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Journal of Chromatography A, 1045 (2004) 29–35
JOURNAL OF CHROMATOGRAPHY A
www.elsevier.com/locate/chroma

Application of single-drop microextraction to the determination of dialkyl phthalate esters in food simulants

Ramón Batlle*, Cristina Nerín

Department of Analytical Chemistry, Aragón Institute of Engineering Research i3A, CPS-University of Zaragoza, Torres Quevedo Bldg., María de Luna St. 3, E-50018 Zaragoza, Spain

Available online 8 July 2004

Abstract

A fast and simple method, using static single-drop microextraction (SDME), has been developed to facilitate the identification and quantification of seven dialkyl phthalate esters in the three aqueous food simulants. The simulants were: A, distilled water; B, 3% (w/v) acetic acid/water; and C, 15% (v/v) ethanol/water. The extraction is performed by simply suspending a drop of organic solvent in the aqueous sample using a conventional gas chromatography (GC) microsyringe. Following extraction, the organic phase is withdrawn into the syringe and analyzed by gas chromatography and flame ionization detection (FID). The optimized method yields a linear calibration curve over three orders of magnitude for all the simulants, and method detection limits (MDLs) allowing detection of all the studied compounds at concentrations below migration limits established by the European Union. The accuracy of the SDME method was tested and compared to that of solid-phase microextraction (SPME) by recovery experiments using spiked samples, with results ranging from 85 to 115% in most cases.

Keywords: Single-drop microextraction; Experimental design; Food analysis; Dialkyl phthalate esters

1. Introduction

Single-drop microextraction (SDME) is a fast and inexpensive extraction technique where a microdrop of organic, water-immiscible solvent is suspended at the end of a microsyringe needle, which is then immersed in a stirred aqueous sample solution for a specified period of time [1–5]. Like solid-phase microextraction (SPME), the technique offers significant advantages over liquid–liquid extraction (LLE) or solid-phase extraction (SPE) including near-total elimination of the use of toxic solvents, high enrichment factors due its comparatively small ratio of amount extracting solvent to sample, and integration of extraction and injection in a simple device. The main drawbacks with SPME are that extraction fibers are expensive and have a limited life [6], and sample carry-over between extractions has been reported for some analytes [7]. In contrast with the limited amount of SPME fibers commercially available, any extraction solvent immiscible with water (for extracting aqueous matrices) can be used in SDME, it requires only common laboratory equipment and it is essentially carry-over free.

Further developments of the technique have encompassed the introduction of dynamic microextraction approaches [8,9], the use of ionic liquids as extraction solvents [10], and the use of a hollow fiber to enhance extraction efficiency and to stabilize the extracting solvent drop [11–13]. Review articles have covered different aspects of SDME [14,15], and a review devoted specifically to the technique has been published recently [16]. In spite of the large number of variables that could potentially influence the results obtained from SDME, only the univariant sequential technique for method optimization has been applied in the scientific literature. In this work, chemometric approaches, including Plackett–Burman experimental design followed by a response surface design, were used to provide method optimization as well as some insight into the relevant factors.

Dialkyl phthalate esters (hereafter referred to as phthalates) are ubiquitous in the environment due to their widespread use in various commercial products since 1930s and their slow degradation. The toxicity of several phtalates has been evaluated in animals and the results have led to suspicious that native phthalates as well as their primary

* Corresponding author. Tel.: +34 976 761000x5040; fax: +34 976 762388.
E-mail address: r13bat@unizar.es (R. Batlle).

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doi:10.1016/j.chroma.2004.06.001

metabolites (mainly monoesters [17,18]) may have carcinogenic and estrogenic properties, and can adversely affect human health [19–22]. One of the markets in which they have found many applications is the food packaging industry, where they are used as plasticizers, adhesives, offset printing inks and lacquers. Restrictions, known as specific migration limits (SMLs) [23,24], on the quantities of substances capable of migrating into the packaged food are imposed on materials intended to come into contact with it. Compliance with these limits has to be checked using food simulants as model for different categories of food [25].

