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Orthogonal array designs for the optimization of solid-phase extraction

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Abstract

A systematic approach based on orthogonal array designs for the optimization of solid-phase extraction (SPE) is described. As an example, an off-line SPE approach for extracting 30 pesticides from water was optimized based on the examination of the relevant parameters by orthogonal array designs. The advantages and the disadvantages of the method are discussed.

1. Introduction

Solid-phase extraction (SPE) is a very attractive choice for the trace enrichment of samples prior to instrumental analysis owing to its many advantages over conventional liquid–liquid extractions, such as the decreased use of hazardous solvents, extractions that are not hindered by the formation of emulsions, high extraction efficiency and convenience in automation [1,2]. In recent years there have been many studies leading to a better understanding of various effects on SPE and extended application of this technique [1–11]. This knowledge is also very helpful to those who wish to develop SPE methods for specific purposes. The process of developing an SPE method often involves the investigation of many variables which may affect the efficiency of SPE and the selection of suitable levels for each variable (optimization). The optimization can be achieved either by the trial and error method, the one factor at a time method or systematic methods. Generally, systematic methods are more efficient than trial and error and one factor at a time methods, especially when the number of variables to be tested is large and the interactions between the variables are important [12].

In recent years, some systematic methods, such as simplex optimization and factorial design, have been adopted to search efficiently for optimum conditions for an analysis [13–16]. Factorial designs have an advantage over simplex optimization that in the region preceding the optimum, a large amount of quantitative information about the significance of various effects and interactions can be obtained [17]. Also, factorial designs can deal with both continuous and discrete factors, whereas simplex optimization can only deal with continuous factors. One obvious disadvantage of the factorial de-

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signs is the large number of experiments required when several variables are examined. However, the number of the experiments can be considerably reduced by the use of fractional factorial designs, such as orthogonal array designs.

Orthogonal array designs, the origin and characteristics of which have been described in detail elsewhere [18], are a sophisticated time- and cost-saving testing strategy that draws an orthogonal array to pinpoint areas where variations may be reduced [19]. Besides retaining the merit of routine fractional factorial designs, the interaction effects between variables can be considered as independent factors and estimated by orthogonal array design along with the corresponding linear graphs or triangular tables [19,20].

In this study, an off-line SPE approach for extracting 30 pesticides from water was optimized by orthogonal array designs, just as an example, to demonstrate the application and potential of this systematic optimization technique.

2. Experimental

2.1. Chemicals

HPLC-grade acetonitrile and methanol were obtained from Fisher Scientific (Fair Lawn, NJ, USA). Ascorbic acid was purchased from Merck (Darmstadt, Germany) and was dissolved in HCl-acidified water (pH 2). C_{18} cartridges (Envi-18, 3-ml tubes) and graphitized carbon black cartridges (Envi carb, 3-ml tubes) were obtained from Supelco (Bellefonte, PA, USA). A mixture of humic acid was supplied by Kasei (Tokyo, Japan). Humic acid solutions having concentrations equivalent to organic carbon contents of about 2 and 10 mg l^{-1} were prepared according to a previously reported procedure [6]. The pH of the solutions was adjusted to 8.5 or 3.5 with 0.1 *M* NaOH solution or HCl. Pesticides (listed in Table 6) were obtained from Supelco and had purities greater than 98%. Individual standard solutions were prepared by dissolving 20 mg of each pesticide in 20 ml of methanol. As it was very difficult to separate all 30 of the pesticides considered in a single chromatographic run, the pesticides were divided into two groups and studied separately. Group 1 contained nineteen and group 2 eleven pesticides.

