L^{-1}, prepared in methanol. The sample was left to stand for 30 min before extraction.

PFE procedure

The obtained mixture was transferred to a 11-mL stainless steel cell. The remaining space left in the cell was completely filled with Hydromatrix. The PFE instrument used as an extraction solvent a mixture of acetone–hexane 1:1 and ethyl acetate–hexane 2:1 and 1:1. These solvent mixtures were transferred to the cell, which then was heated and pressurized to the selected conditions. The recovered extract was collected in amber glass vials, and the cell was flushed and purged with gaseous nitrogen.

Extract partitioning

The obtained extract was evaporated to 5 mL approximately under a gentle nitrogen stream. Afterwards, 3 mL of a 0.6% K_2CO_3 aqueous solution were added to the vial; the hexanic phase was recovered and the remaining aqueous phase was extracted in 3×3 mL hexane. Then, the hexane phase was percolated through a florisil–$MgSO_4$ column. This procedure rendered the neutral fraction, where neutral and basic analytes were recovered, namely tonalide, nonylphenol, dibenz[a,h]anthracene, pyrene, chlorothalonil, lindane, and atrazine. Subsequently, 3 mL of ethyl acetate and 75 μl of 5% HCl were added to the aqueous phase. Then, the organic phase was recovered and the aqueous phase was further extracted 2×3 mL ethyl acetate. The organic phase was percolated through a Na_2SO_4 column. This procedure rendered the acid fraction, where acid analytes were recovered, namely triclosan, ibuprofen,, diclofenac, clofibric acid, and bisphenol A. Though carbamazepine is not of acid nature, it was recovered in the acid fraction due to its low affinity for hexane, which was the solvent used to recover neutral and basic compounds. Both neutral and acid fractions were gently evaporated to approximately 300 μl; this step was followed by the addition of 246 ng of triphenylamine as internal standard. The neutral fraction was directly analyzed by GC–MS, while the acid fraction was derivatized by adding 10 μl of TMSH to a 50-μl sample aliquot. The derivatization reaction took place in the chromatograph injector port at 250 °C. The determination was performed by GC–MS.

Validation

Linearity of the GC–MS method was proven because the coefficient of determination R^2 values were always >0.99 for the linear regression equations of all analytes, for six concentration levels; quantitation was performed on the basis of the internal standard procedure (Table 1).

Results and discussion

Optimization

Screening phase

Prior to the screening design, the effect of solvent on the extraction yield was evaluated in the PFE at medium operating conditions. The acetone–hexane 1:1 mixture was found to be the most suitable (Table 2) taking into account the widely different physicochemical properties of the target analytes and the complex nature of the matrix. Then, low and high values for extraction time and temperature were selected according to previous knowledge on the process. Since extraction yield depends on several factors, in order to find those which exert the largest influence, a 2^3 full factorial design was applied (Table 3). The analyzed factors were temperature, extraction time, and cycle number. A one-way analysis of variance was performed to the experimental data obtained, which showed that interaction between extraction time and temperature followed by single factors had the largest effect (positive or negative) on the response of most of analytes (not shown) but in most of the cases this is not statistically significant ($p>0.05$). From low to high temperatures, viscosity and solvent surface

Table 1 Selected parameters for GC–MS determination

Parameter	Description
Injection method	Splitless mode (0.5 min)
Injection volume	2 μl
Injector temperature	270 °C
Capillary column	TRB-5MS (30 m×0.25 mm×0.25 μm) from Teknokroma (Spain)
Carrier gas	Helium
Flow rate	1.4 mL/min (constant flow)
Temperature program	Initial 50 °C (2 min) ramped at 15 °C/min to 120 °C, at 4 °C/min to 160 °C, at 7 °C/min to 220 (5 min), at 5 °C/min to 290 °C (5 min), and at 15 °C/min to 320 °C (5 min).
Ionization	EI mode at 70 eV
Analysis mode	Full scan, two scans per second
	Mass range, 50–500 *m*/*z*