From the foregoing, it is clear that there is a need for analytical methods that allow rapid and reliable quantitation of phthalates in aqueous samples. Conventional multi-step sample pretreatment methods as LLE [26,27] and SPE [28,29] are commonly employed as for the determination of phthalate esters in aqueous matrices requiring extensive sample handling and appreciable amount of solvent [30]. The use of SPME [31–33], the recently introduced carbon nanotubes (CNT) [34], or hollow-fiber liquid-phase microextraction techniques [35] for the extraction of several phthalate esters from water samples enable determination at very low ($\mu g\,L^{-1}$) concentrations and simultaneously reduces the risk of secondary contamination during sample handling. Nevertheless, most of the reported applications of these techniques have been restricted to pure water matrices. Thus, the aim of the present study is to investigate the applicability of SDME to the extraction of phthalates from aqueous food simulants.

2. Experimental

2.1. Standards and reagents

The analytes used were selected from those reported in the scientific literature to be found in food packaging materials [36–38]. Diethylhexyl phthalate (DEHP), dibutyl phthalate (DBP), diisobutyl phthalate (DiBP), dimethyl phthalate (DMP), diisopropyl phthalate (DiPP), and diethyl phthalate (DEP) (98.0% or better) were obtained from Sigma-Aldrich (Madrid, Spain). Di-*n*-octyl phthalate (DOP > 99.5%, Fluka, Buchs, Switzerland) was added to the analyte mixture as a quality check for the technique since it has been reported to constitute a severe contamination problem. 2,6-Di-*tert*-butyl-*p*-cresol (BHT, >99.0%) was supplied by Fluka. BHT is an antioxidant and was included in this study in order to investigate the possibility of expanding the proposed method to a wider range of constituents of food packaging materials. Spiking test solutions containing the analytes were made by adding different amounts of standard methanol solutions to volumes of the food simulant, with the final sample having a maximum methanol content of 1%.

3,5-Di-*tert*-butyl-4-hydroxyanisol (bBHA, internal standard, >98.0%) was also purchased from Fluka. Internal standard solutions were prepared each week by diluting of an *n*-hexane stock solution ($100\,\mu g\,g^{-1}$) with the solvent being studied (original solvent in the final solution <0.1%). Mixtures were prepared as required by direct mixing of bBHA solutions. Table 1 shows some physico-chemical characteristics of the analytes and the internal standard.

Table 1
Physicochemical properties of the analytes studied

Analyte	CAS	Molecular weight	Water solubility ($mg\,L^{-1}$)	log *P*	SML ($mg\,kg^{-1}$)
DMP	131-11-3	194	4000	1.60	3.0
DEP	84-66-2	222	1080	2.42	12.0
DiPP	605-45-8	250	332	2.83	–
DBP	84-74-2	278	11.2	4.50	3.0
DiBP	84-69-5	278	6.20	4.11	3.0
DEHP	117-81-7	390	0.27	7.60	3.0
DOP	27554-26-3	390	0.09	8.39	–
BHT	128-37-0	220	0.60	5.10	3.0
bBHA	489-01-0	236	213	4.56	–

Food simulants used in the study were as follows: distilled water (simulant A); 3% (w/v) acetic acid/water solution (simulant B), and 15% (v/v) ethanol water solution (simulant C) [25]. Methanol, ethanol, isopropanol (gradient HPLC grade), hexane, cyclohexane, diethyl ether, isooctane, and dichloromethane (gas chromatography (GC) residue analysis) were obtained from Scharlab (Barcelona, Spain). Toluene, acetone, and glacial acetic acid (for analysis) were supplied by Merck (Darmstadt, Germany). Water was provided by a Milli-Q purification system (Millipore Ibérica SA, Madrid, Spain). All glassware used in the study was previously washed with a tetrahydrofuran–methanol mixture, and then rinsed with isopropanol, hexane, and finally acetone before each use.

2.2. Instrumentation

Chromatographic analysis was performed on a Hewlett-Packard (Palo Alto, CA, USA) 5890 Series II gas chromatograph equipped with a split/splitless injector used in splitless mode and a flame ionization detector (FID). Separations were conducted using a DB-5, 30 m × 0.32 mm capillary column with a 0.25 μm stationary phase thickness (J&W, Folsom, CA, USA). The carrier gas was C-50 nitrogen (Carburos Metálicos, Barcelona, Spain) at a flow rate of 1.0 mL/min. The GC conditions were as follows: injector temperature 260 °C; splitless time 1.0 min; detector temperature 300 °C; initial oven temperature 60 °C for 1 min, increased to 120 °C at a rate of $25\,^{\circ}C\,min^{-1}$, and a second ramp to 285 °C at a rate of $10\,^{\circ}C\,min^{-1}$.