2.2. Procedure for recovery determination

Aqueous samples (0.5 l) were fortified with know volumes of either group 1 or group 2 working standard solutions. For tap water, 0.25 g of sodium thiosulphate was added to 0.5 l of water before pesticides were added to prevent the oxidation of some pesticides. The water was forced to pass through a preconditioned cartridge by vacuum from a circulating pump. After the water had passed through the cartridge, the pump was disconnected. The cartridge was turned upside down and a 5-ml pipette tip was attached to the outlet of the cartridge as a solvent reservoir. The cartridge was washed with 10 ml of distilled water by the back-flush method. If the distilled water was unable to percolate through the cartridge, pressure was applied to the top of the solvent reservoir. The trap was air dried for 0.5 min by vacuum. The analytes were then eluted by front flushing the cartridge with 5 ml of methanol. The eluate collected in a 100-ml flask was concentrated to *ca.* 0.5 ml using a rotary evaporator set at 45°C. Isobutanol (0.2 ml) was added to the eluate as a "keeper solvent". The concentrated eluate was transferred into a 5-ml graduated cylinder using a Pasteur pipette. The flask was rinsed with 0.5 ml of methanol. The solvent was also transferred into the graduated cylinder. The volume of the liquid in the cylinder was made up to 1 ml for HPLC analysis.

2.3. Liquid chromatographic analysis

Liquid chromatographic analysis was carried out with an LC-6A liquid chromatograph (Shimadzu, Kyoto, Japan) equipped with a UV–Vis detector. The injection volume was 20 μl. The wavelength of the detector was set at 215

nm. An LC-ABZ column (25 cm × 4.6 mm I.D.) from Supelco was used for the separation. The mobile phase was acetonitrile–phosphate buffer solution (pH 2.6) (45:55).

2.4. Experimental design

The first experiment was designed to optimize the extraction using graphitized carbon black cartridges. Four variables that may affect the extraction efficiency and the possible interactions were examined by using a two-level orthogonal array design: the volume of water sample, the pesticide concentration in water, the elution method and the time for air-drying the trap. The average recovery of the pesticides in group 1 was used as the response. The selection of the variables and their levels was based on previous knowledge of SPE. For example, Di Corcia *et al.* [4] reported that back-flushing was better than the conventional front-forward elution method when a graphitized carbon black cartridge was used. A comparison between the two elution methods was made in the first experiment to see whether this statement was still true with the pesticides selected. The selection of the air-drying time as a variable was based on the consideration that the effluent air passing through the cartridge may cause evaporative losses of some volatile analytes. As the evaporation loss of the pesticides from the sorbent in the air-drying step is less likely to be affected by the other three variables, its interactions with them were neglected.

In the application of fractional factorial designs, previous knowledge of the variables is very helpful in arranging the experiment. In the first experiment, the sorbent type was not tested because each type of sorbent may have its own optimum conditions and it will be "fairer" to compare their extraction efficiencies under their own optimum conditions. Therefore, the conditions for the graphitized carbon black cartridge were optimized first. In the second experiment, it was compared with a C_{18} cartridge under conditions favouring the graphitized carbon black cartridges. If a C_{18} cartridge is better than a graphitized carbon black cartridge, C_{18} will be selected for the analysis. Otherwise, another comparison may be conducted after the optimum conditions for C_{18} have been found.

It has been reported that pre-eluting graphitized carbon black cartridges with ascorbic acid solution after conditioning with methanol can prevent partial irreversible adsorption of some compounds, and that the addition of sodium thiosulphate to tap water can prevent the oxidation of some compounds [4]. In addition to the comparison between the graphitized carbon black and C_{18} cartridges, the effects of these two treatments were also tested in the second experiment. Consideration was also given to the interaction effects between the variables.

In the analysis of real samples, a large amount of humic substances may decrease the extraction efficiency [2,4,6]. The pH and salinity may also affect the extraction [2,7]. Liska *et al.* [2] observed that the adverse effect of humic acid was more serious at lower pH. There is a possibility of decreasing this adverse effect by adjusting the pH and increasing the salinity. The third experiment was accordingly designed to test this possibility by examining the effects of humic substances, pH and salinity and their interactions. In the first experiment, the two elution methods (back-flush and front-forward) were compared with a graphitized carbon black cartridge. The result may differ if a C_{18} cartridge is used. Therefore, in the third experiment, the two methods were compared again with a C_{18} cartridge. The assignment of the factors and the levels is shown in Table 1. Details on the assignment of factors in the orthogonal array designs have been given elsewhere [19,20].