Table 2 Recoveries according with solvent mixture

Solvent mixture	Analyte group	Average recovery[b], %
Ethyl acetate–hexane (2:1)	Acids	82 (46–91)
	Neutrals	17 (5–58)
Ethyl acetate–hexane (1:1)	Acids[a]	80 (35–128)
	Neutrals	62 (11–126)
Acetone–hexane (1:1)	Acids	70 (46–91)
	Neutrals	75 (54–94)

[a] Carbamazepine was not recovered

[b] Values between parentheses correspond to highest and lowest recovery

tension decrease, while its solvent strength and rate of diffusion into the sample increase, making this factor and its interaction with other factors evidently important to this process for neutral and inert molecules (i.e., lindane, pyrene, etc.). Nevertheless, functionalized molecules (i.e., carbamazepine, clofibric acid, etc.) are more labile and prone to by-product formation at higher temperatures leading to a negative effect usually interacted with other factors. Cycle number was found to exert the lowest effect on the extraction yield; therefore, it was fixed and kept constant at two in the following optimization experiments and only the rest of the factors were considered.

Response surface design

In order to obtain further information on the effect of factors in the extraction yields of the analytes, a response surface design methodology was applied. A central composite design was performed, it consisted of 11 runs, which were a combination of the chosen factors within the following ranges: extraction temperature (76–104 °C) and extraction time (6–14 min), while keeping the cycle number was fixed at two (Table 4). Maximum extraction yield was highly satisfactory for most of the analytes; mean maximum yield for acid compounds was 92% (54–116%) with a relative standard deviation (RSD) ranging form 5% to 19%. For neutral compounds, mean maximum yield was 83% (65–95%) with an RSD ranging from 2% to 4%. Only two out of the 13 compounds showed yields under 70% that was the case of clofibric acid and chlorothalonil.

Response variable namely extraction yield of all analytes was fitted to polynomial models. The model coefficient was calculated by a multiple regression. In Table 5, the R^2 regression coefficient for all analytes and their corresponding model are shown; broad differences in compound nature were reflected in model order. In this regard, acid analytes and atrazine fitted better to a second-order model, while the behavior of the remaining compounds was best described by a cubic model; still, all but three of the resulting models explained more than 70% of the target analyte variance.

Figure 1a shows the response plot for atrazine as time and temperature were varied. Temperature does not exert a remarkable influence on the extraction yield but, as extraction time increases, it increases the extraction yield, which is in good agreement with the model for this analyte in which the most significant term is the quadratic time ($p<0.05$). Moreover, Fig. 1b shows the response plot for diclofenac; a minimum is observed at mean time and temperature; the highest extraction yield is reached in the zone of maximum time and temperature; the behavior of this analyte is clearly influenced by both time and temperature, reflected in the significance ($p<0.05$) of both quadratic factors in the model for this compound. The same behavior is exhibited by ibuprofen (not shown), for which the quadratic terms for time and temperature are, as in the case of diclofenac, significant in the model ($p<0.05$). The resemblance in these compound behavior could be explained by similarities in their properties such log Kow (ibuprofen 3.79, diclofenac 3.18), which could mean that compound affinity for the extractive solvent behaves similarly in the different extraction conditions evaluated.

Clofibric acid behavior, as extracting factors were varied, was described by two maxima in yield, one in the zone of maximum time and temperature and the other at minimum time and temperature. In the zone of medium

Table 3 Factors and levels of the 2^3 full factorial design

Factors	Levels		Run										
	1	2	1	2	3	4	5	6	7	8	9	10	11
(X1) Extraction temperature, °C	80	120	100	120	80	120	80	100	80	120	80	120	100
(X2) Extraction time, min	5	15	2	1	4	4	1	2	1	1	4	4	2
(X3) Cycle number	1	4	10	15	15	15	5	10	15	5	5	15	10