2.3. Single-drop microextraction (SDME)

Before every extraction, the syringe was rinsed 10–15 times with the organic extraction solvent to avoid formation of air bubbles and the carryover of compounds between extractions. Then, 5 μL of extraction solvent were drawn into the syringe and suspended over the vial using a metal stand.

A Hamilton 85RN (26S/51 mm/needle type 2) 5 μL syringe (Hamilton Bonaduz AG, Bonaduz, Switzerland) was used in all the extractions. The needle was immersed to a given depth and the plunger was depressed in order to expel 1.5–3.5 μL of the solvent (depending on the desired drop volume). The drop formed was discarded and the plunger was then totally depressed to generate a 1.5–3.5 μL droplet of solvent on the needle tip. Meanwhile, the solution was constantly stirred (when required), to promote the diffusion of the analytes from the matrix into the solvent drop. With the extraction finished, the drop was retracted, leaving 0.5 μL in the solution to ensure that no aqueous entered the GC system. The syringe was then taken out of the vial, the needle tip cleaned carefully with a tissue, and the solvent injected into the GC. All the extractions were performed in 20 mL sylanized glass vials (Teknocroma, Barcelona, Spain).

Experiments based on a fractional factorial Plackett–Burman design were performed to identify significant experimental parameters affecting SDME. The results were used to develop a response surface design (central composite circumscribed (CCC) design) to optimize the single-drop extraction process. All statistical calculations were performed using Modde 4.0 for Windows by Umetri (Umeå, Sweden).

2.4. Solid-phase microextraction (SPME)

SPME was used as described by Psillakis and Kalogerakis [35]. No further optimization of the method was performed to extract the acidic simulants. In brief, a 65 μm polydimethylsiloxane-divinylbenzene (PDMS-DVB) fiber (Supelco, Bellefonte, CA, USA) was used to extract 14 g of each simulant. The stirred solution (1000 rpm) was sampled at 50 °C for 20 min. In accordance with the manufacturer's specifications, the fiber was conditioned before its first use.

Once the extraction was finished, the fiber was retracted and transferred to the heated injection port (260 °C) of the GC-FID. Injection was performed in splitless mode for 2 min, but the fiber remained in the injector block for 10 min to ensure complete desorption and to prevent carryover. However, blank analyses were performed every 12 samples, and the rejection criteria for all the analytes was a detectable raw signal above 1% of a 25 μg L^{-1} liquid injection solution.

3. Results and discussion

3.1. SDME optimization

Several solvents, with different chemical characteristics (i.e. polarity, volatility, solubility in water, dipole moment and viscosity), were tested. Table 2 lists the solvents studied. Solvents were evaluated for a triplicate extraction of a 10 g simulant sample containing 25 μg L^{-1} of each analyte. The stirred solution (600 rpm) was sampled at 50 °C for 25 min using a 2 μL drop at a 1 cm depth of the appropriate organic solvent. Two optimization criteria were used. The first was the enrichment factor, calculated as the ratio of the strength of signal obtained for each analyte extracted to that obtained following direct liquid injection of a 25 μg L^{-1} analyte solution. The second, refers to drop integrity calculated as the ratio of the signal for the internal standard (bBHA) obtained following extraction to that obtained following direct injection of the appropriate bBHA solution.

The best results were obtained with 7:3 DCM:hexane (w/w) when working with simulants A and C. In contrast, 1:9 DCM:hexane (w/w) was required with simulant B, because the use of percentages of dichloromethane above 20% resulted in impracticably high levels of drop loss (more than 50%). Working with simulants A and C an estimated 30% of the droplet volume was lost when using dichloromethane as the extraction solvent, whereas only approximately a 15% was lost using hexane. Nevertheless, the bBHA signal observed following extraction with DCM was comparable to that observed using hexane. Therefore, it seems that, when using dichloromethane-enriched drops, evaporative losses are significant (one has to remember that boiling point for DCM is 40 °C and extraction temperature is 50 °C). When hexane is the principal component of the mixture, loss is largely due to drop dissolution. Since hexane has only a very limited solubility in water (see Table 2), we believe that this is related to its relatively low surface tension when compared to dichloromethane, an explanation which is also consistent with the somewhat higher rate of drop loss (estimated at 10%) observed when working with hexane.