3. Results and discussion

The results of the three experiments are given in Table 2. The level means of the average recoveries for each factor were calculated according to the assignment of the experiments. For example, to obtain the level mean of factor *B* at level 2 in the first experiment, the average recovery data of the four trials in which the level of *B* was set at 2 (trials 3, 4, 7 and 8; see Table

Table 1
Assignment of factors and levels of the OA_7 (2^7) matrix for investigating the effects of the factors on the recoveries of pesticides from water

Experiment	Level	Column No.						
		1	2	3	4	5	6	7
		Factor[a]						
		A	*B*	*A* × *B*	*C*	*A* × *C*	*B* × *C*	*E*
First	1	0.5	60		Back-flush			5
	2	1.0	10		Front-flush			30
Second	1	C_{18}	200		0.5			
	2	GCB	0		0			
Third	1	2	3.5		0			Front-flush
	2	10	8.5		10			Back-flush

[a] For the first experiment: *A* = volume of the sample (l); *B* = concentration of the pesticides in water ($\mu g\ l^{-1}$); *C* = elution method; *E* = air-drying time (min). For the second experiment: *A* = type of cartridge (GCB = graphitized carbon black); *B* = amount of ascorbic acid used for cartridge conditioning (mg); *C* = concentration of sodium thiosulphate in water ($g\ l^{-1}$); *E* = unassigned column. For the third experiment: *A* = concentration of dissolved organic substances ($mg\ l^{-1}$); *B* = pH of water; *C* = concentration of sodium chloride in water (%); *E* = elution method. *A* × *B*, *A* × *C* and *B* × *C* mean the interactions between the factors.

2) were pooled and divided by the number of the trials: $B_2 = (69.5 + 75.0 + 85.9 + 57.9)/4 = 72.1$. The means at the two levels of a variable reveal how the response will change when the level of the variable is changed. When significant interactions exist between two variables, say *A* and *B*, the level means for *B* were calculated according to the level of *A*. Thus, to obtain the mean for variable *B* at level 1 when *A* was set at level 2, the average recovery data of the two trials in which *A* was set at level 2 and *B* was set at level 1 (trials 5 and 6) were pooled and divided by 2.

Fig. 1 shows the relationship between the level means of average recovery and the variable levels of significant variables. The analysis of variance tables were constructed for testing the significance of the effects (Tables 3–5). The sum of squares for an effect was calculated by using

Table 2
An OA_8 (2^7) matrix along with the results of the three experiments

Trial No.	Column No.							Average recovery (%)[a]		
	1	2	3	4	5	6	7	I	II	III
1	1	1	1	1	1	1	1	87.8	83.8	95.3
2	1	1	1	2	2	2	2	59.3	91.9	84.1
3	1	2	2	1	1	2	2	69.5	89.5	72.2
4	1	2	2	2	2	1	1	75.0	87.3	72.3
5	2	1	2	1	2	1	2	84.5	78.1	69.1
6	2	1	2	2	1	2	1	80.9	86.1	60.6
7	2	2	1	1	2	2	1	85.9	79.6	51.4
8	2	2	1	2	1	1	2	57.9	75.5	63.1

[a] Average recovery of the pesticides studied; I = the firsts experiment; II = the second experiment; III = the third experiment.