Table 4 Factors and levels of the central composite design

Factors	Levels			Star point (α=1.41421)		Run										
	Low (−1)	Central (0)	High (+1)	−α	+α	1	2	3	4	5	6	7	8	9	10	11
(X1) Extraction temperature, °C	76	90	104	70	110	70	76	104	90	76	90	110	90	90	104	90
(X2) Extraction time, min	6	10	14	5	15	10	6	14	10	14	10	10	15	10	6	5

extractive conditions, a clear minimum in yield is observed. Figure 1c shows the response plot for triclosan; the highest response was achieved at high temperatures and medium time; this trend was shared by bisphenol A (figure not shown). Temperature seemed to exert the largest influence on both triclosan and bisphenol A response, in spite of lack of significant terms in their models ($p<0.05$). Chlorothalonil (Fig. 1d), tonalide, nonylphenol, dibenz[a,h]anthracene, and pyrene exhibited a similar behavior. For this set of compounds, the minimum in extraction yield was found at minimum time and temperature; inversely maximum yield was attained at maximum time and temperature. In the polynomial models fitted to these compounds, no significant terms are present at $p<0.05$. However, time appears to be the most influencing factor in the behavior of this set, especially at high temperatures where the increase in extraction yield becomes more evident as time increases. It is interesting to note that four out of the five compounds have high log Kow, dibenz[a,h]anthracene 6.7, tonalide 6.35, nonylphenol 5.99, pyrene 5.08, and chlorothalonil 3.66. When analyzing carbamazepine behavior, it can be seen that a maximum in response is reached at maximum time and low temperature (figure not shown). An increase of yield with time is observed at high temperatures, even though temperature appears to have a negative effect on response at long extraction times. The response for lindane was characterized by a maximum yield obtained at maximum time and minimum temperature; time appears to have the largest effect in response because at both low and high temperatures best yield is obtained with larger extraction time (figure not shown).

The individual response plots revealed conflicting optimum parameter levels for the extraction yield. Intrinsic differences in physicochemical nature of the analytes played a visible role outside the experimental design domain; their importance was visible because parameters exerted different magnitude and even direction on the response variable depending on the analyte.

Table 5 Model characteristics of target analytes

Analyte	Model order	Coefficient of determination, R^2	Significant terms in the model ($p<0.05$)
Tonalide	3	0.71	None
Nonylphenol	3	0.79	None
DBA	3	0.73	None
Pyrene	3	0.95	None
Lindane	3	0.55	None
Atrazine	2	0.63	$X2^2$
Chlorothalonil	3	0.62	None
Ibuprofen	2	0.96	$X2^2$, $X1^2$
Carbamazepine	3	0.97	X1, $X1^2$, $X2^2X1$
Diclofenac	2	0.90	$X2^2$, $X1^2$
Clofibric acid	2	0.89	X1X2, $X1^2$
Triclosan	3	0.88	None
Bisphenol A	3	0.81	None

X1 temperature, *X2* time

Optimization for multiple responses

To overcome differing responses of individual analyte response, a multiple response optimization approach was performed. Desirability is an objective function that ranges from zero outside of the set limits to one at the goal [40]. The numerical optimization finds a point that maximizes a function; then, the desirability function D was used to simultaneously optimize responses of all target analytes. In multiple response, a desired weight is given to each response; in the present study, when building this function, higher desirable values were given to those analytes with lower recoveries. Figure 2a, b shows the overall desirability plot when extraction time and temperature were varied. The overall desirability values were lowest in the region of low to medium extraction time and low to medium extraction temperature, while it reached its maximum at 0.68 in the region of higher temperature and time. It is important to note that the goal of optimization is to find the best set of conditions in which all responses are maximized not to get a desirability value of 1. This value is completely dependent on how closely the lower and upper limits are set relative to the actual optimum. According to the results obtained, the optimal condition for the D function is obtained with time set at 13.5 min and temperature at 104 °C. Theoretical recoveries reached by the desirability function are shown in Table 6.