The use of a third solvent in the extracting mixture can help alleviate these problems. As shown in Table 2, toluene is the solvent of choice since it has both a high boiling point (thus reducing evaporative losses) and high surface

Table 2
Extraction solvent candidates[a]

Extraction solvent	Water solubility (mg L^{-1}, 25 °C)	log *P*	Surface tension (dyn cm^{-1})	Dipole (*D*)	Viscosity (cP)	Boiling point (°C)
Diethyl ether	**6 × 10⁴**	*0.89*	*17.06*	0.24	**1.15**	*34.5*
n-Hexane	*9.5*	3.90	17.91	0.31	*0.08*	68.7
Dichloromethane	1.3 × 10^4	1.25	28.12	**1.14**	0.44	40
Toluene	526	2.73	**28.53**	0.08	0.59	**110.6**
Cyclohexane	55	3.44	–	*0*	1.0	80.7
Isooctane	2.44	**4.09**	18.77	*0*	0.50	99.2

[a] Bold and italic characters represent maximum and minimum values, respectively, of the parameters among the solvents tested.

Table 3
Factors and levels tested (coded values in parentheses) for SDME screening and CCC experimental design

Factor[a]	Low level[b]	Medium level[b]	High level[b]
Extraction time (*T* (min))	2	16	***30***
Extraction temperature (Te (°C))	30	***55***	80
Amount of salt (*S* (%))	***0***	5	10
Stirring rate (*R* (rpm))	0	350	***700***
Drop volume (*D* (μL))	1	***2.5***	4
Sample mass (*M* (g))	*8*	14	**20**
Sampling depth (Sa (mm))	3	***6.5***	10

[a] Bold factors were selected for RSM design for simulants A/C whereas italic factors were selected for simulant B.
[b] Bold and italic characters represent optimum values found within the experimental domain for simulants A/C and B, respectively.

tension, increasing cohesive forces at the interface and thus reducing solvent re-dissolution. Moreover, its log *P* value is intermediate among the solvents under studied, so it would not be expected to cause any major changes to the extracting properties of the solvent mixtures. Mixtures with proportions of toluene ranging from 1 to 25% (w/w, $n = 3$) were experimented with. In all cases, solvent losses were reduced, but, when using higher concentrations detrimental changes (i.e. peak doubling and tailing in the early eluting compounds resulting in poor chromatography) were observed. Toluene content was, therefore, fixed at a 5% (w/w) of the extracting solvent in both cases. So the optimum solvent conditions were fixed as follows: simulants A and C (7:3:0.5 DCM:hexane:toluene); simulant B (1:9:0.5 DCM:hexane:toluene).

In a first optimization step, a Plackett–Burman [39,40] experimental design including seven experimental variables at two levels was employed, including eight experiments plus three replicates at the central point. Two replicates of the design were performed for each simulant under study. Samples were spiked by adding the appropriate amount of either blank methanol (blank sets) or standard methanol solution to food simulant. Then glass vials housing the samples were then wrapped in aluminum foil, and allowed to equilibrate for at least 7 days at 4 °C (the "aging" procedure) prior to analysis. Blank analyses were performed every 10 runs using the blank set sample. No detectable signal for any of the analytes under study was detected, which is especially relevant for DOP, as explained previously. Table 3 shows the factors selected for study.

Coefficients *R* and *T* appeared to correlate positively with the set criteria, while *D* and *M* seemingly correlate negatively, but these conclusions should be treated with caution, since interactions between individual factors are not included in this model. For simulant B, coefficient *S* was also relevant, but only by a narrow margin. Thus, a response modeling design (CCC) was constructed including the relevant factors as presented in Table 3. The designs consisted of 24 randomized experiments (plus five replicates at the central point, two replicates of the design performed) for simulants A and C, and 26 randomized experiments (plus five central point replicates, two replicates) for simulant B.