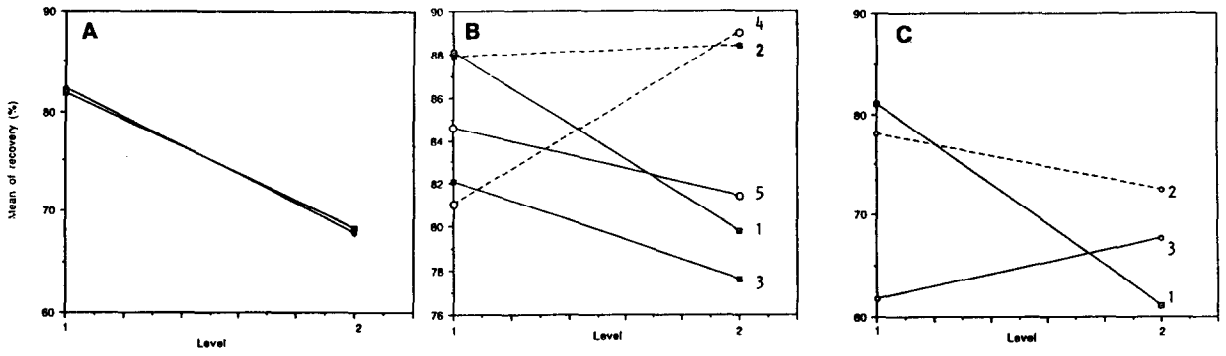

Fig. 1. Relationship between the level mean of average recoveries and the factor level. (A) The first experiment; □ = elution method (back-flush and front forward elution), ◆ = air-drying time (5 and 30 min). (B) The second experiment; 1 = cartridge type (C_{18} and GCB), 2 = use of ascorbic acid with C_{18} cartridge (used and not used), 3 = use of ascorbic acid with GCB cartridge (used and not used), 4 = addition of sodium thiosulphate with ascorbic acid (added and not added), 5 = addition of sodium thiosulphate without ascorbic acid (added and not added). (C) The third experiment; 1 = concentration of humic acid (2 and 10 mg l^{-1}), 2 = concentration of sodium chloride at pH 3.5 (0 and 10%), 3 = concentration of sodium chloride at pH 8.5 (0 and 10%).

Table 3
An ANOVA table for the first experiment

Source of variance	Sum of squares	Degrees of freedom	Mean square	*F* value	Significance[a]
Volume of sample (*A*)	38.7	1	38.7	3.72	
Concentration (*B*)	73.2	1	73.2	7.04	
Elution method (*C*)	372.6	1	372.6	35.8	$P<0.05$
Air-drying time (*E*)	426.3	1	426.3	41.0	$P<0.05$
$A \times B$	49.0	1	49.0	4.71	
Pooled error[b]	20.8	2	10.4		
Total	980.6	7			

[a] The critical *F* value is 8.53 at 90% confidence and 18.5 at 95% confidence.
[b] Pooled error result from pooling negligible effects ($A \times C$, $B \times C$).

Table 4
An ANOVA table for the second experiment

Source of variance	Sum of squares	Degrees of freedom	Mean square	*F* value	Significance[a]
Type of cartridge (*A*)	137.8	1	137.8	285	$P<0.01$
Ascorbic acid (*B*)	8.0	1	8.0	16.7	$P<0.1$
Sodium thiosulphate (*C*)	13.0	1	13.0	23.7	$P<0.05$
$A \times B$	12.0	1	12.0	25.0	$P<0.05$
$B \times C$	62.7	1	62.7	131	$P<0.01$
Pooled error[b]	0.95	2	0.48		
Total	233.9	7			

[a] The critical *F* value is 8.53 at 90% confidence, 18.5 at 95% confidence and 98.5 at 99.0% confidence.
[b] Pooled error result from pooling negligible effect ($A \times C$) and unassigned column effect.

Table 5
An ANOVA table for the third experiment

Source of variance	Sum of squares	Degrees of freedom	Mean square	F value	Significance[a]
Humic acid (A)	792.0	1	792.0	29.2	$P < 0.05$
Water pH (B)	312.5	1	312.5	11.5	$P < 0.05$
NaCl (C)	8.0	1	8.0	0.3	
$B \times C$	128.8	1	128.8	4.8	
Pooled error[b]	81.4	3	27.1		
Total	1322.7	7			

[a] The critical F value is 5.54 at 90% confidence, 10.1 at 95% confidence and 34.1 at 99.0% confidence.
[b] Pooled error result from pooling negligible effects ($A \times B$, $A \times C$ and E).

the equation $SS_i = [(M_2 - M_1) \cdot 4]^2/8$, where M_2 and M_1 are the means for effect i at levels 2 and 1, 4 is the number of data used to calculate the mean and 8 is the number of data produced by the experiment. The importance of each effect was calculated using the relative contribution (RC), which was calculated by using the equation $RC_i = SS_i/\Sigma SS$. As the trials in the experiments were not repeated, the error was estimated by combining the mean squares of negligible effects. The negligible effects were selected by using the method described by Montgomery [16].

The ANOVA results of the first experiment (Table 3) indicate that the air-drying time and the elution method have significant effects on the average recovery ($RC = 38.0\%$ for elution method and 43.5% for air-drying time), whereas the effects of the sample volume and the concentration of the pesticide are not significant. Fig. 1 suggests that back-flush elution is better than front-forward elution and a shorter air-drying time is better. The results with the elution method confirmed Di Corcia *et al.*'s results [4], although the effect of the air-drying time had not been expected to be so important before. The flow-rate of air passing through the cartridge was 3 l min^{-1}. Such a high flow-rate can possibly cause considerable evaporative losses of pesticides from the cartridge. Even 5 min may still be too long for air-drying. In subsequent experiments, the air-drying time was decreased to 0.5 min and the back-flush method was adopted for elution.