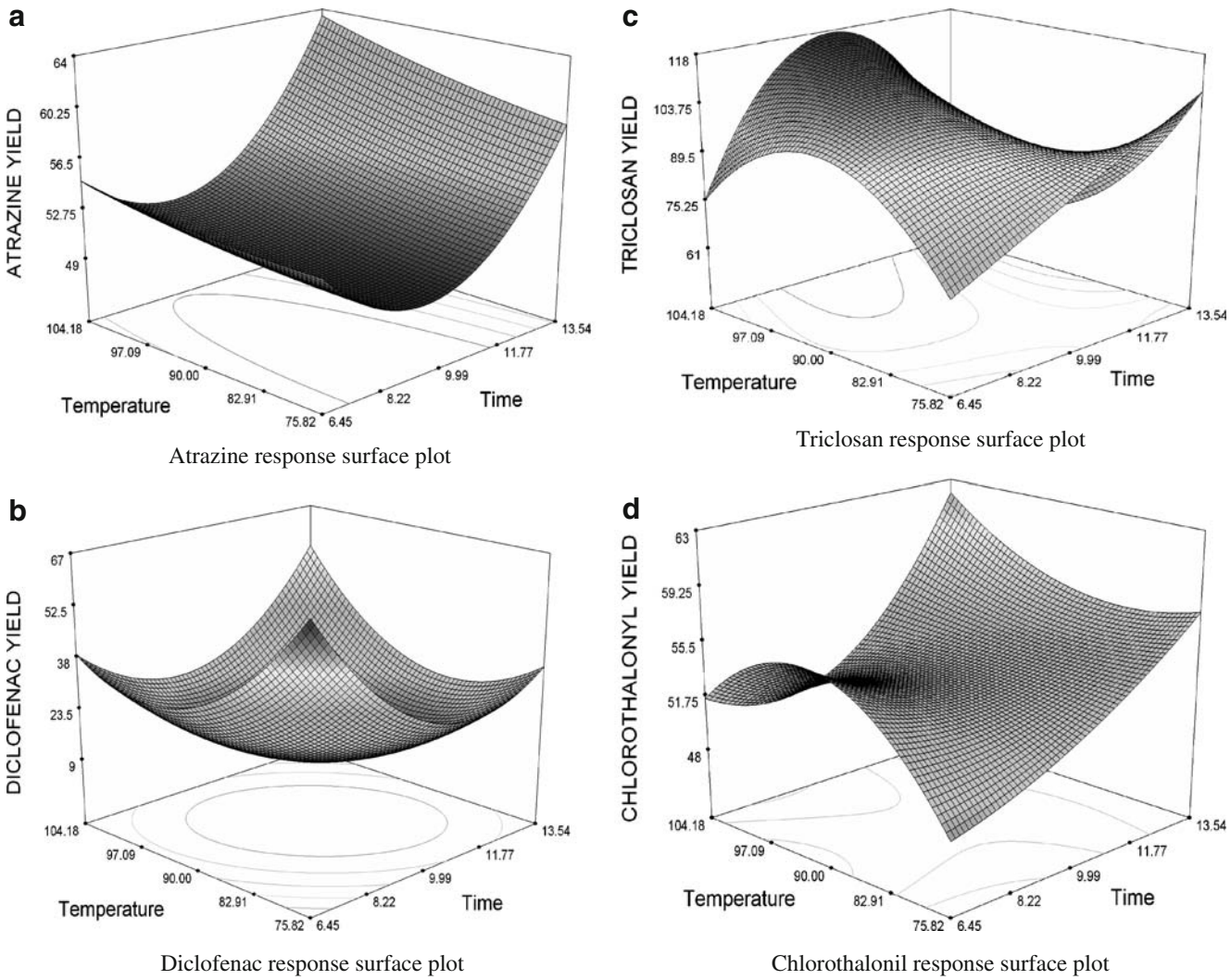


Fig. 1 **a** Atrazine response surface plot. **b** Diclofenac response surface plot. **c** Triclosan response surface plot. **d** Chlorothalonil response surface plot