Since each replicate of the model had to be performed on 2 different days, the block effect had to be evaluated prior to further data analysis. It was found to be negligible at the 95% confidence level, indicating that performing the runs over a number of days would introduce no additional bias. Fig. 1 shows the significant factors and their coefficients, as well as the descriptive values, R^2 and Q^2. Again, similar results were obtained for simulants A and C (for clarity, only simulant A coefficients are shown), whereas the acidic simulant B produced different results.

For simulants A and C (upper part of Fig. 1) it can be seen that factors *R* and *T* are the only significant factors that correlate positively with efficiency of extraction. It is easy to understand that an increase in the stirring rate, *R*, will

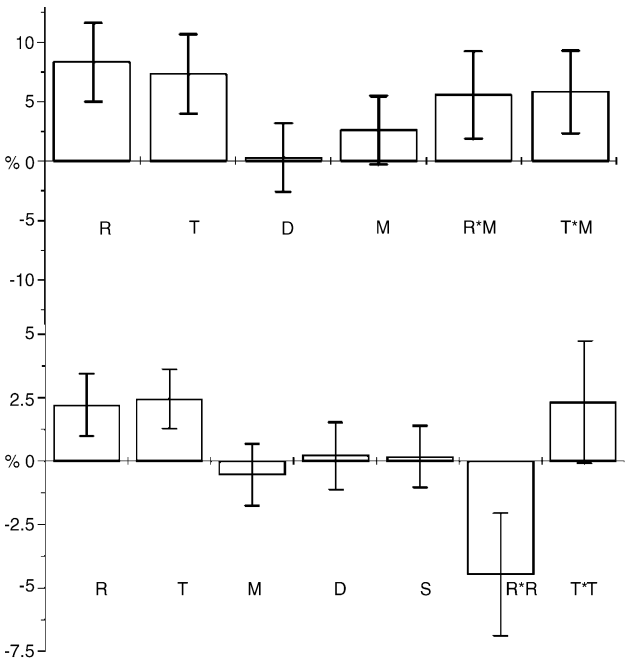

Fig. 1. Scaled and centered coefficients for significant factors in the response surface modeling CCC design. Upper panel, simulant A (analogous in form to the one found for simulant C); lower panel, simulant B. For the identifications of factors, see Table 3. Numbers in parentheses refer to coefficients for simulant C; those in italics to coefficients for simulant B.

increase the amount of analyte extracted by reducing the thickness of the stagnant film, in which only slow diffusion can take place and which therefore constitutes the bottleneck of the extraction process, as suggested by general diffusion theory. The positive result for the extraction time, *T*, suggests that equilibrium has not been reached within the tested time span, and so increasing the extraction time increases the extracted amount of analytes. It must be emphasized that even if a single coefficient is not directly relevant (as in the case of *M*), this does not mean that it cannot have any influence on the optimized process, through cross-interaction terms, as can be seen in Fig. 1.

For simulant B (lower panel, Fig. 1) the significance of all the cross-interaction terms was extremely low, indicating that no interaction between variables occurs. Again, *R* and *T* were the only relevant factors, both correlating positively with the response. Table 3 also shows the optimum values selected within the experimental domain. An extraction time of 30 min was chosen, but this can be reduced to match the time required for chromatography (approximately 23 min including cooling and post-run stabilization) to maximize sample output, while maintaining an 85% of the average response for all the analytes. Fig. 2 shows typical chromatograms obtained working with different simulants.

3.2. Analytical performance

In order to evaluate it, the proposed method's repeatability (expressed as CV (%)), linearity and method detection limit (MDL) were investigated under optimized conditions. Calibration curves were generated for each simulant and their linearity was evaluated by extracting them with the appropriate extracting phase (containing 10 $\mu g\,L^{-1}$ of bBHA) from 50 to 0.01 $\mu g\,L^{-1}$. Most of the analytes gave linear curves in the range 0.1–50 $\mu g\,L^{-1}$ for simulants A and C, the two exceptions were DOP and DEHP which had a narrower range (from 0.5 $\mu g\,L^{-1}$). For simulant B, the dynamic range was shorter for all the analytes, in this case from 50 to 0.3 $\mu g\,L^{-1}$ (DOP and DEHP, 0.75 $\mu g\,L^{-1}$).