The ANOVA results of the second experiment (Table 4) suggest that the cartridge type (A), ascorbic acid (B) and sodium thiosulphate (C) have significant effects on the average recovery, among which the cartridge type is the most important ($RC = 58.9\%$). Significant interactions also exist between the cartridge type and ascorbic acid treatment ($A \times B$) and between ascorbic acid treatment and the addition of sodium thiosulphate ($B \times C$). Fig. 1 suggests that a C_{18} cartridge is better than a graphitized carbon black cartridge and that ascorbic acid treatment can improve the extraction efficiency when graphitized carbon black cartridges are used, but has no effect when C_{18} cartridges are used. Fig. 1 also suggests that the addition of sodium thiosulphate to tap water can increase the recovery if the cartridge is not pre-eluted with ascorbic acid solution, but can decrease the recovery if the cartridge is pre-eluted with ascorbic acid solution. Therefore, the two treatments should not be used together. To explain this observation, further investigation is needed. As sodium thiosulphate will not be used in analyses of real samples, the problem will not exist.

The ANOVA results of the third experiment (Table 5) indicate that humic acid (A) and water pH (B) have significant effects on the recovery, among which humic acid is the most important factor ($RC = 60\%$). The interaction effect between pH and NaCl ($B \times C$) is near the significant level. The two elution methods (back-flush and front-forward elution) make no difference in recovery when C_{18} cartridges are used. When the

concentration of dissolved organic substances was increased from 2 to 10 mg l^{-1}, the recovery dropped from 81 to 61%. When the pH was lowered from 8.5 to 3.5, the recovery increased from 65% to 77%. At pH 3.5 addition of sodium chloride can decrease the recovery and at pH 8.5 addition of sodium chloride can increase the recovery. Although the effects of humic acid and pH can be explained based on the results of Johnson *et al.* [6] and Liska *et al.* [2], the interaction between pH and salinity can only be an observation here. As there are no significant interactions between humic acid and pH and between humic acid and sodium chloride, it is impossible to decrease the adverse effects of humic acid through adjustment of the pH and the concentration of salt.

Based on the results of the three experiments, the conditions for extraction of pesticides from water were chosen as follows: C_{18} as extraction cartridge, methanol as preconditioning solvent (10 ml) and as eluent (5 ml), elution by the front-forward method, air-drying time 0.5 min and addition of sodium thiosulphate when the recoveries of pesticides from tap water are to be determined.

Table 6
Recoveries of pesticides from water by solid-phase extraction (duplicated results)

Pesticide	Retention time (min)	Recovery (%)[a]		
		A	B	C
Simazine	3.96	96, 112	94, 97	88, 84
Isoprocarb	5.70	73, 61	64, 108	84, 83
Fenobucarb	7.70	84, 103	93, 125	106, 110
Methyldymiron	8.80	95, 105	83, 113	89, 99
Napropamide	10.1	85, 95	87, 91	94, 97
Isoprothiolane	11.2	86, 95	90, 106	99, 123
Mepronil	13.4	81, 93	82, 83	88, 99
Flutolanil	14.6	93, 107	94, 122	103, 106
Diazinon	16.4			84, 85
Thiobencarb	22.0	84, 96	84, 87	84, 87
Iprodione	23.5	26, 49	84, 89	85, 89
Terbutol	25.0	88, 103	90, 98	90, 95
Isofenphos	28.7	121, 132	122, 123	119, 129
Pencycuron	30.9	99, 108	99, 101	96, 103
Butamifos	33.0	98, 101	96, 97	99, 106
EPN	37.3	77	87	83, 90
Pendimethalin	54.4	70, 79	73, 79	59, 67
Chlorpyrifos	56.4	49, 71	71, 79	65, 69
Balan	70.9	63, 73	66, 69	61, 64
Dichlorvos	3.85	82, 123	49, 89	67, 88
Thiram	5.50	2, 20	0, 3	15, 17
Captan	9.25	19, 25	13, 13	0, 0
Pyridaphenthion	11.2	75, 95	79, 95	101, 112
Chloroneb	12.7	77, 106	79, 106	62, 78
Proamide	13.4	66, 105	90, 109	90, 98
Chlorothalanil	15.2	57	83	82, 91
Etridiazole	16.8	49, 82	20, 76	32, 85
Bensulfite	30.4	122, 138	99, 156	110, 117
Tolclofos	32.1	85, 105	81, 96	75, 83
Isoxathion	39.4	60, 60	108, 143	115, 139