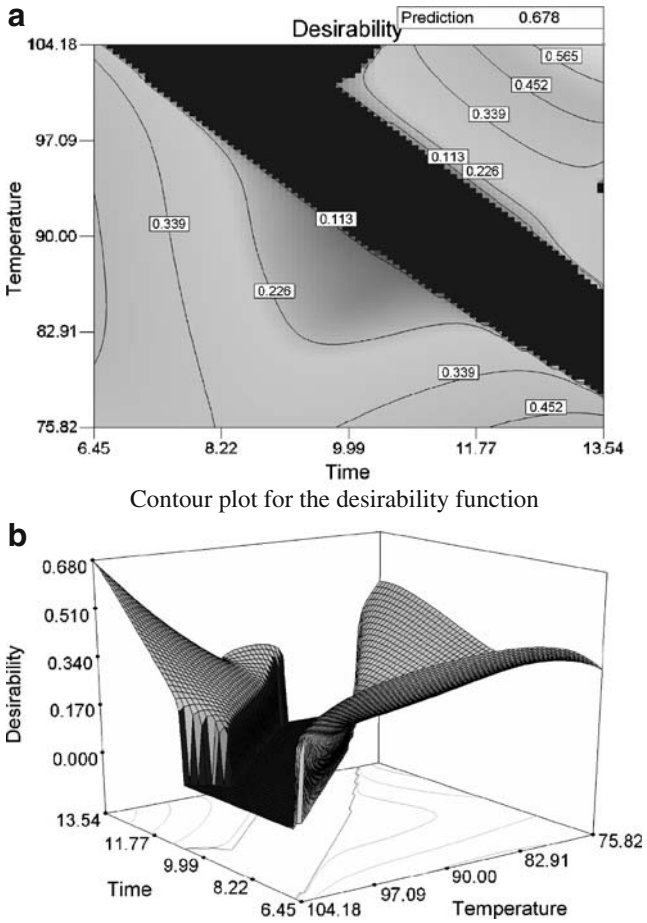
Method validation

Validation of global optimal operating conditions was carried out by running those conditions and evaluating analyte recovery at two spiking levels for neutral compounds (0.1 and 0.5 mg kg^{-1}) and at one spiking level for acid compounds (0.3 mg kg^{-1}; Table 6). Recoveries and relative standard deviations were calculated from a triplicate carried out on the same day at all concentrations. The obtained recoveries were overall acceptable; average recoveries for neutral and acid analytes were 70.5% and 71.8%, respectively. In case of the acid analytes, the mean deviation of the actual and theoretical recoveries was 29.9%. Indeed, the compound whose actual recovery had the highest deviation from the predicted recovery was clofibric acid with 71% being not immediately apparent due to its good model fitting. For neutral compounds, the mean deviation of the actual recovery and theoretical one was 27.5% for the low spiking level and 28.2% for the high one. Compounds which exhibited the worst recovery deviation were lindane with 72.6% and chlorothalonil with 50.2%. Nevertheless, both of these compounds had a poor model fitting (R^2_{lindane}=0.55 and $R^2_{\text{chlorothalonil}}$=0.62), which could explain this deviation in their recoveries.

Method performance

Linearity and figures of merit

Linearity for neutral analytes ranged from 0.006 to 2.40 mg kg^{-1}, while for acid analytes it was found to be between 0.005 and 2.41 mg kg^{-1}. The limits of detection (LOD) of the method were defined as the mean background noise in a blank triplicate, namely matrix sample, plus three times the



Contour plot for the desirability function

Response surface plot for the desirability function

Fig. 2 **a** Contour plot for the desirability function. **b** Response surface plot for the desirability function