To determine the precision of the overall method, 15 samples of each simulant were spiked at 0.5 $\mu g\,L^{-1}$ (DOP and DEHP, 1.0 $\mu g\,L^{-1}$). Table 4 shows the average results, together with method detection limits. To determine these limits for each analyte, MDLs were then calculated as the product of the standard deviation of the 15 replicates and the two-tailed *t*-value for 14 degrees of freedom at the 95% confidence level ($t = 2.14$) [41,42].

As can be seen, MDLs are in the low μg per L range. Since the method is designed to monitor phthalate migration from packaging materials, it is interesting to compare these values with the SMLs listed in Table 1. As can be seen, the lowest SML for these analytes is 3.0 $mg\,kg^{-1}$ of packaged food, so in the worst case 3 μg of analyte will be transferred to each gram of food (i.e. simulant). Thus, MDLs are well below the required standards. Moreover, the method can be used to

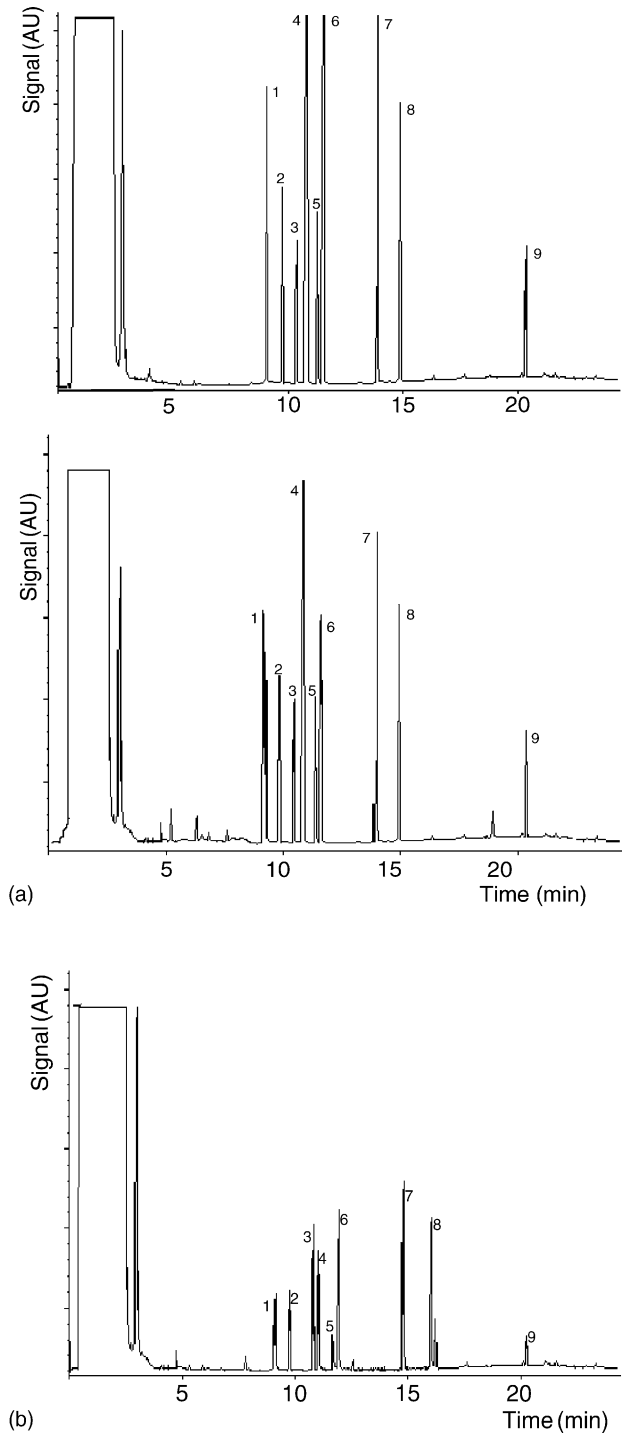

Fig. 2. Chromatograms obtained in the extraction of simulants under study. (a) upper panel, distilled water, simulant A; lower panel 15% (v/v) ethanol solution, simulant C. (b) 3% (w/v) acetic acid solution, simulant B. Peak identification: (1) DMP; (2) BHT; (3) bBHA (internal standard); (4) DEP; (5) DOP; (6) DiPP; (7) DiBP; (8) DBP; (9) DEHP.