[a] A = Extracted from tap water with graphitized carbon black cartridge; B = extracted from tap water with C_{18} cartridges; C = extracted from sea water with C_{18} cartridges.

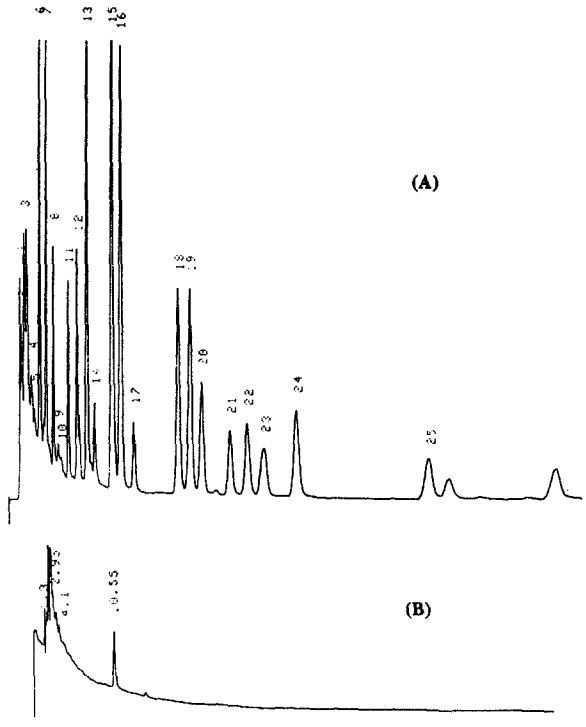

Fig. 2. Chromatograms of sea water samples. (A) Fortified with group 1 pesticides at 10 $\mu g\ l^{-1}$ level (6 = simazine; 8 = isoprocarb; 11 = fenobucarb; 12 = methyldymiron; 13 = napropamide; 14 = isoprothiolane; 15 = mepronil; 16 = flutolanil; 17 = diazinon; 18 = thiobencarb; 19 = aprodione; 20 = terbutol; 21 = isophenfos; 22 = pencycuron; 23 = butamifos; 24 = EPN; 25 = pendimethalin; 26 = chlorpyrifos; 27 = balan). (B) Blank sea water (0.5 l) extracted with a C_{18} cartridge following the same procedures as fortified samples.

Under the optimum conditions, the recoveries of the pesticides from tap water and sea water at the 10 $\mu g\ l^{-1}$ level were determined. The results are given in Table 6. The chromatograms of fortified and blank sea water samples are given in Fig. 2.

4. Conclusions

The concept of the optimum in systematic optimization is a conditional one; it depends on the goals one wants to achieve and the experimental conditions available. In this study, the recoveries of some pesticides were not satisfactory under the selected conditions. It is possible that some variables that may affect the extraction of these pesticides have not been studied or some important levels have been missed. In the case of the sorbent type, more levels may be tested to improve the recoveries of the pesticides. Although the optimization by factorial designs is regarded as a simultaneous method, the optimum is actually located step by step as in sequential approaches. In this study, the second experiment was designed based on the results of the first experiment, and the third experiment was based on the first and the second experiments. This process can be continued with new variables and more accurate levels to achieve better results. It should be mentioned that orthogonal array designs, as with other factorial designs, cover a predefined region. Problems appear in situations where the initial values of the effects are too close together to give a significant difference, or are too far apart, giving a large but useless significant difference. Therefore, it is necessary to rely on previous knowledge of the system, past experience and intuition when the levels of the variables are chosen [16]. Previous knowledge is also necessary in interpreting the results, otherwise certain observations will remain mere observations.

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