Table 7 Figures of merit

Analyte	LOD (μg kg^{-1})	LOQ (μg kg^{-1})
Tonalide	18.2	27.4
Nonylphenol	58.1	61.7
DBA	35.9	40.3
Pyrene	10.7	13.1
Lindane	18.4	21.3
Atrazine	33.0	39.6
Chlorothalonil	53.7	54.2
Ibuprofen	16.1	16.9
Carbamazepine	18.5	24.5
Diclofenac	23.2	25.4
Clofibric	30	30.6
Triclosan	6.6	7.6
Bisphenol A	13.6	15.3

standard deviation of the background; the limits of quantitation (LOQ) were defined as the mean background noise in a blank triplicate, namely matrix sample, plus ten times the standard deviation of the background. In Table 7, the figures of merit for all the analytes are shown. The LOD for target analytes ranged from 6.6 to 58 μg kg^{-1}, while LOQ values were between 7.6 and 61.7 μg kg^{-1}.

Repetitivity

Method accuracy and repetitivity were evaluated by performing recovery studies using a lettuce spiked at two concentrations, 0.1 and 0.5 mg kg^{-1} in the case of neutral compounds and 0.3 mg kg^{-1} for acid compounds. Samples were spiked with 25 μl of the appropriate mixed standard solution in methanol. All experiments were performed in triplicate on the same day at both concentrations. The

Table 6 Recovery data obtained from lettuce matrix spiking

Neutral analytes	Theoretical recovery	0.1mg kg^{-1}		0.5mg kg^{-1}		Acid analytes	Theoretical recovery	0.3mg kg^{-1}	
		R%	RSD%[a]	R%	RSD%[a]			R%	RSD%[a]
Tonalide	92	106	13.4	87.0	8.4	Ibuprofen	92	83.2	0.88
Dibenzo[a,h] anthracene	84	57.3	9.3	50.8	12.4	Diclofenac	55	69.5	2.8
Pyrene	94	93.6	21.5	59.7	6.5	Clofibric acid	29	50.2	1.1
Lindane	68	117	10.1	73.7	6.9	Triclosan	74	91.9	0.5
Atrazine	63	59.3	9.6	79.5	3.0	Bisphenol A	76	61.1	0.2
Nonylphenol	95	79.3	11.1	54.6	9.9				
Chlorothalonil	62	30.9	14.3	37.8	8.8				
Carbamazepine[b]	59	75.0	14.6	na	na				

na not available

[a] Mean recovery and variance (expressed as relative standard deviation) from analysis of spiked samples (n=3)

[b] Spiking level was 0.3 mg kg^{-1}

relative standard deviations are shown in Table 6. Larger variability was obtained for neutral analytes. Their relative standard deviation values ranged from 3% to 21.5%, whereas for acid compounds they were much smaller ranging from 0.2% to 14.8%.

Analysis of a real sample

The efficiency of the method developed was evaluated by analyzing a nonspiked lettuce sample bought at a local market. The sample was processed in triplicate as described in the "Experimental" section. Ibuprofen was identified and quantitated on the basis of the internal standard procedure, and it was found to be at a concentration of 28.5 ng g^{-1}; the relative standard deviation was 10.54%.

Conclusions

A multiresidue methodology for the determination of 13 emerging and priority pollutants in lettuce based on MSPD combined with PFE and GC–MS determination was successfully developed. RSM was used to optimize the parameters of PFE for each analyte. The use of the desirability function allowed for the simultaneous optimization of all analytes in spite of their conflicting responses to yield global optimal extraction conditions. Theoretical results obtained with this function were validated by running these conditions at different spiking levels, the recoveries obtained were overall acceptable. The deviation of the actual recoveries from the theoretical values could be explained by the poor fit to the model exhibited by some analytes. The use of experimental design and RSM along with the application of the desirability function yields reliable data obtained with the minimum of experimentation. Good results with respect to accuracy and repetitivity were attained in the range of concentrations studied for most of the analytes of interest. Finally, an incurred pharmaceutical could be identified in a lettuce sample obtained from local sources.

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