accomplish with US Environmental Protection Agency (EPA) recommendations of closely monitoring concentrations of DEHP above 0.6 $\mu g\,L^{-1}$ in drinking water [43]. Compared to other techniques, MDLs obtained in water are similar to those reported for in-tube SPME [32]

Table 4
Analytical performance

Analyte	Simulant	MDL ($\mu g\,L^{-1}$)	CV (%)	0.5 ($\mu g\,L^{-1}$) SDME/SPME[a]	CV (%)	5 ($\mu g\,L^{-1}$) SDME/SPME[a]
DMP	A	0.07	7.0	98/102	7.0	97/95
	B	0.21	8.0	96/94	12	99/106
	C	0.08	7.0	99/101	7.0	98/96
BHT	A	0.05	5.0	104/116	6.0	101/109
	B	0.20	6.5	82/64	8.0	92/86
	C	0.09	5.0	106/108	7.0	100/105
DEP	A	0.02	3.5	95/101	4.5	95/100
	B	0.13	6.0	85/91	6.0	81/92
	C	0.03	4.5	91/102	5.0	87/90
DOP	A	0.15	10	85/102	8.0	87/101
	B	0.40	16	81/85	17	77/86
	C	0.21	10	87/95	12	89/96
DiPP	A	0.04	5.0	91/92	6.0	93/96
	B	0.20	7.0	78/72	11	78/70
	C	0.09	6.0	90/93	5.0	89/95
DiBP	A	0.02	3.5	81/90	4.0	86/93
	B	0.10	6.0	78/85	5.0	75/89
	C	0.03	4.0	81/91	5.0	80/90
DBP	A	0.03	4.5	110/86	5.0	98/83
	B	0.16	8.0	86/82	12	85/79
	C	0.07	4.5	112/95	5.0	99/85
DEHP	A	0.12	8.0	116/90	7.5	118/102
	B	0.31	15	80/70	16	85/75
	C	0.20	10	111/95	12	115/97

[a] $n = 5$. Expressed as recovery percentage.

or carbon nanotubes [34], but are higher by an order of magnitude than those reported for SPME [33] or hollow-fiber LME [35]. No results listing MDLs for other techniques for the other simulants could be found in the literature, and therefore no comparison with these simulants was possible.

The performance of the method was compared with that of the SPME method described in Section 2.4. For this purpose, sets of five samples prepared in both simulants were spiked again at the two concentration levels (0.5 (DOP and DEHP 1.0) and 5.0 $\mu g\,L^{-1}$), and extracted and quantified using both techniques. Table 4 shows the comparison between the average recoveries found. No significant differences in the means or precision were found between the two methods (ANOVA, confidence level 95%, data not shown).

4. Conclusions

This paper describes the use of single-drop microextraction for sampling food simulants containing traces of dialkyl phthalate esters. The proposed method has been shown to be highly practical because of its high reproducibility, convenient dynamic range and method detection limits, as well as its overall robustness, with respect to matrix characteristics (direct application to alcoholic or acidic matrices has been shown) and ubiquitous pollutants (DOP study). The proposed methodology reduces the amount of solvent necessary for the whole procedure to $\sim 5\,\mu L$ thus eliminating the need for additional cleaning or concentration steps.

The determination of BHT as a model compound has been used to test the applicability of SDME as a routine control technique for migration testing, since it is cheap, easy to use, and does not require specific training or equipment, and provides high sample output. Further research should therefore focus on applying the proposed methodology to the determination of other potentially migrant packaging constituents, such as UV stabilizers, antioxidants, or lubricants in food simulants.

The analysis of fatty food simulants (simulant D, olive oil or proposed substitute) is another challenge. In such cases, direct exposure is not an option, and it is necessary to protect the extracting phase, by using membranes or hollow fiber approaches.

Acknowledgements

This work was financed by the Spanish Projects AGL-2001-1808 and CAL 01-084-INIA. R. Batlle gratefully acknowledges the Spanish Ministry of Science and Technology for personal funding through the Ramón y Cajal program.

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